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ABSTRACTS

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1. Toxicity in Children: Comparative Aspects

Bond GR.
Cincinnati Drug and Poison Information Center, Cincinnati Children's Hospital, Cincinnati, US

Introduction: The sources of pediatric toxicology include developmental biology, lifetime exposure duration, size difference, the helplessness of the child and developmental exploratory behavior. *Developmental kinetics:* Absorption, distribution, metabolism and elimination are most dramatically different in the neonatal period, particularly the first post natal month, but still do not fully approach the adult pattern until near puberty. Variation from the adult pattern results in a concentration and duration of exposure that can produce unexpected but classic dose dependent toxic impact. Infants have relatively less stomach acid, less mature intestinal villi, relatively longer gut, less conjugated bile salts, a different set of gut metabolic enzymes and transporter proteins, a faster ventilatory rate, more skin surface area, thinner *stratum corneum* and more moist and perfused skin.[1] Depending on the agent these factors can dramatically decrease or increase absorption. Infants have relatively less fat but more total body water and extracellular water. Individual organ perfusion and xenobiotic uptake (related to transporters and tissue binding) can change in dramatic but variable ways.[1] The blood brain barrier is relatively more porous in infants (or relatively less is actively transported out). Phase I and Phase II enzymes are expressed differently in the liver, and in other organs and the pattern changes with age.[1,2] The liver is relatively larger in the infant and child, but this does not always explain increased metabolism when present. Non-hepatic metabolism plays a lesser or greater role in children, depending on the agent.[1,2] Renal blood flow and elimination rises significantly in the first month of life.[1] Bioaccumulation, resulting from the lack of an ability to metabolize and eliminate a compound (generally due to a "sink" in fat or bone) makes some highly toxic compounds particularly concerning.[4] *Developmental toxin dynamics:* With regard to therapeutic agents children have fewer well characterized dynamic differences from adults, particularly mechanistically.[1,4] There is some age related variation in receptor density which affects dosing requirements and toxicity risk of therapeutic agents. However, the development of children allows unique mechanistic opportunities for the toxic action of xenobiotics—therapeutic and environmental.[2–4] Interference with unique messengers directing gene expression, cell-cell signalling, organogenesis and cellular differentiation makes *in utero* exposure the time of greatest risk. Brain development, linear growth and sexual maturation make several non-therapeutic agents of particular concern post-natally.[5] Lead impairs neuronal growth and the rapidly progressing synaptogenesis which characterizes the first years of life. Thus the pattern of toxicity is different than that seen in adults. Studies show an impact on long term IQ even at levels below 10 mcg/dL.[6] The impact may not be observable at an individual level but may have a profound population impact. A variety of substances have been suggested to "disrupt" the estrogen/androgen axis.[7] Given the promoting role of hormones directly and via gene regulation prior to and during the course of puberty, exposure to non-plant xenoestrogenic substances, including phthalates, has been suggested as an explanation for observed earlier onset of thelarche and menarche, reduced sperm count in some populations and smaller phallic size.[7] *In vitro* receptor research has suggested plausible molecular mechanisms, but official EU and WHO bodies are among those who note that *in vivo* and human population research is insufficient to establish causality.[7] Some experts are specifically sceptical that the additive impact of these xenoestrogens are significant next to the plant estrogens in modern diets.[3] To specifically accommodate pediatric exposure risks, including any unknown dynamic impact, when setting allowable exposure limits for environmental agents the US EPA requires an additional ten-fold reduction beyond all other reductions from the no-observed adverse effect level. *Longer lifetime exposure to xenobiotics:* Earlier and prolonged exposure to an environmental agent may make the lifetime risk of disease or cancer higher or result in disease or cancer at an earlier age. For example, recent human reports link both arsenic and bisphenol A to insulin resistance, diabetes and hypertension.[8,9] *Size:* Size affects the relative risk for and consequence of dosing error. The total mg doses are smaller as are the dose volumes. Errors, including 10 fold and greater errors occur. Size is also key to the toxicity following unintentional ingestion of adult therapeutic agents. *Helplessness:* Limited communication and physical dependence means a child cannot identify and refuse too much or the wrong medication, express specific symptoms of toxicity early or leave an unhealthy environment. They also make a child particularly vulnerable to abuse involving medications (Munchausen's by proxy, sedation by a caregiver and sexual exploitation). Some deaths linked to cough and cold medications resulted from intentional administration of the agent to sedate a healthy child. *Exploratory behavior:* The exploratory behavior of young children (and developmentally challenged older children) leads to classic unintentional exposure to drugs and other xenobiotics. *Conclusion:* Our understanding of pediatric toxicity remains limited yet is foundational to appropriate preventive intervention. Because the causes are so broad, in addition to traditional "poison prevention" activities, a range of actions are required including: pediatric specific drug research; multipoint regulatory intervention; hospital, pharmacy and home care systems revision; and criminal prosecution. *References:* 1. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology-drug disposition, action, and therapy in infants and children. N Engl J Med 2003; 349:1157–1167. 2. Brent RL, Weitzman M. 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2. Poisoning in Special Patient Groups: The Elderly

Bateman DN, Sandilands E.
NPIS Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, UK

Background: The epidemiology of poisoning in the elderly differs from that in younger patients for several reasons. *Epidemiology:* Firstly the mortality rate per self-harm event is generally higher, and a variety of hypotheses may be considered to explain this. Elderly patients who self harm may have a clearer strategy to achieve a completed suicide. In addition they are more likely to have ready access to more toxic agents, due to the need to treat the increasing frequencies of illness seen in the ageing population. Drug ingestion is favoured by females, and as in younger age groups, more violent methods of self-harm tend to be used by males. Other cultural factors affect self-harm methods, and in countries where there is widespread availability of firearms these achieve greater prominence as a cause of death. There is also data to support the hypothesis that elderly patients with self harm have a greater risk of completed suicide than younger patients, some studies putting the excess risk as high as seven fold.[1] Social isolation, depression, early dementia, chronic ill-health and poverty may all be additional risk factors. There is good evidence that increasing numbers of concurrent diseases also increases risk of completed suicide.[2] A number of studies have shown that the pattern of drug ingestion in the elderly is different to the young in overdose. The key implication here is that drug availability affects the agent taken in overdose. *Pathophysiology*: Even apparently healthy older patients are more likely to have a deterioration in renal and cardiovascular function that will potentially affect susceptibility to toxins. They may have co-morbid conditions that influence their decision to self-harm but also that increase the potential toxicity of ingested agents due to impaired pathophysiological responses.[3] Deliberate self-harm in the elderly is more likely to include a drug ingestion than in other age groups.[4,5] Quantification of the excess risk of mortality within individual drug groupings is more difficult because of the problem in linking dose to effect in different patient populations. Studies on patients with major paracetamol poisoning suggest that in this situation age is a determinant of risk of renal dysfunction, which in turn relates to poor outcome. This finding is independent of dose ingested and appears therefore to indicate impaired ability to respond to the effects of paracetamol. Whether this is due to existing renal dysfunction, nutritional deficiency in patients ingesting the drug or other factors requires further exploration. Age has been identified as an independent risk factor for hepatotoxicity from paracetamol poisoning, but may also be associated with increased regular alcohol consumption and late presentation – both of which increase risk of hepatotoxicity.[6] Diminished elimination of renally excreted compounds occurs as the body ages, and thus accumulation of agents such as digoxin and lithium are more likely. There is some

evidence that the cardiac effects of digoxin are greater in the elderly thus further complicating the clinical scenario. Elderly patients who have ingested agents that alter acid base balance are less able to resist these changes and this is particularly a feature of aspirin poisoning. Fortunately the incidence of this condition has reduced but in those patients who ingest large quantities physicians' lack of familiarity with this poison may mean patients are not adequately treated. The pharmacokinetics of drugs may change in the elderly. With reduced muscle and fat mass the apparent volume of distribution may change, therefore altering the relationship between ingested dose and plasma concentration. The impact of this on outcome in poisoning is difficult to evaluate. Evidence that drug metabolism changes significantly in old-age in a way which affects outcome is also more difficult to establish, although there is some evidence that hepatic clearance of some agents is reduced in the elderly. This may be one factor in the apparent excess mortality seen with benzodiazepines in the elderly.[4] Some of these changes in metabolism may be related to changes in organ mass rather than enzyme activity. *Implications*: Elderly patients appear to have a higher rate of successful suicide indicating the need to be more aware of their higher suicide intentionality. Managing underlying diseases optimally may assist in prevention of recurrence. There is some evidence to suggest that elderly patients who ingest similar doses may have worse outcomes than younger ones.[3] Management strategies need therefore to be appropriately targeted and correct physiological abnormalities. Delayed excretion and increased susceptibility of end organs, particular the heart and brain, may also contribute to excess mortality. Targeting poisons information for the elderly poisoned patient is more difficult as physiological responses may not be so readily predictable as in the young. *References:* 1. Lawrence D, Almeida O, Hulse G, et al. Suicide and attempted suicide among older adults in Western Australia. Psychol Med 2000; 30:813–821. 2. Juurlink D, Herrmann N, Szalai J, et al. Medical illness and the risks of suicide in the elderly. Arch Intern Med 2004; 164:1179–1184. 3. Eddleston M, Dissanayake M, Sheriff MHR, et al. Physical vulnerability and fatal self-harm in the elderly. Br J Psychiatry 2006; 189:278–279. 4. De Leo D, Padoani W, Scocco P, et al. Attempted and completed suicide in older subjects: results from the WHO/EURO Multicentre study of suicidal behaviour. Int J Geriatr Psychiatry 2001; 16:300–310. 5. Cattell H, Jolley D. One hundred cases of suicide in elderly people. Br J Psychiatry 1995; 166:451–457. 6. Schmidt LE. Age and paracetamol self-poisoning. Gut 2005; 54:686–690.

3. Pharmacogenetics of Drug Toxicity

Daly A.
Institute of Cellular Medicine, Newcastle University Medical School, Newcastle upon Tyne, UK

Pharmacogenetics is concerned with the study of genetic factors affecting drug disposition and drug response. Currently, the role of genetic variability in drug disposition is generally well understood but our knowledge and understanding on drug targets, including those that contribute to drug toxicity, is more limited. Examples of drugs where toxicity may arise due to impaired metabolism include coumarin anticoagulants, immunosuppressants and antipsychotic drugs. In each of these cases, low activity or absence of activity for the cytochrome P450 enzyme that contributes to metabolism, CYP2C9, CYP3A5 and CYP2D6 respectively for these drug classes, is an important contributor to this toxicity.[1] The genetic basis of the low activity in these enzymes is well understood and individuals can now be genotyped to predict their enzyme activity, with the possibility of dose adjustment tailored to genotype to avoid toxicity.[2] Our knowledge of genetic variability in drug targets has improved as a result of projects such as the Human Genome project and HapMap. These have led to the realization that most genes are subject to polymorphism which may result in physiologically and pharmacologically relevant interindividual variation. In the case of the coumarin anticoagulants, genetic polymorphism in the VKORC1 gene is an important determinant of dose requirement and appears relevant to both over and undercoagulation.[3] However, unlikely the common P450 polymorphisms, the important polymorphism in VKORC1 is a regulatory polymorphism which affects level of expression rather than causing very low or absent activity.[4] Other examples of drug targets where genetic polymorphism appears to contribute to drug response include the beta-2 adrenergic receptor[5] and angiotensin converting enzyme (ACE).[6] Susceptibility to idiosyncratic drug toxicity where drug concentration appears less important in determining toxicity is also likely to be genetically determined but, apart from emerging information on immune factors that are important in some forms of toxicity, information is very limited. Paracetamol in overdose is associated with serious hepatotoxicity but there is interindividual variability in severity of response to similar overdoses, suggesting that genetic factors may determine disease severity. Genes relevant to metabolism, cell signalling and oxidative stress are all potential determinants of risk but, due to a variety of factors including the complexity of the toxicity response and the overlapping substrate specificity of the various metabolizing enzymes, no clear associations have yet been described. If suitable DNA collections can be obtained, genome-wide association studies focussing on all genes rather than selected candidates may prove the best way for identifying risk genes. This approach has recently been used successfully to identify a major genetic determinant of statin-induced myopathy[7] and is also likely to be of value for studies on other idiosyncratic toxicities. *References:* 1. Daly AK Pharmacogenetics of the major polymorphic metabolizing enzymes. Fundamen Clin Pharmacol 2003; 17:27–41. 2. Ingelman-Sundberg M, Sim SC, Gomez A, et al. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. Pharmacol Ther 2007; 116:496–526. 3. Sconce EA, Khan TI, Wynne HA, et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. Blood 2005; 106:2329–2333. 4. Wang D, Chen H, Momary KM, et al. Regulatory polymorphism in vitamin K epoxide reductase complex subunit 1 (VKORC1) affects gene expression and warfarin dose requirement. Blood 2008; 112:1013–1021. 5. Israel E, Chinchilli VM, Ford JG, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. Lancet 2004; 364:1505–1512. 6. Jeunemaitre X. Genetics of the human renin angiotensin system. J Mol Med 2008; 286:637–641. 7. SEARCH Collaborative Group, Link E, Parish S, et al. SLCO1B1 variants and statin-induced myopathy-a genomewide study. N Engl J Med 2008; 359:789–799.

4. Chronic Kidney Diseases and Poisoning

Groszek B.
Department of Clinical Toxicology, Jagiellonian University, Kraków, Poland

Pathophysiology: The kidney plays an important role in the elimination of numerous hydrophilic xenobiotics, including drugs, toxins, and endogenous compounds. It has developed high-capacity transport systems to prevent urinary loss of filtered nutrients, as well as electrolytes, and simultaneously to facilitate tubular secretion of a wide range of organic ions. The majority of drugs are eliminated as inactive metabolites, but a large number of drugs are excreted in the urine unchanged or as active metabolites. Three basic renal processes determine the rate of drug excretion in the urine - glomerular filtration, active secretion by the tubule cells, and passive reabsorption. The contribution of filtration to drug elimination is a function of the glomerular filtration rate (GFR), the plasma concentration of the unbound (filterable) drug, and the extent of passive reabsorption of the drug following its filtration. Active secretion results in the net transfer of the drug from the peritubular capillaries into the tubule lumen. It is a much more efficient mechanism of drug elimination than glomerular filtration particularly for drugs that are highly protein bound. There are two independent secretory systems, both of which are located in the proximal tubule. The organic anion transport system is responsible for secreting acidic substances, the organic cation transport system specializes in the secretion of basic (cationic) compounds. Renal function and dysfunction considerably contribute to the morbidity and mortality of poisoned patients. Kidney failure results in life-threatening complications, affecting virtually every organ system in the body. Renal failure may be acute or chronic. The onset of acute renal failure is relatively rapid, but the injury to the renal tissue may be partially or completely reversible. Chronic renal failure develops as a result of a progressive, irreversible tissue damage resulting in irreversible nephron loss. The state of gradually and slowly declining renal function is referred to as chronic kidney disease (CKD). CKD is defined as a progressive, irreversible loss of nephrons and nephron function. The degree of renal deficiency and the severity of kidney disease are generally reflected in the decline of glomerular filtration rate (GFR). Renal insufficiency can markedly alter one or more of the pharmacokinetic and pharmacodynamic parameters.[1,2] *Pharmacokinetic changes in CKD:* Patients with CKD have alterations in all of the pharmacokinetic parameters: absorption, distribution, metabolism and elimination. The absorption of drug can be reduced or slowed in the CKD patient due to delayed gastric emptying. The absorption of many drugs is affected by gastric pH. Gastric acidity is reduced in CKD patients compared to healthy people. The volume of distribution (Vd) for patients with renal failure can be altered due to volume overload, decreased protein binding, hypoalbuminemia or alterations in tissue binding. It has been postulated that the albumin molecule itself has a different conformation in renal failure and that change affects protein binding. As kidney function declines so does the kidneys ability to metabolize drugs. The brush border of the kidney is responsible for the metabolism of many drugs, and this also declines as glomerular filtration rate (GFR) declines. Chronic renal failure (CRF) and end-stage renal disease (ESRD) can alter drug disposition by reducing the systemic clearance of renally cleared drugs and by affecting protein and tissue binding. Many studies have shown that loss of renal function can result in decreased hepatic clearance of drugs. Both drug metabolizing enzymes and uptake and efflux transporters are important determinants of drug metabolism and drug clearance by the liver. Retention of unspecified retained uremic molecules may affect hepatic enzyme activity. Although reduced metabolic enzyme activity can be responsible for the reduced non-renal clearance of drugs in a number of cases, other mechanisms, such as alterations in transporter systems or transporter activity, may also be involved in decreasing the clearance of drugs in renal failure. Another important drug elimination consideration in CKD patients is the accumulation of renally eliminated drug metabolites. Many drugs have metabolites that have pharmacologic activity. Some of these metabolites are also active drugs with similar activity in their own right. Some retained metabolites in CKD have therapeutic activity that differs from the parent compound. The mechanisms responsible for altered dynamic responses of some agents in renally compromised patients include enhanced receptor sensitivity secondary to the accumulation of endogenous uraemic toxins and competition for secretion to the renal tubular site of action.[1–5] *Clinical implications:* Renal insufficiency is associated with an increased risk of adverse and toxic effects with many classes of medications, even in therapeutic doses. The risk of toxic effects is generally linked to the patient's degree of residual renal function, may be the result of inappropriate individualisation of the dose, those medicines that are primarily eliminated by the kidney, or an alteration in the pharmacodynamic response as a result of renal insufficiency.[6–10] All these pharmacokinetic and pharmacodynamic changes will also aggravate the clinical course in overdose situation. *References:* 1. Churchwell MD, Mueller BA. Selected pharmacokinetic issues in patients with chronic kidney disease. 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5. Poisoning in Patients with Eating Disorders and Nutritional Abnormalities

Kupferschmidt H.
Swiss Toxicological Information Centre, Zurich, Switzerland

Nutrition disorders and eating disorders including anorexia nervosa and bulimia nervosa are typically associated with disturbances of body weight (low body weight, cachexia or obesity) and nutritional abnormalities, but this association may not invariably be present in these conditions. In addition eating disorders are frequently associated with psychiatric illness including compulsive disorders,[1] and these patients are at a higher risk of self-harm including intentional self-poisoning. As a consequence these patients would be expected to be overrepresented in poisoned patients. Therefore clinical toxicologists must be aware of particular issues and conditions associated with this type of disorder, but have to keep in mind that there are specific risks associated with a pathological body weight, and specific risks associated with eating disorders. An extremely decreased body weight, either due to voluntary or forced malnutrition, and after bariatric surgery, may be associated with deficiencies in macronutrients (proteins) or micronutrients (iron, calcium, folate, vitamins) thus causing a change in susceptibility to a variety of xenobiotics and poisons. Anorectic individuals are shown to have reduced glutathione stores with a potential to an increased risk of paracetamol-induced liver injury.[2] A very low or extremely high percentage of fat tissue can alter pharmacokinetic and toxicokinetic parameters, volume of distribution being one of the most important in acute poisoning, which may not only change the clinical response to toxicants but also have implications in treatment strategies including dosing of medications (e.g. antidotes). Many of the pharmaceutical therapies are dosed on a per kilogram bodyweight basis. This may not be appropriate if the lean body mass to fat tissue ratio is outside the normal range. Taking the mass of fat tissue in account is not a regular practice in clinical medicine or intensive care. Most concern in this regard is for markedly lipophilic and hydrophilic pharmaceuticals, as hydrophilic substances tend to be overdosed in obese individuals, as are lipophilic substances in patients with very low fat tissue. Delayed gastric emptying and gut transit in bulimia nervosa can change toxicant absorption and adversely affect orally administered therapies.[1] Anorectic and obese patients may have concomitant diseases associated with their weight disorders, including diabetes mellitus, sleep apnoea, cardiovascular disease, addiction and their complications.[1] These can be adversely associated with outcome in acute or chronic poisoning. Further aspects of pharmaceuticals related to weight disturbances are body weight disturbances in psychopharmacology and the use and abuse of anorexigenic agents.[3] Psychiatric illness is not only associated with eating disorders but psychopharmaceuticals may also affect appetite and lead to weight gain as an adverse drug effect,[4,5] most pronounced in neuroleptics, which eventually decreases treatment adherence (low compliance) and self-medication with appetite suppressants or misuse of other pharmaceuticals and illicit drugs as appetite suppressants. Adverse drug reactions to and poisoning with these drugs are a potential consequence. Many appetite suppressants have an unfavorable adverse drug reaction risk profile (e.g. phentermine, fenfluramine, rimonabant).[3] Lastly obesity may have a toxicological etiology as findings suggest that endocrine disruption during development may lead to obesity in later life.[6] *References:* 1. Klein DA, Walsh T. Eating disorders: clinical features and pathophysiology. Physiol Behav 2004; 81:359–374. 2. Zenger F, Russmann S, Junker E, et al. Decreased glutathione in patients with anorexia nervosa. Risk factor for toxic liver injury? Eur J Clin Nutr 2004; 58:238–243. 3. Newbold RR, Padilla-Banks E, Snyder RJ, et al. Perinatal exposure to environmental estrogens and the development of obesity. Mol Nutr Food Res 2007; 51:912–917. 4. Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for obesity and overweight. Cochrane Database Syst Rev 2003; 4:CD004094. 5. Schwartz TL, Nihalani N, Jindal S, et al. Psychiatric medication-induced obesity: a review. Obesity Rev 2004; 5:115–121. 6. Vieweg WV, Levy JR, Fredrickson SK, et al. Psychotropic drug considerations in depressed patients with metabolic disturbances. Am J Med 2008; 121:647–655.

