

AMERICAN ACADEMY OF CLINICAL TOXICOLOGY
HERBS & DIETARY SUPPLEMENTS ABSTRACTING SERVICE

January 31, 2009

1. Heise LA, Wagener BM, Vigil JR, Othman M, Shahinpoor P. Hemorrhagic Colitis Secondary to Acute Elemental Mercury Vapor Poisoning. *Am J Gastroenterol*. 2009. PMID: 19174799
2. Zhang X, Li HS, Zhu QH, Zhou J, Zhang S, Zhang L, Sun CY. Trends in suicide by poisoning in China 2000-2006: age, gender, method, and geography. *Biomed Environ Sci*. 2008;21(3):253-6. PMID: 18714825
OBJECTIVE: This study analyzed patterns of suicide and suicide attempts by poisoning as reported through a national poison control system for the purpose of improving intervention and prevention. METHODS: During the period of 2000 to 2006, 6440 cases of poisoning suicide were reported to the telephone consultation service system of The National Center for Poisoning Control (Chinese Center for Disease Control and Prevention). Among these records, 4728 cases had completed data for this analysis in terms of age, sex, trend of time and location, and type of poisons. RESULTS: There were 60.6% female cases with the age from 10 to 90 years old. The age of cases from 20 to 39 years accounted for 54.5% of all age groups. Both the numbers and percentage in record related to poisoning consultation of oral poisoning suicide showed an increasing tendency during the 7 years. In particular, there was a drastic increase from 2004 to 2006. In addition, the high frequency of cases occurred from May to October. Hebei, Shandong, Henan, and Anhui Provinces had the highest number of cases. Pesticide poisonings were the most common method in these cases of consultation for suicide and suicide attempts. CONCLUSION: This study describes epidemiological characteristics in the oral poisoning suicide cases and provides scientific basis for suicide prevention interventions.
3. Faber WD, Pavkov KL, Gingell R. Review of reproductive and developmental toxicity studies with isopropanol. *Birth Defects Res B Dev Reprod Toxicol*. 2008;83(5):459-76. PMID: 18924148
Published studies for reproductive and developmental toxicity conducted with isopropanol have been conducted by the inhalation and oral gavage routes of administration. Interpretation of the data from these studies has resulted in discussions regarding NOAELs and additional benchmark dose modeling publications. Unpublished reproductive and developmental toxicity studies administered in the drinking water were also conducted by BIBRA, and the results of those studies are presented here. In addition, all of the reproductive and developmental toxicity studies conducted with isopropanol are summarized and evaluated for concordance of effects and NOAELs. Endpoints of concern for regulatory agencies were decreases in male mating index and reductions in postnatal pup survival. Original study reports were evaluated and data collated to address these two endpoints, and the data summarized. Data are presented suggesting that there were technical problems in the study that implied a decrease in male mating index, and based on the results from the drinking water studies, the weight of evidence suggests that isopropanol does not affect male mating or fertility at dose levels of up to 1000 mg/kg/day. The weight of evidence suggests that isopropanol can cause decreases in postnatal pup survival following oral gavage administration of 1000-1200 mg/kg/day to the dams. The NOAEL for this endpoint with oral gavage administration was 700 mg/kg/day. Indications of maternal toxicity were also an important predictor for decreased postnatal survival. Decreased postnatal pup survival was also noted in the drinking water studies with isopropanol with a LOAEL of 2278 mg/kg/day and a NOAEL of 1947 mg/kg/day.
4. Carratu MR, Coluccia A, Modafferi AM, Borracci P, Scaccianoce S, Sakamoto M, Cuomo V. Prenatal methylmercury exposure: effects on stress response during active learning. *Bull Environ Contam Toxicol*. 2008;81(6):539-42. PMID: 18787750
The long-term impact of prenatal methylmercury (MeHg) exposure on the stress response during active learning was investigated. Pregnant rats were gavaged MeHg (8 mg/kg) on gestational day 15. Ninety-day-old rats born to both MeHg- and saline-treated dams were

subjected to an active avoidance test. The active avoidance-experienced rats (AAERs) with prenatal exposure to MeHg showed significant impairment in learning ability and exhibited higher levels of corticosterone than the untreated AAERs. The present findings suggest that the abnormal increase in plasma corticosterone levels could contribute to the poor performance of MeHg-treated AAERs in this learning task.

