

American Academy of Clinical Toxicology
Special Interest Group: Herbs & Dietary Supplements
Literature Summary Service
May 13, 2008

1. Creemers L, Van den Driessche M, Moens M, Van Olmen A, Verschaeren J, T'Syen M, Desmet K, Moerman J. Safety of alternative medicines reconsidered: lead-induced anaemia caused by an indian ayurvedic formulation. *Acta Clin Belg.* 2008;63(1):42-5. PMID: 18386765
We report two cases of Belgian women diagnose with a lead poisoning. Both patients presented with abdominal pain and a normochromic normocytic anaemia. The diagnosis was based on the clinical symptoms, the anaemia, the basophilic stippling of erythrocytes and the elevated blood lead level Upon further questioning, both patients reported the use of Ayurvedic medications. Toxicological analysis of the different pills revealed that, in both, the same orange-red pills contained a remarkably high amount of lead. Cases of lead poisoning associated with the use of Ayurvedic formulations are emerging around the world. However, to our knowledge, these are the first reported cases in Belgium.
2. Gamma-aminobutyric acid (GABA), Monograph. *Altern Med Rev.* 2007;12(3):274-9. PMID: 18072823
3. *Urtica dioica*; *Urtica urens* (nettle). Monograph. *Altern Med Rev.* 2007;12(3):280-4. PMID: 18072824
4. Sun J. D-Limonene: safety and clinical applications. *Altern Med Rev.* 2007;12(3):259-64. PMID: 18072821
D-limonene is one of the most common terpenes in nature. It is a major constituent in several citrus oils (orange, lemon, mandarin, lime, and grapefruit). D-limonene is listed in the Code of Federal Regulations as generally recognized as safe (GRAS) for a flavoring agent and can be found in common food items such as fruit juices, soft drinks, baked goods, ice cream, and pudding. D-limonene is considered to have fairly low toxicity. It has been tested for carcinogenicity in mice and rats. Although initial results showed d-limonene increased the incidence of renal tubular tumors in male rats, female rats and mice in both genders showed no evidence of any tumor. Subsequent studies have determined how these tumors occur and established that d-limonene does not pose a mutagenic, carcinogenic, or nephrotoxic risk to humans. In humans, d-limonene has demonstrated low toxicity after single and repeated dosing for up to one year. Being a solvent of cholesterol, d-limonene has been used clinically to dissolve cholesterol-containing gallstones. Because of its gastric acid neutralizing effect and its support of normal peristalsis, it has also been used for relief of heartburn and gastroesophageal reflux (GERD). D-limonene has well-established chemopreventive activity against many types of cancer. Evidence from a phase I clinical trial demonstrated a partial response in a patient with breast cancer and stable disease for more than six months in three patients with colorectal cancer.
5. Chawla S, Asmar A, Smith CA. Rhabdomyolysis: a lesson on the perils of exercising and drinking. *Am J Emerg Med.* 2008;26(4):521 e3-4. PMID: 18410842
Acute abdomen is a common presentation to the emergency department (ED), accounting for 5% to 10% of ED visits. Of these, 10% require surgery, and 25% go undiagnosed. Usually, most of the cases of undiagnosed abdominal pain are in young women with pelvic etiologies, although occasionally, unusual causes of abdominal pain lead to diagnostic dilemmas and can have adverse clinical outcomes. We present an unusual etiology of abdominal pain in a young man, who presented with acute onset of right lower quadrant pain accompanied by nausea and vomiting. He

was an amateur boxer who had recently intensified his training regimen and admitted to binge drinking for several days before presentation. The initial diagnosis was acute appendicitis, but a computed tomographic scan done revealed a normal appendix. Creatine kinase level was then checked and found to be significantly elevated, and a diagnosis of isolated abdominal wall rhabdomyolysis was made.