6. Genetic Basis of Drug-Induced Liver Injury Linked to Commonly Prescribed Drugs

Daly A.
Institute of Cellular Medicine, Newcastle University Medical School, Newcastle upon Tyne, UK

Hepatotoxicity is a common reason for discontinuation of drug development. A number of currently licensed drugs are also associated with idiosyncratic liver injury. This drug-induced liver injury (DILI) is relatively rare but potentially serious, sometimes leading to death or requiring a liver transplant. The genetic basis for susceptibility to this disease is still poorly understood. The DILIGEN study is a UK-wide study on the genetics of DILI. In the UK, the drugs most commonly associated with DILI are the antimicrobials co-amoxiclav and flucloxacillin. The disease seen with these drugs usually, but not always, shows a cholestatic phenotype. We have collected DNA samples from cases of DILI due to these drugs and also from controls where drug exposure has not resulted in DILI. Samples have been genotyped for a range of candidate genes selected either on the basis of previous reports or biological relevance. More recently, genome-wide association studies have been initiated. The strongest associations seen by both the candidate gene and genome-wide association studies were with the MHC locus on chromosome 6. Associations with HLA class II DRB1 alleles were detected for both co-amoxiclav and flucloxacillin. For co-amoxiclav, DRB1*15 was found at a frequency of 52% in cases compared with 30% in community controls giving an odds ratios of 2.5 (95% CI 1.4–4.8; pc=0.041), confirming the previously reported DRB1*15 association for this drug.[1] DRB1 genotyping found that 70% of flucloxacillin DILI cases were positive for DRB1*07 compared with 26% of those exposed to flucloxacillin without toxicity giving an odds ratios of 6.5 (95% CI 2.9–14.3; pc=0.000021). Limited high resolution sub-typing of DRB1*07 positive cases and controls found the significant increase in DRB1*07 frequency was due to an increased frequency of the DRB1*0701-DQB1*0303 haplotype (odds ratio 17.4; 95% CI 6.3 to 48.2; p<alpha SNPs tested two, T-1031C and G-238A, were–0.0001). Of five TNF statistically significant for flucloxacillin-related DILI. The strongest effect at TNF-alpha was with the −238 SNP with an odds ratio for disease development in individuals carrying −238A of 31.2 (95% CI 10.3 to 95.0; p<0.0001), comparing cases to drug-exposed controls. The HLA class II and TNF markers are part of the extended B57.1 MHC haplotype present in approx. 6% of Europeans which also includes the class I HLA allele B*5701. All flucloxacillin cases and drug-exposed controls were therefore genotyped for B*5701. An odds ratio of 80.6 (95% CI 22.8–284.9) was obtained, with 84% of cases positive for B*5701 compared with 6% of controls. This haplotype is also strongly associated with hypersensitivity to abacavir but this is the first report of an association between B*5701 and DILI. There is now evidence that an abacavir metabolite interacts specifically with CD8-positive T cells expressing the B*5701 antigen but the mechanism involved in flucloxacillin DILI is still unclear. A genome-wide association study on the flucloxacillin cases confirms that B*5701 is the main risk allele for flucloxacillin toxicity with some evidence for a weaker effect for a gene on chromosome 3 which is currently under further investigation. These findings suggest that the mechanisms underlying DILI due to co-amoxiclav and flucloxacillin are different but that a specific HLA component is involved in each case. DILI due to other drugs, e.g. diclofenac or drugs used in TB treatment, does not show a strong HLA association. Polymorphisms affecting drug disposition or oxidative stress may be more important predictors of susceptibility to DILI relating to these drugs. *References:* 1. O'Donohue J, Oien KA, Donaldson P, et al. Co-amoxiclav jaundice: clinical and histological features and HLA class II association. Gut 2000; 47:717–720. *Acknowledgements:* These studies were funded by the UK Department of Health and the International Serious Adverse Events Consortium.

7. Airway Control and Ventilation – To Intubate or Not?

Bedry R.
Forensic Medicine Department, Pellegrin University Hospital, Bordeaux, France

Objective: To describe the indications and techniques of ventilatory support in poisoned patients. *Methods:* The three main questions are 1. What are the indications for respiratory support in a poisoned patient?, 2. How to ventilate such patients? 3. Is there a need for additional sedation in case of mechanical ventilation? *Results:* Airway control is one of the main items of emergency life support. The objectives of ventilation usually include correction of hypoxaemia or respiratory acidosis, respiratory muscle support, prevention and treatment of atelectasis, as well as facilitation of sedation.[1] Only a few studies have focused on the ventilatory support of poisoned patients. In 1996, poisonings represented the third etiology of calls to mobile intensive care services in Paris (10% of 3594 patients). 21% of them were intubated.[2] In 2005, a prospective, multi-center survey on health care practices was conducted in 153 ICUs and 104 mobile emergency services in France, Belgium, and Switzerland, during a 1-month period. The aim was to describe the practice of ventilatory support of poisonings in the pre-hospital and hospital phases: the main indications for ventilatory support were coma and/or aspiration either in the pre-hospital or hospital management.[3] 1. Indications for ventilatory support were defined in the recently published recommendations by the experts of the French Society of Critical Care Medicine (SRLF):[4] whatever the origin of the coma or the respiratory failure (type I: ventilation/perfusion alteration as in aspiration pneumonia or type II as in coma) there is no indication for non-invasive ventilation. Intubation and mechanical ventilation are indicated when the level of consciousness is depressed (coma: the most useful tool remains the Glasgow Coma Scale score (GCS) where intubation is needed if GCS<8, or in case of permanent seizures), if signs of respiratory exhaustion occur despite adequate oxygenation and in case of hemodynamic failure. The nature of the ingested toxicant is not a determinant criterion for deciding to intubate.[5] 2. Parameters used to monitor mechanical ventilation in patients with poisoning are the same as in other conditions. However, close respiratory and hemodynamic monitoring is required due to the risk of hemodynamic failure (toxin-induced vasoplegia syndrome), barotrauma (cocaine), or acid-base imbalance.[4] The more frequently used mode of ventilation was assisted/controlled ventilation in the previously mentioned prospective study,[3] with initial 60% inspired fraction of O_2 and mean tidal volume of 7.5 ml/kg before first arterial blood gas analysis. The only particularity of mechanical ventilation is the need for a charcoal cartridge on the expiratory circuit of the ventilator in case of volatile solvent intoxication. The cartridge is then used to prevent diffusion of the gas into the room. 3. The need for sedation to intubate a comatose poisoned patient is related to the risk of aspiration: airway protective reflexes are suppressed at different levels of narcosis, and the cough as well as the laryngeal reflexes are abolished later than the gag reflex,[6,7] so aspiration can occur during pre-oxygenation or intubation. It is necessary

to sedate the patient before intubation, and several studies have shown the usefulness of a rapid sequence induction with a hypnotic drug associated with a neuromuscular blocking agent.[8] The need for sustained sedation after induction in intoxicated comatose patients has not been clearly evaluated, but it may be necessary to ensure a secure airway and make easier care and adaptation to the ventilator. For example, it appears necessary in the case of a life-threatening situation (collapse, convulsions, severe hypoxemia: ARDS, aspiration), continuing coma, excessive agitation in a patient not fully awake or in case of required gastrointestinal decontamination. *References:* 1. Slutsky AS. ACCP Consensus Conference on Mechanical Ventilation. Chest 1993; 104:1833–1859. 2. Ould-Ahmed M, Drouillard I, Savio C, et al. [Experience with 361 acute poisonings managed by mobile intensive care units]. Rean Urg 1999; 8:93–97. 3. Bedry R, Nouts C, Guisset O. Ventilatory Management of Poisoned Patients: Prospective Multi-Center Survey. Clin Toxicol 2006; 44:755–756. 4. Mégarbane B, Donetti L, Blanc T, et al. ICU management of severe poisoning with medications or Illicit substances. Experts recommandations. Réanimation 2006; 15:343–353. 5. Mégarbane B, Loulizi C, Lino M, et al. [Does the need for assisted ventilation in toxic coma depend on the clinical status of the patient or the toxic agent?] Réanimation 2001; 10:107S (abstract). 6. Kulig K, Rumack BH, Rosen P, et al. Gag reflex in assessing level of consciousness. Lancet 1982; 1:565. 7. Moulton C, Pennycook A, Makower R. Relation between Glascow coma scale and the gag reflex. BMJ 1991; 303:1240–1241. 8. Bergen JM, Smith DC. A review for etomidate for rapid sequence intubation in the emergency department. J Emerg Med 1997; 15:221–230.

8. Conventional Cardiovascular Support and Extracorporeal Life Support in Acute Poisonings Involving Cardiotoxicants

Mégarbane B, Baud FJ.
Réanimation Médicale et Toxicologique, Hôpital Lariboisière and Université Paris-Diderot, Paris, France

Objective: To review the conventional treatments of drug-induced cardiac failure in order to define the place of extracorporeal life support (ECLS) in poisonings. *Methods:* Review of the international literature. *General considerations:* Despite significant improvement in critical care, drug-induced cardiovascular failure remains a leading cause of death. "Cardiotoxicants" include not only cardiovascular drugs but also various other toxicants like antidepressants, H1-antihistaminic agents, meprobamate, chloroquine, cocaine, organophosphates, cyanide, and plants. Among 2,403,539 exposures in adults reported to the American Association of Poison Control Centers in 2006, cardiovascular drugs were involved in 3.3% of the cases. However, they accounted for 21% of the total of 1,229 fatalities, representing the third toxicant category responsible for death.[1] In this register, calcium channel blockers (CCB) and beta-blockers (BB) accounted for 36% of cardiovascular drug exposures, while CCB represented the second cause and cardiac glycosides the first cause of cardiovascular agent-related death. Usually, severe cardiotoxicity appears either at presentation or during the course of poisoning with the sudden onset of hypotension, high-degree atrio-ventricular block, asystole, pulseless ventricular tachycardia or fibrillation.[2] Other critical features include mental status deterioration, seizures, hyperlactacidemia, and respiratory failure. Neurological alteration is generally subsequent to cerebral hypoperfusion. Cardiovascular effects generally occur within 6 hours after massive ingestions. However, delay depends on the drug type, pharmaceutical formulation, and dose. Thus, intensive cardiac monitoring is mandatory as soon as the patient is admitted in the intensive care unit (ICU). *Conventional management:* Determination of the mechanism of cardiovascular failure is mandatory to improve the patient management.[3] Cardiac failure mainly results from a decreased systolic myocardial contractility. However, numerous other mechanisms may also be implicated, including diastolic dysfunction, alteration in the geometry of heart contraction, myocarditis, or acute coronary syndrome. Overdoses with CCB, BB, and membrane-stabilizing agents (MSA) result in myocardial negative inotropic effects as well as arterial dilatation. Toxicity is generally reversible following toxicant elimination. Prognostic factors remain poorly investigated, except for digitalis, colchicine, theophylline, and antidepressants. They are specific for a class of toxicants. Interestingly, the prognostic value of blood concentrations remains also to be determined. Poisoning management includes non-specific and specific treatments. Non-specific supportive care aims to correct hypoxia, hypotension, acid/base, and electrolyte disorders. Tracheal intubation and mechanical ventilation are required in case of coma, severe collapse, or cardiac arrhythmia. In case of cardiac arrest, basic and advanced life support should be immediately provided. Cardioversion is indicated for life-threatening ventricular arrhythmia. Multidose activated charcoal is not helpful except for sustained-release preparations. Due to large volumes of distribution and high protein binding ratios, extracorporeal elimination enhancement techniques are not feasible options. Catecholamines represent the first-line therapy for cardiovascular support if hypotension persists despite initial rapid IV saline infusion. Sodium bicarbonate is required if ventricular conduction is delayed as in MSA poisonings. In chloroquine poisonings, combining early mechanical ventilation with diazepam and epinephrine administration is life-saving.[4] Regarding cardiac glycoside poisonings, digoxin-specific Fab fragments represent the treatment of life-threatening events if atropine fails as first-line anti-arrhythmic therapy to correct bradycardia.[5] In CCB poisonings, despite controversial clinical efficacy, calcium salts are still recommended. Based on animal data and single case reports, insulin/glucose therapy (1 UI/kg IV bolus followed by 0.5–1.0 IU/kg/h) should be used early as adjunctive treatment, mainly if vasopressors failed to improve haemodynamic function or conduction disturbances.[6] In BB poisonings, glucagon remains largely used, despite lack of clinical studies to support its beneficial effects.[7] Isoproterenol is life-saving in sotalol-related bradycardia, as QT interval prolongation may cause torsade-de-pointes or favour sustained ventricular dysrhythmia. Various other antidotes have been shown promising, including phosphodiesterase inhibitors (milrinone), vasopressin analogues, levosimendan, as well as potassium-channel-antagonists (4-aminopyridine and 3,4-diaminopyridine). However, the interest in all these agents is only based on animal studies or if tested, single human cases. Moreover, their availability still limits their utilization. *Place of ECLS:* Despite optimal supportive and antidotal treatments, management of drug-induced cardiovascular failure remains difficult. Ventricular arrhythmia, sudden cardiac arrest, and refractory cardiovascular failure may cause death, despite aggressive resuscitative measures and vasopressors. Prognostic factors predictive of refractoriness to conventional treatments are lacking. The interest of ventricular pacing can only be considered if the inotropic heart function is preserved. Similarly, the interest in use of intra-aortic balloon pumps appears limited due to the need for intrinsic cardiac rhythm for synchronization and diastolic augmentation. ECLS for reversible cardiac toxicity has a sound basis but clinical experience is still limited in toxicology with insufficient evidence to conclude for its recommendation (grade C).[8,9] The purpose of ECLS is to take over the heart function during refractory cardiac shock until recovery can occur, thus minimizing myocardial work, improving organ perfusion, and maintaining the renal and biliary elimination of the toxicant.[2] Two experimental randomized studies supported the hypothesis that ECLS is life-saving in comparison with ACLS.[10,11] However, only single cases or small series of drug-induced refractory cardiovascular failures or cardiac arrests treated with ECLS have been published.[12,13] Regarding the different mechanisms of drug-related shock, ECLS should not be considered in predominant arterial vasodilatation, justifying thereby the necessity of a systematic evaluation of the cardiac index using any adequate technique in the ICU. Interestingly, we demonstrated that emergent ECLS is feasible in medical ICU.[10] To date, we have treated about 60 severely poisoned patients with ECLS in our medical ICU, allowing a 45%-survival rate in patients suffering from cardiogenic shock and permitting survivors among poisoned patients with prolonged refractory cardiac arrests despite extremely high predicted death rates. However, femoral cannulation for ECLS remains an invasive technique, not lacking in potential severe risks. We thus believe that this technique should only be performed by trained multidisciplinary medico-surgical teams. *Conclusion:* Cardiotoxicants are responsible for life-threatening poisonings resulting in multiple organ failure and leading to death. Supportive and antidotal treatments are usually efficient. Due to a persistent high-rate of mortality, there is a need for a more aggressive management in patients not responding to conventional treatments. Clarification of prognosticators of refractoriness to conventional treatment is thus mandatory. Usefulness of ECLS remains a matter of debate. To date, only experimental studies and case reports support the hypothesis that peripheral ECLS may be life-saving. Further studies are still needed to clarify indications and usefulness of ECLS. *References:* 1. Bronstein AC, Spyker DA, Cantilena LR Jr, et al. 2006 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS). Clin Toxicol 2007; 45:815–917. 2. Baud FJ, Mégarbane B, Deye N, et al. Clinical review: aggressive management and extracorporeal support for drug-induced cardiotoxicity. Crit Care 2007; 11:207. 3. Mégarbane B, Aslani AA, Deye N, et al. Pharmacokinetic/pharmacodynamic modeling of cardiac toxicity in human acute overdoses: utility and limitations. Expert Opin Drug Metab Toxicol 2008; 4:569–579. 4. Riou B, Barriot P, Rimailho A, et al. Treatment of severe chloroquine poisoning. 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9. Why do Patients Die in Organophosphorus Poisoning Despite Effective Relief of the Cholinergic Crisis?

Thiermann H,[1] Worek F,[1] Kehe K,[1] Zilker T.[2]
[1]Bundeswehr Institute of Pharmacology and Toxicology, Munich; [2]Toxicological Department of 2nd Medical Clinic, Technical University, Munich, Germany

Objective: Inhibition of acetylcholinesterase is generally regarded as the most important toxic mechanism in poisoning by organophosphorus compounds (OP). Although experimental data showed that oximes are able to reactivate inhibited acetylcholinesterase (AChE),[1] its usefulness in a clinical situation is an ongoing matter of debate.[2] *Methods:* OP-poisoned patients were treated with obidoxime (250 mg bolus, followed by 750 mg/24h) and activity of red blood cell (RBC)-AChE activity, reactivatability of RBC-AChE and neuromuscular transmission were analysed. *Results:* In 33 patients RBC-AChE activity was inhibited by more than 70%. In 12 of them marked sustained reactivation was achieved. In 8 patients RBC-AChE activity decreased below 20% of normal after initial substantial reactivation. In 13 patients no reactivation could be achieved. An increase above some 30%

residual activity was associated with nearly unimpaired neuromuscular transmission. Three patients with substantial sustained reactivation, 2 with transient reactivation and 2 patients with absent reactivation died. Only in 2 patients, cholinergic crises persisted until death. In the others, severe complications developed during intensive care therapy (e.g. peritonitis due to septic duodenal ulcer, severe lung embolism, pneumothorax) or were probably due to delayed emergency treatment (e.g. aspiration, leading to ARDS in combination with circulatory failure). These complications finally resulted in death. *Conclusion:* In OP poisoned patients oximes are able to reactivate inhibited RBC-AChE, thereby restoring impaired neuromuscular transmission indicating clinical benefit. However, frequent complications develop during the clinical course of OP-poisoning finally leading to death. The reason may be due to mechanisms that occur prior to therapy (aspiration and local lung effects due to solvents or unknown toxic effects of OPs) or after the subsiding of the cholinergic crises. Such complications cannot be attributed to oximes but have to be considered when assessing oxime effectiveness by survival rates. *References:* 1. Eyer P. The role of oximes in the management of organophosphorus pesticide poisoning. Toxicol Rev 2003; 22:165–190. 2. Hmouda H, Ben Salem C, Bouraoui K. Management of acute organophosphorus pesticide poisoning. Lancet 2008; 371:2169–2171.

10. Should you Treat Every Paracetamol-Poisoned Patient?

Dalhoff K,[1] Gesser K,[2] Rasmussen M.[2]
[1]*Dept of Clinical Pharmacology, Bispebjerg Hospital, Copenhagen;* [2]*Faculty of Pharmacy, University of Copenhagen, Copenhagen, Denmark*

Objective: To investigate whether the Danish recommendation of treating all patients suspected of paracetamol-poisoning with 36 hours N-acetylcysteine (NAC) infusion influenced morbidity or mortality. *Methods:* Register-based study with data from the Danish Medicines Agency. Sale, hospital admissions and deaths secondary to the use of dextropropoxyphene, paracetamol (pcm) and acetylsalicylic acid in the period 1989 to 2007 were extracted and reviewed with special reference to the periods before and after 1996. In 1996 the Danish Association of the Study of the Liver recommended that all patients admitted with a suspicion of paracetamol poisoning should receive treatment with NAC IV for 36 hours. *Results:* In the whole period the sale of pcm increased from 31 (1989) to 61 (2007) Defined Daily Dose (DDD)/1,000inhabitants/day. Also the number of admissions due to poisonings with uncategorised non-opioid analgesics increased in the period from 1090/y in 1989 to 4766/y in 2007. However, due to changes in the WHO disease coding system, it was not possible to distinguish between poisonings from the various drugs after 1993. In the period 1989 to 1993 admissions with pcm poisonings alone increased from 271/y to 745/y. The pcm deaths/sale ratio was unchanged in the whole period from 0.42 to 0.44 deaths/(DDD/1,000inhabitants/day). However, this is based on the assumption that 50% of the uncategorised cases were due to pcm poisonings. *Conclusion:* The Danish recommendations probably led to an increasing number of admissions due to pcm poisonings. However, the deaths per sale ratio did not decrease in the period, suggesting that other means to avoid pcm poisonings have to be discussed.

11. Risk Genes for Multiple Chemical Sensitivity: A Pilot Study

Bornschein S,[1,2] Hausteiner C,[3] Zilker T,[1] Förstl H,[2] Riemenschneider M.[2]
[1]*Section of Clinical Toxicology and Environmental Medicine, Technical University of Munich;* [2]*Department of Psychiatry and Psychotherapy, Technical University of Munich;* [3]*Department of Psychosomatic Medicine, Technical University of Munich, Munich, Germany*

Objective: Multiple Chemical Sensitivity (MCS) has been hypothesized to be genetically determined. Despite interesting preliminary findings, evidence of a genetic basis of MCS is limited. In this pilot project, various enzymes involved in the metabolism of xenobiotics were investigated using a "whole-gene approach" by genotyping of densely spaced single nucleotide polymorphisms (SNPs) in patients with MCS and population-based controls. *Methods:* DNA samples of 387 patients with MCS and 280 controls from a normal population were analyzed for 170 SNPs in 22 genes coding for enzymes involved in the metabolism of xenobiotics. Allelic and genotypic frequencies in patients and controls were compared with c2, respectively logistic regression analysis considering corrections for multiple testing. *Results:* Strong associations with MCS were identified for polymorphisms in the genes for CYP2E1 (rs2031920, pcorr.< 0.001; OR= 3.6 [2.04 – 6.23]), MPO (rs8067377; pcorr = 0.001; OR = 18.4 [2.4 – 142]), and PON1 (rs3917564, pcorr. = 0.04, OR = 6.3 [1.3 – 29.3]). *Conclusion:* This pilot study examining a multitude of single nucleotide polymorphisms in genes of xenobiotic metabolizing enzymes in a large sample of patients with a clearly described clinical picture of MCS is the first to indicate the existence of risk genes for this condition of still unclear aetiology and pathogenesis. It is the first indication of a potential importance of CYP2E1 and MPO (myeloperoxidase) genes as risk factors for MCS.

12. Pediatric Death from Cough and Cold Medicines: A Modern Day Mystery

Dart RC.
Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, Denver, US

Fatalities have been reported with the use of nonprescription cough and cold products in children, creating a debate regarding whether these products should be available for use in children. Although the same cough and cold products have been used widely for decades, it is alleged that typical therapeutic use of these products may cause the death of children 0 to 12 years of age. It is also alleged that these products are proven ineffective; therefore any risk is unacceptable. Case reports are the basis of safety allegations regarding cough and cold products. Until recently, there have been no peer-reviewed reports regarding the underlying cause of pediatric deaths associated with cough and cold products. The debate has highlighted several important issues: 1. Why are fatal cases coming to attention now? 2. Could recommended doses of cough and cold products be lethal to some children? 3. Are these pediatric deaths actually caused by the cough and cold product? 4. How should we integrate case information when assessing the safety of a product? 5. If some or all of the deaths were causally related to the use of a cough and cold product, what is the root cause of the deaths? What was the caregivers' intent? Several recent reports have been published. Most reports focus on accidental exposures leading to adverse effects and the interventions needed to prevent medication errors; for example, children accidentally ingesting a product or caregivers inadvertently administering an overdose of the medication. The causes underlying these accidental exposures is often unclear, but attention has focused on medication errors, including the use of multiple products containing the same ingredients simultaneously, using an improper measuring device, and multiple caregivers administering the same medicine too frequently, among others.[1,2] A retrospective study of deaths of children associated with cough and cold products was completed in 2007.[3] Each case was reviewed by an independent panel of five experts (pediatrics, pediatric toxicology, clinical toxicology, forensic toxicology) using explicit definitions to assess the causal relationship between medication ingestion and death. In the original study, 103 deaths involving a nonprescription cough and cold medicine were identified. Of these, the expert panel concluded that an overdose had occurred in 88 (85%) cases; the dose could not be determined in the remaining 15 cases. Several contributing factors were identified: age younger than 2 years, use of the medication for sedation, use in a day-care setting, use of two medicines with the same ingredient, failure to use a measuring device, product misidentification, and use of a nonprescription product intended for adult use. The study also identified a root cause not previously addressed – intentional nontherapeutic use of cough and cold medications. Of the 103 nonprescription medication cases, the person administering the medicine was an adult in 79 (77%) cases, a child (self-administered) in 18 (17%) cases, and was not identified in 6 (6%) cases. The 79 cases of adult administration included 19 with therapeutic intent, 34 with unknown intent, and 26 with nontherapeutic intent. Among the cases with nontherapeutic intent, child abuse and purposeful administration of an overdose to sedate a child were identified. Remarkably, 20% of fatal cases with a site recorded occurred in a day care center. Typical measures to prevent child access or increase parental understanding of instructions are unlikely to deter these types of fatalities. Following the initial retrospective study, the same methods have been used for ongoing surveillance for adverse events and fatalities that involved a child younger than 12 years and one of 8 cough and cold ingredients. The benefit of cough and cold products is currently unclear. Although it is claimed that the products have been proven ineffective, the scientific rationale behind their use in children is logical and the research suggesting ineffectiveness seriously flawed. Convincing evidence of efficacy exists in adults. Therefore, appropriate timed and controlled studies with objective endpoints are needed to assess efficacy in children before they are pronounced ineffective. Pediatric cough and cold products were deemed effective and safe by the US FDA in the 1970s. This had the unintended effect of stifling further research and development. Since that time rare deaths have occurred. Analysis of the root cause shows that most of the cases resulting in death involve overdose. Traditional approaches to reduce pediatric overdose (changes in product packaging, improved package instructions for parents) are important and may prevent some causes of overdose. However, in a substantial portion of fatal cases, these medications are intentionally administered by a caregiver with the intent of altering behavior or overtly harming the child. *References:* 1. Gunn VL, Taha SH, Liebelt EL, et al. Toxicity of Over-the-Counter Cough and Cold Medications. Pediatrics 2001; 108:e52. 2. Schaefer MK, Shehab N, Cohen AL, et al. Adverse Events From Cough and Cold Medications in Children. Pediatrics 2008; 121:783–787. 3. Dart RC, Paul IM, Bond GR, et al. Pediatric Fatalities Associated With Over the Counter (Nonprescription) Cough and Cold Medicines. Ann Emerg Med 2009; 53:411–417.

