



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

July 2, 2011

1. Geng CA, Wang LJ, Zhang XM, Ma YB, Huang XY, Luo J, et al. Anti-hepatitis B virus active lactones from the traditional Chinese herb: *Swertia mileensis*. *Chemistry*. 2011;17(14):3893-903. PMID: 21365705

Swerilactones H-K (1-4), which are four novel lactones with an unprecedented C₂₉ skeleton, were isolated from *Swertia mileensis* (Qing-Ye-Dan), an endemic Chinese herb used for treating viral hepatitis. Their structures were determined by extensive spectroscopic and X-ray crystallographic diffraction analyses. Swerilactones H-K exhibit potent anti-hepatitis B virus activity against HBV DNA replication with IC₅₀ values ranging from 1.53 to 5.34 μM. For the first time, a plausible biogenetic pathway for swerilactones H-K, together with the previously reported swerilactones A-D is proposed. From a biogenetic point of view, swerilactones A-D are ascribed as secoiridoid dimers, and swerilactones H-K as secoiridoid trimers.

2. Jones R, Jones J, Causer J, Ewins D, Goenka N, Joseph F. Yew tree poisoning: a near-fatal lesson from history. *Clin Med*. 2011;11(2):173-5. PMID: 21526705

3. Carstairs SD, Cantrell FL. The spice of life: an analysis of nutmeg exposures in California. *Clin Toxicol (Phila)*. 2011;49(3):177-80. PMID: 21495887

BACKGROUND: Nutmeg is widely used as a household spice. Numerous citations in the medical literature report its abuse as a psychoactive agent, primarily for its purported hallucinogenic effects that are thought to be due to the compound myristicin; these are primarily limited to case reports.

METHODS: We performed a retrospective review of the California Poison Control System database for the years 1997-2008 for all cases of single-substance human exposure to nutmeg. **RESULTS:** There were a total of 119 single-substance exposures to nutmeg. Eighty-six (72.3%) exposures were intentional. Patients intentionally abusing nutmeg were more likely to be between the ages of 13 and 20 than those with unintentional exposure to the spice (80.2% vs. 9.1%, $p < 0.05$). Abusers were significantly more likely to require medical evaluation than nonabusers (61.6% vs. 33.3%, $p < 0.05$). Patients who abused nutmeg were significantly more likely ($p < 0.05$) to experience tachycardia and agitation than those whose exposure was unintentional. No major effects and no deaths were reported to occur in either group. **CONCLUSIONS:** Although nutmeg exposure is uncommonly encountered, clinical effects from

ingestion can be significant and can require medical intervention. While clinically significant effects were common, life-threatening toxicity and death did not occur in this series.

4. Krenzelok EP, Mrvos R. Friends and foes in the plant world: a profile of plant ingestions and fatalities. *Clin Toxicol (Phila)*. 2011;49(3):142-9. PMID: 21495882

INTRODUCTION: Plants are beneficial as foodstuffs and many have medicinal properties. However, some plants also have the potential to produce toxicity. The objective of this study was to characterize plant exposures that involve humans and to discuss those that are associated with morbidity and mortality, as well as some that have undeserved bad reputations. **MATERIALS AND METHODS:** The American Association of Poison Control Centers (AAPCC) 1983-2009 annual reports were reviewed to identify all plant-related fatalities. The 2000-2009 AAPCC Toxic Exposure Surveillance System and the National Poison Data System databases were queried to identify all plant ingestions. The data were analyzed to identify the specific plants, the age and gender of those who were exposed, the reason for the exposures and patient outcome. **RESULTS:** During the decade of 2000-2009, 668 111 plant ingestion exposures were reported, 621 109 were single substance exposures with no co-ingestants, and the age was known in 611 708 of the exposures. There has been a steady decline in the number of plant exposures reflected as a percentage of all exposures reported to US poison centers. A total of 8.9% of all exposures involved plants in 1983, 6.0% in 1990, 4.9% in 2000, and 2.4% in 2009. Males accounted for 52.2% of the ingestions and over 60% of the moderate and major outcomes occurred in males. Morbidity was related directly to the reason for the exposure with the most severe outcomes occurring in those who ingested plants intentionally for self-harm or substance abuse. Children \leq 5 years of age accounted for 81.2% of plant ingestion exposures. Within this age category, there were 497 002 ingestions over the 10-year period where a known age was recorded and 57.8% occurred in children less than 1 year of age. Only 45 fatalities were recorded between 1983 and 2009. *Datura* and *Cicuta* species were responsible for 35.5% of the fatal outcomes. **CONCLUSIONS:** Plant ingestion exposures remain a common call to poison information centers. However, the volume of those calls has decreased steadily over the last three decades. Most plant ingestion exposures occur in children, specifically children \leq 5 years of age. Within this age group, there were an inordinate number of exposures in children $<$ 1 year of age, a previously unidentified finding with an unknown epidemiological basis. Morbidity and mortality associated with plant ingestion exposures were very low relative to the total number of reported exposures.