6. Shavit I, Hoffmann Y, Shachor-Meyouhas Y, Knaani-Levinz H. Delayed hypersensitivity reaction from black henna tattoo manifesting as severe facial swelling. *Am J Emerg Med.* 2008;26(4):515 e3-4. PMID: 18410830
We report on a 14-year-old boy who was presented to the emergency department with an acute swelling of the face and scalp 3 days after using a new hair dye. The patient had applied a black henna tattoo 1 year earlier. Patch testing revealed an allergy to the potent skin sensitizer paraphenylenediamine, a common ingredient of hair dyes and also found in black henna tattoo. It is important for emergency physicians to be aware of the possibility of a delayed type-IV hypersensitivity reaction from black henna tattoos manifesting as an acute contact dermatitis. These patients may have gross facial swelling but should not be treated for angioedema.
7. Beuth J, Schneider B, Schierholz JM. Impact of complementary treatment of breast cancer patients with standardized mistletoe extract during aftercare: a controlled multicenter comparative epidemiological cohort study. *Anticancer Res.* 2008;28(1B):523-7. PMID: 18383896
OBJECTIVES: To investigate the safety and efficacy of complementary treatment of breast cancer patients with the standardized mistletoe extract (sME) HELIXOR in routine practice during aftercare through a multicenter comparative epidemiological cohort study with 53 randomly selected hospitals/practices representatively distributed in Germany, including oncologists, gynaecologists and general practitioners. PATIENTS AND METHODS: Data from 741 screened patients fulfilling the inclusion/exclusion criteria were checked. Of these, 681 patients were eligible for the final analysis of the study group (with sME n = 167) and the control group (n = 514). Efficacy (development of disease/therapy-induced signs and symptoms; quality of life) and safety (number and severity of adverse events) of complementary treatment in breast cancer patients treated with sME in the aftercare period were determined. RESULTS: Complementary treatment of breast cancer patients with sME during the aftercare period of approximately 5 years after terminating recommended standard therapies resulted in significantly fewer ($p < 0.001$) complaints of patients (56.3% study group versus 70.0% control group). The reduced number of disease/therapy-related sign/symptoms (e.g. mucositis, fatigue, pain, headache) correlated to a significantly improved quality of life. Adverse drug reactions to the sME treatment were mostly mild and self limiting. CONCLUSION: Complementary treatment with the sME HELIXOR proved to be beneficial for breast cancer patients since it significantly improved quality of life and significantly reduced persistent signs/symptoms of the disease/treatment during the validated aftercare period of approximately five years.
8. Preziosi P, Minotti G. Beyond poisons and problems: toxicology in Italy. *Chem Res Toxicol.* 2008;21(4):771-4. PMID: 18422367
9. Gupta S, Ashrith G, Chandra D, Gupta AK, Finkel KW, Guntupalli JS. Acute phenol poisoning: a life-threatening hazard of chronic pain relief. *Clin Toxicol (Phila).* 2008;46(3):250-3. PMID: 17852157
BACKGROUND: Phenol (carbolic acid, a higher alcohol) has been used for local analgesic therapy for a long time. Several complications of phenol therapy can occur by exposure through inhalational, oral, and dermal routes. Renal and pulmonary toxicity arising from the exposure to injectable phenol, however, has only been reported in a few case reports. CASE PRESENTATION: A 50-year-old man inadvertently received 10 cc of 89% phenol injection. It

resulted in the development of acute respiratory and renal failure requiring intubation and hemodialysis, respectively. He improved clinically with the recovery of renal function. However, the chest x-ray and CT scan showed persistent nodular pulmonary infiltrates which resolved by six months. **CONCLUSION:** We report here an unusual case of acute respiratory and acute renal failure following accidental overdose of phenol. The case highlights potential development of multiple organ failure with persistence of organ dysfunction, an unusual danger associated with the overdose of injectable phenol for neurolysis.