13. Liver and Kidney Toxicity of Diethylene Glycol Results from its Metabolism

McMartin KE, Besenhofer LB, Cain M, Latimer B.
Department of Pharmacology, Toxicology & Neuroscience, LSU Health Sciences Center, Shreveport, US

Objective: Mistaken use of medicines adulterated with diethylene glycol (DEG) has led to mass epidemic poisonings. DEG targets the kidneys, liver and nervous system, but the mechanism for the organ damage and the role of DEG or its metabolites in the toxicity are unknown. This study was designed to define the role of metabolism in the toxicity and to relate the accumulation of specific metabolite(s) with the development of the toxicity. *Methods:* Male rats were treated in four groups: water, low dose DEG (2 g/kg), high dose DEG (10 g/kg), or high dose DEG+fomepizole, an inhibitor of the presumed DEG metabolic pathway. Urine and blood samples were collected at timed intervals to 48 h, when rats were anesthetized for collection of liver and kidney tissues. *Results:* DEG produced a time- and dose-dependent metabolic acidosis that was completely inhibited by fomepizole. In the high dose animals only, kidney and liver toxicity began at about 24 h post DEG. No signs of toxicity were observed in the DEG+ fomepizole treated group throughout the 48 h. Histopathologic analysis of the livers showed mild to severe damage in 4 of 6 rats at the high dose, with no evidence of damage in any rat at the low dose or in rats co-treated with fomepizole. Similar analysis of the kidneys showed damage in 5 of 6 rats at the high dose, with 4 showing severe damage. Kidneys in the rats at the low dose or in rats co-treated with fomepizole were not affected. *Conclusion:* These studies demonstrate, for

the first time, that a metabolite of DEG, rather than DEG itself, is responsible for its toxicity and that metabolic inhibition should be used to treat these poisonings. The variability in toxicity at the high dose is unusual, but is a key to determining which metabolite is responsible for the organ damage. Blood, urine and organ levels of the various metabolites are being studied to relate accumulation of a specific metabolite with the organ damage and to begin to understand the mechanism of DEG toxicity.

14. The "Diagnostic Pathways in Toxicology" Project – A Multidisciplinary Approach

Hallbach J.
Toxicology Laboratory, Städt. Klinikum München, Munich, Germany

Objective: In acutely diseased patients, depending on the anamnesis, clinical examination and cardinal symptoms, the process of differential diagnosis requires a fast, secure and efficient diagnostic strategy. In practice laboratory medicine plays a major rule to distinguish between the relevant and conceivable possibilities. Therefore laboratory investigations are involved in nearly every differential diagnostic procedure, often in combination with sonography, X-ray, CT, ECG and others. Laboratory tests can be performed stepwise with increasing specificity and can not only substantiate or confirm the suspicion of an intoxication, but also can help to rule out other medical possibilities like metabolic or neurological disorders. In many clinical cases a possible intoxication is not the suspected diagnosis in the first instance, even though in many cases an intoxication will be the cause of coma, loss of consciousness, suddenly developing arrhythmias or neurological symptoms. A battery of clinical chemistry parameters, i.e. RBC, WBC, platelets, INR, D-dimer, sodium, calcium, glucose, urea, creatinine or cystatin C, AST, ALT, GGT, CK, CHE, troponin, anion gap, osmolar gap, prolactin, blood gas parameters, lactate, urine stick and sediment, microproteins in urine, may help to increase the evidence of an intoxication and are therefore generally recommended. For example, an osmolar gap can support the evidence for a methanol intoxication[1] or others of the previously listed tests can support an alternative diagnosis. In combination with the previously mentioned parameters, toxicological tests for ethanol, paracetamol, benzodiazepines and others can be performed with the same routine analysers within a few minutes and can help to confirm or exclude some specific poisons.[2] More dedicated tests and strategies will be introduced and discussed in the second part of the session. *Methods:* Two years ago the German society for laboratory medicine DGKL introduced interdisciplinary expert groups which were to develop diagnostic strategies for frequent clinical symptoms like chest pain, abdominal pain or neurological disorders. One group (Degel, Desel, Felgenhauer and Hallbach) has focussed on acute poisoning. *Results:* The first project of the expert group was suspected paracetamol intoxication which is not yet completed. A preliminary rational strategy with 5 steps was defined. 0. Estimation of exposure. 1. Assessment of risk: no further action, if dose is below 150 mg/kg body weight and no other relevant substances and no suicidal tendency. 2. Therapy controlled by symptoms and measure of basal chemistry parameters including ALT, GGT, HST, TBIL and determination of paracetamol in blood. 3. Where required antidote therapy. 4. Monitoring of progression, i.e. ALT, prothrombin ratio (INR), TBIL, creatinine. *Conclusion:* The role of emergency clinical toxicological testing cannot be definitely evaluated following the rules of evidence based medicine because the database in the literature is very small and nobody has evaluated data from outside well-known centres. Furthermore, the existing studies rely often on a restricted battery of tests. Therefore the recommendation from literature.[3] and scientific communities should be followed to establish regional centres for specialized toxicology testing. The time schedule of the whole process (transportation of samples and analysis) is critical for acute clinical decisions and should be defined. *References:* 1. Hunderi OH, Hovda KE, Jacobsen D. Use of the osmolal gap to guide the start and duration of dialysis in methanol poisoning. Scand J Urol Nephrol 2006; 40:70–74. 2. Hallbach J, Guder WG. Mechanized toxicological serum tests in screening hospitalized patients. Eur J Clin Chem Clin Biochem 1991; 29:537–547. 3. Wu AH, McKay C, Broussard LA, et al. National academy of clinical biochemistry laboratory medicine practice guidelines: recommendations for the use of laboratory tests to support poisoned patients who present to the emergency department. Clin Chem 2003; 49:357–379.

15. Systematic Toxicological Analysis – the Broad Approach Far Beyond Immunochemical Limitations

Maurer HH.
Department of Experimental and Clinical Toxicology, Saarland University, Homburg (Saar), Germany

Objective: Rational diagnosis or definite exclusion of an acute or chronic intoxication should be supported by efficient toxicological analysis. The analytical strategy includes screening, confirmation and identification followed by quantification of relevant compounds and interpretation of the results.[1] Some papers have been published on strategies of clinical toxicological analysis services, showing that depending on the country and/or the tasks to be covered different statements were made.[2–6] The tasks may cover besides support for diagnosis and prognosis of poisonings, help for indications for (invasive) treatment, monitoring of the efficiency of detoxification, support in differential diagnostic exclusion of poisonings, drug determinations in the context of brain death diagnosis, monitoring of polytoxicomaniacs, detection of adverse drug reactions or interactions, monitoring of Munchhausen Syndrome patients, and finally monitoring of non-compliant patients. *Methods:* Gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS) are the gold standards in clinical and forensic toxicological analysis due to their universality, reliability, high sensitivity and specificity.[7–9] *Results:* GC-MS and LC-MS are used for target and comprehensive screening, library-assisted identification, and validated quantification of drugs, poisons and their metabolites in blood and/or urine. Examples will help to understand when and why competent analytical results available within 1-2 h may change the initial clinical considerations and decisions. *Conclusion:* Reliable analytical and reference data are a prerequisite for correct interpretation of toxicological findings. Unreliable analytical data and/or their interpretation could lead to wrong treatment of the patient or might be contested in court and finally, they could lead to unjustified legal consequences for the defendant. Reliable analytical data, however, are, in combination with well-documented clinical data, important for the toxicological risk assessment e.g. of chemicals as well as for assessing the clinical outcome in the sense of evidence-based medicine. *References:* 1. Maurer HH, Kraemer T, Kratzsch C, et al. What is the appropriate analytical strategy for effective management of intoxicated patients? In: Balikova M, Navakova E, eds. Proceedings of the 39th International TIAFT Meeting in Prague, 2001. Prague, Czech Republic: Charles University, 2002:61–75. 2. Maurer HH. Demands on scientific studies in clinical toxicology. Forensic Sci Int 2007; 165:194–198. 3. Flanagan RJ. Developing an analytical toxicology service: principles and guidance. Toxicol Rev 2004; 23:251–263. 4. Wu AH, McKay C, Broussard LA, et al. National academy of clinical biochemistry laboratory medicine practice guidelines: recommendations for the use of laboratory tests to support poisoned patients who present to the emergency department. Clin Chem 2003; 49:357–379. 5. Boyer EW, Shannon MW. Which drug tests in medical emergencies? Clin Chem 2003; 49:353–354. 6. Bailey B, Amre DK. A toxicologist's guide to studying diagnostic tests. Clin Toxicol (Phila) 2005; 43:171–179. 7. Maurer HH. Position of chromatographic techniques in screening for detection of drugs or poisons in clinical and forensic toxicology and/or doping control. Clin Chem Lab Med 2004; 42:1310–1324. 8. Maurer HH. Hyphenated mass spectrometric techniques - indispensable tools in clinical and forensic toxicology and in doping control. J Mass Spectrom 2006; 41:1399–1413. 9. Maurer HH. Current role of liquid chromatography-mass spectrometry in clinical and forensic toxicology. Anal Bioanal Chem 2007; 388:1315–1325.

16. Fatal Toxicity from Symptomatic Hyperlactemia: Factors Implicated with Chronic Nucleoside Reverse Transcriptase Inhibitor Use

Leung L,[1] Wilson D,[2] Manini AF.[1]
[1]Department of Emergency Medicine, Mount Sinai School of Medicine, New York, US; [2]Department of Internal Medicine, Edendale Hospital, Pietermaritzburg, South Africa

Objective: HIV antiretroviral regimens based on nucleoside reverse transcriptase inhibitors (NRTI) are prevalent in resource-poor countries due to ease of use and lower cost compared with alternative regimens. Chronic NRTI use poisons mitochondrial DNA-polymerase (gamma) which may result in symptomatic hyperlactatemia (SH), a toxicity that can be life-threatening.[1] We determined the factors associated with fatality in patients with SH due to chronic NRTI therapy. *Methods:* This was a retrospective cohort study at a 900-bed tertiary care hospital in South Africa over four years (2005–08). Consecutive inpatients with chronic NRTI use, SH (lactate >2 mmol/L), and no source of infection (determined by adjudication) were included. Patients with missing follow-up data and subsequent inter-hospital transfer were excluded. The primary outcome was in-hospital fatality. Data collection included demographics (age, gender), CD4 counts, duration of NRTI use, initial blood pressure, symptom type and duration, altered mental status (GCS <15), and relevant serum laboratory data (including lactate, A-a gradient, anion gap, WBC, and creatinine). Statistical analysis was performed to calculate univariate odds ratios (OR), chi-squared (nominal variables) and t-test (continuous variables), using SPSS computer software. *Results:* 87 patients met inclusion criteria, of whom 8 were excluded (6 missing data, 2 transfers). Of 79 patients analyzed (mean age 37.9, 97% female, mean CD4 count 197) there were 46 fatalities (58%). Age, CD4 count, symptom duration, initial vital signs, and length of NRTI therapy were not associated with fatality (using the t-test). Factors associated with fatality included initial lactate > 10 mmol/L (OR 4.5, $p = 0.003$), initial pH<7.2 (OR 6.6, $p = 0.002$), and altered mental status on presentation (OR ∞, $p = 0.03$). *Conclusion:* SH due to chronic NRTI use occurred largely in females and carried high in-hospital mortality. Factors associated with fatal toxicity included initial lactate, initial pH, and altered mental status. We recommend aggressive management for patients with these high-risk features, and prospective study is warranted. *References:* 1. Wester CW, Okezie OA, Thomas AM, et al. Higher-than-expected rates of lactic acidosis among highly active antiretroviral therapy-treated women in Botswana: preliminary results from a large randomized clinical trial. J Acquir Immune Defic Syndr 2007; 46:318–322.

17. Need for Laboratory Investigation Support in Diagnosis and Treatment of Poisonings – Results of a EAPCCT Membership Survey

Desel H.
GIZ-Nord Poisons Centre, University Medical Centre Göttingen, Göttingen, Germany

Objective: Besides the EAPCCT there are other European scientific communities concerned with the best management of human poisonings. The Scientific Committee 'Clinical Toxicology' of the Society of Toxicological and Forensic Chemistry (SCCT-GTFCh) is preferentially dealing with technical and medical aspects of laboratory support for diagnosis and clinical management of intoxications. To prepare a joint symposium of EAPCCT and SCCT-GTFCh on this topic a survey was conducted to evaluate the role of laboratory service in routine clinical toxicology in Europe. *Methods:* A short 5-item questionnaire form was prepared and distributed by the General Secretary via email to the EAPCCT membership. Feedback was requested within

3 weeks. *Results:* 58 questionnaires were returned (about 19%): 46 from Europe, 5 from America, 4 from Asia and 3 from Australia. 14 members responding are working in a toxicological laboratory (24%), 6 of them in addition to their work in a poisons centre (PC) or hospital treating poisoned patients (HOS). 57% of all responders and 45% of responders not working in a laboratory stated that lab investigations play a major role in their daily work. Only 2 responders indicated that there is no role for laboratory investigations. A systematic (non-target) toxicological analysis (STA, reliable toxicological screening) designed to identify toxic agents in blood or urine samples that have not been expected from the patient's history, was assessed to be 'of major importance' by 79% of the lab workers and 39% of the non-lab scientists. Only one lab scientist (7%) and 20% of the responders without lab experience did not see any role for this type of analysis. The preferred methods for STA are high performance screening methods such as gas chromatographic coupled to mass spectrometry (GC/MS 52%) and various liquid chromatographic methods (42%). Besides STA, a set of target compound analyses in biological sample materials were considered valuable: ethanol, paracetamol, carboxyhemoglobin and carbamazepine were marked as important parameters in >70% of all answers, met-hemoglobin, salicylate, ethylene glycol, digoxin, lithium, methanol and valproate were evaluated as important by more than 60% of responders, while theophylline, tricyclic antidepressants, phenobarbital, and methanol were still considered important by the majority. 4-hydroxybutyrate and amanitines were only important in few countries. Some laboratories were considering rare parameters as important featuring their scientific interests: red blood cell cholinesterase, toxic anions (F-, Br-, CN-, SCN-), glycol ethers, metformin or orellanine. A WWW-connected database of toxicological laboratories and parameters that was developed recently by SCCT-GTFCh was considered interesting by 72% of responders and 54% of them are ready to include their own knowledge into this system. *Conclusion:* A substantial subgroup of EAPCCT members are working at least part time in toxicological laboratories and may be interested in discussions on the role of analytical investigations for poisoning management. Furthermore, the broad majority of members responding to the questionnaire was regularly involved with laboratory analyses in the management of poisoning cases in PC or hospital. A frequent need is directed to toxicological screening for unknown agents. Besides this, several target analyses were considered as highly important from the members' point of view. Traditions are different in European countries.

18. Matched Comparison of Plasma Lactate Concentrations in Cyanide Poisoned and Drug Poisoned Patients

Baud FJ, Lapostolle F.
Medical and Toxicological Critical Care Department, Assistance Publique - Hopitaux de Paris, France

Objective: Cellular hypoxia indicated by lactic acidosis may be a useful marker of cyanide poisoning. However, it is not known to what extent lactic acidosis is a direct result of cyanide effects on oxidative phosphorylation versus a secondary response to shock and hypoperfusion. We conducted a retrospective chart review to compare plasma lactate concentrations in patients with acute poisoning due to cyanide or other agents who were matched for age, sex, blood pressure, and catecholamine use. *Methods:* Plasma lactate concentrations, blood chemistry/gases, and vital signs were measured in 12 patients admitted to a toxicology intensive care unit with acute cyanide poisoning (other than smoke inhalation) and 12 patients with acute non-cyanide poisoning due to psychotropic drugs (5/12), cardiotropic drugs (4/12), and opiates (3/12) The two groups were compared using the Wilcoxon signed rank test. Correlations were made using the Spearman test. *Results:* Plasma lactate concentrations were significantly greater in patients with acute cyanide poisoning (median 15.6 mmol/L) than in patients with similar vital signs suffering acute poisonings not involving cyanide (median 3.3 mmol/L, $p < 0.001$). Compared with non-cyanide poisonings, heart rate and blood glucose levels were significantly increased and HCO_3 and PaO_2 significantly decreased in the cyanide poisoned patients. Plasma lactate concentration positively correlated with blood cyanide ($r = -0.783$, $p = 0.017$) concentrations in cyanide poisoned patients. In both groups, plasma lactate was inversely correlated with systolic blood pressure. *Conclusion:* This study supports the hypothesis that the lactic acidosis seen in acute cyanide poisoning results from the direct toxicity of cyanide rather than a secondary response to cardiovascular disturbances.

19. Toxicokinetic Calculations Based on Drug Blood Levels – Pro

Binscheck TB.
Institute of Toxicology, Clinical Toxicology and Poison Information Centre BBGes, Berlin, Germany

Objective: Toxicokinetic calculations based on drug levels require a highly available and sensitive quantitative toxicological analysis. Appropriate mathematical models have to be applied to measured blood levels in order to calculate individual kinetic parameters. The obtained data should be suitable for the assessment of the patient's individual risk and the support as well as monitoring of therapeutic decisions. All these activities require substantial technical, personal, logistic and - last but not least - financial resources. Therefore it is important to ask, if any benefit from toxicological computation can be expected when treating intoxications. To address this issue, the following principles have to be evaluated in the first line: 1. In therapeutic drug monitoring it is accepted, that an individual correlation between drug blood level and clinical effect exists. 2. In modern drug development therapeutic reference concentrations are well established. 3. Exceeding the upper therapeutic concentrations will result in specific and intensifying unwanted drug effects which can also be judged as toxic effects. 4. Combining drug quantification and pharmacokinetic modelling allows the individualisation of dose rate also regarding the patient's specific conditions (e.g. type of metabolizer, renal or hepatic impairment, abnormal absorption or distribution etc). Clinical toxicologists adhere to these principles only in intoxications with selected substances: the hepatotoxic risk and the decision for antidote therapy in paracetamol poisoning are often based on drug blood levels. With some restrictions the same is true for intoxications with salicylate, digitalis glycosides, and lithium. A loose correlation between dose and effect can be found in gradual effects like CNS depression by benzodiazepines, which is dose-related in a single individual but not between different patients. No dose related data exist on stochastic risks like late arrhythmias elicited by tricyclic antidepressants or delayed seizures in intoxications with serotonin reuptake inhibitors like fluoxetine. It is unknown whether the knowledge of drug levels and toxicological computation would be of predictive value in these cases. *Methods:* (a) In order to test if pharmacokinetic data for drugs are valid also under the specific conditions of acute intoxication, a database containing more than 10,000 cases of acute intoxications were analyzed for computed individual toxicokinetic parameters. Individually computed elimination half-life times from acute intoxications with amitriptyline, carbamazepine, clozapine, diazepam, diphenhydramine, doxylamine, nitrazepam, propranolol, promethazine, trichlorethanol, and trimipramine were statistically analyzed and compared to those of published population pharmacokinetic data. (b) Time courses of drug blood levels from intoxications with unexpected course or secondary detoxification were analysed to identify the putative reason or to check the effectiveness of secondary detoxification, respectively. *Results:* Based on consecutive measurements of drug blood levels in acute intoxications, toxicokinetic computation can provide the patient's individual elimination half-life time, total clearance, and the area under the curve (AUC). From these basic parameters, the following data can be derived: bioavailable dose, the maximum blood level Cmax, and the period of time until blood concentration falls below maximum therapeutic levels, thus the symptoms being expected to resolve. (a) The mean±S.D. of computed half-life time in intoxications with amitriptyline (n = 42), carbamazepine (n = 42), clozapine (n = 7), diphenhydramine (n = 25), doxylamine (n = 18), nitrazepam (n = 40), propranolol (n = 13), promethazine (n = 16), trichlorethanol (n = 12), and trimipramine (n = 13) did not differ significantly from published population data which were found under therapeutic conditions. (b) A patient with clozapine poisoning had an initial serum concentration of 4.36 µg/mL and an individual half-life time of 13.5 hrs resulting in an initially estimated absorbed dose of 2112.85 mg of clozapine. After 68.4 hrs of treatment the serum concentration of clozapine had increased to a Cmax of 5.28 µg/mL resulting in an absorbed dose of 8280.8 mg. In this case, computation of elimination kinetics clearly indicates a substantial delayed absorption which probably was due to an insufficient gastrointestinal detoxification. In a similar case absorption of carbamazepine was delayed approx. 54.6 hrs with an elimination half-life time of 10.3 hrs being in good accordance to population data. Delayed absorption is a common reason for prolonged symptoms in acute oral intoxications; it can easily be detected by toxicokinetic computation. Another cause for delayed recovery can be found in a decreased clearance leading to an extended half-life time: a comatose and respiratory insufficient adult male was diagnosed as poisoned with trichlorethanol (the active metabolite of sedative chloral hydrate) at an initial blood level of 141.8 µg/mL (therapeutic up to 20 µg/mL). As population half-life time of trichlorethanol is approx. 8 hrs, the patient was expected to recover within 24 hrs. As the patient was still deeply comatose at that time, consecutive blood samples were analyzed revealing an individual half-life time of 44.28 hrs, allowing the prediction that he would recover after approx. 96 hrs. After four days he was awake and had no symptoms. Another important reason for toxicokinetic modelling can be found in the evaluation of secondary detoxification. In an intoxication with organophosphorus insecticide dimethoate effectiveness of hemodialysis was monitored by computing the decrease in elimination half-life time and significant reduction of the AUC. This approach also allows comparison of the effect of hemodialysis vs. hemoperfusion in two severe intoxications with parathion-methyl indicating that only repeated hemoperfusion substantially reduced the patient's burden of this highly toxic organophosphorus compound leading to immediate clinical improvement. *Conclusion:* Toxicokinetic computation on drug blood levels is a feasible approach in managing acute intoxication. In most cases kinetic data from therapeutic drug monitoring are valid to evaluate the time course and possible risks of intoxications. Especially, when the individual course of intoxication deviates from expectation (e.g. more severe and/or prolonged symptoms), toxicological computation can provide valuable information on possible reasons and can assist the clinical management by adjusting the prognosis and detecting possible individual risks of the patient. Furthermore it is a useful instrument to monitor the effectiveness of primary and secondary detoxification, which is of special interest in substances where less is known about their toxicokinetic properties.