5. Zajicek JP, Apostu VI. Role of cannabinoids in multiple sclerosis. *CNS Drugs*. 2011;25(3):187-201. PMID: 21323391

Although extracts from the cannabis plant have been used medicinally for thousands of years, it is only within the last 2 decades that our understanding of cannabinoid physiology and the provision of evidence for therapeutic benefit of cannabinoids has begun to accumulate. This review provides a background to advances in our understanding of cannabinoid receptors and the endocannabinoid system, and then considers how cannabinoids may help in the management of multiple sclerosis (MS). The relative paucity of treatments for MS-related symptoms has led to experimentation by patients with MS in a number of areas including the use of cannabis extracts. An increasing amount of evidence is now

emerging to confirm anecdotal reports of symptomatic improvement, particularly for muscle stiffness and spasms, neuropathic pain and sleep and bladder disturbance, in patients with MS treated with cannabinoids. Trials evaluating a role in treating other symptoms such as tremor and nystagmus have not demonstrated any beneficial effects of cannabinoids. Safety profiles of cannabinoids seem acceptable, although a slow prolonged period of titration improves tolerability. No serious safety concerns have emerged. Methodological issues in trial design and treatment delivery are now being addressed. In addition, recent experimental evidence is beginning to suggest an effect of cannabinoids on more fundamental processes important in MS, with evidence of anti-inflammation, encouragement of remyelination and neuroprotection. Trials are currently under way to test whether cannabinoids may have a longer term role in reducing disability and progression in MS, in addition to symptom amelioration, where indications are being established.

6. Vitalone A, Menniti-Ippolito F, Moro PA, Firenzuoli F, Raschetti R, Mazzanti G. Suspected adverse reactions associated with herbal products used for weight loss: a case series reported to the Italian National Institute of Health. *Eur J Clin Pharmacol.* 2011;67(3):215-24. PMID: 21243344

PURPOSE: The aim of this study was to describe suspected adverse reactions (ARs) associated with herbal products used for weight control in Italy. **METHODS:** Spontaneous reports of suspected ARs associated with herbal products used for weight control were collected by the Italian National Institute of Health (April 2002 to June 2010), and the causality assessment was performed. **RESULTS:** Forty-six of the suspected ARs were associated with herbal products used for weight control. Women were involved in 85% of the reports. The reactions affected mainly the cardiovascular system, the skin, the digestive system, the central nervous system, and the liver. A large proportion of ARs were serious. In more than half of the suspected ARs, the use of other therapies (herbs and/or drugs) was reported, while concomitant conditions were present in 22% of the reports. **CONCLUSIONS:** The use of herbal dietary supplements for weight loss is associated with several ARs. Considering the risk/benefit ratio, consumers should pay attention when using these products.