10. Knudsen K, Greter J, Verdicchio M. High mortality rates among GHB abusers in Western Sweden. *Clin Toxicol (Phila)*. 2008;46(3):187-92. PMID: 18344100
BACKGROUND: GHB is a drug of abuse and acute poisonings have been an increasing medical problem over the last decade in Sweden. **OBJECTIVES:** To document all cases of GHB poisonings in Gothenburg during 1995-2004 and to record drug-related deaths to compare the toxicity of GHB with other illicit drugs, such as heroin and amphetamine. **METHODS:** The number of GHB-poisoned patients treated at the Sahlgrenska University Hospital has been recorded with the help of an in-house database. The number of deaths by illicit drugs was recorded during 2004. Seizures of the drugs GHB, 1,4-butanediol, and GBL were registered between 1996 and 2004. **RESULTS:** The number of poisoned patients was 259. The number of seizures with GHB was 743, GBL 343, and 1,4-butanediol 236. In 2004 the number of deaths was 6 with heroin, 7 with GHB, 32 with amphetamine, 6 with cocaine, and one with methadone. One patient with GHB poisoning died during hospital care. **CONCLUSIONS:** Intoxication by GHB has substantial morbidity and abuse of GHB has substantial mortality. The acute prognosis is good but long-term prognosis is insecure with an increased risk for drug dependency and an early death.
11. Duan X, Zhou L, Wu T, Liu G, Qiao J, Wei J, Ni J, Zheng J, Chen X, et al. Chinese herbal medicine suxiao jiuxin wan for angina pectoris. *Cochrane Database Syst Rev*. 2008(1):CD004473. PMID: 18254051
BACKGROUND: Suxiao jiuxin wan is widely used in China for angina pectoris. **OBJECTIVES:** The objective of this review is to determine the effects (benefits and harms) of suxiao jiuxin wan in the treatment of angina pectoris. **SEARCH STRATEGY:** We searched the Cochrane Central Register of Controlled Trials on The Cochrane Library (issue 4 2005), Medline (1995 to 2005), EMBASE (1995 to 2005), the Register of Chinese trials developed by the Chinese Cochrane Centre (to 2006), and the Chinese Biomedical Database (1995 to 2005), and handsearched 83 Chinese journals. We also searched reference lists, databases of ongoing trials and the Internet. Date of last search: November 2005. **SELECTION CRITERIA:** Randomised controlled trials of suxiao jiuxin wan compared to standard treatment in people with angina. Studies with a treatment duration > 4 weeks were included. **DATA COLLECTION AND ANALYSIS:** Two reviewers independently applied the inclusion criteria, assessed trial quality and extracted the data. **MAIN RESULTS:** Fifteen trials involving 1776 people were included. There was weak evidence that suxiao jiuxin wan compared with nitroglycerin (xiaoxintong) improved ECG measurements (RR 1.16, 95% CI 1.05 to 1.27), reduced symptoms (RR 1.09, 95% CI 1.04 to 1.13), reduced the frequency of acute attacks of angina (difference in means -0.70, 95% CI -0.90 to -0.50), reduced diastolic pressure (difference in means -3mmHg, 95% CI -5.73 to -0.27) and reduced the need for supplementary nitroglycerin (difference in means of -0.60, 95% CI -0.94 to -0.26). There was also weak evidence that suxiao jiuxin wan compared with *Salvia miltiorrhiza* (danshen) reduced symptoms (RR 1.21, 95% CI 1.11 to 1.31) and improved ECG measurements (RR 1.55, 95% CI 1.30 to 1.84). There was no significant difference when comparing suxiao jiuxin wan with isosorbide dinitrate (xiaosuananyishanlizhi) both for ECG improvement (RR 1.34, 95% CI 0.91 to 1.98) and for symptom improvement (RR 1.11, 95% CI 0.86 to 1.43). **AUTHORS' CONCLUSIONS:** Suxiao jiuxin wan appears to be effective in the treatment of angina pectoris

and no serious side effects were identified. However, the evidence remains weak due to poor methodological quality of including studies.

12. Wei J, Ni J, Wu T, Chen X, Duan X, Liu G, Qiao J, Wang Q, Zheng J, et al. Chinese medicinal herbs for acute bronchitis. *Cochrane Database Syst Rev.* 20081):CD004560. PMID: 18254054
BACKGROUND: Acute bronchitis is one of the most common diagnoses made by primary-care physicians. It is traditionally treated with antibiotics (although the evidence for their effectiveness is weak and modest at best), and other even less effective treatments. Chinese medicinal herbs have also been used as a treatment. OBJECTIVES: This review aimed to summarise the existing evidence on the comparative effectiveness and safety of Chinese medicinal herbs for treating uncomplicated acute bronchitis. SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2007, Issue 1), which includes the Cochrane Acute Respiratory Infections Group's specialised register; MEDLINE (1966 to March Week 1, 2007); EMBASE (1988 to January 2007); The Chinese Cochrane Centre's Controlled Trials Register (up to January 2007); and the Chinese Biomedical Database (CBM) (1980 to January 2007). SELECTION CRITERIA: Randomised controlled trials (RCTs) comparing Chinese medicinal herbs with placebo, antibiotics or other Western medicines for the treatment of uncomplicated acute bronchitis. DATA COLLECTION AND ANALYSIS: At least two review authors independently extracted data and assessed trial quality. MAIN RESULTS: No studies met the inclusion criteria for this review. One study with 300 participants but uncertain randomisation was analysed. The study showed that treatment with the Chinese medicinal herb Huoke granules leads to a shorter duration of cough, fever and sputum compared to using penicillin and Xiaoer Shangfeng Zhike tangjiang syrup. However, the study also lacked allocation concealment and blinding. There was a high possibility of conflict of interest as the Huoke granules were made by the trial author's hospital. AUTHORS' CONCLUSIONS: There is insufficient quality data to recommend the routine use of Chinese herbs for acute bronchitis. Study-design limitations of the individual studies meant that no conclusion about the benefits of Chinese herbs could be taken. In addition, the safety of Chinese herbs is unknown due to the lack of toxicological evidence on these Chinese herbs, though adverse events were reported in some case reports.
13. Schnitzer SA, Londre RA, Klironomos J, Reich PB. Biomass and toxicity responses of poison ivy (*Toxicodendron radicans*) to elevated atmospheric CO₂: comment. *Ecology.* 2008;89(2):581-5; discussion 585-7. PMID: 18409446
14. Areia M, Gradiz R, Souto P, Camacho E, Silva MR, Almeida N, Rosa A, Xavier da Cunha MF, Leitao MC. Iron-induced esophageal ulceration. *Endoscopy.* 2007;39 Suppl 1(E326). PMID: 18273777
15. Dussault EB, Balakrishnan VK, Sverko E, Solomon KR, Sibley PK. Toxicity of human pharmaceuticals and personal care products to benthic invertebrates. *Environ Toxicol Chem.* 2008;27(2):425-32. PMID: 18348646
Despite concerns about potential risks associated with the presence of pharmaceuticals and personal care products (PPCPs) in the environment, few toxicological data address the effects of these compounds. In aquatic systems, which often represent the final repository for PPCPs, increasing toxicological information regarding aquatic biota is improving our capacity to assess potential risks. However, responses of key biota, such as benthic invertebrates, have not been investigated as widely. In the present study, we examined the toxicity of four PPCPs -- the lipid regulator atorvastatin (ATO), the antiepileptic drug carbamazepine (CBZ), the synthetic hormone 17alpha-ethinylestradiol (EE(2)), and the antimicrobial triclosan (TCS) -- to the midge *Chironomus tentans* and the freshwater amphipod *Hyalella azteca* in 10-d waterborne exposures.