5. Setz JM, van der Linde AA, Gerrits GP, Meulstee J. EEG findings in an eleven-year-old girl with mercury intoxication. *Clin EEG Neurosci.* 2008;39(4):210-3. PMID: 19044221
An 11-year-old female was seen at our outpatient clinic with a broad variety of symptoms that were due to elemental mercury intoxication. Electromyography and sequential electroencephalography findings obtained at days 2, 36, 88 and 148 are described. The patient was treated with chelation therapy during which she clinically improved considerably. A profound decrease in urinary mercury concentration occurred as well as normalization of the electroencephalogram.
6. Baxter AJ, Krenzelok EP. Pediatric fatality secondary to EDTA chelation. *Clin Toxicol (Phila)*. 2008;46(10):1083-4. PMID: 18949650
BACKGROUND: Chelation therapy has emerged as a popular treatment modality to remove heavy metals that are thought to cause autism. We report a fatality that occurred as a consequence of chelation therapy for autism when the incorrect form of EDTA was administered. CASE REPORT: A five-year-old autistic male was being chelated in a physician's office. While receiving his third treatment he went into cardiac arrest. It was not determined until after the child's death that he had been given edetate disodium rather than edetate calcium disodium, causing profound hypocalcemia and triggering the cardiac events that led to his death. DISCUSSION: In 1991, the CDC recommended using only edetate calcium disodium, not edetate disodium, to children because edetate disodium may induce tetany and possible hypocalcemia as illustrated in this case. CONCLUSION: The use of chelation therapy in autistic children has not been validated and can have tragic consequences.
7. Bronstein AC, Spyker DA, Cantilena LR, Jr., Green JL, Rumack BH, Heard SE, American Association of Poison Control C. 2007 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 25th Annual Report. *Clin Toxicol (Phila)*. 2008;46(10):927-1057. PMID: 19065310
BACKGROUND: This report is the 25th Annual Report of the American Association of Poison Control Centers (AAPCC; <http://www.aapcc.org>) National Poison Data System (NPDS). During 2007, 60 of the nation's 61 U.S. Poison Centers upload case data automatically. The median upload time is 14 [5.3, 55] (median [25%, 75%]) min creating a real-time national exposure 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. Fatalities were reviewed by a team of 29 medical and clinical toxicologists and assigned to 1 of 6 categories according to Relative Contribution to Fatality. RESULTS: Over 4.2 million calls were captured by NPDS in 2007: 2,482,041 human exposure calls, 1,602,489 information requests, and 131,744 nonhuman exposure calls. Substances involved most frequently in all human exposures were analgesics (12.5% of all exposures). The most common exposures in children less than age 6 were cosmetics/personal care products (10.7% of pediatric exposures). Drug identification requests comprised 66.8% of all information calls. NPDS documented 1,597 human fatalities. CONCLUSIONS: Poisoning continues to be a significant cause of morbidity and mortality in the United States NPDS represents a valuable national resource to collect and monitor U.S. poisoning exposure cases. It offers one of the few real-time surveillance systems in existence, provides useful data, and is a model for public health surveillance.
8. Sahoo R, Hamide A, Amalnath SD, Narayana BS. Acute demyelinating encephalitis due to *Abrus precatorius* poisoning--complete recovery after steroid therapy. *Clin Toxicol (Phila)*. 2008;46(10):1071-3. PMID: 18763153
INTRODUCTION: Poisoning from *Abrus precatorius* is attributed to a toxalbumin (abrin) that acts by inhibiting protein synthesis and rarely can cause immuno-mediated

demyelination. We report a case of abrin poisoning with demyelination. **CASE REPORT:** A 19-year-old man presented with a history of ingesting crushed *Abrus precatorius* seeds following a family quarrel. He developed vomiting, abdominal pain, and bloody diarrhea, followed by a seizure and an altered sensorium. Magnetic resonance imaging (MRI) of the brain showed demyelination in the bilateral-medial temporal lobes. The patient was treated with supportive care, and intravenous methylprednisolone followed by oral prednisone, and recovered fully. **DISCUSSION:** Abrin is an immuno-modulator that may cause immune-mediated demyelination. We report the clinical course of a patient with demyelination after abrin poisoning, treated with corticosteroids, and document his clinical recovery. **CONCLUSION:** Demyelination is a rare complication of *Abrus precatorius* poisoning. In our case, the demyelination was demonstrated by MRI. Although our patient appeared to recover completely following methylprednisolone therapy, the suggestion that methylprednisolone or other corticosteroids might be useful in treating this demyelination needs experimental verification and clinical validation before concluding that it is a beneficial therapy.

9. Choi AL, Cordier S, Weihe P, Grandjean P. Negative confounding in the evaluation of toxicity: the case of methylmercury in fish and seafood. *Crit Rev Toxicol.* 2008;38(10):877-93. PMID: 19012089
In observational studies, the presence of a confounding factor can distort the true association between an exposure and a toxic-effect outcome, if the confounding variable is not controlled for in the study design or analysis phase. While confounding is often assumed to occur in the same direction as the toxicant exposure, the relationship between the benefits and risks associated with fish and seafood consumption is a classic example of negative confounding: the exposure to methylmercury occurs with fish and seafood, which are also associated with beneficial nutrients, and the signs of mercury toxicity are thereby counteracted. Mercury and nutrients may affect the same epidemiological outcomes, but most studies addressing one of them have ignored the potential for negative confounding by the other. This article reviews the existing evidence of effects of both nutrient and contaminant intakes as predictors of neurodevelopmental and cardiovascular outcomes. Substantial underestimation of the effects of mercury toxicity and of fish benefits occurs from the lack of confounder adjustment and imprecision of the exposure parameters. Given this inherent bias in observational studies, regulatory agencies should reconsider current dietary advice in order to provide better guidance to consumers in making prudent choices to maintain a nutritious diet with seafood that is low in mercury concentrations. Attention should also be paid to the occurrence of negative confounding in other connections.
10. Bandyopadhyay A, Ghoshal S, Mukherjee A. Genotoxicity testing of low-calorie sweeteners: aspartame, acesulfame-K, and saccharin. *Drug Chem Toxicol.* 2008;31(4):447-57. PMID: 18850355
Low-calorie sweeteners are chemicals that offer the sweetness of sugar without the calories. Consumers are increasingly concerned about the quality and safety of many products present in the diet, in particular, the use of low-calorie sweeteners, flavorings, colorings, preservatives, and dietary supplements. In the present study, we evaluated the mutagenicity of the three low-calorie sweeteners in the Ames/Salmonella/microsome test and their genotoxic potential by comet assay in the bone marrow cells of mice. Swiss albino mice, *Mus musculus*, were orally administered with different concentrations of aspartame (ASP; 7, 14, 28, and 35 mg/kg body weight), acesulfame-K (ASK; 150, 300, and 600 mg/kg body weight), and saccharin (50, 100, and 200 mg/kg body weight) individually. Concurrently negative and positive control sets were maintained. The animals were sacrificed and the bone marrow cells were processed for comet assay. The standard plate-incorporation assay was carried with the three sweeteners in *Salmonella typhimurium* TA 97a and TA 100 strains both in the absence and presence of the S9 mix. The comet parameters of DNA were increased in the bone marrow cells due to the sweetener-induced DNA strand breaks, as revealed by increased comet-tail extent and percent DNA in the tail. ASK and saccharin were found to induce greater DNA damage than ASP. However, none could act as a potential mutagen in the Ames/Salmonella/microsome test. These findings are important, since they represent a potential health risk associated with the exposure to these agents.