7. Tezer H, Erkocoglu M, Kara A, Bayrakci B, Duzova A, Teksam O, et al. Household poisoning cases from mercury brought from school. *Eur J Pediatr.* 2011;170(3):397-400. PMID: 20924603

Mercury has a number of unique and fascinating properties. It is present in the environment in several forms, both organic and inorganic. Each of these forms has somewhat unique properties that differentiate them from the other forms, but all are toxic to humans in one way or the others. Mercury has been proven to be a potential source of poisoning in children as a result of the inappropriate handling of a liquid mercury. The cases of metallic mercury vapor intoxication not associated with occupational exposure may occur in school science laboratories, from mercury dust and powders, from latex paint containing a mercury-based fungicide, and from normal wear or installation of dental amalgam fillings. Another source of toxic mercury exposure can be broken thermometers, barometers, or sphygmomanometers that may occur in the home, and children are often victims of environmental exposure. In this paper, we present three members of a family who were exposed to mercury brought home from school by a family member. Since the mercury exposure was not known, the initial presentation and clinical picture suggested a misdiagnosis, a contagious infectious disease, because the

onset of symptoms occurred at different times in the same family members. A subsequent change to a diagnosis of mercury intoxication and chelation therapy with meso-2,3-dimercaptosuccinic acid was started.

8. Frohlich S, Lambe E, O'Dea J. Acute liver failure following recreational use of psychotropic "head shop" compounds. *Ir J Med Sci.* 2011;180(1):263-4. PMID: 21063803

The recreational use of the so-called "legal-highs" has been in both the medical and political arena over the last year as a result of the appearance of "head shops" in many towns in Ireland. These shops specialized in selling new psychotropic compounds that circumvented established drug legislation. Little is known about the potentially harmful effects of these substances but case reports suggest a plethora of harmful psychological and physical effects. Our case describes for the first time acute liver failure associated with the ingestion of two of these amphetamine type compounds.

9. Jomova K, Jenisova Z, Feszterova M, Baros S, Liska J, Hudecova D, et al. Arsenic: toxicity, oxidative stress and human disease. *J Appl Toxicol.* 2011;31(2):95-107. PMID: 21321970

Arsenic (As) is a toxic metalloid element that is present in air, water and soil. Inorganic arsenic tends to be more toxic than organic arsenic. Examples of methylated organic arsenicals include monomethylarsonic acid [MMA(V)] and dimethylarsinic acid [DMA(V)]. Reactive oxygen species (ROS)-mediated oxidative damage is a common denominator in arsenic pathogenesis. In addition, arsenic induces morphological changes in the integrity of mitochondria. Cascade mechanisms of free radical formation derived from the superoxide radical, combined with glutathione-depleting agents, increase the sensitivity of cells to arsenic toxicity. When both humans and animals are exposed to arsenic, they experience an increased formation of ROS/RNS, including peroxy radicals (ROO*), the superoxide radical, singlet oxygen, hydroxyl radical (OH*) via the Fenton reaction, hydrogen peroxide, the dimethylarsenic radical, the dimethylarsenic peroxy radical and/or oxidant-induced DNA damage. Arsenic induces the formation of oxidized lipids which in turn generate several bioactive molecules (ROS, peroxides and isoprostanes), of which aldehydes [malondialdehyde (MDA) and 4-hydroxy-nonanal (HNE)] are the major end products. This review discusses aspects of chronic and acute exposures of arsenic in the etiology of cancer, cardiovascular disease (hypertension and atherosclerosis), neurological disorders, gastrointestinal disturbances, liver disease and renal disease, reproductive health effects, dermal changes and other health disorders. The role of antioxidant defence systems against arsenic toxicity is also discussed. Consideration is given to the role of vitamin C (ascorbic acid), vitamin E (alpha-tocopherol), curcumin, glutathione and antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase in their protective roles against arsenic-induced oxidative stress.