The toxicity of the four compounds varied between 0.20 and 47.3 mg/L (median lethal concentration), with a relative toxicity ranking of TCS > EE(2) > ATO > CBZ. *Hyalella azteca* was more sensitive than *C. tentans* to these compounds. The toxicity data were used in a hazard quotient approach to evaluate the risk posed by the four PPCPs to benthic invertebrates and other aquatic organisms. For each compound, a hazard quotient was calculated by dividing the lowest toxicity value by the highest exposure value found in the literature, to which an uncertainty factor was applied. With hazard quotients of 3.55 to 11.5, we conclude that potential risks exist toward benthic invertebrates for the toxicity of TCS and CBZ and that further investigations of these compounds are required to characterize more completely the risks to benthic organisms. In contrast, our data also indicate that considering the low concentrations currently detected in the environment, ATO and EE(2) pose negligible risks to benthic invertebrates.

16. Benyamina A, Lecacheux M, Blecha L, Reynaud M, Lukasiewicz M. Pharmacotherapy and psychotherapy in cannabis withdrawal and dependence. *Expert Rev Neurother.* 2008;8(3):479-91. PMID: 18345976
Cannabis has long been perceived as a drug causing questionable dependence. Only recently has a clinically recognized withdrawal syndrome been described, thus laying the foundations for specific treatment evaluations. Six different pharmacotherapies have been studied in cannabis withdrawal. Of these, only oral tetrahydrocannabinol, and perhaps mirtazapine, have shown some promise in the specific treatment of withdrawal symptoms. In cannabis dependence, rimonabant, and perhaps buspirone, have shown promising results. Clinical trials of oral tetrahydrocannabinol were less convincing. Cognitive and behavioral therapies and motivational enhancement therapies have proven their efficacy in several randomized controlled trials. Brief therapies have also been associated with good compliance and efficacy. Combinations with voucher incentives in certain populations have been associated with improved treatment compliance and reduced cannabis use. Only two studies have analyzed the cost-efficacy of psychotherapies. It would seem that brief combined cognitive and behavioral therapies, and motivational enhancement therapies are the most cost effective. For the moment, it is uncertain whether the additional treatment costs associated with voucher incentives are proportional to the accrued abstinence duration.
17. Stenfors Arnesen LP, Fagerlund A, Granum PE. From soil to gut: *Bacillus cereus* and its food poisoning toxins. *FEMS Microbiol Rev.* 2008. PMID: 18422617
Bacillus cereus is widespread in nature and frequently isolated from soil and growing plants, but it is also well adapted for growth in the intestinal tract of insects and mammals. From these habitats it is easily spread to foods, where it may cause an emetic or a diarrhoeal type of food-associated illness that is becoming increasingly important in the industrialized world. The emetic disease is a food intoxication caused by cereulide, a small ring-formed dodecadeptide. Similar to the virulence determinants that distinguish *Bacillus thuringiensis* and *Bacillus anthracis* from *B. cereus*, the genetic determinants of cereulide are plasmid-borne. The diarrhoeal syndrome of *B. cereus* is an infection caused by vegetative cells, ingested as viable cells or spores, thought to produce protein enterotoxins in the small intestine. Three pore-forming cytotoxins have been associated with diarrhoeal disease: haemolysin BL (Hbl), nonhaemolytic enterotoxin (Nhe) and cytotoxin K. Hbl and Nhe are homologous three-component toxins, which appear to be related to the monooligomeric toxin cytolysin A found in *Escherichia coli*. This review will focus on the toxins associated with foodborne diseases frequently caused by *B. cereus*. The disease characteristics are described, and recent findings regarding the associated toxins are discussed, as well as the present knowledge on virulence regulation.
18. Mudipalli A. Lead hepatotoxicity & potential health effects. *Indian J Med Res.* 2007;126(6):518-27. PMID: 18219078
Occupational and environmental exposures to lead (Pb), one of the toxic metal pollutants, is of