11. Pokras MA, Kneeland MR. Lead poisoning: using transdisciplinary approaches to solve an ancient problem. *Ecohealth*. 2008;5(3):379-85. PMID: 19165554
Conservation medicine examines the linkages among the health of people, animals, and the environment. Few issues illustrate this approach better than an examination of lead (Pb) toxicity. Lead is cheap and there is a long tradition of its use. But the toxic effects of Pb have also been recognized for many years. As a result, western societies have eliminated or greatly reduced many traditional uses of Pb, including many paints, gasoline, and solders because of threats to the health of humans and the environment. Legislation in several countries has eliminated the use of lead shot for hunting waterfowl. Despite these advances, a great many Pb products continue to be readily available. For example, wildlife agencies recognize that angling and shooting sports deposit thousands of tons of Pb into the environment each year. In recent years, our knowledge of the lethal and sublethal effects of Pb has grown dramatically. This discussion reviews the effects of lead on wildlife, humans, and domestic animals. It also discusses the importance of bringing together all interest groups to find safe alternatives, to develop new educational and policy initiatives, to eliminate many current uses of Pb, and to clean up existing problems.
12. Forsberg S, Hojer J, Enander C, Ludwigs U. Coma and impaired consciousness in the emergency room: characteristics of poisoning versus other causes. *Emerg Med J*. 2009;26(2):100-2. PMID: 19164617
OBJECTIVES: Unconscious patients represent a diagnostic challenge in the emergency room (ER), but studies on their characteristics are limited. The aim of this study was to investigate the frequency, characteristics and prognosis of different coma aetiologies with special focus on poisoning. DESIGN: An observational study of consecutive adults admitted to the non-surgical ER, with a Glasgow coma scale (GCS) score of 10 or below. The GCS score on admission was prospectively entered into a study protocol, which was complemented with data from the medical record within one month. RESULTS: 938 patients were enrolled. Poisoning caused unconsciousness in 352 cases (38%). In the remaining 586 cases (non-poisoning group) the underlying cause was a focal neurological lesion in 24%, a metabolic or diffuse cerebral disturbance in 21%, epileptogenic in 12%, psychogenic in 1% and was still not clarified at hospital discharge in 4%. Among patients below the age of 40 years, the coma was caused by poisoning in 80%, but among those over 60 years, poisoning was the cause in only 11%. The median GCS score on admission was identical in the two study groups. Hospital mortality rates were 2.8% and 39% in the two groups, respectively. CONCLUSION: Poisoning was the most common cause of coma and young age was a strong predictor of this condition. The prognosis was favourable among poisoned patients but poor in the rest of the study population as a group.
13. Lin GZ, Peng RF, Chen Q, Wu ZG, Du L. Lead in housing paints: an exposure source still not taken seriously for children lead poisoning in China. *Environ Res*. 2009;109(1):1-5. PMID: 18976991
After prohibitions on lead gasoline additives, which have proved to be a public health accomplishment world wide, many countries focus on other exposure source of children lead poisoning. Removing lead from paints is one of the important measures. Although there have been regulatory limits on lead in paints in China, evidence reported in this article indicates that lead-based paints were very common in new paints available for housing and in existing residential paints. Twenty-nine of 58 new paint samples (50%) had lead content equal to or exceeding 600 ppm, including 14 (24%) equal to or exceeding 5000 ppm. The highest sample contained 153,000 ppm lead, about 15% of the paint weight. Thirty-two new paints (55%) contained "soluble" lead exceeding 90 ppm, the current lead limit on paints in China. Of the existing paints, 16 of 28 samples of existing paint (57%) collected from 24 kindergartens and primary schools had lead concentrations equal to or exceeding 600 ppm, including six samples (21%) equal to or exceeding 5000 ppm. The highest concentration sample contained 51,800 ppm lead, accounting for 5.2% of the paint weight. It has been shown in many areas that paint lead is a major exposure source for lead poisoning in children. This is particularly true after the phasing out of lead from gasoline. Effective limitation on lead content in new paint, and lead hazard control measures directed towards existing paint, could reduce children blood lead levels (BLLs). There has been a lead standard

for paints in China since 1986 and a stricter limit was introduced in recent years. Governments should take it seriously and enforce regulations, commit a long-term challenge to eliminate paint lead as it is the threat to current and the next generation.