10. Li T. Avoiding adverse drug reactions to Chinese medicine injections. *J Evid Based Med.* 2010;3(1):44-9. PMID: 21349039

A total of 109 varieties of Chinese medicine injections (CMI) have been approved by the State Food and Drug Administration of China, all of which have the potential to induce adverse drug reactions (ADRs). Major ADRs include systemic anaphylaxis, anaphylactic shock, acute intravascular hemolysis, hepatorenal damage, skin lesion, cardiac damage, respiratory system injury, and gastrointestinal

disorders. Contributing factors of ADRs include healthcare workers' inadequate attention to ADRs of CMI, complex ingredients, allergic uncertainties, and inappropriate drug use in children and the aged. To decrease ADRs resulting from CMI, it is essential to improve the selection of drug indications, delivery of proper dosage regimens, compliance with drug instructions, and selection of solvents for the drugs.

11. Wang L, Cui X, Cheng L, Yuan Q, Li T, Li Y, et al. Adverse events to Houltuynia injection: A systematic review. *J Evid Based Med.* 2010;3(3):168-76. PMID: 21349062

OBJECTIVE: To systematically assess the main clinical features of Houltuynia injection-associated adverse drug reactions (ADRs), as described in published reports, and to contribute to the post-marketing re-evaluation and clinical practices of Houltuynia injection. **METHOD:** We searched the electronic databases- PubMed, EMBASE, the Chinese National Knowledge Infrastructure (CNKI), the Chinese Science and Technology Journal Full-text Database (VIP) and the Chinese Biomedical Disc (CBMdisc), for articles published through June 2010. We then extracted and analyzed the data. **RESULTS:** A total of 645 articles were included, with a total of 1232 ADR cases reported. Respiratory diseases accounted for 52.44% of all cases of Houltuynia injection ADRs, followed by reproductive system diseases (4.30%) and urinary system diseases (3.73%). Multiple systems or organs were involved in the ADRs, the top five were: respiratory system (37.42%), skin (34.66%), digestive system (25.49%), circulatory system (25.41%), and nervous system (23.96%). Serious systemic adverse reactions accounted for 22.56% of total ADRs. Of the reported 1,232 ADR cases, 286 ADR cases reported previous allergies in detail; allergy to penicillin accounted for 15.03% of the total cases with the allergic history, followed by unknown drugs (8.05%), and sulfonamides (3.15%). Among the ADR cases, Houltuynia injection was commonly used together with cephalosporins, penicillins, and macrolides. Macrolides combined with Houltuynia injection showed higher ADR risk than Houltuynia injection used alone (RR = 8.80, 95% CI 6.12 to 12.65, P < 0.0001). The ADR risk for intravenous injection of Houltuynia injection was higher than that of intramuscular injection (OR = 6.86, 95% CI 1.88 to 56.95, P= 0.0016). We used the WHO ADR Classification Criteria to divide the ADR cases into four grades. There were 22.56%, 36.28%, 16.48%, and 24.68% cases of Grade I, II, III, and IV, respectively. Anaphylactic shock accounted for 58.99% of the most serious ADRs (Grade I). All cases of death were caused by allergic shock, except one, who died of multiple organ failure caused by anaphylactic purpura. The fastest-onset three ADR cases occurred in one minute after injection. **CONCLUSION:** The respiratory system was the most common system treated in Houltuynia injection ADR cases. It was also the most common site of ADR symptoms. The ADRs of Houltuynia injection were serious. The precautions should be taken to prevent the anaphylactic shock. Intravenous injection and the combination with cephalosporins, penicillins, and macrolides increased the ADR risk of Houltuynia injection.