global concern. Health risks are increasingly associated with environmental exposures to Pb emissions from, for example, the widespread use of leaded gasoline in developing countries. Exposure occurs mainly through the respiratory and gastrointestinal systems, and the ingested and absorbed Pb is stored primarily in soft tissues and bone. Autopsy studies of Pb-exposed patients have shown a large amount (approximately 33%) of the absorbed Pb in soft tissue stored in liver. In addition to neuronal encephalopathy observed in persons after exposure to very high concentrations of Pb, gastrointestinal colic (abdominal pain, constipation, intestinal paralysis) is a consistent early symptom of Pb poisoning in humans. Such severe gastrointestinal effects are consistently observed in patients with a blood Pb range of 30 to 80 microg/dl. Ingestion of Pb is one of the primary causes of its hepatotoxic effects. Hepatocarcinogenic effects of Pb reported in animal toxicology studies have led to new research into the biochemical and molecular aspects of Pb toxicology. Gains in the molecular understanding of Pb effects on hepatic drug metabolizing enzymes, cholesterol metabolism, oxidative stress, and hepatic hyperplasia suggest a potential role for Pb in damaging extrahepatic systems, including the cardiovascular system. This review also discusses the therapeutic potential of chelation therapy in treating Pb-induced hepatotoxicity in animals.

19. Dogru MI, Dogru AK, Gul M, Esrefoglu M, Yurekli M, Erdogan S, Ates B. The effect of adrenomedullin on rats exposed to lead. *J Appl Toxicol.* 2008;28(2):140-6. PMID: 17503410
Adrenomedullin (AdM) was originally discovered as a vasorelaxant peptide. The antioxidative properties of AdM have been reported recently. Through its antioxidative effect, adrenomedullin can protect organs from damage induced by stressors. Lead, commonly detected in air, soil, water and food, is a major source of oxidative stress. The effect of AdM in the liver of rats exposed to lead was investigated. Twenty-four female Wistar rats were divided into four groups: a control group (C), adrenomedullin group (AdM), lead (Pb) group and lead + adrenomedullin (Pb + AdM) group. In the Pb-treated groups, the animals were exposed to lead in drinking water containing 250 ppm PbCl₂ for 4 weeks. In the AdM-treated group, the animals received an i.p. injection of AdM (3000 ng kg(-1) body weight) in the third week of lead treatment for 1 week. The activities of catalase (CAT), glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) and the level of malondialdehyde (MDA) were determined in the liver of rats. Histological changes in the liver were examined by light and electron microscopy as well. The MDA levels were increased significantly in the Pb-treated groups, but in the Pb + AdM group the MDA levels were decreased significantly when compared with the Pb group. AdM reduced hepatic damage in the Pb + AdM group, but the difference in the total histopathological scores between the Pb and Pb + AdM groups was not significant. When the results are taken together, it can be concluded that AdM may have protective or compensating effects in lead toxicity.
20. Hawton K, Harriss L. Deliberate self-harm by under-15-year-olds: characteristics, trends and outcome. *J Child Psychol Psychiatry.* 2008;49(4):441-8. PMID: 18081755
BACKGROUND: Relatively little information is available about the characteristics and long-term outcome of children and adolescents aged under 15 years who present to general hospitals because of deliberate self-harm (DSH). METHOD: Information was collected on 710 consecutive under-15-year-olds presenting to a general hospital in central England with DSH over a 26-year period (1978-2003). Outcome in terms of death was investigated from national statistics in 464 cases presenting during the first 20 years of the study. RESULTS: Most individuals were aged 12-14 years. In this age group the female:male ratio was 6.5:1. Nearly all (680/710, 95.8%) had taken overdoses, over half of these episodes involving paracetamol (acetaminophen). Few had a history of prior (7.7%) or current psychiatric treatment (7.7%), although a quarter (150/559, 26.8%) had a history of previous DSH. Suicidal intent was usually low. The most frequent problems were difficulties in relationships with family members (77.3%) and with friends (38.9%), and school/study problems (37.9%). The long-term risk of suicide was low, 1.1% (N =

5) having died by probable suicide after a mean follow-up period of 11 years 2 months.
CONCLUSIONS: DSH in children and young adolescents is usually related to life problems, is generally of low suicidal intent, and is associated with a relatively low long-term risk of suicide.