14. Teschke R, Schwarzenboeck A, Hennermann KH. Kava hepatotoxicity: a clinical survey and critical analysis of 26 suspected cases. *Eur J Gastroenterol Hepatol.* 2008;20(12):1182-93. PMID: 18989142
BACKGROUND/AIMS: Hepatotoxicity has been previously suspected by national regulatory agencies in 26 patients in causal relationship with the treatment by kava extracts commonly used as herbal anxiolytic drugs. METHODS: A quantitative causality assessment was undertaken using the system of the Council for International Organizations of Medical Sciences, scale of objective probability scoring. RESULTS: Causality was unassessable, unrelated, or excluded in 16 patients owing to lack of temporal association and causes independent of kava or comedicated drugs. Low Council for International Organizations of Medical Sciences scores additionally resulted in excluded or unlikely causality assessments (n=2), leaving a total of eight patients with various degrees of causality for kava +/- comedicated drugs. Only one out of these eight patients adhered to the regulatory recommendations regarding both daily dose (<or=120 mg kavapyrones) and duration of therapy (<or=3 months) and experienced toxic liver injury with a probable causality for kava. In six cases with kava overdose and/or increased duration of kava treatment causality for kava was possible (n=3) and for kava together with the comedicated drug(s) possible (n=2) or probable (n=1). CONCLUSION: Kava taken as recommended is associated with rare hepatotoxicity, whereas overdose, prolonged treatment, and comedication may carry an increased risk.
15. Bentur Y, Lurie Y, Cahana A, Lavon O, Bloom-Krasik A, Kovler N, Gurevych B, Raikhlin-Eisenkraft B. Poisoning in Israel: annual report of the Israel Poison Information Center, 2007. *Isr Med Assoc J.* 2008;10(11):749-56. PMID: 19070280
BACKGROUND: The Israel National Poison Information Center, Rambam Health Care Campus, provides telephone consultations on clinical toxicology as well as drug and teratogen information around the clock. The Center participates in research, teaching and regulatory activities and also provides laboratory services. OBJECTIVES: To analyze data on the epidemiology of poisonings and poison exposures in Israel. METHODS: We conducted computerized queries and a descriptive analysis of the medical records database of the IPIC during 2007. RESULTS: Overall, 26,738 poison exposure cases were recorded, a 118.5% increase compared to 1995. Children under 6 years old were involved in 45% of cases; 73% of the calls were made by the public and 25.5% by physicians; 74.4% of exposures were unintentional and 9.2% intentional. Chemicals were involved in 37.9% of cases, pharmaceuticals in 44.2%, bites and stings in 4.3% and poisonous plants in 1.2%. Substances most frequently involved were analgesics, cleaning products and antimicrobials. Clinical severity was moderate/major in 3.5%. Substances most frequently involved in moderate/major exposures were insecticides, drugs of abuse and corrosives. Eight fatalities were recorded - three unintentional exposures (all chemicals) and five intentional (chemicals, medications, drugs of abuse). CONCLUSIONS: The rates of poison exposures and poisonings in Israel have increased significantly, contributing substantially to morbidity and mortality. The IPIC database is a valuable national resource for collecting and monitoring cases of poison exposure and can be used as a real-time surveillance system. It is recommended that reporting to the IPIC become mandatory and that its activities be adequately supported by national resources.
16. Lurie Y, Fainmesser P, Yosef M, Bentur Y. Remote identification of poisonous plants by cell-phone camera and online communication. *Isr Med Assoc J.* 2008;10(11):802-3. PMID: 19070291
17. Sawalha AF. Poison Control and the Drug Information Center: the Palestinian experience. *Isr Med Assoc J.* 2008;10(11):757-60. PMID: 19070281
BACKGROUND: The Palestinian Poison Control and Drug Information Center was established in 2006 to provide up-to-date information on medications and to help in the early

diagnosis and management of poisoning cases. OBJECTIVES: To summarize the activities carried out by the PCDIC in the past 2 years. METHODS: Documented inquiries received at the PCDIC were analyzed and the Center's activities were extracted from the files. RESULTS: During the first 2 years of the Center's existence, 323 enquiries were received, mainly (67.2%) from physicians; 70% of the calls were from the city of Nablus. Unintentional poisoning was the leading type of call (62.8%) followed by suicidal poisoning (20.7%). Medications were the major category of toxicants encountered (48.9%), followed by pesticides (23.5%). In 67.9% of the cases, the calls were initiated before any treatment was provided. The advice provided by the PCDIC was based on the nature of the call. During these 2 years the PCDIC has conducted both academic and non-academic activities. The Center introduced the concept of poison prevention weeks in Palestine and has conducted two so far. The PCDIC has published several articles in the fields of toxicology, rational drug use, complementary and herbal therapy, pharmacoepidemiology, and self-medication. CONCLUSIONS: Documentation of all enquiries is mandatory for analysis, evaluation, comparative purposes and quality assurance. More information campaigns are needed to encourage people to use the services provided by the PCDIC.