12. Zhang L, Hu J, Xiao L, Zhang Y, Zhao W, Zheng W, et al. Adverse drug reactions of Shenmai injection: a systematic review. *J Evid Based Med.* 2010;3(3):177-82. PMID: 21349063

OBJECTIVE: To analyze adverse drug reactions (ADRs) associated with Shenmai injection and possible contributing factors. **METHODS:** We searched all clinical studies and ADR reports of Shenmai injection from the China National Knowledge Infrastructure (CNKI) database, the Data Bank of Chinese Scientific Journals (VIP), and Chinese Biomedical (CBM) database. We collected relevant information such as

gender, age, allergic history, and diseases treated in ADR cases; types, occurrence times, and severity of ADRs; and menstruum and compatibility of Shenmai injection. RESULTS: Of the 1828 clinical studies of Shenmai injection, 146 (7.99%) mentioned 576 ADR cases; 181 ADR reports mentioned 246 ADR cases. The most commonly affected age group was 40 to 69 (57.32%). In 36 (14.63%) cases, patients were described as having an allergic history. The diseases treated in ADR cases were principally heart failure and coronary artery heart disease. Thirty-eight (15.45%) of the 246 ADR cases in ADR reports described anaphylactic shock, while the most common ADR reported in clinical studies was headache/dizziness. Of the 822 total reported ADR cases, 99 (12.04%) were class III, and 637 (77.50%) were class IV, and there were no fatalities. The menstruum of most Shenmai injections was 5% glucose. Incompatible drugs were given in 68 ADR cases. In ADR cases, the most common dosage of Shenmai injection was 40 to 60 ml; 215 (80.90%) ADR cases occurred in first time medication, mainly in the first 30 minutes after injection. CONCLUSIONS: Current evidence shows that Shenmai injection had lower ADR occurrence, but some potential factors such as irrational compatibility, dosages may lead to a high risk of ADR. In future, clinicians should follow indications or functions to promote rational use of Chinese Medicine Injections .

13. Takahashi M, Li W, Koike K, Sadamoto K. Clinical effectiveness of KSS formula, a traditional folk remedy for alcohol hangover symptoms. *J Nat Med.* 2010;64(4):487-91. PMID: 20559749

A formula (KSS formula) containing the pith of Citrus tangerine Hort. et Tanaka (Kitsuraku), the rhizome of Zingiber officinale (Shokyo), and brown sugar has been traditionally used in China for the treatment of discomfort and cold sensation in the abdomen after ingestion of large amounts of alcohol. We evaluated the clinical effectiveness of this formula on signs and symptoms of alcohol hangover (AH). Of the twenty-two symptoms listed, significant decreases in severity scores were shown in nausea, vomiting, and diarrhea when the formula was administered in scheduled prophylactic doses. The score in overall well-being, ranging from 0 to 100 (worst possible condition), was 68.9 +/- 16.5 (mean +/- SD) in the control group and it decreased to 46.9 +/- 27.3 and to 44.4 +/- 26.4 in the two groups that included a dosing point prior to alcohol ingestion. Regardless of dosing schedules, KSS formula did not alter the time required for complete recovery from AH symptoms. These findings suggest the possibility that KSS formula may become a candidate for AH remedy when administered prophylactically.

14. Yoshida M, Suzuki M, Satoh M, Yasutake A, Watanabe C. Neurobehavioral effects of combined prenatal exposure to low-level mercury vapor and methylmercury. *J Toxicol Sci.* 2011;36(1):73-80. PMID: 21297343

We evaluated the effects of prenatal exposure to low-level mercury (Hg(0)) or methylmercury (MeHg) as well as combined exposure (Hg(0) + MeHg exposure) on the neurobehavioral function of mice. The Hg(0) exposure group was exposed to Hg(0) at a mean concentration of 0.030 mg/m³ for 6 hr/day during gestation period. The MeHg exposure was supplied with food containing 5 ppm of MeHg from gestational day 1 to postnatal day 10. The combined exposure group was exposed to both Hg(0) vapor and MeHg according to above described procedure. After delivery, when their offspring reached the age of 8 weeks, behavioral analysis was performed. Open field (OPF) tests of the offspring showed an increase and decrease in voluntary activity in male and female mice, respectively, in the MeHg exposure group. In addition, the rate of central entries was significantly higher in this group than in the control