20. Limitations of Toxicokinetic Calculations Based on Blood Levels in the Poisoned Patient

Jaeger A.
Direction de la Qualité, de la Coordination des Risques et de Relations avec les Usagers, Hôpitaux Universitaires, Strasbourg, France

Introduction: Over the last 30 years, toxicokinetics gained an important place in clinical toxicology mainly due to the progress in analytical techniques with the development of specific and sensitive analytical methods. Ideally, toxicokinetics should help to answer the following questions: - do the symptoms correlate with the blood concentrations? - are the kinetics in a given patient similar or different to the known kinetics of the poison? - which kinetic parameters may be useful for the evaluation of severity or prognosis and for the indications of specific treatments? Toxicokinetic studies in the poisoned patient are mostly based on plasma or blood concentrations. However, toxicokinetics are a

complex process including numerous factors, which may be responsible for variations and difficulties in the interpretation of blood concentrations especially in the poisoned patient. Therefore, kinetic studies based only on blood concentrations are subject to limitations and need to be carefully interpreted. Calculated parameters based on blood concentrations. The plasma concentration (Cp) depends on the amount bioavailable (AmB) and the volume of distribution (VD): Cp = AmB/VD. The plasma concentration at a given time (Cpt) depends on the concentration at time 0 (Cpt0) and on the elimination constant (Ke): (Cpt)=Cpt0 e-Ket . The calculated plasma half-life (T1/2) depends on the elimination constant: T1/2= Log 2/ Ke. The total body clearance (ClT) can be calculated according to the T1/2 (or Ke), the VD and the patients weight (W): (ClT) = Log 2 × VD × W / T1/2) (or Ke × VD × W). Limitations of the calculated kinetic parameters in the poisoned patient: In poisoned patients the AmB is often difficult to estimate because the amount ingested and the time of ingestion are not exactly known. While the VD is known for pharmaceutical drugs, it has mostly not been determined for other poisons and, therefore, the total clearance cannot be estimated. It cannot also be excluded that the VD may change with the dose ingested. However, the major limitation of kinetic parameters based only on blood concentrations is that they reflect only a very small part of the whole kinetic process especially for poisons with a high VD. Plasma concentrations alone provide no information concerning the different elimination routes (renal and metabolic), protein binding and multicompartment kinetics. If specific treatments which may interfere or change the poisons kinetics are used, it is mandatory to analyse other parameters in order to evaluate their efficacy. For instance, the efficacy of extracorporeal techniques (haemodialysis, haemodiafiltration) must take into account the clearance of the extracorporeal procedure (ClEC) which needs the measurements of the concentrations at the inlet and outlet sides of the device and of the blood flow rate (Qs): ClEC = (Cin – Cout) × Qs/C in. For some drugs such as lithium it is necessary to use the plasma flow rate instead of the blood flow rate in order to avoid an overestimation of the extracorporeal clearance. Moreover, it is necessary to estimate the amount removed and to compare it with the amounts eliminated by other routes. Therefore, the kinetic efficacy can be based neither on the decrease of plasma concentrations, nor on the comparison of the procedure clearance with the renal clearance, nor on the decrease of the plasma half-life, but only on the comparison of the procedure clearance with the spontaneous clearance and on the amount of drug really in fact eliminated. If antidotal treatments such as chelating agents are used, the evaluation of their efficacy cannot only be based on the variations of blood concentrations but must take into account the changes of the amounts eliminated by the renal route. Limitations of blood concentrations for the interpretation of the kinetic-dynamic relationship. Apart from a diagnostic point of view, the interest in measurements of blood concentrations is the evaluation of severity, prognosis and efficacy of specific treatments. For many poisons (psychotropic, cardiovascular drugs for instance) severity and prognosis is based rather on clinical symptoms or biomedical parameters than on blood concentrations. Although in these cases a kinetic-dynamic relationship may exist, the measurement of blood concentrations has mostly a small impact on the management of the patient. Moreover, for the kinetic-dynamic relationship it is sometimes necessary to determine not only the parent drug but also possible active metabolites but these are mostly not analysed. For many poisons the interpretation must also take into account different factors: the type of poisoning: acute or chronic (lithium, theophylline, barbiturates, digoxin), the duration of the exposure (carbon monoxide), the age (theophylline), underlying diseases (cardiovascular drugs, theophylline), drug tolerance (barbiturates, ethanol, opiates). For some drugs which have a bi-compartment kinetic (lithium for instance), there is a delay between the evolution of the symptoms and the plasma concentrations. The mechanism of toxicity has a major role in the interpretation of the kinetic-dynamic relationship. For functional poisons (psychotropic and cardiovascular drugs, lithium), there is usually a good relationship between the clinical signs and the blood concentrations if these are related to the poisons concentrations at the target organs. For poisons which induce tissue or cellular damage (colchicine, paracetamol, paraquat, heavy metals), the blood concentrations have a good prognostic value if the delay between ingestion and measurement of concentrations is taken into account. However, at a given moment symptoms are not related to the blood concentrations if cellular damage has occurred. *Conclusion:* Toxicokinetics are complicated processes which depend on numerous factors especially in the poisoned patient. Although toxicokinetic calculations based on blood level may provide some information, it is necessary to take into account other parameters in order to avoid misinterpretations. *References:* 1. Jaeger A, Sauder P, Kopferschmitt J, et al. Toxicokinetics in clinical toxicology. 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21. Laboratory Investigations in Diagnosis and Treatment of Poisonings – The Lab Chemist's Point of View

Degel F.
*Institute of Clinical Chemistry and Laboratory Medicine – Central Laboratory, Klinikum Nuremberg, Nurembe*rg*, Germany*

Objective: The integration of toxicological analyses into the workflow of a hospital laboratory should be encouraged. These analyses are essential for poisoning diagnosis or exclusion, as well as for follow-up of acute intoxications. A basic panel of selected target quantitative tests in serum or plasma and qualitative toxicology tests in urine has been proposed by Wu et al,[1] which should be provided by each hospital laboratory (tier 1 testing). Among the target quantitative tests in serum / plasma are paracetamol, salicylates, carbon monoxide oximetry, cholinesterase, iron, lactate and several therapeutic drugs such as digitalis glycosides, lithium, carbamazepine, valproic acid, phenobarbital and ethanol. As the main job of hospital laboratories is clinical chemistry including therapeutic drug monitoring (TDM), tier 1 analyses from this field are easily available and can be determined in a short turn around time (TAT). Larger hospital laboratories should provide additional analyses for methanol, isopropanol and ethylene glycol, and for amanitines (tier 2 testing). Additional comprehensive toxicological screening or targeted quantitative analyses (tier 3 testing) using mass spectrometric techniques should be realized in larger hospitals, too, or at least in regional centers for specialized toxicology testing. *Methods:* While urine is the preferred specimen for qualitative toxicology screening, blood (serum or plasma) is the material of choice for selected target quantitative analyses. For some well described agent classes, e.g. drugs of abuse (DAU), a qualitative toxicological prescreening in urine can be performed using immunochemical methods (DAU testing) in order to set the course for dedicated analytical procedures. However, the limitations of those assays should be kept in mind, and a toxicologically experienced clinical chemist or a laboratory physician should always communicate these limitations together with the analytical results to the clinician. This immunochemical prescreening has to be followed in most cases by more reliable investigations. As a general-purpose method to detect all xenobiotics is not available, usually a combination of methods is applied to optimize laboratory turnaround times with maximum analytic efficiency. Gold standard for comprehensive screening is gas chromatography-mass-spectrometry (GC-MS). Large spectra databases are available for library – assisted identification of drugs and chemicals.[2,3] High performance liquid chromatography with Diode-Array-Detection (HPLC-DAD) or tandem-mass-spectrometry (LC-MS/MS, ion trap- or time of flight technology) can be used alternatively or better complementarily (multi-target screening or –quantitation, growing databases are yet available[4]). Gas chromatographic headspace analysis (particularly with mass-spectrometric detection, HSGC-MS) is the preferred technique for alcohols, solvents and other volatile substances (developing database[5]). All of those techniques can be used for qualitative (screening) and quantitative (targeted) analyses. *Results:* Tier 1 testing: Analysis of the aforementioned stat panel (selected target quantitative tests in serum or plasma) can be realized in a hospital lab within less than 60 minutes (TAT). Anyway, in many hospitals most of these assays are included in the typical all-emergency panels. Clinical chemistry findings can also substantially support toxicological diagnosis. Some findings can be indicative for dedicated poisonings like state of acidosis, osmolal and/or anion gap for alcohols and ethylene glycol, a high lactate acidosis for e.g. metformin overdosage. Tier 2 testing: Short chain alcohols such as methanol are determined via headspace gas chromatography within 1 hour. Determination of ethylene glycol via gas chromatography takes the same TAT. The targeted analysis of alpha-amanitin in suspected cases of mushroom poisoning takes maximum 3 hours. Tier 3 testing: A further broad spectrum tier of testing is needed whenever a patient remains comatose for unknown reasons in spite of supportive emergency therapy. It is usually performed by GC-MS, HPLC-DAD or LC –MS/MS with TAT less than 120 min. GC-MS or even LC-MS/MS instrumentation is going to be standard equipment in bigger hospital laboratories, nowadays. So, in a pertinent equipped laboratory all of these tests can be performed in parallel and thus, there is no need for a stepwise proceeding. In many cases, identification of toxins should be followed by quantification in blood (urine). This is done by established, validated methods or by an *ad hoc* method with at least semiquantitative results, wherever an established quantification method does not exist. Hospitals that do not have adequate resources to perform a broad spectrum screening can elect to send these specimens to a regional toxicology laboratory centre. *Conclusion:* According to our experience delivery of a comprehensive toxicological information in a short TAT time can often positively influence treatment and hospital stay for presumably poisoned patients. The time schedule is strongly dependent on the strategy. A preselection of the appropriate techniques can be essential for getting a quick and comprehensive answer. Therefore an exchange of clinical and analytical information including medical interpretation is very important between the clinician and the lab chemist. *References:* 1. Wu AH, McKay C, Broussard LA, et al. NACB Guidelines: Recommendation for use of laboratory tests to support poisoned patients who present to the emergency department. Clin Chem 2003; 49:357–379. 2. Maurer HH, Pfleger K, Weber AA. Mass spectral library of drugs, poisons, pesticides, pollutants and their metabolites. 4th revised ed. Weinheim, Germany: Wiley-VCH, 2007. 3. NIST02 Mass Spectral Library, U.S. Department of Commerce, National Institute of Standards and Technology, 2002. 4. Weinmann W, Gergov M, Goerner M. MS/MS-Libraries with triple quadrupole tandem mass spectrometers for drug identification and drug screening. Analysis 2000; 28:934–941. 5. Degel F. Screening Procedures for General Unknown Analysis: Gas chromatographic headspace analysis. In: Külpmann, WR, ed. Clinical Toxicological Analysis Procedures, Results, Interpretation. Weinheim, Germany: Wiley-VCH, 2008:165–75.

22. Laboratory Investigations in the Acutely Poisoned Patient: The Clinician and Poison Centre's Point of View

Hoffman RS.
Division of Medical Toxicology, New York University School of Medicine, New York, US

Objective: Toxicology testing has become a highly sophisticated process whereby clinicians have the ability to confirm a remarkable number of potentially poisonous xenobiotics. Technologically advanced reference laboratories offer both an extensive array of individual quantitative analyses, and massive comprehensive test batteries that provide qualitative confirmation of exposure. These tests are often expensive and have relatively slow turn-around times. Although some hospital laboratories offer comprehensive screening, in-hospital testing is

more often focussed based on common overdoses, drugs of abuse, and pharmaceuticals where therapeutic drug monitoring is available. In emergency departments, point of care devices provide rapid qualitative analyses of a very limited number of common toxins that are most often drugs of abuse. The objective is to examine the data to support the utility of emergency toxicologic testing and develop a clinically based rational strategy for an essential panel of emergency tests. Although not of emergent clinical necessity, these tests have implications for society and continued care that warrant their use. *Methods:* An extensive literature review was conducted to identify studies that evaluated the role of emergency toxicology testing in clinical care. Additional information was derived from consensus statements of major societies. An overall synthesis of the data was conducted and recommendations were formulated. A list of essential tests required by clinicians was created with the following two criteria: The results of the test must directly alter clinical care; and, the results must be available in a time frame that is clinically relevant. *Results:* A number of studies evaluated the clinical utility of broad toxicology testing of patients who have intended self harm.[1–4] While it is clear that many more substances can be found in the laboratory than at the bedside, clinical management is rarely if ever altered by identification of these additional substances. Typically toxins that were found but not suspected belonged to the sedative hypnotic class and cannabis. In the absence of a history, physical finding or other marker suggesting a particular substance (anion gap elevation), the only single toxin that is suggested to be routinely screened for is paracetamol,[5] and even this is debated.[6] Only consensus documents helped guide the role of emergency testing based on history or clinical suspicion. *Conclusion:* Existing data do not support broad qualitative testing of patients with intended self harm. Although a case could be made for a more focussed approach, the specific tests should be dictated by regional epidemiology. For example, routine screening for paracetamol in patients with intended self harm in the developing world is likely to be as unproductive as routine testing for paraquat and cholinesterase activity in the developed world. Local consensus documents created among laboratorians and clinicians can be created to provide rational testing guidelines based on the two criteria selected. One example of these guidelines is listed in the table[7] but is clearly not applicable in every region. *References:* 1. Kellermann AL, Fihn SD, Logerfro JP, et al: Impact of drug screening in suspected overdose. Ann Emerg Med 1987; 16:1206–1216. 2. Montague RE, Grace RF, Lewis JH, et al. Urine drug screens in overdose patients do not contribute to immediate clinical management. Ther Drug Monit 2001; 23:47–50. 3. Bjornaas MA, Hovda KE, Mikalsen H, et al. Clinical vs. laboratory identification of drugs of abuse in patients admitted for acute poisoning. Clin Toxicol 2006; 44:127–134. 4. Heyerdahl F, Hovda KE, Bjornaas MA, et al. Clinical assessment compared to laboratory screening in acutely poisoned patients. Hum Exp Toxicol 2008; 27:73–79. 5. Ashbourne JF, Olson KR, Khayam-Bashi H. Value of rapid screening for acetaminophen in all patients with intentional drug overdose. Ann Emerg Med 1989; 18:1035–1038. 6. Dargan PI, Ladhani S, Jones AL. Measuring plasma paracetamol concentrations in all patients with drug overdose or altered consciousness: does it change outcome? Emerg Med J 2001; 18:178–182. 7. Wu AH, McKay C, Broussard LA, et al. National Academy of Clinical Biochemistry Laboratory Medicine. National academy of clinical biochemistry laboratory medicine practice guidelines: recommendations for the use of laboratory tests to support poisoned patients who present to the emergency department. Clin Chem 2003; 49:357–379.

Table. Assays Recommended by the National Academy of Clinical Biochemists

Serum Assays, Quantitative	Urine Assays, Qualitative
Acetaminophen	Amphetamines
Carbamazepine	Barbiturates
Cooximetry (carboxyhemoglobin, methemoglobin, oxygen saturation)	Cocaine Opiates
Digoxin	Propoxyphene
Ethanol	Phencyclidine
Iron (plus transferrin or unfilled iron-binding capacity)	Tricyclic antidepressants
Lithium	
Phenobarbital	
Salicylate	
Theophylline	
Valproic acid	

23. Inquiries to a Poison Centre Concerning Patients with Severe Metabolic Acidosis: A Prospective Study

Höjer J, Persson H, Karlson-Stiber C, Landgren A, Personne M.
Swedish Poisons Information Centre, Karolinska Institute, Stockholm, Sweden

Objective: Inquiries to poison centers concerning patients presenting with severe metabolic acidosis are common. The aetiology of the acidosis is often unclear at the time of consultation. In order to clarify the most common underlying conditions and to analyse the characteristics of these cases, we performed a prospective follow-up study. *Methods:* Inquiries to the SPIC from Jan 2007 to Nov 2008 concerning patients with a base excess below –15 mmol/l were documented. Pertinent data were collected from the medical records. *Results:* Seventy-two cases (aged 14–83 years) were included. Fifty-three (74%) were male and 38 (53%) chronic alcoholics. Forty-three patients (60%) were treated with dialysis and the hospital mortality rate was 17/72 (24%). The number of cases with a poisoning-related acidosis (either as is a direct toxic effect, or secondary to seizures, circulatory shock or hypothermia induced by poisoning) was 47 (65%). All underlying conditions are listed in the following. A. Ethylene glycol intoxication: 14 cases (19%) with a mortality of 1/14; B. Chronic metformin intoxication: 12 (17%) with a mortality of 4/12; C. Poisoning induced seizures: 8 (11%) no fatalities; D. Methanol intoxication: 7 (10%) with a mortality of 3/7; E. Alcoholic ketoacidosis: 6 (8%) no fatalities; F. Non-poisoning circulatory shock: 4 cases with a mortality of 4/4; G. Poisoning induced circulatory shock: 3 cases with a mortality of 2/3; H. Mixture of diabetic ketoacidosis and shock: 3 cases no fatalities; I. Acute renal insufficiency: 3 cases no fatalities; J. Non-poisoning induced seizures: 3 cases no fatalities; K. Unclear aetiology: 2 cases with a mortality of 2/2. The remaining 7 cases were different mixtures of underlying conditions such as hypothermia, metformin accumulation, shock, alcoholic or diabetic ketoacidosis, renal failure and ethanol intoxication with a total mortality of 1/7. *Conclusion:* Ethylene glycol ingestion, chronic metformin intoxication and poisoning induced seizures were the most common poisoning-related underlying conditions while alcoholic ketoacidosis and non-poisoning circulatory shock were predominant among other aetiologies. Seizures, irrespective of origin, explained the acidosis in 15% of the cases and were associated with a favourable prognosis. Approximately one third of all cases had a non-toxic explanation for the acidosis.

24. REACH Regulation (EC) N. 1907/2006: Update from Poison Centre Perspective

Butera R, Caldiroli A, Manzo L.
Poison Control Center, IRCCS Maugeri Foundation and University of Pavia, Pavia, Italy

The Regulation (EC) N. 1907/2006 sets up a system for the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and represents a great innovation in the assessment and management of risks posed by chemicals to the health and the environment, emphasizing the need for a deeper knowledge of chemicals and shifting to industry the responsibility to demonstrate the safety of chemicals. Main companies' obligations under REACH: After 1 June 2008, companies manufacturing or importing chemical substances in the EU in quantities of 1 tonne or more per year are required to register them under REACH. Registration requires the submission of relevant and available information on intrinsic properties of substances, and when this is not available, the generation of information, including testing. Moreover, for most substances manufactured or imported in quantities of 10 tonnes or more, a chemical safety assessment has to be done and documented in a chemical safety report, which has to be submitted together with the registration dossier. Since it is for manufacturers, importers and downstream users to ensure that they manufacture, place on the market or use such substances that do not adversely affect human health or the environment, the goal of the assessment is not to establish whether or not there is a risk, but to identify and describe the conditions under which the risks are controlled. This last point includes the possibility of identifying uses advised against, according to the toxicological profile and exposure assessment of a chemical. Relevance of human data in the registration process: In the registration process, the health impact of chemicals can be predicted, extrapolating to humans the data obtained from *in silico* and/or *in vitro* models and from *in vivo* animal studies. However, this approach has inherent weaknesses due to modelization limits, interspecies differences and different exposure patterns. Human data (case series and even single, well documented case reports) can contribute in several ways to the knowledge of chemicals required in the registration process by reducing, refining and/or replacing the need for testing. Firstly, when experimental data are lacking but clinical observations clearly and consistently document an effect of a given chemical in humans, human data may avoid at all the need for animal testing. Secondly, human data may strengthen weak experimental observations and reduce the need for further confirmatory testing. Thirdly, clinical experiences of unusual effects may address basic research and trigger proper generation of further information. Finally, in the identification of uses advised against, the experience from cases of accidental acute poisoning may be helpful in identifying exposure patterns and uses at high risk. In all cases, toxicological observations in humans contribute to the ultimate scope of REACH, that is to ensure a high level of protection of human health. These remarks are in tight agreement with REACH Regulation, which clearly states that before new tests on substances are carried out, all available data (including historical human data) shall be assessed first (Annex VII). Poison Centers, Clinical Toxicology Departments and/or EAPCCT as data holders: The risk assessment process required in order to register substances focuses mainly on long term-effects of chemicals, but data on acute exposures are of great value too. Poison Centers and Clinical Toxicology Departments (as individuals and/or at societal level) are a unique reservoir of knowledge on chemicals' intrinsic properties and dose-response relationships (especially after acute exposure), as well as on exposure patterns and operational conditions that may cause poisoning. Starting from January 2009, there is the possibility for data holders to communicate to the European Chemicals Agency (ECHA) interest in a given substance, in order to provide information on the substance to registrants. This data sharing can have both professional, scientific and economic revenues for the data holders. Chiefly, however, it is a great chance for our discipline: our experience and expertise can make the difference in the assessment and control of the risks posed by chemicals.