18. Meng MB, Cui YL, Guan YS, Ying Z, Zheng MH, Yuan CK, Zhang RM. Traditional Chinese medicine plus transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma. *J Altern Complement Med.* 2008;14(8):1027-42. PMID: 18990050
OBJECTIVES: To compare the efficacy and safety of Traditional Chinese Medicine (TCM) plus transcatheter arterial chemoembolization (TACE) with that of TACE alone (therapy I versus therapy II, respectively) in treating unresectable hepatocellular carcinoma (UHCC) through a meta-analysis of all available randomized controlled trials. METHODS: Literature retrieval was conducted using the Cochrane Library, MEDLINE, EMBASE, CBMdisk, and CNKI in any language. Meta-analysis was performed on the results of homogeneous studies. Analyses subdivided by TACE frequency (subgroup A, <3 times; subgroup B, > or =3 times) were also performed, but were not done for both therapy I and therapy II. RESULTS: Based on our search criteria, we found 37 trials involving 2653 patients. Our results showed that therapy I, compared with therapy II, improved patient survival, quality of life, alleviation of symptoms, and tumor response, and was thus more therapeutically beneficial. Further analysis showed that subgroup A proved to be better for patients' survival and alleviation of symptoms, while the two subgroups were similar in improved tumor response. No serious adverse events were reported. CONCLUSIONS: Therapy I benefited patients with UHCC. Subgroup A improved the survival of patients and the amelioration of symptoms more than subgroup B. As in some trials, there were flaws in the methodological quality, and the data therefore have a risk of bias and of being insufficient for determining the effects of therapy I and subgroup A. Hence, further large-scale trials are warranted.
19. Gerson D, Sriganeshan V, Alexis JB. Cutaneous drug eruptions: a 5-year experience. *J Am Acad Dermatol.* 2008;59(6):995-9. PMID: 19022101
BACKGROUND: The diversity of cutaneous drug eruptions encompasses many clinicopathologic entities. METHODS: Cases with a pathologic diagnosis of drug eruption from 2000 to 2005 were retrieved from our institution. The histologic slides were reviewed, the patterns of inflammatory changes were recorded, and a chart review was performed. RESULTS: The majority of the cases (94%) were "morbilliform"-type rashes. Eighty-two percent of cases exhibited an inflammatory infiltrate confined to the superficial dermis. Eighty percent exhibited a perivascular and interstitial pattern of dermal infiltrate. The infiltrate was composed of lymphocytes and eosinophils in approximately 29% of cases, lymphocytes and neutrophils in approximately 10% of cases, and lymphocytes, eosinophils, and neutrophils in approximately 21% of cases. Eosinophils were present in only 50% of cases. Approximately half (53%) of the cases exhibited epidermal-dermal interface changes. LIMITATIONS: The cases were limited to those with a pathologic diagnosis of cutaneous drug reaction, thereby excluding any cases with drug-induced disease not specifically diagnosed (histologically) as such. CONCLUSIONS: While the histologic features of most drug eruptions are not entirely specific, the finding of superficial infiltrates composed variably of lymphocytes, neutrophils, and eosinophils, either with or without interface changes, should suggest the possibility of a morbilliform drug eruption. Clinical correlation is

very helpful to confirm the diagnosis. To our knowledge, this study is the most extensive documenting the histologic findings in morbilliform drug eruptions.

20. Chan KH, Pan RN, Hsu MC, Hsu KF. Urinary elimination of ephedrine following administration of the Traditional Chinese Medicine preparation Kakkon-to. *J Anal Toxicol.* 2008;39(9):763-7. PMID: 19021932
Kakkon-to is one of the most common Traditional Chinese Medicine preparations for the attenuation of colds. Ephedrae Herba is one of the prescriptions of Kakkon-to. The major ingredients of Ephedrae Herba, ephedrine, are banned substances on the World Anti-Doping Agency (WADA) list. The purpose of this study was to investigate the elimination of urinary ephedrine after administering Kakkon-to and to determine the possibility of urinary positive ephedrine test results. Six healthy volunteers took one single dose of 2.5 g Kakkon-to extract granules. The concentrations of urinary ephedrine were analyzed by high-performance liquid chromatography. The result showed that ephedrine and norpseudoephedrine were excreted in the urine after taking one single dose of Kakkon-to. However, the highest amount of ephedrine in urine was ephedrine and the peak concentration was 4.35 +/- 1.82 microg/mL (mean +/- standard deviation), which was lower than the WADA permitted value (10 microg/mL). The estimated elimination half-lives of ephedrine, norephedrine, pseudoephedrine, and norpseudoephedrine following administration of this preparation were: 5.2 +/- 1.2, 4.2 +/- 1.3, 4.2 +/- 0.9, and 6.5 +/- 2.8 h, respectively. This study concluded that the urine would not violate the rule of doping after administering a single dose of Kakkon-to. Nevertheless, a further study on administering the preparation for 3 times per day for 3 days showed a positive ephedrine result. Athletes should be careful when taking more than a single dose of Kakkon-to.
21. Chan K, Poon R, O'Brien PJ. Application of structure-activity relationships to investigate the molecular mechanisms of hepatocyte toxicity and electrophilic reactivity of alpha,beta-unsaturated aldehydes. *J Appl Toxicol.* 2008;28(8):1027-39. PMID: 18626890
Covalent binding of reactive electrophiles to cellular targets is a molecular interaction that has the potential to initiate severe adverse biological effects. Therefore, a measure for electrophilic reactivity with biological nucleophiles could serve as an important correlate to toxic effects such as hepatocyte death. To determine if electrophile reactivity correlates with rat hepatocyte cytotoxicity, the inherently electrophilic alpha,beta-unsaturated aldehydes were chosen for investigation. Reactivity was measured with simple assays that used glutathione, a soft nucleophile, and butylamine, a harder nucleophile, as models for protein thiol and amine nucleophilic sites, respectively. Despite their higher reactivity with thiols, a linear relationship was only observed between hepatocyte cytotoxicity and amine reactivity. Structure-activity relationships were also investigated for hepatocyte toxicity, and results showed toxicity was well modelled by log P and electronic parameters E(LUMO) and partial charge of the carbonyl carbon (C'(carb)). Hydrophobicity and electronic descriptors were only significant in separate distinct models, suggesting that there were simultaneously occurring mechanisms that affected toxicity. Log P was linked to the ease of oxidation by a microsomal aldehyde dehydrogenase enzyme, while the electronic descriptors and amine reactivity were linked to direct alkylation. Even with the presence of electrophile characteristics, alpha,beta-unsaturated aldehyde hepatocyte toxicity could not be predicted exclusively by electrophilic reactivity as oxidative metabolism was also a factor for toxicity.
22. Palikhe NS, Kim SH, Park HS. What do we know about the genetics of aspirin intolerance? *J Clin Pharm Ther.* 2008;33(5):465-72. PMID: 18834360
Although acetylsalicylic acid is prescribed for a broad range of diseases, it can induce a wide array of clinically recognized hypersensitivity reactions, including aspirin-intolerant asthma (AIA) with rhinitis and aspirin-intolerant urticaria (AIU) with anaphylaxis. Altered eicosanoid metabolism is the generally accepted mechanism of aspirin intolerance; the overproduction of cysteinyl leucotrienes has been suggested to play a causative role in both AIA and AIU. Genetic markers suggested for AIA include HLA-DPBI*0301, leucotriene C4 synthase (LTC4S), ALOX5, CYSLT, PGE2, TBXA2R and TBX21. Similarly, HLA-DB1*0609, ALOX5, FCER1A and HNMT have been identified as possible genetic markers for AIU. An additional low-risk genetic marker for AIA is MS4A2, which encodes the beta-chain of