group. The results of OPF tests in the Hg(0) + MeHg exposure group were similar to those in the MeHg exposure group in both males and females. The results in the Hg(0) exposure group did not significantly differ from those in the control group in males or females. Passive avoidance response (PA) tests revealed no significant differences in avoidance latency in the retention trial between the Hg(0), MeHg, or Hg(0) + MeHg exposure group and the control group in males or females. Morris water maze tests showed a delay in the latency to reach the platform in the MeHg and Hg(0) + MeHg exposure groups compared with the control group in males but no significant differences between the Hg(0), MeHg, or Hg(0) + MeHg exposure group and the control group in females. The results of OPF tests revealed only slight effects of prenatal low-level Hg(0) exposure (0.03 mg/m³), close to the no-observable-effect level (NOEL) stated by the WHO (0.025 mg/m³), on the subsequent neurobehavioral function. However, prenatal exposure to 5 ppm of MeHg affected exploratory activity in the OPF test, and, in particular, male mice were highly sensitive to MeHg. The MeHg and Hg(0) + MeHg exposure groups showed similar neurobehavioral effects. Concerning the effects of prenatal mercury exposure under the conditions of this study, the effects of MeHg exposure may be more marked than those of Hg(0) exposure.

15. Chau W, Ross R, Li JY, Yong TY, Klebe S, Barbara JA. Nephropathy associated with use of a Chinese herbal product containing aristolochic acid. *Med J Aust.* 2011;194(7):367-8. PMID: 21470089

16. Al-Braik FA, Rutter PM, Hasan MY, Brown DT. Potential adverse reactions to herbal medicines in patients attending a nephrology clinic in Abu Dhabi, United Arab Emirates. *Saudi Med J.* 2011;32(2):171-6. PMID: 21301765

OBJECTIVE: To provide data on herbal medicine (HM) use and safety in patients attending a nephrology clinic at Sheikh Khalifa Medical City (SKMC), Abu Dhabi, United Arab Emirates (UAE). **METHODS:** A prospective, 3-month study between June and September 2007, investigated all patients presenting to the Nephrology Clinic of the Sheikh Khalifa Medical center (SKMC) in Abu Dhabi, UAE. A structured questionnaire determined previous and current HM use, and descriptions of associated adverse reactions. Corroborating evidence was sought from the patient's medical records. Causality was assessed by consensus from an expert panel using the Naranjo algorithm. **RESULTS:** The HM use was widespread (468 of 688; 68%). Over two-thirds (69%) reported currently taking 3 or more herbal preparations. Patients reported using over 100 different HMs, many of them compounded mixtures; 35% could not identify a single ingredient of these mixtures, and 70% had not informed the clinic doctors that they were taking HMs. Just 2 patients had HM use recorded in their medical record. Twenty-eight HM-related adverse reactions were identified in 26 (5.6%) patients; 12 probably and 16 possibly related to HMs. Seven involved HMs alone and 21, a HM/prescription medication (PM) interaction. **CONCLUSION:** The use of HMs in patients with underlying kidney problems was extensive and contributed additional pathology to the underlying renal disease, either alone or in combination with PMs. The reluctance of patients to inform their healthcare providers of concurrent use highlights a need to take a thorough drug history on clinic registration.

17. Reckziegel P, Dias VT, Benvegna D, Bouffleur N, Silva Barcelos RC, Segat HJ, et al. Locomotor damage and brain oxidative stress induced by lead exposure are attenuated by gallic acid treatment. *Toxicol Lett.* 2011;203(1):74-81. PMID: 21402136