25. Requirements of Product Notification in EU-GHS as a First Step Towards European Harmonisation

Brekelmans PJAM,[1] de Groot R,[1] Meulenbelt J.[1,2,3]
[1]*National Poisons Information Centre, National Institute for Public Health and the Environment, Bilthoven;* [2]*Institute for Risk Assessment Sciences, Utrecht University;* [3]*Division Intensive Care Centre, University Medical Centre, Utrecht, The Netherlands*

Objective: Changes in article 45 of EU-GHS makes European harmonisation of product notification possible. As a first step to harmonisation, a proposal is made on how the 1989 EAPCCT requirements on product composition and ingredient concentration could be translated in terms of the new EU-GHS classification. This could be the starting point for further discussion on the required product information. *Background:* Notification of

Table. Requirements of product notification in EU-GHS as a first step towards European harmonisation

EU-GHS		Option 1	Option 2	Option 3
Hazard class	**Categories**	**EAPCCT proposal (direct translation)**	**Division based on EU-GHS Pictograms**	**Division based on EU-GHS Signal word**
Acute toxicity Oral	1, 2, 3, 4	1, 2, 3 (partial)	1, 2, 3	1, 2, 3
Acute toxicity Dermal	1, 2, 3, 4	1, 2, 3 (partial)	1, 2, 3	1, 2, 3
Acute toxicity Inhalation	1, 2, 3, 4	1, 2, 3	1, 2, 3	1, 2, 3
STOT* - single exp.	1, 2, 3	1	1, 2	1
STOT* - repeated exp.	1, 2	1	1, 2	1
Aspiration hazard	1		1	1
Skin corrosion/irritation	1ABC, 2	1ABC	1ABC	1ABC
Eye damage/irritation	1, 2		1	1
Respiratory sensitisation	1		1	1
Skin sensitisation	1			
Carcinogenicity	1AB, 2	1AB	1AB, 2	1AB
Germ cell mutagenicity	1AB, 2	1AB	1AB, 2	1AB
Reproductive toxicity	1AB, 2	1AB	1AB, 2	1AB
Effects on/via lactation				
* Specific Target Organ Toxicity		Based on cut-off limits for T^+, T and C as used in 1999/45/EC	Pictograms: Skull/crossbones Health hazard Corrosion	Signal word: Danger

dangerous products by companies to a governmental authority (GA) and/or a Poisons Information Centre (PIC) in EU Member States is regulated by national legislation, based on article 17 of the Preparations Directive (1999/45/EC). This article states that the appointed GA/PIC in each Member State shall have at their disposal all information necessary to carry out tasks for which they are responsible. In case of the PIC "… to meet any medical demand for formulating preventive and curative measures, in particular in case of emergency." In a our report[1] on notification of dangerous products in the EU it was concluded that article 17 was differently implemented in EU Member States, resulting in different notification procedures. The reason is that article 17 does not define which information should be notified and in what way. It would be beneficial to both GAs/PICs and suppliers to harmonise notification of product information at an EU level and have it implemented in EU legislation. The new EU-GHS regulation replacing the Preparations Directive (1999/45/EC) offers an opportunity for this harmonisation. By joint efforts of industry, country representatives and the EAPCCT, article 45 in EU-GHS (which replaces article 17 of the Preparations Directive) was extended with a provision that the European Commission (EC) should review the possibility to harmonise product notification to GAs/PICs. After entry-into-force (planned at the end of 2008), the EC has three years to review this possibility, which also includes establishing a format and possibly incorporating the result in an Annex to the EU-GHS regulation. In article 45, the EAPCCT is recognised as an important stakeholder to be consulted. How to move forward: The first step towards harmonisation is to reach consensus amongst the EU PICs on the required product information. When comparing the differences in requirements between EU Member States, the 1989 EAPCCT proposal[2] on product notification still seems a reasonable compromise. The following requirements were proposed for the composition and concentration of the notified products. All constituents whatever their toxicity must be mentioned. Actual concentrations on very toxic (T+), toxic (T) and corrosive (C) constituents should be mentioned and specified concentration ranges for the others (0–1%,1–5%,5–10%,10–20%,20–30%,30–50%,50–75%,>75%). In our experience suppliers are willing to provide a complete composition (without thresholds. Although requiring an exact concentration for all constituents is the most straightforward approach, a division between exact concentration for some constituents and ranges for others still seems a suitable compromise. In that case, it is necessary to translate the requirements in terms of the new EU-GHS classification. EU-GHS introduces new hazard classes that are subdivided in hazard categories (see table). It should be defined for which hazard classes and categories an exact concentration is required. The first option could be a direct translation of the EAPCCT proposal into EU-GHS. In this way the EU-GHS categories are included that correspond with the classification T+, T and C of the Preparations Directive (1999/45/EC) (see table). Because EU-GHS uses different cut-off limits, the constituents classified as acute toxicity category 3 are only partially included, which is inconvenient. A second option could be a division based on the EU-GHS hazard pictograms 'skull and crossbones', 'health hazard'(new) and 'corrosion'. These pictograms are used for the more hazardous categories of the health hazards. The table shows that more categories are included using these pictograms than in option one. The reason is that the pictogram 'health hazard' is not only assigned to categories in EU-GHS that are classified as T+ and T in the Preparations Directive (1999/45/EC) but also as Xn (harmful). A third option is a compromise between option 1 and 2 and is based on signal words. EU-GHS introduces the signal word 'danger' (for more hazardous categories) and 'warning' (for less hazardous categories). To require an exact concentration for constituents in categories with the signal word 'danger' will be closest to the exact translation of the EAPCCT proposal and still presents a clear division in terms of EU-GHS classification. *Conclusion:* It is proposed to require an exact concentration for all constituents with the EU-GHS signal word 'danger' and to allow specified ranges for the other constituents with the signal word 'warning'. This presents a clear division in terms of the new EU-GHS classification and remains close to the EAPCCT requirements expressed in 1989. This could be a starting point for further discussion on the required product information to reach European harmonisation on product notification. *References:* 1. de Groot R, Brekelmans PJAM, Meulenbelt J. Article 17 of the Preparations Directive 1999/45/EC is differently implemented in EU member states. RIVM report 233900001/2007; 2. EAPCCT newsletter of April 1996.

26. The DeNaMiC Project: Description of the Nature of Accidental Misuse of Chemicals and Chemical Products

Tempowski J,[1] Wyke S,[2] Duarte-Davidson R,[2] Wagner R,[3] Desel H,[3] Bauer K,[3] Mathieu-Nolf M,[4] Jumeau F,[4] Edwards N,[5] McParland M,[5] Pelclova D,[6] Mrazova K,[6] Heiland A, [7] Heinemeyer G,[7] Lindtner O.[7]
[1]International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland; [2]Health Protection Agency, Chemical Hazards and Poisons Division, Didcot, UK; [3]GIZ-Nord Poisons Centre, University Medical Centre, Göttingen, Germany; [4]Centre Antipoison - Toxicovigilance, Centre Hospitalier Régional Universitaire, Lille, France; [5]Guy's & St Thomas' Poisons Unit, Medical Toxicology Unit, London, UK; [6]Toxicology Information Centre, Prague, Czech Republic; [7]Bundesinstitut für Risikobewertung, Berlin, Germany

Objective: To determine the availability of information from poisons centres and other sources that would characterise the nature of accidental exposure to household chemical products to improve risk management. The DeNaMiC project was funded by European Chemical Industry Council (CEFIC) and was carried out by the poisons centres in Göttingen, Lille, London and Prague, the German Federal Institute for Risk Assessment, the World Health Organization and the Health Protection Agency (UK). *Method:* The project involved developing an analytical tool to compare data on accidental poisoning obtained from the published literature, poisons centre annual reports and official mortality and morbidity statistics, and comparing and mapping the data collection and product classification schemes used by three poisons centres (Göttingen, Lille and London). A retrospective analysis of 3 years of enquiry data from Göttingen and Lille was also carried out to determine routinely available data on circumstances of exposure. European poisons centres were surveyed to determine the availability of data useful for product risk assessment. In addition, an analysis of published literature on toxicovigilance and a survey of toxicovigilance activities of European poisons centres was carried out. Finally, the project explored the feasibility of using poisons centres to obtain additional information about circumstances of exposure through a prospective follow-up study. *Results:* A range of publicly available data on accidental exposures was found; however, this provided little on the circumstances of exposure and could only be compared qualitatively. The product classification schemes used by three poisons centres showed some degree of comparability for household products. European poisons centres collected the same base data set but varied in collecting data relevant for risk assessment. European poisons centres varied in their understanding of 'toxicovigilance' but most stated that they perform it. It was possible to collect additional prospective data on exposures to household products relevant for risk assessment and management. *Conclusions:* Poisons centres are an important potential source of data useful for product risk assessment and management. In most cases, however, this requires additional work that needs to be resourced. Cooperation between poisons centres and industry can contribute to improving product safety.

27. Prevalence of Acute Renal Failure in Children's Poisoning – 10 Years Study

Ulmeanu C, Nitescu V, Ulmeanu A.
Paediatric Poison Centre, Emergency Clinical Hospital for Children Grigore Alexandrescu, Bucharest, Romania

Objective: To evaluate the prevalence of acute renal failure (ARF) in poisoned children in a toxicology department. *Methods:* We performed a retrospective study of children with acute poisoning admitted to the toxicology department over a period of 10 years (1998–2007). The following criteria were used for the definition of ARF: the onset of progressive oliguria and azotaemia over a period of hours or days caused by a sudden decrease

in glomerular filtration rate and leading to an acute rise of blood urea nitrogen and creatinine. *Results:* 6453 patients with acute poisoning were admitted between 1998 and 2007. Out of the total of 6453 patients, 56 children (0.86%) presented with renal dysfunction. ARF was reported from poisoning with the following agents: organophosphates 3 cases, *Amanita phalloides* 42 cases, ethylene glycol 6 cases, formaldehyde 3 cases and potassium dichromate 2 cases. The age distribution was the following: 12–18 years – 27 (48.20%), 3–6 years – 13 (23,21%), 6–12 years – 10 (17.40%), 1–3 years – 6 (10.71%). Of the 56 patients, 39 were girls (69.80%). We used extracorporeal treatment in the majority of cases (53 cases; 96,42%). We registered 23 deaths (41%) with mushroom poisoning being responsible in all cases. *Conclusion:* We conclude that ARF is not a frequent entity in children's poisoning, representing less than 1% of total cases. Even so, it can have a severe outcome needing extracorporeal treatment in the majority of cases. *References:* Rees L, Webb NJA, Brogan PA. Acute renal failure. In: Paediatric Nephrology, Oxford, England: Oxford University Press, 2007: 359–376.

28. The Treatment of the Severe Corrosive Acute Oesophagitis Due to Alkali Ingestion in Children: Comparative Results of Two Management Protocols

Nitescu V, Ulmeanu CE.
Paediatric Poison Centre, Emergency Clinical Hospital for Children Grigore Alexandrescu, Bucharest, Romania

Objective: To compare the results of two management protocols used in the treatment of severe corrosive acute oesophagitis due to alkali ingestion in children. *Methods:* We analyzed two groups of patients with severe corrosive acute oesophagitis due to alkali ingestion. The first group includes patients admitted between 1988–1998 treated by the following protocol: endovenous rehydration, corticosteroids, antibiotics, endoscopy 21 days post ingestion. The second group includes patients admitted between 1999–2008 managed by the following protocol: endoscopy within 24–48 hours post ingestion, placing a nasogastric tube with double role: feeding and calibration, partial parenteral nutrition, corticosteroids, antibiotics. We studied the following aspects: the clinical and endoscopic evolution, acute and late complications. *Results:* The first group included 65 patients. In the acute period 16 children presented with perforation of the oesophagus, 39 patients had gastrointestinal haemorrhage, 2 patients had perforation of the stomach and 52 children presented upper airways obstruction; 18 deaths were reported. The late complications registered in the first group were the following: oesophageal stricture requiring oesophageal dilatation in 47 patients, oesophageal perforation during the dilatations in 19 patients; 17 deaths were noted. The second group included 61 patients. The acute complications were the following: perforation of the oesophagus in 2 cases, gastrointestinal haemorrhage in 25 cases, perforation of the stomach in 2 children, pyloric stenosis in 1 case, upper airways obstruction in 49 patients; 2 patients died. The late complications were the following: oesophageal stricture in 56 patients; out of the 56 patients 14 presented with perforation of the oesophagus during the dilatations; 8 deaths were reported and oesophagoplasty was performed in 8 cases. *Conclusion:* Early endoscopy offered a rapid means of obtaining diagnostic and permits initiating precise treatment. The partial parenteral nutrition combined with placing the nasogastric tube for feeding and calibration significantly improved the survival of the patients in the acute period. *References:* Fulton J, Rao R. Caustics. In: Goldfrank LR, Hoffman RS, Howland MS, et al., eds. 8th ed. New York, USA: McGraw-Hill, 2006:1405–1413.

29. Decontamination in Response to Natural Anthrax Incidents

Snook CP.
National Decontamination Team, US Environmental Protection Agency, Cincinnati, US

Introduction: Achieving consensus on how to respond to anthrax incidents became a key goal in terrorism preparedness following the 2001 attacks involving the U.S. postal system resulting in 22 cases of anthrax and 5 deaths. *Results:* In a review of CDC responses prior to 2001,[1] anthrax occurred with infection of cattle in agricultural settings; in the U.S., human infection was limited to cases of cutaneous disease associated with direct contact with infected animals. In the developing world, gastrointestinal anthrax occurred as well associated with the eating of inadequately cooked, infected meat. In U.S. textile mills, almost 80% of cases were cutaneous, and occurred in association with the handling of infected, unprocessed hides; approximately 20% of cases were inhalational resulting from exposure to spores during an aerosol-generating activity. Measures to mitigate the threat to the public health consisted primarily of vaccination and/or quarantine along with improved work practices in agricultural settings, and improvements in industrial hygiene, vaccination and antibiotics in industrial settings. Environmental remediation was seldom utilized. In contrast, the pattern of disease observed during the 2001 attacks on the U.S. postal system was unusual. 50% of the cases were inhalational and public health authorities were unable to fully characterize the pathway of exposure for at least 2 cases. These events, given weaponization of the agent and a maliciously chosen means of dissemination, elicited a more elaborate response. Fumigation was used extensively. A cleanup goal of no growth on post-decontamination samples was chosen. Since 2001, several anthrax incidents have occurred in the U.K. and the U.S. involving individuals making drums with unprocessed hides in homes. These incidents involved naturally occurring forms of *B. anthracis*. The role of decontamination in response to these events has ranged from none to extensive without clear consensus as to what it should be. *Conclusion:* Further research, discussion, and consensus are needed to define the role of environmental decontamination in response to anthrax cases from the agent in its natural form. *References:* 1. Bales ME, Dannenberg AL, Brachman PS, et al. Epidemiologic Response to Anthrax Outbreaks: Field Investigations, 1950–2001. Emerging Infectious Diseases 2002; 8:1163–1174.

30. Gas Chromatographic – Mass Spectrometric Method for Estimating Clozapine Blood Levels

Urazaev TH,[2] Gofenberg MA,[2] Brusin AN,[2] Brusin KM,[2] Sentsov VG.[1]
[1]The Ural State Medical Academy, Ekaterinburg; [2]Regional Centre of Acute Poisoning, Ekaterinburg, Russia

Objective: Poisonings with clozapine happen frequently in Russia (6.7% of pharmaceutical intoxications during the period of 2002 – 2006 according to the data of Sverdlovsk Regional Centre of Clinical Toxicology). It is difficult to estimate the blood level of clozapine and there are only a few data concerning correlation of severity of poisoning with blood levels of clozapine. *Methods:* We observed 29 patients with acute clozapine poisoning in the period 2006–2008. According to the PSS scale there were moderate symptoms in 12 and severe in 17 cases. 18 patients were in coma, 16 were intubated and underwent ventilation for between 5 and 192 hours. The clozapine concentration was measured by gas chromatographic/mass spectrometric (GS/MS) method just after admission and during treatment. For isolation of clozapine from the blood we used the method of liquid-liquid extraction with chloroform with clearing from co-extracted substances at pH 2.5 to 3. Concentration of substance was defined on GC/MSD Agilent 6890/5973 with capillary column HP-5 ms EVDX in a SIM-mode. Papaverine has been used as an internal standard. Simultaneously with measuring the clozapine concentration in blood, bicarbonate and lactate levels were estimated; consciousness was evaluated according to the Glasgow scale (GCS). *Results:* Clozapine concentration in blood with moderately poisoning patients was 1.03 ± 0.16 microg/ml, GCS was 12.83 ± 0.55; with patients with severe poisoning – 2.50 ± 0.55 microg/ml and 5.35 ± 0.51, respectively. The correlation of the concentration of clozapine in blood with the level of consciousness according to GCS was $rs = -0.517$ ($p<0.01$), with lactate concentration was $r = 0.577$ ($p<0.05$) and with bicarbonate concentration was $r = -0.451$ ($p<0.05$). *Conclusion:* The estimation of clozapine concentration in the blood in severe clozapine poisonings correlated with the level of consciousness and with the laboratory parameters describing the degree of metabolic shifts. It can be used to control the efficiency of clozapine removal.

31. A Simultaneous Determination of 23 Benzodiazepine Derivatives in Blood Using a Gas Chromatography – Mass Spectrometric Method. Applications in Clinical and Forensic Toxicology

Papoutsis I, Nikolaou P, Athanaselis S, Spiliopoulou C, Maravelias C.
Department of Forensic Medicine and Toxicology, University of Athens, Athens, Greece

Objective: Benzodiazepine derivatives are used widely in daily clinical practice, due to their multiple pharmacological actions. These drugs present significant differences in their pharmacokinetic properties and chemical affinity with the benzodiazepine receptors. The pharmacological action is well differentiated and the clinical usefulness of each derivative varies considerably.[1,2] The multiple incidents of poisoning, as well as the frequent problems caused by the wide use of benzodiazepines, led to the necessity for the development of a precise, sensitive and rapid method for the simultaneous determination of 23 benzodiazepine derivatives (diazepam, nordiazepam, oxazepam, bromazepam, alprazolam, lorazepam, medazepam, flurazepam, fludiazepam, tetrazepam, chlorodiazepoxide, clobazam, midazolam, flunitrazepam, 7-amino-flunitrazepam, triazolam, prazepam, nimetazepam, nitrazepam, temazepam, lormetazepam, clonazepam, camazepam) in blood. *Method:* A gas chromatographic method combined with mass spectrometer detector was developed, optimized and validated for the determination of the above substances. This assay includes liquid-liquid extraction with chloroform and two stages of derivation using TMAH and propyliodide for the propylation, as well as mixture of triethylamine:propionic anhydrate for the propionylation. *Results:* Recoveries were more than 72% for all the benzodiazepines. The calibration curves were linear in the corresponding dynamic ranges with correlation coefficient more than 0.991. The limits of detection and quantification were estimated with S/N 3:1 and 10:1, respectively. Accuracy and precision were also calculated and were found to be less than 15%. The method has been successfully applied and contributed to the investigation of both forensic and clinical toxicological cases of accidental and suicidal poisoning. *Conclusion:* The acceptance and establishment of the method developed in the daily analytic practice of toxicology laboratories will constitute a useful tool in the hands of the toxicologists and will give them the possibility of investigating easily, immediately and correctly each incident in which a benzodiazepine derivative is involved either in the frame of Forensic or Clinical Toxicology. *References:* 1. Rosenbaum JF. Attitudes toward benzodiazepines over the years. J Clin Psychiatry 2005; 66:4–8. 2. Voshaar RC, Verkes RJ, van Luijtelaar GL, et al. Effects of additional oxazepam in long-term users of oxazepam. J Clin Psychopharm 2005; 25:42–50.

32. Determination of Phenobarbital in the Urinary Tests Performed in the Analytical Toxicology Laboratory in 2007

Ionica M,[1] Caragea G,[1] Macovei R,[1,2] Danescu I.[2]
[1]Army Center of Medical Research, Bucharest; [2]ICU II Toxicology, Emergency Clinical Hospital, Bucharest, Romania

Objective: Phenobarbital is a barbiturate, nonselective CNS depressant witch is primarily used as a sedative hypnotic and also as an antiseizure drug. Much easier accessibility of this drug, observed during the last year, may account for the increasing number of acute poisoning with phenobarbital. *Methods:* In the last year (2007) the Analytical Toxicology Laboratory of the ICU II Toxicology, Emergency Clinical Hospital Bucharest performed 3216 urinary samples by GC/MS for toxicological drugs testing. The obtained data show

that the method is very useful for diagnosis of diverse compounds and drugs poisoning. It used a computerized Varian Chrompack System. Sample preparation: 50 ml urine sample is mixed with 4.5 ml of dichloromethane, chloroform, dichlorethane (1:1:1) and 2 ml phosphate buffer, and 0.5 ml midazolam solution 1:20 as internal standard. Mixture was stirred 10 min, centrifuged 3-min/ 5000 rot/min, dried and then resolved in the same three solvents. *Results:* From 3216 tests, 14.1% (454) of the samples were positive for phenobarbital. The highest incidence - in the first three months of the year (52.9%). Sex repartition: women 29.8% (135), men 70.2% (319). In women: phenobarbital and other drugs 58.3%, phenobarbital alone 41.7%. In men: phenobarbital and other drugs 72.3%, phenobarbital alone 27.7%. *Conclusion:* Regarding the facts it is obvious that GC/MS analysis offers to the clinician a more comprehensive view into the exposure of the patient presenting with a known or unknown drug ingestion. Gas Chromatography/Mass Spectrometry - GS-MS systems represents one of the most accurately analytical techniques for drug poisoning diagnosis.

33. The Graphite Furnace Atomic Absorbtion Spectrometry for Measurement of Stable Strontium in Whole Blood of Chronic Dialyzed Patients

Caragea G,[1] Ionica M,[1] Danescu I,[2] Macovei R.[1,2]
[1]Army Center of Medical Research, Bucharest; [2]ICU II Toxicology, Emergency Clinical Hospital, Bucharest, Romania

Objective: Studies in dialysis patients demonstrated that strontium (Sr) levels and strontium/calcium ratios were elevated in the bone of osteomalacia patients compared with other types of renal osteodystrophy. High strontium levels present in dialysis fluids correlated with strontium serum content. Medical exposure to such trace metals should be evaluated to establish toxic thresholds and to eliminate the possibility of associated renal osteopathy. *Methods:* We developed a method for determination of the element in whole blood by using graphite furnace atomic absorption spectrometry, for biological monitoring of Sr in chronic renal failure patients. Samples were diluted 1:10 with a Antifoam-A and 1.6 M HNO_3 mixture whereas dialyzed fluid where diluted 1:10 with HNO_3. For both type of samples we used new rational calibration curve in 3 points (0, 20 and 50 microg/L). Detection limits were 1.6 microg/L (whole blood) and 3.02 microg/L (dialyzed liquid). *Results:* Mean Sr concentration assessed in blood of 15 subjects with normal renal function was 25.2±9.03 microg/L. This corresponds well with the concentration range of the data reported in the literature. Mean blood Sr concentration in 37 dialyzed patients was 58.5±9.7 microg/L at the beginning and 37.4±4.2 microg/L at the end of dialysis ($p = 0.05$, PS=2.048). Mean for dialysis fluid Sr concentrations was 38.17±7.74 microg/L. The dialysis fluid plays an important role in the accumulation of the element in the dialyzed patients. Hemoglobin range was 7.5–13.7 g/dl, PCR range was 0.1–12 UI and albumin range was 2.6–4.21 g/L. *Conclusion:* We conclude that the present methods are accurate and precise and may be useful for routine applications for strontium determination in whole blood of chronic renal failure patients. Sr determination in the monitoring and diagnosis of Sr overload/deficiency and treatment follow-up might become important because Sr has a potential therapeutic value in the prevention and treatment of osteopenic disorder.