FCER1. Other single and sets of two or more interacting genetic markers are currently being investigated. Analyses of the genetic backgrounds of patients with AIA and AIU will promote the development of early diagnostic and therapeutic interventions, which may reduce the incidence of AIA and AIU.

23. Sekizawa J. Low-dose effects of bisphenol A: a serious threat to human health? *J Toxicol Sci.* 2008;33(4):389-403. PMID: 18827439
The author tried to review and summarize low-dose effects of endocrine disrupting chemicals (EDCs) through an extensive literature survey of toxicological studies with bisphenol A (BPA), taking BPA as an example for which many studies were published. Data on low-dose effects with BPA, especially on neurobehavioral effects after fetal or early postnatal exposures, suggested that there would be new aspects to be considered. Specific mention for future tasks was made. Firstly, toxicity tests should be designed with more elaboration to ensure a sufficient number of animals with careful handling of litters to allow adequate statistical analysis and appropriate selection of dosages to obtain insight in dose-response relationship. Secondly, precise measurement of plasma levels in both humans and rodents and construction of relevant physiologically-based pharmacokinetic models would help obtain quantitative estimates of intake and target-organ exposure relationship. Thirdly, biological backgrounds, particularly differences and similarities in endocrinological, neurological and immunological aspects among species, should be revisited. Fourthly, mechanistic deliberations on the possibilities of epigenetic mechanism and examinations of putative neurobehavioral effects or a presumptive link of miscarriage with BPA exposures are requested. Finally, general public concerns must be addressed in a thoughtful way so that a simple precautionary approach is not pursued, but uncertainties of the new toxicological aspects should be carefully explained. Further researches and internationally concerted efforts on elucidating risk of low-dose effects by integrating knowledge will contribute to setting new directions in toxicology and improving chemical risk assessments.
24. Ono T, Hayashida M, Uekusa K, Lai CF, Hayakawa H, Nihira M, Ohno Y. An accidental case of aconite poisoning due to Kampo herbal medicine ingestion. *Leg Med (Tokyo).* 2008. PMID: 19121599
An accidental case of aconite intoxication occurred after a patient took a therapeutic dose of Kampo herbal medicine containing Aconiti tuber, Uzu but had used the wrong decoction procedure. The poisoning was likely caused by an increased level of Aconitum alkaloids in the decoction; the patient developed aconite intoxication due to incomplete decoction. Aconitum alkaloid levels in the leftover solution which the patient had drunk and in the decoction extracted from 3g Uzu were determined. It was found that decoction makes the medicine safer to drink. Older individuals, especially those with dementia, have a higher risk of aconite poisoning because they sometimes do not boil the medicine appropriately.
25. Quilliam DN, Simon PR. Evaluation of case management services for lead poisoned children in Rhode Island. *Med Health R I.* 2008;91(12):384-5. PMID: 19170316
26. Ralston NV, Ralston CR, Blackwell JL, 3rd, Raymond LJ. Dietary and tissue selenium in relation to methylmercury toxicity. *Neurotoxicology.* 2008;29(5):802-11. PMID: 18761370
Selenium (Se) supplementation in the nutritionally relevant range counteracts methylmercury (MeHg) toxicity. Since Se tends to be abundant in fish, MeHg exposures alone may not provide an accurate index of risk from fish consumption. Molar ratios of MeHg:Se in the diets and Hg:Se in tissues of exposed individuals may provide a more accurate index. This experiment compared MeHg toxicity in relation to MeHg exposure vs. Hg:Se molar ratios in diets and tissues. Diets were prepared using low-Se torula yeast basal diets supplemented with Na₂SeO₄ to contain 0.1, 1.0, or 10.0 micromol Se/kg (approximately 0.01, 0.08, or 0.8 ppm Se), reflecting low-, adequate-, or rich-Se intakes, respectively. Diets contained either low or high (0.5 micromol or 50 micromol MeHg/kg) (approximately 0.10 or 10 ppm Hg). Sixty weanling male Long Evans rats were distributed into six weight-matched groups (three Se levels x two MeHg levels) that were supplied with water and their respective diets ad libitum for 18 weeks. No Se-dependent differences in growth were noted among rats fed low-MeHg diets, but growth impairments among rats fed high-MeHg were inversely related to dietary Se.