We investigated the antioxidant potential of gallic acid (GA), a natural compound found in vegetal sources, on the motor and oxidative damages induced by lead. Rats exposed to lead (50 mg/kg, i.p., once a day, 5 days) were treated with GA (13.5mg/kg, p.o.) or EDTA (110 mg/kg, i.p.) daily, for 3 days. Lead exposure decreased the locomotor and exploratory activities, reduced blood ALA-D activity, and increased brain catalase (CAT) activity without altering other antioxidant defenses. Brain oxidative stress (OS) estimated by lipid peroxidation (TBARS) and protein carbonyl were increased by lead. GA reversed the motor behavior parameters, the ALA-D activity, as well as the markers of OS changed by lead exposure. CAT activity remained high, possibly as a compensatory mechanism to eliminate hydroperoxides during lead poisoning. EDTA, a conventional chelating agent, was not beneficial on the lead-induced motor behavior and oxidative damages. Both GA (less) and EDTA (more) reduced the lead accumulation in brain tissue. Negative correlations were observed between the behavioral parameters and lipid peroxidation and the lead levels in brain tissue. In conclusion, GA may be an adjuvant in lead exposure, mainly by its antioxidant properties against the motor and oxidative damages resulting from such poisoning.

18. Johansson I, Ingelman-Sundberg M. Genetic polymorphism and toxicology--with emphasis on cytochrome p450. *Toxicol Sci.* 2011;120(1):1-13. PMID: 21149643

Individual susceptibility to environmental, chemical, and drug toxicity is to some extent determined by polymorphism in drug-metabolizing enzymes, in particular the cytochromes P450 (CYPs). This polymorphism is in particular translated into risk differences concerning drugs metabolized by the highly polymorphic enzymes CYP2C9, CYP2C19, and CYP2D6, whereas CYP enzymes active in procarcinogen activation are relatively well conserved without important functional polymorphisms. Examples of drug toxicities that can be predicted by P450 polymorphism include those exerted by codeine, tramadol, warfarin, acenocoumarol, and clopidogrel. The polymorphic CYP2A6 has a role in nicotine metabolism and smoking behavior. Besides this genetic variation, genome-wide association studies now allow for the identification of an increasing number of predictive genetic biomarkers among, e.g., human leukocyte antigens and to some extent drug transporters that provide useful information regarding the choice of the drug and drug dosage in order to avoid toxicity. The translation of this information into the clinical practice has been slow; however, an increasing number of pharmacogenomic drug labels are assigned, where the predictive genotyping before drug treatment can be mandatory, recommended, or only for informational purposes. In this review, we provide an update of the field with emphasis on CYP polymorphism.

19. Thompson KJ, Molina RM, Donaghey T, Savaliya S, Schwob JE, Brain JD. Manganese uptake and distribution in the brain after methyl bromide-induced lesions in the olfactory epithelia. *Toxicol Sci.* 2011;120(1):163-72. PMID: 21177252

Manganese (Mn) is an essential nutrient with potential neurotoxic effects. Mn deposited in the nose is apparently transported to the brain through anterograde axonal transport, bypassing the blood-brain barrier. However, the role of the olfactory epithelial cells in Mn transport from the nasal cavity to the blood and brain is not well understood. We utilized the methyl bromide (MeBr) lesion model wherein the olfactory epithelium fully regenerates in a time-dependent and cell type-specific manner over the course of 6-8 weeks postinjury. We instilled $(^{54}\text{MnCl}_2)$ intranasally at different recovery periods to study the role of specific olfactory epithelial cell types in Mn transport. $(^{54}\text{MnCl}_2)$ was instilled at 2, 4, 7, 21, and 56 days post-MeBr treatment. (^{54}Mn) concentrations in the blood were measured over the first 4-h period and in the brain and other tissues at 7 days postinstillation. Age-matched control rats were similarly studied at 2 and 56 days. Blood and tissue (^{54}Mn) levels were reduced initially but returned to control values by day 7 post-MeBr exposure, coinciding with the reestablishment of sustentacular cells. Brain (^{54}Mn) levels also decreased but returned to control levels only by 21 days, the period near the completion of neuronal regeneration/bulbar reinnervation. Our data show that Mn transport to the blood and brain temporally correlated with olfactory epithelial regeneration post-MeBr injury. We conclude that (1) sustentacular cells are necessary for Mn transport to the blood and (2) intact axonal projections are required for Mn transport from the nasal cavity to the olfactory bulb and brain.