34. Do not Judge a Book by its Cover, a Bottle by its Ingredients

Akhtar J,[1] Abesamis MG,[2] Carlson JN,[2] Krenzelok EP.[1]
[1]Pittsburgh Poison Center, University of Pittsburgh Medical Center Schools of Pharmacy and Medicine, Pittsburgh; [2]University of Pittsburgh Affiliated Residency in Emergency Medicine, Pittsburgh, US

Objective: The societal dimension of parsimony is critical to healthcare: providing the appropriate care, at the appropriate time, without waste is the responsibility of the health care provider. Toxicologists are renowned cost savers and choose decision paths judiciously. We report a case where "right" testing would have resulted in a missed diagnosis. *Case report:* A 73-year-old man presented after overdose of a windshield de-icer fluid. The bottle "Hot Energy windshield de-icer" was brought with the patient and the ingredients on the bottle were listed as ethylene glycol, isopropyl alcohol and surfactant. The patient's physical examination was unremarkable. His initial pH was 7.37, CO_2 11 meq/L, Cr 0.3 mg/dl and anion gap 6.8. The patient was given an ampoule of bicarbonate and started on the loading dose of fomepizole. Repeat pH 31/2 hours later was 7.5, CO_2 23 meq/L, Cr 0.9 mg/dl and anion gap 6.0. Based on the listed content of the bottle an ethylene glycol level was sent out and was reported as 64 mg/dl. The plan was to continue the patient on fomepizole and monitor levels and anion gap. However, the laboratory called back later with a methanol level of 305 mg/dl. The methanol level was done by the lab even though not ordered because ordering for any toxic alcohol results in automatic checking of a toxic alcohol screen which includes methanol, ethylene glycol and isopropyl alcohol. Based on this new information the patient was started on hemodialysis, and did well. *Conclusion:* The art of the clinical process lies in seeking the relevant information to achieve the goal of optimal care. This involves the use of diagnostic tests. It is important that physicians remain parsimonious, but not when it comes to testing for toxins which have similar clinical presentation. They need to do be open-minded and more comprehensive to prevent missed or delayed diagnosis.

35. Lactic Acidosis and Rhabdomyolysis in a Buformin Self-Poisoning

Danescu I,[1] Macovei R,[1,2] Voicu VA.[2]
[1]ICU II Toxicology, Emergency Clinical Hospital, Bucharest; [2]Army Center of Medical Research, Bucharest, Romania

Introduction: Buformin is an oral antihyperglycemic drug of the biguanide class, chemically related to metformin and phenformin. Biguanides decrease gluconeogenesis from alanine, pyruvate, and lactate, with accumulation of lactic acid and development of lactic acidosis. It is a type of high anion gap metabolic acidosis and is associated with various pathological processes: disturbances of consciousness, Kussmaul's respiration, shock, hypothermia, hypoglycemia. *Case report:* We present the case of a 19 year old previously healthy patient admitted in our department for suicidal ingestion of 30 tablets (1 tb.=100 mg, total dose=3 g) of Silubin retard (mother's medication) ten hours from hospital presentation. On admission: altered general status, conscious but confuse, spontaneous and normal breathing, BP=140/70 mmHg, 70 beats/min., diffuse abdominal pain, diarrhea. Arterial blood gas test: pH= 7.36, lactate=5.5 mmol/l, HCO_3=21 mmol/l, BE=4.5 mmol/l. The patient started treatment with fluids, bicarbonate, analgesics. The patient status did not improved, he became more agitated, with severe abdominal pain, high breathing rate and increasing lactic acidosis; 12 hours after admission he became hemodynamically unstable and was initiated vasopressor support. The laboratory tests show increasing elevated values for CK, CK-Mb, LDH, liver and pancreatic enzymes, with up and down variations of glycemia. Continuous venovenous haemodialysis (CVVHD) and ventilator support was initiated. The hemodialysis was performed over 4 days until complete correction of metabolic acidosis and decrease of muscular enzymes. The patient was weaned from ventilator support after 6 days; the laboratory tests normalized. Psychiatric examination revealed only a reactive depression (an argument with the girlfriend). He was discharged after 14 days with normal mental status and no other sequelae. *Conclusion:* Buformin poisoning induced lactic acidosis is a life-threatening event and should be suspected in patients presenting with high-anion gap metabolic acidosis and high blood lactate concentration. Clinical presentations are non-specific, but it may show severe complications like severe hypotension, rhabdomyolysis and respiratory failure. Therapeutic approach for buformin-associated lactic acidosis includes adequate supportive care, correction of acidemia, acceleration of lactate metabolism and elimination of the offending drug by renal excretion or dialysis. Dialysis techniques are the recommended treatment of lactic acidosis since it rapidly corrects the acid-base disorders.

36. Emerging Epidemic of Fatal Human Self Poisoning with a Washing Powder in Southern Sri Lanka: A Prospective Observational Study

Gawarammana IB,[1] Ariyananda PL,[2] Dawson AH.[3]
[1]Department of Clinical Medicine and South Asian Clinical Toxicology Research Collaboration, University of Peradeniya, Sri Lanka; [2]Department of Clinical Medicine, University of Ruhuna, Sri Lanka; [3]South Asian Clinical Toxicology Research Collaboration, University of Peradeniya, Sri Lanka and School of Population Health, University of Newcastle, Australia

Introduction: A new laundry detergent consisting of two sachets of 1.2 g of potassium permanganate ($KMNO_4$) and 12.5g of oxalic acid (OA) has become a popular agent for self poisoning in the south of Sri Lanka. We report the first case series. *Case series:* Prospective clinical data, major outcomes and post-mortem findings were recorded in patients admitted to a referral hospital. Serial biochemistry was performed in 20 patients. Retrospective case analysis was done in 4 referring hospitals. *Results:* There were 37 deaths reported from the study hospitals. 26 patients were admitted to one of the referring hospitals and 12 died (case fatality ratio of 46.2% (95% CI 27.9–65.2). Eleven patients died in transit to the hospital while the 12th died soon after admission. At the referral hospital, there were 103 (61 females, median age 22.5 years) patients. There were twice as many patients in 2008 compared to 2007. Four died within 24 hours while 2 died within 2 weeks due to renal failure and septicaemia. Of the 20 patients who ingested both $KMNO_4$ and OA, the median serum creatinine estimated on day 2 was 1.7mg/dL (IQR 0.91 –4.4) and 28% had evidence of renal failure. There were 19 deaths in the other referring hospitals. All the fatalities ingested OA while some ingested both OA and $KMNO_4$. Ingestion of more than one sachet is associated with a significantly higher risk of death (risk ratio 12.43, (95% CI 3–51, $p<0.05$) Postmortem findings revealed mucosal ulcerations in the majority while 2 had congested lungs. *Discussion:* This case series brings to light an emerging fatal self poisoning in Sri Lanka. As the number of cases has doubled in two years more deaths are likely to be reported in the coming years if the manufacture and sale of this product is not regulated. Postmortem examination revealed no apparent cause of death. The cause of death is most probably cardiac in origin. As deaths occur soon after ingestion medical management of these patients is bound to be difficult. *Conclusion:* This case series highlights a fatal mode of self poisoning that has become popular amongst the youth of Sri Lanka.

37. Dexmedetomidine in Withdrawal Syndromes: A Case Report Describing Dexmedetomidine in Acute Intrathecal Baclofen Pump Withdrawal and Review of the Literature Regarding Alpha2-adrenergic Agonist Use in Sedative-Hypnotic Withdrawal

Ward SM,[1] Morin S,[2] Sullivan JK,[3] Peredy T,[4] Wiegand TJ.[4]
[1]Department of Medicine, Maine Medical Center; [2]Department of Pulmonary and Critical Care Medicine, Maine Medical Center; [3]Department of Neurology, Maine Medical Center; [4]Northern New England Poison Control, Maine Medical Center, Portland, US

Objective: Acute withdrawal from intrathecal baclofen is a potentially life-threatening illness.[1,2] We describe the use of dexmedetomidine, a selective alpha2-adrenergic agonist, as primary therapy in severe intrathecal baclofen pump failure. Additionally, we review the literature regarding dexmedetomidine use in withdrawal syndromes. *Case report:* A 37-year-old paraplegic man presented with an intrathecal baclofen-pump site

infection. Attempts to preserve catheter function failed and the pump was emergently removed. Within twenty-four hours, he developed progressive, severe baclofen withdrawal with spasticity, hypertension, tachycardia and fever. Intravenous dexmedetomidine was initiated with rapid symptomatic improvement. Intubation was avoided. The patient was successfully weaned from dexmedetomidine and continued on oral baclofen and antibiotics. *Conclusion:* GABA and NMDA agonists are used adjunctively for intrathecal baclofen withdrawal syndrome until pump replacement.[3] However, alpha2-adrenergic agonists decrease central sympathetic outflow and noradrenergic activity. Dexmedetomidine has a favorable side-effect profile compared to barbiturates and propofol, and may be administered with minimal respiratory depression compared to standard therapies for severe withdrawal states.[4,5] A small but growing literature describes successful use of dexmedetomidine as adjuvant and even primary treatment of opiate, sedative-hypnotic and refractory alcohol withdrawal.[5] Dexmedetomidine may be an effective agent for treatment of withdrawal syndromes. Discussion and further study is warranted. *References:* 1. Reeves RK, Stolp-Smith KA, Christopherson MW. Hyperthermia, rhabdomyolysis, and disseminated intravascular coagulation associated with baclofen pump catheter failure. Arch Phys Med Rehabil 1998; 79:353–356. 2. Greenleaf MI, Hendrickson RG. Baclofen withdrawal following removal of an intrathecal baclofen pump despite oral baclofen replacement. J Toxicol Clin Toxicol 2003; 41:83–85. 3. Ackland GL, Fox R. Low-dose propofol infusion for controlling acute hyperspasticity after withdrawal of intrathecal baclofen therapy. Anesthesiology 2005; 103:663–665. 4. Gerlach AT, Dasta JF. Dexmedetomidine: An Updated Review. Ann Pharmacother 2007; 41:245–252. 5. Darrouj J, Puri N, Prince E, et al. Dexmedetomidine infusion as adjunctive therapy to benzodiazepines for acute alcohol withdrawal. Ann Pharmacother 2008; 42:1703–1705.

38. Sub-Acute High-Dose Nitrous Oxide (N_2O) Exposure Produces Severe Peripheral Neuropathy

Morrissey RP,[1,2] Alt RS,[2] Howland MA,[1,2,3] Nelson LS,[1,2] Hoffman RS.[1,2]
[1]New York City Poison Control Center; [2]Department of Emergency Medicine, New York University Medical Center; [3]College of Pharmacy, St John's University, New York, US

Objective: Peripheral neuropathy from chronic, intermittent exposure to N_2O is well described.[1] We report a case of peripheral neuropathy secondary to subacute use of high-dose N_2O. *Case report:* A 24 year-old man presented to the ED complaining of tingling of hands and feet and difficulty walking, writing, using utensils, or buttoning clothing. He denied weakness, headache, vision change, vertigo, falls, dysarthria, dysphagia, bowel/bladder changes, confusion, or mood change. He reported using approximately 240 (8-gram) N_2O canisters daily for 2 weeks. Although he used N_2O intermittently for several years, he never had similar symptoms. Physical examination revealed lucid speech without latency, PERRLA, EOMI without nystagmus, and no glossal fasciculations. He had constant repetitive finger flexing/extending and fingertip rubbing on palms while conversing, but was able to temporarily abstain when directed. He had a steppage gait, markedly poor proprioception, fine intention tremor, and was dysmetric finger to nose bilaterally. Vibratory sensation was decreased distal to right tibial tuberosity and left malleoli. Remaining neurologic examination was normal. Labs revealed grossly abnormal markers of B12 deficiency [methylmalonic acid 49.17 (normal 0 – 0.4 mcmol/L; and homocysteine 39.4 (normal 7 – 15 mcmol/L)], yet normal B12, folate, CBC, BMP, LFT, TSH, and HbA1c. Brain and cervical spine MRI revealed no abnormalities. He did not improve during his four-day hospitalization, but demonstrated safe ambulation and ADLs, so was discharged on daily B12 supplements. He failed to follow-up at one week in neurology clinic as prescribed. *Conclusion:* This case demonstrated neuropathic changes more acutely than has been previously described. N_2O irreversibly oxidizes and inactivates the cobalt in methylcobalamin, ultimately inhibiting the synthesis of myelin and thymidine, and resulting in axonopathy and megaloblastic anemia, respectively.[2,3] Proposed treatments include supplementation of methionine and vitamin B12.[4] *References:* 1. Layzer RB, Fishman RA, Schafer JA. Neuropathy Following Abuse of Nitrous Oxide. Neurology 1978; 28:504–506. 2. Nunn JF. Clinical Aspects of the Interaction Between Nitrous Oxide and Vitamin B12. Br J Anaesth 1987; 59:3–13. 3. Amess JA, Burman JF, Rees GM, et al. Megaloblastic Haemopoiesis in Patients Receiving Nitrous Oxide. Lancet 1978; 2:339–342. 4. Stacy CB, DiRocco A, Gould RJ. Methionine in the Treatment of Nitrous Oxide Induced Neuropathy and Myelopathy. J Neurology 1992; 239:401–403.

39. Atrioventricular Block in Acute Ethanol Poisoning

Brvar M,[1,3] Bunc M.[2]
[1]Poison Control Centre, University Medical Centre; [2]Department for Cardiology, University Medical Centre; [3]Department for Cardiology, University Medical Centre, Ljubljana, Slovenia

Objective: Acute ingestion of ethanol in healthy adults can induce prolongation of the PR and QTc interval, but searching Medline, we have found only one report of Wenckeback-type atrioventricular block in severe ethanol poisoning. First-degree atrioventricular block is also reported in 1% of young healthy adults. We present a patient with atrioventricular block in acute ethanol poisoning. *Case report:* A 17-year-old woman with a non-contributory medical history ingested 3dcl of vodka and was found comatose. On arrival at the Emergency Department she was somnolent with tympanic temperature 36.0°C, pulse 70 counts/min, blood pressure 90/60 mmHg, respiratory rate 12 counts/min and SpO2 96% on room air. She had nausea and vomited several times. Blood ethanol level was 130mg/dL; other blood laboratory test results were normal. ECG revealed sinus rhythm, first-degree atrioventricular block with a PR interval of 0.280 seconds and intermittent second- and third-degree atrioventricular blocks with up to 3 second-long pauses that appeared 15–30 seconds after each vomiting. She was given oxygen, thiethylperazine, pantoprazolum and a continuous infusion of glucose. Nausea and vomiting resolved within an hour and during subsequent treatment she had a normal heart rate. On discharge 12 hours after admission, ECG revealed a sinus rhythm and first-degree atrioventricular block with a PR interval of 0.236 seconds. Subsequent toxicology analysis by gas chromatography coupled to mass spectrometry revealed no drugs in the patient's blood and urine samples. One month later she was re-examined and she denied any symptom of bradycardia. A sinus rhythm and first-degree atrioventricular block with a PR interval of 0.210 seconds was noted on ECG. Holter revealed a sinus rhythm with a frequency of 50–150/min and first-degree atrioventricular block with a PR interval of 0.210 seconds. The echocardiogram was normal. The serology for borealis's and antinuclear antibodies were negative. Vagal manoeuvres did not provoke second- or third-degree atrioventricular block. *Conclusion:* Acute ethanol poisoning has the potential to prolong the PR interval in young healthy adults with first-degree atrioventricular block and provoke intermittent second- and third-degree atrioventricular blocks, possibly by its direct inhibitory action on the conduction system and increasing parasympathetic tone due to nausea and vomiting.

40. Miller-Fisher Syndrome Presenting as Botulism

Aleguas A, Grygiel K.
MA/RI Poison Control Center, Children's Hospital, Boston, US

Objective: The differential diagnosis of rapid onset of cranial neuropathies accompanied by gastrointestinal symptoms syndrome (GBS), and Miller Fisher syndrome includes botulism, Guillain-Barré (MFS). MFS was first clinically described in 1956.[1] The triad of ataxia, areflexia, and ophthalmoplegia was initially considered an unusual variant of GBS which is characterized by limb weakness and areflexia. While some patients who present with MFS may progress to GBS (with an incidence of 1–2 per 100,000),[2] the current thinking is that while both syndromes may have an infectious relationship to *Campylobacter jejuni*, each triggered by a specific strain.[3] We report a patient initially thought to have botulism, with a course of gastrointestinal symptoms and the development of cranial neuropathies, and a final diagnosis of MFS. *Case report:* A 68 year-old female presented to the ED with a 6-day history of nausea, vomiting, and diarrhea starting 2 hours after ingesting food from street vendor. Her GI symptoms lasted 3–4 days, and 2 days prior to presentation she complained of diplopia, dizziness, with some difficulty. The patient was admitted for a complete workup with the possible diagnosis of botulism. The Department of Health was notified. The nursing staff reported diplopia, and a unilateral ptosis. A lumbar puncture, magnetic resonance imagining, and cultures for salmonella, shigella, and campylobacter were performed. A neurology consult noted no ptosis, some vertical diplopia, no dysarthria or dysphagia, and an absence of deep-tendon reflexes in the lower extremities, which appeared to be her baseline. No acute process was noted on the MRI and she had a normal LP, and carotid evaluation by echo and ultrasound. Acetylcholine R binding antibody, anti-nuclear antibody, and IGG antibody to GQ1b gangliosides were negative. *Conclusion:* A diagnosis of Miller Fisher variant of Guillain-Barré (GB) syndrome was made and the patient was discharged for follow-up. *References:* 1. Fisher M. An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia, and areflexia). New Engl J Med 1956; 255:57–65. 2. Hughes R, Rees J. Clinical and epidemiologic features of Guillain-Barré syndrome. J Infect Dis 1997; 176:S92–S98. 3. Yuki N, Koga M. Bacterial infections in Guillain-Barré Fisher syndromes. Curr Opin Neurol 2006; 19:451–457.

41. Cases of Quinine Poisoning Referred to a Poisons Information Service for Specialist Advice

Good AM, Bateman DN.
NPIS Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, UK

Objective: To investigate the epidemiology of cases of quinine poisoning referred from a poisons information service for specialist advice. *Methods:* Medical professionals in the UK use TOXBASE (on-line poisons database) extensively. NPIS specialists in poisons information are the first-line for subsequent telephone enquiries, with more serious cases being referred to a national rota of consultant clinical toxicologists. All cases referred to the UK National Poisons Information Service (NPIS) on-call consultant clinical toxicologists for the period 1 April 2006 to 30 September 2008 concerning quinine were reviewed for age, gender and features. *Results:* There were 32 enquiries available for analysis involving 30 patient incidents. In the UK quinine is predominantly used for treatment of night cramps, especially in the elderly. The age of patients referred varied from 1–87 years (mean 43.9 years; median 40 years) including 2 children<5 years. There were 13 males and 17 females. In 22 cases the overdose was deliberate (3 accidental, 3 accidental therapeutic errors, one therapeutic and one unknown). Two patients took additional doses because their cramps had not resolved. In 12 cases quinine was taken alone. The most common co-ingestant in other cases was paracetamol (6). Cardiac features (17) were common and included tachycardias (6), prolonged QT/QTc (6), bradycardia (3; probably related to other factors), hypotension (3), atrial fibrillation (2), wide QRS (2). Two patients suffered cardiac arrest but in neither case was this thought to be directly related to the overdose. Other features included visual impairment (13), drowsiness/reduced GCS (7), auditory change (4). Four patients were reported to have dilated pupils. Other ocular features varied from slight blurring after 2.4 g to varying degrees visual loss through complete blindness after 2.8–15 g. Referrals were for general advice, use of multiple dose

activate charcoal and management of cardiac problems and blindness. *Conclusion:* Cardiac and visual features were common. Care should be taken when prescribing this drug. *Acknowledgement:* NPIS consultants and staff for the data.

42. Fatal Foodborne Botulism in an Infant Caused by Home-Canned Baby Food

Lonati D,[1] Bigi S,[1] Giampreti A,[1] Vecchio S,[1] Petrolini V,[1] Fenicia L,[2] Anniballi F,[2] Landri PA,[3] Locatelli C,[1] Manzo L.[1]
[1]*Poison Control Centre and National Toxicology Information Centre, IRCCS Maugeri Foundation and University of Pavia;* [2]*National Reference Centre for Botulism, Istituto Superiore di Sanità, Rome;* [3]*Intensive Care Unit, S. Maria della Speranza Hospital, Battipaglia, Italy*

Objective: Botulism is a neuroparalytic disease caused by the blockage of the transmission in the cholinergic synapses by botulinum neurotoxins (BonTs) produced by neurotoxigenic Clostridia. We describe, to our knowledge, the youngest European fatal case of foodborne-botulism (FBo) caused by ingestion of improperly home-canned baby food. *Case report:* An 8-month-old female (9 kg bw) was brought at about 8 a.m. by her parents to the emergency department (ED) for a progressive worsening of weakness and acute respiratory failure. At ED-admission, she presented with poor oral intake, weak cry, lethargy, and floppiness; hyperglycaemia (328 mg/dL), severe respiratory hypoxia and acidosis (pH 6.89; pCO_2 121 mmHg; pO_2 36.4 mmHg; $SatO_2$= 48.4%, HCO_3^- 12.5 mEq/L; BE −9.4; lactate 2.2 mmol/L) were present. *Ab ingestis* pneumonia was suspected and orotracheal intubation and continuous mechanical ventilation were applied. The child appeared lethargic, diffusely hypotonic and weak, mydriatic with non reactive pupils, presented poor gag and suck, absence of peristalsis and tendon reflexes. Chest radiograph, encephalic CT-scan, magnetic resonance imaging, and electroencephalography were normal, as well as biochemical tests, cerebrospinal fluid analysis, viral tests and muscular biopsy. The patient received fluids, corticosteroids, aerosol therapy, large spectrum antibiotics and enteral nutrition. A further investigation revealed that the patient had eaten, the day before, an home-canned baby food. FBo was suspected and biological and food samples were analysed: BonTs type A was identified in the food leftover. Trivalent botulinum antitoxin (250 ml) was intravenously administered in 6 hours followed by activated charcoal (5 g) and prostigmine (0.05 mg/kg bid). The patient worsened with a clinical and laboratory (procalcitonin 37.34 ng/ml) picture of sepsis, and died on day twelve. *Conclusion:* Prevention of food's contamination remains the most relevant step to counteract foodborne botulism. Botulism poisoning should be suspected in any infant presenting with feeding difficulties, constipation, descendent paralysis or acute respiratory failure. Supportive treatment and antidotal therapy should be performed as soon as a clinical diagnosis is made.