21. Alexiades-Armenakas M. Parabens toxicity to skin and other organs. *J Drugs Dermatol.* 2008;7(1):77-8. PMID: 18246703
Laser and Cosmetic News covers the latest advances in laser surgery, light technology, phototherapy, and cosmetic surgery. New and emerging therapies, noteworthy publications, and exciting meeting developments will be highlighted. Controversies and opinions about the future in this field will be addressed. The aim of this column is to keep you abreast of the cutting edge in laser and cosmetic surgery.
22. Massart F, Meucci V, Saggese G, Soldani G. High growth rate of girls with precocious puberty exposed to estrogenic mycotoxins. *J Pediatr.* 2008;152(5):690-5, 695 e1. PMID: 18410776
OBJECTIVE: To test the hypothesis that human puberty timing can be advanced by environmental estrogen exposure. STUDY DESIGN: We analyzed serum mycoestrogen contamination via high-performance liquid chromatography (HPLC) in 32 girls affected by central precocious puberty (CPP) and in 31 healthy female control subjects. All 32 patients received triptorelin (TR) for more than 12 months after diagnosis. RESULTS: Increased serum levels of zearalenone (ZEA; 933.7 +/- 200.3 pg/mL; 95% CI, 723.5-1143.9) and of its congener alpha-zearalenol (106.5 +/- 1.9 pg/mL; 95% CI, 104.5-108.5) contaminated 6 girls with CPP, who were from a bounded Tuscany area. At diagnosis, ZEA levels correlated with patient height ($r = 0.906$, $P < .05$) and weight ($r = 0.887$, $P < .05$), but not with bone age. In patients who were mycotoxin-positive, height ($F = 4.192$; $P < .01$), weight ($F = 3.915$; $P < .01$), and height velocity ($F = 2.777$, $P < .05$) were higher than patients who were mycotoxin-negative during 12-months TR treatment. Height correlated with weight both in patients who were mycotoxin-positive ($r = 0.986$, $P < .001$) and in patients who were mycotoxin-negative ($r = 0.994$, $P < .001$). Body mass index, bone age, and gonadal secretion was not different in patient groups before and during TR treatment ($P > .05$). CONCLUSIONS: Mycoestrogenic zearalenone is suspected to be a triggering factor for CPP development in girls. Because of its chemical resemblance to some anabolic agents used in animal breeding, ZEA may also represent a growth promoter in exposed patients.
23. Gunja N, Doyle E, Carpenter K, Chan OT, Gilmore S, Browne G, Graudins A. Gamma-hydroxybutyrate poisoning from toy beads. *Med J Aust.* 2008;188(1):54-5. PMID: 18021061
A 2-year-old boy and a 10-year-old girl presented to the emergency department with a decreased level of consciousness. The girl had had persistent vomiting and a seizure. Urine metabolic screening tests were positive for gamma-hydroxybutyrate (GHB). Samples from toy beads ingested by both children contained 1,4-butanediol, which is metabolised to GHB in humans. Regulatory authorities were notified, leading to an international recall of the toy beads.
24. Meyer PA, Brown MJ, Falk H. Global approach to reducing lead exposure and poisoning. *Mutat Res.* 2008. PMID: 18436472
Lead poisoning is an important environmental disease that can have life-long adverse health effects. Most susceptible are children, and most commonly exposed are those who are poor and live in developing countries. Studies of children's blood-lead levels (BLLs) are showing cognitive impairment at increasingly lower BLLs. Lead is dangerous at all levels in children. The sources of lead exposure vary among and within countries depending on past and current uses. Sources of lead may be from historic contamination, recycling old lead products, or from manufacturing new products. In all countries that have banned leaded gasoline, average population BLLs have declined rapidly. In many developing countries where leaded gasoline is no longer used, many children and workers are exposed to fugitive emissions and mining wastes. Unexpected lead

threats, such as improper disposal of electronics and children's toys contaminated with lead, continue to emerge. The only medical treatment available is chelation, which can save lives of persons with very high BLLs. However, chelating drugs are not always available in developing countries and have limited value in reducing the sequelae of chronic low dose lead exposure. Therefore, the best approach is to prevent exposure to lead. Because a key strategy for preventing lead poisoning is to identify and control or eliminate lead sources, this article highlights several major sources of lead poisoning worldwide. In addition, we recommend three primary prevention strategies for lead poisoning: identify sources, eliminate or control sources, and monitor environmental exposures and hazards.