After 3 weeks on the diet, growth impairments were evident among rats fed high-MeHg with low- or adequate-Se and after 10 weeks, rats fed low-Se, high-MeHg diets started to lose weight and displayed hind limb crossing. No weight loss or hind limb crossing was noted among animals fed high-MeHg, rich-Se diets. Methylmercury toxicity was not predictable by tissue Hg, but was inversely related to tissue Se ($P < 0.001$) and directly related to Hg:Se ratios ($P < 0.001$). Methylmercury-selenocysteine complexes (proposed name; pseudomethionine) appear likely to impair Se bioavailability, interrupting synthesis of selenium-dependent enzymes (selenoenzymes) that provide antioxidant protection in brain. Therefore, selenoenzymes may be the molecular target of methylmercury toxicity.

27. Rice DC. Overview of modifiers of methylmercury neurotoxicity: chemicals, nutrients, and the social environment. *Neurotoxicology*. 2008;29(5):761-6. PMID: 18722469
It has been known for decades that methylmercury is a potent neurotoxicant, and that the developing brain is more susceptible to impairment as a result of methylmercury exposure than is the adult. Exposure to methylmercury is exclusively through consumption of fish and marine mammals. In recent years, the potential for protection against methylmercury toxicity by nutrients present in fish, particularly omega-3 fatty acids and selenium, has been explored in both epidemiological and experimental studies. There is evidence from several studies that fish consumption per se and methylmercury body burden act in opposition with regard to neuropsychological outcomes, whereas the evidence for a protective effect of specific nutrients is contradictory in both epidemiological and experimental studies published to date. The potential for methylmercury to interact with other chemicals present in marine food, particularly PCBs, has been explored in both animal models and human studies. Results may be both exposure- and endpoint-dependent. The Seychelles Islands study has explored the potential for the social environment to modify the effects of developmental methylmercury exposure. An understanding of the interactions of the multiple factors that determine the final behavioral outcome of exposure to methylmercury is crucial to risk assessment and risk management decisions.
28. Ferriero DM. Cannabinoids--can what hurts you make you stronger? Commentary on the article by Alvarez et al. on page 653. *Pediatr Res*. 2008;64(6):590-1. PMID: 19034198
29. Greene SL, Wood DM, Gawarammana IB, Warren-Gash C, Drake N, Jones AL, Dargan PI. Improvement in the management of acutely poisoned patients using an electronic database, prospective audit and targeted educational intervention. *Postgrad Med J*. 2008;84(997):603-8. PMID: 19103819
PROBLEM: The need to improve the clinical assessment and management of acutely poisoned patients presenting to an NHS hospital emergency department (ED). DESIGN: Creation of an electronic clinical toxicology database to prospectively collect all aspects of clinical information on poisoned-patient presentations. Systematic analysis of collated information to identify shortfalls in patient assessment and management. Bimonthly audit meetings, and design and implementation of educational interventions to address identified shortfalls. Ongoing audit to demonstrate continued improvement in patient care. BACKGROUND AND SETTING: ED in tertiary-level inner-city London teaching hospital. Study conducted by staff from the ED and clinical toxicology service. KEY MEASURES FOR IMPROVEMENT: Demonstration of overall reduction in the incidence of predefined shortfalls in patient assessment and management during 12-month study period. Strategies for improvement: Targeted educational lectures and case-based clinical scenarios addressing identified deficiencies in the knowledge required to effectively manage poisoned patients. Weekly case-based anonymised feedback report sent electronically to staff involved in caring for poisoned patients. EFFECTS OF CHANGE: Implementation of targeted teaching of ED staff and regular electronic distribution of teaching cases. Between the first and second 6 months of the study, there was a significant increase in the proportion of presentations for which clinical management was graded as "good" (77.6% to 89.4%, $p < 0.0001$) and a significant reduction in the proportion of "major" (9.9% to 5.8%, $p = 0.012$) and "minor" (12.6% to 4.8%, $p < 0.0001$) shortfalls. LESSONS LEARNED: Systematic collection of clinical information, using a dedicated electronic database and subsequent review and audit of collated data by interested clinicians, enabled design and implementation of targeted

educational interventions to address shortfalls in patient management. This process has led to significant improvements in the clinical care of acutely poisoned patients presenting to the ED.