43. Fentanyl-Contaminated Heroin: "Get High or Die Tryin"

Mangili AC,[1] Roth R,[1] Brooks DE.[2]
[1]*Department of Emergency Medicine, University of Pittsburgh Medical Center, Pittsburgh;* [2]*Banner Poison Control Center, Banner Good Samaritan Medical Center, Phoenix, US*

Background: In the months of June and July 2006 Pittsburgh, PA experienced an unusually high volume of EMS calls due to fentanyl-contaminated heroin use among unsuspecting heroin abusers. These overdoses coincided with the circulation of a batch of heroin sold on the street as "Get High or Die Tryin" (GHDT). Reports of abuse, including many deaths were uncovered throughout the northeast United States. We report our local experience and mention several specific cases. *Case series:* Patient one, a 23 year old male, was found unresponsive with minimal respirations and myosis after a minor MVC. After administration of four mg of IM naloxone he became alert and reported purchasing and using one bag of GHDT. Gas chromatography and mass spectroscopy testing of the patient's urine and his confiscated GHDT were positive for fentanyl and heroin. Patient two, a 40 year old male, was found unresponsive with an oxygen saturation of 40%. The patient responded after eight mg of IM naloxone. Family confirmed he had just used GHDT. Patient three, a 34 year old male, was found unresponsive with an oxygen saturation of 32% but responded to four mg of IM naloxone. He subsequently reported using GHDT, the same heroin batch that his relative had died from using the previous week. *Discussion:* Higher rates of adverse morbidity and mortality were experienced after the use of heroin, unknowingly contaminated with fentanyl. When compared to the preceding and subsequent months the total number of heroin-related EMS calls during this period was 270% higher, and nearly 200% higher than the same time period in 2005. Many of our patients reported using their "typical" amount of heroin but experiencing 'atypical' sedation. *Conclusion:* Adulteration of illicit drugs continues to be associated with morbidity and mortality. EMS and ED staff should consider adulteration when encountering 'atypical' clinical effects from substance abuse. Collaboration between EMS and regional poison centers may enhance toxico-surveillance and limit morbidity and mortality.

44. Complications of Fentanyl Patch Ingestion

Prosser JM,[1,2] Howland MA,[1,2,3] Jones BE,[2] Hoffman RS,[1,2] Nelson LS.[1,2]
[1]*Toxicology and Emergency Medicine, New York City Poison Control Center;* [2]*New York University School of Medicine;* [3]*St. John's University School of Pharmacy, New York, US*

Objective: Fentanyl is the second most common drug associated with death and serious outcomes in the FDA Adverse Event Reporting System data. Fentanyl patches [FP] are likely to account for a substantial portion of the morbidity and mortality related to fentanyl. FP morbidity can occur via dermal application, or following ingestion, insufflation, or injection of the contents. The amount of fentanyl in the FP is potentially lethal after ingestion despite a low GI bioavailability of 32%. We report a series of patients with ingestion of FPs. *Case series:* The records of 20 cases of FP ingestions reported to our poison center from 2000–2008 were reviewed. Eleven patients developed symptoms (Table 1). The intent was either abuse or suicide in all. Nine either received naloxone or were intubated. One patient had a seizure, one developed acute lung injury, and two had troponin elevation. One death, from apnea and anoxic brain injury, occurred in a patient who had a FP adherent to her pharyngeal mucosa during intubation. *Conclusion:* A 100 mcg/hr FP contains 10 mg of fentanyl. Despite the poor GI bioavailability of fentanyl, ingestion of one patch may result in consequential clinical effects. Transmucosal absorption in the oropharynx may be important in some cases. Patches that are cut or chewed may be associated with enhanced toxicity as a result of increased release of fentanyl. Fentanyl patch ingestion may result in life-threatening complications.

45. Experimental Study of Alcohol Influence on Biological Effects of Antidepressants

Kutcher EO, Shevchuk MK, Petrov AN.
Institute of Toxicology, Federal Medical-Biological Agency of Russia, Saint-Petersburg, Russia

Objective: It is well known that many antidepressants have extremely significant side effects. This fact is important since many patients require these drugs for long periods of time and unpleasant side-effects may cause refusal of or non-compliance with subsequent treatments. Additionally, patients suffering from depression are frequently inclined to alcohol abuse.[1] Not only may alcohol have a negative influence on clinical course of depression, but it can also strengthen intensity of antidepressant side effects. The object of this study was to analyze the influence of alcohol on biological effects of antidepressants. *Methods:* The study was conducted on white out-bred male rats. Study substances were introduced intra-gastrically during 4 weeks at doses equivalent to the average daily therapeutic doses in mg/kg for man (8.43 mg/kg for fluvoxamine (Faverin®) and 12.64 mg/kg for amitriptyline). Ethanol was introduced as 40° solution at dose 3.2 g/kg. *Results:* The results showed that the combination of fluvoxamine with ethanol caused notable increase in excitability and lowering of blood pressure compared with administration of fluvoxamine only or an amitriptyline/ethanol combination. At the same time some stimulatory action in terms of behavioural response was observed with the fluvoxamine/ethanol combination and with fluvoxamine alone. Amitriptyline with ethanol causes greater educational disturbances, greater hole reflex disturbances, and increased cardiac conduction disturbances compared with amitriptyline only, ethanol only or the combination of fluvoxamine with ethanol. *Conclusion:* Co-ingestion of ethanol intensifies the sedative effects of amitriptyline. In a clinical setting it may cause aggravation of depressive symptoms and possibly increase suicide risk. Combination of fluvoxamine with ethanol increases risk of liver function and blood pressure disorders. Intensification of the side-effects and signs may lead to serious health problems and/or refusal of treatment. *References:* 1. Powell, BJ, Read, M, Penick, E, et al. Primary and secondary depression in alcoholic men: an important distinction. J Clin Psychiat 1987; 48:98–101. 2. Bauer M, Bschor T, Pfenning A, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders in Primary Care. World J Biol Psychiatry 2007; 8:67–104.

Table 1. Symptoms of 11 patients who ingested fentanyl patches

Age	Amount	#	Patch (mcg)	Naloxone	Intubation	Symptoms
Adult	Licked	1	unkn			"stoned"
50	Gel extracted	2	100	Y	N	lethargic, hypoxic
25	Gel extracted	1	100	N	N	Ten episodes of emesis
28	Ingested	1	50	Y	N	Unconscious
Adult	Ingested	3	100	Y	N	Unconscious, cyanotic, hypoxic
35	Sucked	1	unkn	N	Y	Seizure, respiratory failure, hypotension, elevated troponin
52	Ingested	0.5	100	Y	N	Respiratory arrest
34	Ingested	1	unkn	Y	N	Unconscious, hypoxic, acute lung injury, elevated troponin
51	Adhered to pharyngeal mucosa	1	100	Y	Y	Unconscious, hypoxic, elevated troponin, creatine and liver function tests, anoxic brain injury, death

46. Injectable 'Crack' Cocaine: A Case Report and Discussion of the Method of Preparation and Complications Associated with Use

Wiegand TJ,[1] Pickering CE.[2]
[1]*Department of Medicine and Emergency Medicine, Maine Medical Center and Northern New England Poison Control, Portland;* [2]*Department of Emergency Medicine, Kuakini Medical Center, Honolulu, US*

Objective: A method for converting an insoluble base form of cocaine, 'crack cocaine', to an injectable, soluble, acid-salt using an acidic solution such as acetic acid (e.g. vinegar) has emerged. Increased morbidity is associated with this practice. Physicians need to be aware of evolving methods of drug administration in order to reduce harm and effectively diagnose and manage complications associated with such practices. A case report describing this phenomenon is presented and the chemistry involved in the manufacture of cocaine-hydrochloride, other, soluble, acidic-salts of cocaine, and various 'base' forms of cocaine are discussed. *Case report:* A 22 year-old Caucasian male presented to the ED with complaint of abscess. He has a history of IVDA; using heroin, cocaine, methamphetamine and "crack". He described attempting to inject a mixture of "crack" and "black-tar" heroin but "missed" the vein and subsequently developed an abscess. In discussing the injection of crack cocaine the patient described converting it to a water soluble form using lemon juice or vinegar. In fact, he stated that whenever he had subsequently "smelled vinegar" he had experienced intense urges for using cocaine. *Conclusion:* Although insoluble ('crack') cocaine base is typically manufactured via addition of an alkaline solution to the soluble cocaine salt, cocaine-HCl, a process for turning 'crack' cocaine back into a soluble salt using acetic acid or other acid-salt has emerged. Novel methods for preparing or using drugs of abuse may carry inherent toxicity which differs from previous methods of administration. Intravenous administration of 'crack' converted to a soluble salt is associated with increased risk of abscess, cellulitis and fungal infection compared to cocaine-HCl injection. Knowledge of emerging or novel practices regarding drug abuse is important for implementing strategies aimed at harm reduction and important to clinicians in diagnosis and management of complications inherent to such practices.

47. A Review of "Methadone – Detected" Deaths in Victoria, 2001–2006

McDonough M.
Addiction Medicine Unit, Western Hospital, Melbourne, Australia

Objective & Method: A retrospective case series review of all deaths reported to the State Coroner where Methadone was detected between January 2001 and December 2006. The rate of reported deaths where Methadone has been detected has been noted as increasing. *Results:* Methadone-Detected Deaths have been increasing in Victoria, a phenomenon noted also in other countries.[1] The common profile of factors identified in many of these cases is consistent with those reported in other similar case series.[2] For example, many deaths appear to have occurred at night and likely during sleep; several cases occurred in close proximity to dosing changes, particularly initial dose induction period and following dose increases etc. There appear no pathognomonic features to identify cases as primarily Methadone caused or secondarily Methadone contributed (e.g. in Combined Drug Toxicity) while in other cases, the cause of death is assumed accidental/homicidal/suicidal. Of concern, there is evidence of the tablet form of Methadone (Physeptone) i.e. a different preparation to the Syrup usually prescribed for Heroin Addiction Treatment, being over-represented amongst the recent increasing numbers of Methadone – Detected deaths. Physeptone tablets are prescribed usually for the treatment of opioid – responsive, chronic pain states; such a practise is also known to be increasing in Victoria. Increasing mortality related to opioid analgesics has been also noted in the US.[3] *Conclusion:* The increased prescribing of Physeptone (Methadone Tablets) for chronic pain appears to be associated with an increased level of Methadone - Detected Deaths, as reported to the State Coroner. Methadone syrup prescription appears to carry less risk of mortality in contrast to tablet prescription.[4] Tablet prescribers may need to adopt practises that reduce the risk of mortality e.g. supply only small amounts, monitor patients more closely etc. *References:* 1. Methadone Mortality - A Reassessment. A report by SAMHSA, US Dept Health & Human Services, Washington DC, July 2007. 2. Caplehorn JR, Drummer OH. Fatal methadone toxicity: signs & circumstances, and the role of benzodiazepines. Aust NZ J Pub Health 2002; 26:358–362. 3. Bacca C, Grant K. Mortality from Opioid Analgesics must not be Ignored. Pain 2007; 128:228. 4. Williamson PA, Foreman KJ, White JM, et al. Methadone-related overdose deaths in South Australia, 1984–1994. How safe is methadone prescribing? MJA 1997; 166:302–305.

48. Synthetic Substituted Amphetamines and the Dangerous Drug Ordinance in Israel: The Never-Ending Story

Lurie Y,[1] Lavon O,[1] Almog S,[2] Bentur Y,[1] Gopher A.[2]
[1]*Israel Poison Information Center, Rambam Health Care Campus, Haifa;* [2]*Institute of Clinical Pharmacology and Toxicology, Sheba Medical Center, Tel Hashomer, Israel*

Objective: Synthetic substituted amphetamines are synthesized in order to by-pass the Dangerous Drug Ordinance. We report the clinical, analytical and legal aspects of an outbreak of severe poisoning due to the newly introduced amphetamine derivatives PMA (para-methoxyamphetamine) and PMMA (para-methoxymethamphetamine) poisoning in Israel during 2007. *Case series:* During 2007, the national forensic laboratory identified a cluster of 22 fatalities in which amphetamines were detected in urine by immunoassays but not by chromatographic assays used for routine screening. At the same time the involvement of new designer drug/s was suspected by the poison center in four patients with alleged severe stimulant poisoning. Reanalysis of biological specimens obtained from the fatality cases and the patients who survived, by GC-MS revealed the presence of PMA and PMMA. Both compounds were detected in 24/26 cases. All patients were young adults; age range 18–40 years, 16 males. PMA and PMMA are hallucinogenic para-methoxy derivatives of phenylethylamines. Their onset of action is slower and toxicity higher than methylenedioxy counterparts. Mortality was reported in several countries.[1,2] An alert was sent to all emergency departments and the Ministry of Health. As a result, PMMA was added to the Israeli Dangerous Drugs Ordinance, PMA was included in 2004. Since October 2007 only one additional case was detected by the national forensic laboratory. However, in 2008, chloramphetamine, a halogenated amphetamine derivative, was found in specimens from three fatal cases. Chloramphetamine is not included in the Dangerous Drugs Ordinance and its toxicity in humans has not been reported. *Conclusions:* Forensic laboratory and poison center cooperation is important in identifying new drugs of abuse. Dangerous Drugs Ordinance should include compounds structurally related to known substances of abuse even before they have been introduced into the market. Exception can be made for chemical entities that might be clinically used. The effort to detect and control new designer drugs is challenging and never-ending. *References:* 1. Lin DL, Liu HC, Yin HL. Recent paramethoxymethamphetamine (PMMA) deaths in Taiwan. J Anal Toxicol 2007; 31:109–113. 2. Caldicott DG, Edwards NA, Kruys A, et al. Dancing with "death": p-methoxyamphetamine overdose and its acute management. J Toxicol Clin Toxicol 2003; 41:143–145.

49. Phenazepam as a Drug of Abuse – High Frequency of Prolonged Symptoms

Rafstedt K,[1] Hultén P,[1] Brusin K.[2]
[1]*Swedish Poisons Information Centre, Stockholm, Sweden;* [2]*Sverdlovsk Regional Centre of Acute Poisoning, Yekaterinburg, Russia*

The long-acting benzodiazepine phenazepam has been used medically in Russia and Belarus since the 1970s. Indications are psychiatric disorders, withdrawal syndrome and epilepsy. Phenazepam has a half-life of approximately 60 hours.[1] Most peer reviewed articles are written in Russian and information about phenazepam is scarce in English language journals. In December 2007, the Swedish Poisons Information Centre (SPIC) first started to receive phone calls concerning phenazepam, used as a drug of abuse and mainly bought over the Internet. *Objective:* In order to assess the acute toxicity of phenazepam a survey was conducted, based on all telephone inquiries and hospital case records received by SPIC. *Case series:* 61 cases were registered at the Swedish centre over a period of 11 months, from December 2007 to October 2008. The ingested dose was unknown in the majority of the cases. The most commonly reported symptoms listed in falling frequency were CNS-depression, impaired balance, slurred speech, confusion, memory loss, ataxia, and hallucinations. There were no severe cases, nor any fatalities. Most noticeable was the long duration of the symptoms. Of 61 patients, at least 14 were still experiencing symptoms more than 5 days after the ingestion. In one case the patient was hospitalized until day 16 after the intake. CNS-depression remained to some degree for more than 3 weeks. Also distinguishable from the typical features of benzodiazepine poisoning was the fluctuating appearance of the symptoms. Flumazenil proved useful when given but the effect was not lasting. *Conclusion:* As a consequence of these cases phenazepam was classified as a narcotic drug in Sweden in September 2008. Phenazepam is not likely to cause severe intoxications and treatment should be given in accordance with other benzodiazepine overdoses. However, it is important that physicians are aware of phenazepam's potential for causing fluctuating and long term symptoms in order to avoid unnecessarily extended medical investigations. *References:* 1. Zherdev VP, Caccia S, Garattini S, et al. Species differences in phenazepam kinetics and metabolism. Eur J Drug Metab Pharmacokinet 1982; 7:191–196.

50. Twenty-Three Deaths with GHB Intoxication in Western Sweden Between 2000–2007

Knudsen K,[1] Jonsson U.[2]
[1]*Department of Anesthesia and Intensive Care, Sahlgrenska University Hospital, Gothenburg;* [2]*Department of Forensic Medicine, Gothenburg University, Gothenburg, Sweden*

Background: Gamma-hydroxybutyrate (GHB) is a drug of abuse that has been marketed by many users as safe and harmless.[1] In spite of this an increasing number of deaths have been recorded during the last years in Sweden.[2] Many drug users mix intake of GHB with alcohol or illicit drugs. It is unclear if coingestion with ethanol or opioids causes death in GHB overdose or if GHB itself is the most important cause of death.[3] *Objective:* The aim of this study was to analyse the cause of death in poisonings involving GHB. *Methods:* All cases of deaths with GHB were recorded between 2000–2007. The deaths were classified as GHB poisonings with no influence of other drugs, with minor influence of other drugs or with major influence of other drugs. *Results:* The total number of GHB-related deaths during the study period in our region was 35. Twenty-three were diagnosed as deaths due to intoxication. 22 cases were GHB poisonings of importance with 91% being male. Age was between 16 and 46. 48 percent of the deaths were classified as GHB intoxication with no influence or minor influence of other drugs. Fifty-two percent were mixed overdoses with illicit drugs. Seven patients also ingested alcohol. Two deaths were intoxicated with GHB only. Mean concentration of GHB in femoral blood was 399 mg/g, and mean urinary concentration was 2368 mg/mL. *Conclusion:* Intoxication by GHB carries substantial mortality. Mixing GHB with other drugs such as amphetamine or cocaine does not prevent lethal overdoses. Mixing GHB with ethanol does not seem to explain the many deaths in our region. The drug itself carries such pharmacological properties that any overdose with GHB is dangerous and may lead to death, alone or in combination with other drugs. *References:* 1. Dean W. GHB demonization proceeds in states: a call to action: stop criminalization of GHB now (http://www.erowid.org/chemicals/ghb/ghb_info2.shtml). 2. Knudsen K, Greter J,

Verdicchio M. High mortality rates among GHB abusers in western Sweden. Clin Toxicol 2008; 46:187–192. 3. Bosman IJ, Lusthof KJ. Forensic cases involving the use of GHB in The Netherlands. Forensic Sci Int 2003; 133:17–21.

51. Development of a Scoring Instrument of Illicit Drugs

Knudsen K,[1] Larsson H,[2] Jennische K.[3]
[1]Department of Anesthesia and Intensive Care, Sahlgrenska University Hospital, Gothenburg; [2]Department of Medicine, Hospital of Trollhattan, Trollhattan; [3]Department of Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden

Objective: To develop a simple scoring instrument of illicit drugs based on toxicological data and social risk parameters for overall toxicity. A similar but not equal scale has been proposed in UK 2007.[1] *Methods:* A simple additive model was designed that would be applicable to any drug. Eight different drugs were assessed for the propensity to cause harm in eleven clinical and social parameters. These parameters were designed to assess risk for 1) life-threatening overdose, 2) drug related death excluding acute overdose, 3) acute psychosis, 4) acute trauma, 5) dependency or chronic use, 6) multiple substance abuse, 7) mental disease with long term use, 8) social inability with long term use, 9) development of somatic disease, 10) increased mortality and 11) criminality. For each clinical parameter a scoring of one to five points was given depending on known toxicity for the explored drug. The parameters of risk for 1) life-threatening overdose, 2) drug related death excluding acute overdose and 10) increased mortality were judged as three times as important as the other parameters and the scoring for these was multiplied with three. The following drugs were scored for overall toxicity; amphetamine, cannabis, ecstasy, GHB, heroin, cocaine, methamphetamine and flunitrazepam. *Results:* The scoring points for overall toxicity became respectively; heroin (68 p), cocaine (58 p), amphetamine (54 points), GHB (48 p), methamphetamine (47 p), flunitrazepam (45 p), cannabis (33 p) and ecstasy (33 p). *Conclusion:* Our instrument is feasible for scoring any kind of drug and allows comparison between drugs for determination of overall toxicity. This model is practical, quick and easy to use. It should be tested further to evaluate reliability and sensitivity. The scoring instrument may be useful for legal authorities in need for classification of new illicit drugs. *References:* 1. Nutt D, King A, Saulsbury W, et al. Development of a rational scale to assess the harm of drugs of potential misuse. Lancet 2007; 369:1047–1053.

52. Opiate Detoxification in an Inpatient Setting in Thessaloniki, Greece. A 12 Year Experience

Nikolaou K,[1] Kovatsi L,[2] Njau SN,[2] Molybda S,[1] Passali M,[1] Chalikia I.[1]
[1]Detoxification Unit, Psychiatric Hospital of Thessaloniki; [2]Laboratory of Forensic Medicine and Toxicology, Aristotle University of Thessaloniki, Thessaloniki, Greece

Objective: The Detoxification Unit in Thessaloniki, Greece is a residential facility running a 21 day detoxification program which provides support (medication and psychotherapy) and preparation for transfer to further treatment (residential therapeutic community or outpatient services). This is a retrospective archives trial aimed at presenting the 12 year experience gained during the operation of the Detoxification Unit. *Methods:* For the needs of this paper we studied the records of the Unit from opening day in 1996 until the end of 2008 and we followed-up our patients in order to evaluate whether they received further treatment in another program or not. *Results:* Based on our records, there are on average 200–300 admissions to our Unit every year. The vast majority (more than 80%) of addicts being admitted are men. Half of the admitted addicts complete the 21 day program, while the rest abandon it prematurely. Among those who do not complete the program, the vast majority abandon it against professional advice and roughly 20% are discharged on the grounds of discordance with the facility's set of rules. The vast majority of those who complete the 21 day program, enter the Residential Therapeutic Community and only a small percentage return to the Rehabilitation Unit or continue in an out-patient program. The percentage of those not receiving any further treatment is also low. *Conclusion:* The completion rate of 50% for the 21 day detoxification program is comparable to previously reported rates.[1] The fact that the vast majority of those completing the 21 day program in the Detoxification Unit, transfer to further treatment is very rewarding for the staff of the Unit. The low number of female admissions does not represent the actual ratio of male/female drug users.[2] Undoubtedly a women's program would increase the female users seeking help. *References:* 1. Day E. Opiate detoxification in an inpatient setting. National Treatment Agency for Substance Misuse 2005, Research Briefing 9. 2. Annual Report of the Greek Focal Point of EMCDDA for the situation on drugs and alcohol in Greece 2007.