25. Ryzhavsikii BY, Lebed'ko OA, Belolyubskaya DS, Baranova SN. Long-term consequences of prenatal exposure to lead on brain development in rats. *Neurosci Behav Physiol.* 2008;38(2):145-9. PMID: 18197380
Administration of single doses of lead citrate (200 mg/kg) to pregnant rats (on day 18 of pregnancy) was followed by the appearance of destructive changes in brains at age 40 days, with cysts, foci of gliocyte proliferation, pyknotic neurons, and decreases in NADH and NADPH diaphorase activities in neocortical and hippocampal neurons. Decreases in the density of neurons in the cortex and decreases in cortical thickness were also observed. The intensity of free-radical oxidation in the cortex increased three-fold, along with a 3.9-fold increase in the concentration of lipid peroxides, providing evidence of oxidative stress. The possible mechanisms by which these alterations develop are analyzed.
26. Zapolanski T, Jacob SE. Avoiding paraphenylenediamine exposure in children. *Pediatr Ann.* 2008;37(2):104-5. PMID: 18335882
Although the allergenic potential of PPD is well known, it was chosen by the American Contact Dermatitis Society as the 2006 "allergen of the year" in order to increase awareness of new patterns of exposure and increasing sensitization. Temporary tattoos are a vehicle of contact with PPD that is particularly relevant to children. They are a risk not only in the United States, but in many international locations frequented by American tourist families. Adolescents dyeing their hair are also at risk. With this in mind, measures should be taken to increase awareness and avoid the unnecessary usage of PPD in children.
27. Levy M, Wofford MM, Powell BL, McLean TW. Hyperleukocytosis from arsenic trioxide. *Pediatr Blood Cancer.* 2008;50(6):1265-7. PMID: 18300308
We report the case of a 14-year-old male treated with arsenic trioxide for recurrent acute promyelocytic leukemia. He developed hyperleukocytosis (WBC 111.6 x 10⁹/L) which then resolved while continuing daily arsenic. Hyperleukocytosis without other complications may not be an indication for adding cytotoxic therapy or steroids, nor for discontinuing arsenic trioxide therapy in children.
29. Phua DH, Cham G, Seow E. Two instances of Chinese herbal medicine poisoning in Singapore. *Singapore Med J.* 2008;49(5):e131-3. PMID: 18465037
Datura metel L. (Yangjinhua) is a toxic herb that contains anticholinergic compounds. Inappropriate consumption of this herb could result in anticholinergic poisoning. Clinical features of such poisoning have not been previously described. We report two such cases. Both patients had taken brews of Datura metel L., and developed poisoning soon afterwards. Prominent clinical features included confusion, dilated pupils, absence of sweating, and the absence of sluggish bowel sounds. No flushing of the face or skin was detected in either case. Both patients recovered fully within 12 hours with supportive measures, and no gastric elimination or antidote was used. The different names ascribed to Datura metel L. in Chinese medicine can be confusing; this confusion resulted in the poisoning of one of our patients. The clinical features of Datura metel L.

poisoning and concerns over inappropriate uses of herbal medicine are discussed.