30. Wada K, Shinoda T. A case report of an anorexia nervosa patient with end-stage renal disease due to pseudo Bartter's syndrome and Chinese herb nephropathy requiring maintenance hemodialysis. *Ther Apher Dial.* 2008;12(5):417-20. PMID: 18937729
The extent of end stage renal disease (ESRD) has not been well documented in anorexia nervosa (AN). We herein describe a 47-year-old female with ESRD who required maintenance hemodialysis (HD) following a 27 year history of AN, and seven years of diuretic and purgative abuse. In spite of HD treatment, her serum inorganic phosphorus level remained elevated (10.2-15.8 mg/dL). Tissue degradation due to catabolism, insufficient dialysis treatment, and use of Chinese herbal medicine, including aristolochic acid, are speculated as the cause of her hyperphosphatemia. We also speculated that the causes of her renal dysfunction are as follows: chronic interstitial nephritis caused by pseudo Barter's syndrome resulting from chronic abuse of diuretics and purgatives, and Chinese herb nephropathy.
31. Auerbach SS, Mahler J, Travlos GS, Irwin RD. A comparative 90-day toxicity study of allyl acetate, allyl alcohol and acrolein. *Toxicology.* 2008;253(1-3):79-88. PMID: 18817840
Allyl acetate (AAC), allyl alcohol (AAL), and acrolein (ACR) are used in the manufacture of detergents, plastics, pharmaceuticals, and chemicals and as agricultural agents. A metabolic relationship exists between these chemicals in which allyl acetate is metabolized to allyl alcohol and subsequently to the highly reactive, alpha,beta-unsaturated aldehyde, acrolein. Due to the weaker reactivity of the protoxicants, allyl acetate and allyl alcohol, relative to acrolein we hypothesized the protoxicants would attain greater systemic exposure and therefore deliver higher doses of acrolein to the internal organs. By extension, the higher systemic exposure to acrolein we hypothesized should lead to more internal organ toxicity in the allyl acetate and allyl alcohol treated animals relative to those treated with acrolein. To address our hypothesis we compared the range of toxicities produced by all three chemicals in male and female Fischer 344/N rats and B6C3F1 mice exposed 5 days a week for 3 months by gavage in 0.5% methylcellulose. Rats (10/group) were dosed with 0-100mg/kg allyl acetate, 0-25mg/kg allyl alcohol, or 0-10mg/kg acrolein. Mice (10/group) were dosed with 0-125mg/kg allyl acetate, 0-50mg/kg allyl alcohol, or 0-20mg/kg acrolein. The highest dose of allyl acetate and acrolein decreased survival in both mice and rats. The primary target organ for the toxicity of all three chemicals in both species and sexes was the forestomach; squamous epithelial hyperplasia was observed following exposure to each chemical. In both species the highest allyl acetate dose group exhibited forestomach epithelium necrosis and hemorrhage and the highest dose of acrolein led to glandular stomach hemorrhage. Liver histopathology was the most apparent with allyl acetate, was also observed with allyl alcohol, but was not observed with acrolein. All chemicals had effects on the hematopoietic system with allyl acetate having the most pronounced effect. When dosed at quantities limited by toxicity, allyl acetate and allyl alcohol produce higher levels of urinary mercapturic acids than the minimally toxic dose of acrolein. This observation is likely due to biotransformation of allyl acetate and allyl alcohol to acrolein that occurs after absorption and suggests that these chemicals are protoxicants that increase systemic exposure of acrolein. Increased systemic exposure to acrolein is likely responsible for the differences in hepatic toxicological profile observed with these chemicals.
32. Stummann TC, Hareng L, Bremer S. Embryotoxicity hazard assessment of cadmium and arsenic compounds using embryonic stem cells. *Toxicology.* 2008;252(1-3):118-22. PMID: 18775467
The Embryonic Stem Cell Test (EST) has been successfully validated as an in vitro method for detecting embryotoxicity, showing a good overall test accuracy of 78% [Genschow, E., Spielmann, H., Scholz, G., Seiler, A., Brown, N., Piersma, A., Brady, M., Clemann, N., Huuskonen, H., Paillard, F., Bremer, S., Becker, K., 2002. The ECVAM international validation study on in vitro embryotoxicity tests: results of the definitive phase and evaluation of prediction models. European Centre for the Validation of Alternative Methods. *Altern.*

Lab. Anim. 30, 151-176]. Methylmercury was the only strong in vivo embryotoxicant falsely predicted as non-embryotoxic making the metal the most significant outlayer [Genschow, E., Spielmann, H., Scholz, G., Pohl, I., Seiler, A., Clemann, N., Bremer, S., Becker, K., 2004. Validation of the Embryonic Stem Cell Test in the international ECVAM validation study on three in vitro embryotoxicity tests. *Altern. Lab. Anim.* 32, 209-244]. The misclassification of methylmercury and the potential environmental exposure to developmental toxic heavy metals promoted our investigation of whether the EST applicability domain covers cadmium and arsenic compounds. The EST misclassified cadmium, arsenite and arsenate compounds as non-embryotoxic, even when including arsenic metabolites (methylarsonate, methylarsonous and dimethylarsinic). The reasons were the lack of higher cytotoxicity towards embryonic stem cells as compared to more mature cells (3T3 fibroblasts) or the absence of inhibition of cardiac differentiation by specific mechanisms rather than general cytotoxicity. Including EST data on heavy metals from the literature (lithium, methylmercury, trivalent chromium and hexavalent chromium) revealed that the test correctly predicted the embryotoxic potential of three out of the seven heavy metals, indicating an insufficient predictivity for such metals. Refinement of the EST prediction model and inclusion of additional toxicological endpoints could expand the applicability domain and enhance the predictive power of the test.