30. Ozer J, Ratner M, Shaw M, Bailey W, Schomaker S. The current state of serum biomarkers of hepatotoxicity. *Toxicology*. 2008;245(3):194-205. PMID: 18291570
The level of serum alanine aminotransferase (ALT) activity reflects damage to hepatocytes and is considered to be a highly sensitive and fairly specific preclinical and clinical biomarker of hepatotoxicity. However, an increase in serum ALT activity level has also been associated with other organ toxicities, thus, indicating that the enzyme has specificity beyond liver in the absence of correlative histomorphologic alteration in liver. Thus, unidentified non-hepatic sources of serum ALT activity may inadvertently influence the decision of whether to continue development of a novel pharmaceutical compound. To assess the risk of false positives due to extraneous sources of serum ALT activity, additional biomarkers are sought with improved specificity for liver function compared to serum ALT activity alone. Current published biomarker candidates are reviewed herein and compared with ALT performance in preclinical and on occasion, clinical studies. An examination of the current state of hepatotoxic biomarkers indicates that serum F protein, arginase I, and glutathione-S-transferase alpha (GSTalpha) levels, all measured by ELISA, may show utility, however, antibody availability and high cost per run may present limitations to widespread applicability in preclinical safety studies. In contrast, the enzymatic markers sorbitol dehydrogenase, glutamate dehydrogenase, paraxonase, malate dehydrogenase, and purine nucleoside phosphorylase are all readily measured by photometric methods and use reagents that work across preclinical species and humans and are commercially available. The published literature suggests that these markers, once examined collectively in a large qualification study, could provide additional information relative to serum ALT and aspartate aminotransferase (AST) values. Since these biomarkers are found in the serum/plasma of treated humans and rats, they have potential to be utilized as bridging markers to monitor acute drug-induced liver injury in early clinical trials.
31. Du W, Guo JJ, Jing Y, Li X, Kelton CM. Drug safety surveillance in China and other countries: a review and comparison. *Value Health*. 2008;11 Suppl 1(S130-6. PMID: 18387057
OBJECTIVES: Drug safety and postmarketing surveillance have become important public health issues in China. This study reviews the relatively new drug safety surveillance system in China and compares it with the systems in the United States and Europe. METHODS: An extensive literature review was conducted in the following four areas: 1) the organizational structure of the State Food and Drug Administration (SFDA) in China; 2) the development of an adverse drug reaction (ADR) monitoring system in China; 3) regulatory issues related to drug safety in China; and 4) similarities and differences between drug safety surveillance in China and surveillance in the United States and Europe. RESULTS: The SFDA oversees an extensive network of drug safety "watchdogs," including the China National Center for ADR Monitoring and 32 regional centers throughout China. China's system has faced a number of recent challenges. It has had to respond quickly to the withdrawal of various high-profile drugs like Vioxx (rofecoxib) and Baycol (cerivastatin) from other markets. Together with China's Ministry of Health, the SFDA has faced several unique drug safety events. Three of those events, involving the injectable form of the heartleaf houttuynia herb (Yu Xing Cao), Armillarisni A injections, and clindamycin glucose infusions (Xinfu), are discussed. The rapid development of drug safety surveillance in China is manifested in extensive organizational structure, development of large databases, and laws and regulations supporting drug safety. The two major laws are the China Drug Administration Law issued in February 2001 and the Regulation for the Administration of ADR Reporting and Monitoring issued in March 2004. The study also discusses and compares recent developments in drug safety surveillance in the United States and the European Union. These developments will most likely have implications for the Chinese system in the near future. CONCLUSIONS: While postmarketing surveillance guidelines are not yet available in China, we

fully expect their eventual issuance after adaptation to the particular culture and clinical practices in China.

32. Begovic V, Nozic D, Kupresanin S, Tarabar D. Extreme gastric dilation caused by chronic lead poisoning: A case report. *World J Gastroenterol.* 2008;14(16):2599-601. PMID: 18442215
Lead is a toxic metal that affects many organ systems and functions in humans. In the majority of adults, chronic lead poisoning comes from exposures to work places and can occur in numerous work settings, such as manufacturing, lead smelting and refinement, or due to use of batteries, pigments, solder, ammunitions, paint, car radiators, cable and wires, certain cosmetics. In some countries, lead is added to petrol. We present a rare case of gastric dilation caused by long-term petrol ingestion. A 16-year-old young man was admitted to our hospital due to a 6-mo history of exhaustion, dizziness, nausea, abdominal cramps and constipation. X-ray examination revealed dilated stomach descending into the pelvis and small bowel distension. After a long clinical observation, we found that the reason for the chronic lead poisoning of the patient was due to a 3-year history of petrol ingestion. The patient spontaneously recovered and stomach returned to its normal position and size. Lead poisoning should be taken into consideration in all unexplained cases of gastric dilation.

33. Shi J, Tong Y, Shen JG, Li HX. Effectiveness and safety of herbal medicines in the treatment of irritable bowel syndrome: a systematic review. *World J Gastroenterol.* 2008;14(3):454-62. PMID: 18200670
AIM: To explore the efficacy and safety of herbal medicines (HM) in the treatment of irritable bowel syndrome (IBS). METHODS: A computer-based as well as manual literature search was performed. We reviewed randomized controlled trials on the treatment of IBS with and without HM. RESULTS: A total of 22 studies with 25 HMs met the inclusion criteria. Four of these studies were of good quality, while the remaining 18 studies involving 17 Chinese herbal medicine (CHM) formulas were of poor quality. Eight of these reports using 9 HMs showed global improvement of IBS symptoms, 4 studies with 3 HMs were efficacious in diarrhea-predominant IBS, and 2 studies with 2 HMs showed improvement in constipation-predominant IBS. Out of a total of 1279 patients, 15 adverse events in 47 subjects were reported with HM. No serious adverse events or abnormal laboratory tests were observed. The incidence of the adverse events was low (2.97%; 95% CI: 2.04%-3.90%). CONCLUSION: Herbal medicines have therapeutic benefit in IBS, and adverse events are seldom reported in literature. Nevertheless, herbal medicines should be used with caution. It is necessary to conduct rigorous, well-designed clinical trials to evaluate their effectiveness and safety in the treatment of IBS.