53. The First Reported Fatality Related to Gamma-Butyrolactone Ingestion

Dargan PI,[1] Button J,[2] Davies S,[2] Holt DW,[2] George S,[3] Garnham F,[4] Wood DM.[1]
[1]Guy's and St Thomas' Poisons Unit, Guy's and St Thomas' NHS Foundation Trust; [2]Analytical Unit, St George's University of London; [3]Department of Histopathology, Guy's and St Thomas' NHS Foundation Trust; [4]Emergency Department, Guy's and St Thomas' NHS Foundation Trust, London, UK

Objective: Gamma-butyrolactone (GBL) is rapidly metabolised to gamma-hydroxybutyrate (GHB) *in vivo*, having similar toxicity to GHB in overdose.[1] There are numerous reported fatalities related to GHB ingestion,[2] but no published fatalities related to isolated GBL ingestion. We report the first case of fatality related to GBL together with the results of post-mortem toxicological analyses and analysis of the ingested GBL. *Case report:* A 25-year old male was found unconscious in bed by his partner. There was a history of ingestion of "GHB" the previous evening, and he had returned home "acting strangely" six hours prior to being found by his partner. On arrival in the ED, 40 minutes after being found collapsed, he was in asystole; basic cardiopulmonary resuscitation had been commenced by his partner and ambulance personnel. He was intubated (note was made of vomit in his airway) and cardiopulmonary resuscitation continued using the ACLS protocols. An arterial blood gas revealed: pO_2 0.9kPa, pCO_2 10.9 kPa, pH<6.80, lactate>15.0. Resuscitation was discontinued after four cycles, in view of the prolonged out of hospital cardiac arrest. Comprehensive toxicological screening of post-mortem blood and urine samples showed a total blood GHB/GBL concentration of 282 mg/L; no ethanol or other recreational/sedative drugs were detected. Analysis of the liquid ingested by the deceased showed that this was pure GBL, with no GHB detected. *Conclusion:* We report the first case of fatality associated with GBL ingestion. Currently GHB is classified under the UK Misuse of Drugs Act, 1971 but GBL is not,[3] although it is likely that it will be classified during 2009. This case, together with reports suggesting increasing use of GBL would support the change in its legal status. *References:* 1. Ingels M, Rangan C, Bellezzo J, et al. Coma and respiratory depression following the ingestion of GHB and its precursors. J Emerg Med 2000; 19:47–50. 2. Mazarr-Proo S, Kerrigan S. Distribution of GHB in tissues and fluids following fatal overdose. J Anal Toxicol 2005; 29:398–400. 3. Wood DM, Warren-Gash C, Ashraf T, et al. Medical and legal confusion surrounding gamma-hydroxybutyrate (GHB) and its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4BD). QJM 2008; 101:23–29.

54. Frequency of Self-Reported Cocaine Use in Patients Presenting to a Large Inner-City European Emergency Department with Chest Pain

Bishop CR, Greene SL, Dargan PI, Wood DM.
Guy's and St Thomas' Poisons Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK

Objective: Recreational use of cocaine is common in the developed world, with >2.5% of those in the UK, USA and Spain using cocaine per year. Cocaine use is associated with a significant risk of cardiac complications, including acute coronary syndrome (ACS). It is clinically important to know in patients presenting with ACS if this is related to cocaine use, as the management of this group of patients differs. The prevalence of cocaine use, using urinalysis for cocaine and its metabolites, in patients presenting with ACS in the US has been reported to be 17%.[1] There is limited data on the true frequency of self-reported cocaine use in patients presenting with chest pain in the UK. *Methods:* All patients presenting to the Emergency Department (ED) between 1st January and 30th June 2008 with an initial diagnosis of suspected ACS were identified retrospectively. Electronically scanned ED patient records were reviewed and analysed by one author (CB) to collect basic demographic data and whether self-reported recent use of cocaine had been recorded in the ED notes at the time of presentation. *Results:* There were 1362 presentations to the ED with an initial diagnosis of suspected ACS during the 6 month study period. Self-reported recent use of cocaine was recorded in the ED notes in 15 (1.1%) of these presentations. The mean age±std dev was significantly lower in those self-reporting cocaine use (30±7.2 yrs) than those who did not (51.9±17.1) ($p<0.0001$, students unpaired t-test). There was no significant difference in the gender distribution between those presentations self-reporting cocaine (12/15) to those not (875/1347). *Conclusion:* A significant minority of patients presenting with suspected ACS self-report recent use of cocaine. There is likely to be under-recording of the true incidence of self-reported cocaine use. There is an urgent need for larger studies looking at not only self-reported cocaine use, but also confirmatory analytical toxicology to determine the true prevalence of cocaine-associated chest pain. *References:* Hollander JE, Todd KH, Green G, et al. Chest pain associated with cocaine: an assessment of prevalence in suburban and urban emergency departments. Ann Emerg Med 1995; 26:671–676.

55. Clinical Experience in Treatment of Patients with Ethanol Dependency and Ademetionine Application for Overcoming Acute Toxic Ethanol Hepatitis and Acute Withdrawal Syndrome

Zlateva S,[1] Alexandrov I,[2] Borisova E.[3]
[1]Department of Toxicology, Naval Hospital Varna; [2]Central Military Commission, Naval Hospital Varna; [3]Department of Neurology and Psychiatry, Naval Hospital Varna, Varna, Bulgaria

Objective: To assess effects of ademetionine, when added to standard therapy of alcohol dependant patients with acute withdrawal syndrome and acute toxic ethanol hepatitis. *Methods:* We studied 88 patients aged between 26 and 71 years, hospitalized during the period 2005–2008 because of acute withdrawal syndrome combined with acute toxic ethanol induced hepatitis. They were divided into two groups – controls (20 patients) and study cases (68 patients). The standard treatment protocol consists of: infusions of glucose and saline solutions, nootropics, thiamine, pyridoxine, L-ornitine-L-aspartate, silymarin. For patients from the study group (68 patients) ademetionine was added to this treatment protocol. All patients were monitored in regard to biochemical markers of hepatitis (ASAT, ALAT, GGTP and bilirubin level). For assessment of withdrawal syndrome the following indices were monitored: anorexia, anxiety, insomnia, general condition, febrile status, hypertension, depression and need for sedative therapy. Mental processes were analyzed using Hamilton methodology, Spilberger questionnaire (STAI-Y-1/2) and Miroshnikov methodology (Health Activation Temper). *Results:* We registered prevalence of the non-icteric form of toxic hepatitis - 86% of the cases, in both groups. In cases where hyperbilirubinaemia was observed, the decrease in bilirubin levels was more rapid in the study group in comparison to the control group. Biochemistry results show more rapid recovery of ASAT level in the study group in comparison to the control group. In 13% of the study patients (and 17% of controls) we observed increase of ALAT and GGTP levels on the 4–5th day. In all patients from the study group ALAT and GGTP levels started to decrease on the 10th day. In 90% of them normal levels were observed

on the 30th day in comparison to the controls where we registered only a decrease in the levels but not normal values. Overcoming the withdrawal syndrome was registered earlier in the study group in comparison with controls. Psychology tests show better results in the study group in comparison to controls. *Conclusion:* Ademetionine possesses considerable therapeutic potential in treatment of patients with alcohol dependency for recovery of liver function as well as for overcoming symptoms of acute withdrawal syndrome.

56. Bowel Perforation and Fatality in a Cocaine "Body Stuffer"

Majlesi N,[1,2] Chan GM,[1,2] Su MK,[1,2] McGuigan MA,[2] Greller HA.[1,2]
[1]Emergency Department/Division of Medical Toxicology, North Shore University Hospital, Manhasset; [2]Long Island Regional Poison and Drug Information Center, Mineola, US

Objective: "Body stuffers" are people who ingest illegal substances to escape detection by authorities. Cocaine "body stuffers" rarely have significant morbidity or mortality. We report the first crack cocaine "body stuffer" bowel perforation and fatality. *Case report:* A 27-year-old alleged crack cocaine dealer presented to the emergency department after being arrested during an illicit drug transaction. He ingested about 5 to 10 grams (g) of crack cocaine stored in small plastic bags. On arrival, vital signs were: heart rate (HR) 150 bpm, blood pressure (BP) 117/94 mm Hg, temperature 37.2ºC, and oxygen saturation 100% on room air. The patient suddenly developed an agitated delirium. The BP and rectal temperature increased to 213/130 mm Hg and 38.2ºC, respectively. The patient underwent rapid sequence intubation. His initial electrocardiogram showed a sinus tachycardia at 150 bpm with a QRS duration of 80 ms and a QTc duration of 378 ms. Lorazepam 2 milligrams (mg) and diltiazem 5 mg/hr was given IV. The regional poison center was consulted. Diltiazem was discontinued, repeat doses of lorazepam were administered and propofol was initiated. Bowel sounds were noted to be normal. Activated charcoal 1 g/kg was administered followed by whole bowel irrigation (WBI) with polyethylene glycol at the rate of 2 liters/hr via nasogastric tube. After sedation, repeat vital signs were HR 130 bpm, BP 100/60, and temperature 37.2ºC. Six hours after initiation of WBI, the patient's abdomen was noted to be distended. WBI was discontinued. Abdominal radiography was interpreted as "unremarkable". Surgery was then consulted to evaluate for mechanical bowel obstruction versus local ischemic effects of cocaine. The patient was observed overnight. In the morning, vital signs were BP 129/65, HR 145 bpm, and rectal temperature 39.4ºC. Piperacillin/tazobactam was initiated for presumed aspiration pneumonia. The abdomen was again noted to be distended. Computed tomography of the abdomen showed bowel perforation with extravasation of contrast into Morrison's pouch. The patient was taken to the operating room and died intraoperatively. *Conclusion:* Bowel perforation and death are rare complications of cocaine "body stuffers" presenting to the ED. Abnormal physical examination findings of the abdomen should prompt aggressive diagnostic and therapeutic interventions.

57. New "Herbal Drugs" of Abuse: Spice and Smoke

Hermanns-Clausen M,[1] Sauer O,[2] Gerber G,[3] Faerber E,[4] Koch IE,[5] Hentschel H,[6] Seidel C,[7] Stedtler U,[1] Auwarter V.[8]
[1]Poisons Information Centre VIZ-Freiburg, Centre for Pediatrics and Adolescent Medicine, Freiburg; [2]Poisons Information Centre Mainz, University Hospital, Mainz; [3]Department of Toxicology, Klinikum rechts der Isar, Munich; [4]GIZ-Nord Poisons Centre, University Hospital, Göttingen; [5]Poisons Information Centre BBGes, Berlin; [6]Poisons Information Centre, Erfurt; [7]Poisons Information Center, Bonn; [8]Institute of Forensic Medicine, University Hospital, Freiburg, Germany

Objective: Herbal smoking mixtures called "Spice" and "Smoke" have been advertised via the internet as a legal alternative to cannabis since 2004 in various European countries. In August one of the main German TV stations gave a report about this herbal "cannabis". In December 2008 the synthetic cannabinoid JHW-018 was identified in "Spice",[1] and in a higher concentration in "Smoke".[2] "Spice" also contains a homolog of the potent synthetic cannabinoid CP-47,497. Additionally, a larger quantity of oleamide was found in "Smoke".[2] The added synthetic compounds were banned in Germany in January 2009. *Methods:* After VIZ-Freiburg Poisons Center had registered 4 calls within 20 days concerning poisoning by new herbal drugs of abuse all poisons centers (PC) in Germany and the centers in Vienna and Zurich were contacted by e-mail or telephone. *Results:* 20 cases of monointoxication with "Spice" or "Smoke" and one case after smoking of both mixtures were registered. Only two exposures had been reported 1–6 months before the TV-report. Eight cases were registered in one PC, all other centers reported fewer cases. Age was 14–25 years, 17 male, 2 female, 2 unknown. Severity was moderate (13) or minor (8). All exposures were intentional (abuse 20, criminal intent 1). All but two patients were treated in hospital. Symptoms reported were agitation, panic, confusion, hallucination, dizziness, changes of perception, tachycardia, ECG-changes, hypertonia, dyspnoea, vomiting. Immunoassays for THC, tricyclic antidepressants, cocaine, amphetamines, ecstasy and metamphetamine were performed in 5 patients yielding negative results. *Conclusions:* Symptoms after smoking "Spice" or "Smoke" were similar in all cases resembling severe cannabis-intoxication, not expected from the declared herbs. The subsequently detected synthetic cannabinoids are most probably responsible for the reported clinical effects. Immunoassays for THC were negative because neither synthetic cannabinoid showed significant cross-reactivity to the used assays (2). For the first time human intoxications by the synthetic cannabinoids JHW-018 and CP-47,497 homolog are reported. In this case series, an increase of poisoning cases by cannabinoid containing herbal drugs mainly marketed via the internet and "headshops" ("Spice", "Smoke") was noticed within 3 weeks after one of the main German TV stations reported them as "legal" cannabis substitutes. *References:* 1. http://www.frankfurt.de/sixcms/detail.php?id=2855&_ffmpar[_id_inhalt] =5219316 2. Auwärter V, Dresen S, Weinmann W, et al. Spice and other herbal blends: harmless incense or cannabinoid designer drugs? JMS 2009; 45:(accepted 30.12.2008) DOI:10.1002/jms.1558

58. Severe Hypoglycemia After Use of Oxandrolone Adulterated with Glyburide

Brenner S, Halcomb SE.
Emergency Division Barnes-Jewish Hospital, Washington University, Saint Louis, US

Objective: Medication safety - severe hypoglycemia after oxandrolone use. *Case report:* Oxandrolone is marketed as a mild and safe anabolic steroid that is FDA approved for patients with muscle wasting or severe burns. It is also widely abused by bodybuilders and athletes as a performance enhancing agent. We report a case of a 36 year-old otherwise healthy male who presented to the emergency department with altered mental status due to severe hypoglycemia after use of oxandrolone that was illegally purchased at a local gym. The patient's hypoglycemia was refractory to several doses of IV dextrose but improved after 50 mcg SQ Octreotide was administered. The initial blood sugar measured 17 mg/dL and repeatedly dropped below 70 mg/dL during the hospital stay. The laboratory identified the presence of the sulfonylurea Glyburide in the patient's blood. *Conclusion:* The non-medicinal use of anabolic agents among professional and amateur body builders and athletes is known.[1] Use of antihyperglycemic agents is becoming increasingly popular. Insulin use to increase muscle mass has been reported.[2] Metformin has been promoted by various informal sources as part of a "ketogenic diet" regimen for bodybuilders.[3] Dosing and off brand use of medications in this particular subculture are often derived from subjective or anecdotal data and therefore confer significant risk of misuse with potentially lethal outcomes. This case report illustrates adulteration of supposedly anabolic agents with a sulfonylurea perhaps in order to mimic hypoglycemic effects. Clinicians should be aware of possible sulfonylurea overdose in athletes presenting with hypoglycemia. *References:* 1. Kutscher EC, Lund BC, Perry PJ. Anabolic steroids: a review for the clinician. Sports Med 2002; 32:285–296. 2. Evans PJ, Lynch RM. Insulin as a drug of abuse in bodybuilding. Br J Sports Med 2003; 37:356–357. 3. Deprospo J. Bodybuilding.com: Militant fat loss tricks sample program. http://www.bodybuilding.com/fun/jon4.htm (last reviewed: 11/14/2008)

59. Trends of Dextromethorphan Abuse in Sweden – from the Year 2000 and Forward

Bäckberg M, Hultén P.
Swedish Poisons Information Centre, Stockholm, Sweden

Background: The antitussive agent, dextromethorphan (DXM), has not been on the Swedish pharmaceutical market since year 2000. During recent years, the Swedish Poisons Information Centre (SPIC) has noticed an increasing number of inquiries concerning DXM overdose. The Swedish government classified DXM as a narcotic September 1, 2008. *Methods:* To elucidate the trends of DXM abuse in Sweden we made a retrospective study from the year 2000 and forward of registered DXM intoxication inquiries, focusing on patients treated in hospital. Collected data included age, sex, dose, coingestants, hospitalization, and clinical features. *Results:* More than one hundred cases DXM overdose were recorded at SPIC since 2000. No inquiries were reported up to January, 2004. A dramatic increase of consultations was observed in the spring of 2005. The number of inquiries was similar during the following years until a new increase of inquiries was observed during the beginning of 2008. However, no inquiries have been registered since summer 2008. We have scrutinized more than fifty hospitalized cases. The patients were mainly men and young adults and the abused dose varied from 250 mg to above 3000 mg. In 25% of the cases, one or several coingestants were involved, mainly ethanol. The most common clinical symptoms reported were varying degree of CNS depression, muscle stiffness, hallucinations, tachycardia, hypertension and mydriasis. Ten patients (17%) were classified as severe and displayed unconsciousness and/or respiratory depression. In total, 8 people have had a lethal outcome in Sweden due to DXM intoxication. *Conclusion:* An increasing number of DXM poisonings have been observed in Sweden since 2004. Hopefully, this trend was broken as a result of the drug's classification as a narcotic in September, 2008.

60. An Unusual Cause of Accidental Death Due to Buflomedil

Dona A, Nikolaou P, Papoutsis I, Spiliopoulou C, Athanaselis S.
Department of Forensic Medicine and Toxicology, University of Athens, Athens, Greece

Objective: Buflomedil hydrochloride is a vasodilator drug commonly used in the treatment of both peripheral and cerebral vascular diseases. Since the buflomedil toxic dose is very similar to the therapeutic dose and the response to the drug is quite different in various subjects, many accidental (in particular among elderly patients) or suicidal intoxications have been reported. Consequently, it is essential to use a specific, sensitive and rapid method for the determination of buflomedil in biological fluids in case of poisoning.[1,2] *Case report:* An 84-year-old man, who suffered from serious vision problems, was found dead in his house. He was currently taking buflomedil, maprotiline and various analgesics. At autopsy, no pathological findings were present and toxicological analysis of biological fluids was necessary in order to investigate the cause of death. Toxicological analysis by gas chromatography-mass spectrometry showed the presence of buflomedil in the following concentrations: 74.7μg/mL blood and 652.8μg/mL urine. Analgesics and maprotiline were not detected in blood

or urine samples of the deceased. *Conclusion:* Taking into consideration the fact that the deceased had no history of suicidal attempts and the results of toxicological analysis, it was assumed that the man, who was constantly in pain, was taking buflomedil tablets by accident instead of analgesics. His inability to see well probably caused this accidental death. Our assumption was reinforced by the fact that the buflomedil tablets missing from the prescription date to the day of death were more than the therapeutic dose. The presentation of this case contributes not only to the investigation of a cause of death, but reminds of the dangers involved when elderly patients suffer from problems of vision and are under pharmaceutical prescription without supervision. *References:* 1. Athanaselis S, Maravelias C, Michalodimitrakis M, et al. Buflomedil concentrations in blood and viscera in a case of fatal intoxication. Clin Chem 1984; 30:157. 2. Neri C, Barbareschi M, Turrina S, et al. Suicide by buflomedil HCl: a case report. J Clin Forensic Med 2004; 11:15–16.

61. Death Due to Mirtazapine Overdose

Nikolaou P, Dona A, Papoutsis I, Spiliopoulou C, Maravelias C.
Department of Forensic Medicine and Toxicology, University of Athens, Athens, Greece

Objective: Mirtazapine is a recently approved medication for the treatment of depression and it is considered to be equally efficacious to many of the current antidepressants, with the advantage of faster onset of symptoms relief. Little is known about mirtazapine in overdose and a limited number of case reports have been published, without any reported deaths due to only mirtazapine overdose.[1,2] We report the first fatal case of mirtazapine overdose in Greece. *Case report:* A 78-year-old female was found dead in her toilet, by her daughter-in-law. The deceased had a medical history of depression and hypertension. Her medications included mirtazapine and olmesartan. The woman usually lived with her relatives, but she was left alone for a few days during summertime. At autopsy, no pathological findings were present and toxicological analysis of biological fluids was necessary in order to investigate the cause of death. Concentrations of mirtazapine in blood and gastric fluids were extraordinarily high, 2.6 and 30.9 μg/mL, respectively. *Conclusion:* So far, mirtazapine has been suggested as a relatively safe drug with respect to overdose and it was believed that the mirtazapine concentrations alone may not have been the sole determinant in any of previously reported deaths related to mirtazapine intake.[1] Nevertheless, Robertson et al in 1999[3] reported the death of a young man attributed to mirtazapine ingestion, although other causes cannot be excluded. The same holds also in our case since no other drugs were found in the deceased specimens. The presentation of this case contributes not only to the investigation of a cause of death, but reminds of the dangers involved when elderly patients are under pharmaceutical prescription without custody. *References:* 1. Kirkton C, McIntyre I. Therapeutic and toxic concentrations of mirtazapine. J Anal Toxicol 2006; 30:687–691. 2. LoVecchio F, Riley B, Pizon A, et al. Outcomes after isolated mirtazapine (RemeronTM) supratherapeutic ingestions. J Emer Med 2008; 34:77–78. 3. Baselt R. Disposition of toxic drugs and chemicals in man. 7th ed. Foster City, California, USA: Biomedical Publications, 2004:752–3.

62. Somatosensory Evoked Potentials and Brain-Stem Auditory Evoked Potentials in Coma Due Venlafaxine Overdose

Akhtar J,[1] Carlson JN,[2] Abesamis MG,[2] Katz KD.[1]
[1]Pittsburgh Poison Center, University of Pittsburgh Medical Center Schools of Pharmacy and Medicine; [2]University of Pittsburgh Affiliated Residency in Emergency Medicine, Pittsburgh, US

Objective: It has been reported that in comatose patients due to severe CNS depressant drug overdose the central somatosensory conduction time after median nerve stimulation and brain-stem auditory evoked potentials demonstrate delayed interpeak latencies. We report a case of a critically sick venlafaxine overdose that had normal limits on testing. *Case Report*: A 28-year-old female was admitted after an overdose of 15 grams of venlafaxine. Her hospital course was complicated with wide complex tachycardia, multiple seizures, and myocardial depression with low cardiac output, intractable hypotension, and acute respiratory failure secondary to ARDS and rhabdomyolysis and renal insufficiency. She was managed aggressively and eventually survived after a 27 days stay in the ICU. Her comprehensive drug screen was positive for benzodiazepine metabolite (nordiazepam), phenobarbital, propofol, nicotine, caffeine, venlafaxine and guaifenesin metabolite. Her venlafaxine levels were reported as 19000 ng/mL and O-Desmethylvenlafaxine level as 1700 ng/mL. Somatosensory evoked potentials (SEP's) and brain-stem auditory evoked potentials (BAEP's) were examined. The median and the peroneal nerve SEP's and the BAEP's were all within normal limit. *Conclusion:* The assessment and care of persons with coma following catastrophic drug overdose is often difficult and filled with diagnostic and prognostic challenges. Somatosensory evoked potentials and brain-stem auditory evoked potentials may not have therapeutic efficacy, nor help predict outcome. Somatosensory evoked potentials and brain-stem auditory evoked potentials may have no role in the care of a comatose drug overdose patient.

63. Acetaminophen-Induced Type B Lactic Acidosis

Wong S,[1] Goto C.[2]
[1]Parkland Memorial Hospital, Dallas; [2]The University of Texas Southwestern Medical Center, Dallas, US

Objective: To report a teenager with large acetaminophen overdose and type B lactic acidosis. *Case report*: A 16-year-old female presented after a large overdose of Tylenol PM®. Vital signs: T 97.9 °F; RR: 20; HR: 106; BP: 134/62 mmHg; oxygen saturation: 99% on room air. Physical examination demonstrated sedation and mild tachycardia. There was no history of hypoxia, hypotension, hyperthermia, or severe agitation. Laboratory results (4 hours post-ingestion) shown in Table 1 demonstrated lactic acidosis, extremely elevated acetaminophen level, and absence of liver injury. Comprehensive urine drug screen was positive for acetaminophen and diphenhydramine. The patient was treated with a 21-hour Acetadote® protocol. Lactic acidosis resolved spontaneously *Conclusion:* We report a 16-year-old female with acetaminophen-induced type B lactic acidosis without hepatic injury. Only one teenager and two toddlers have been previously reported.[1,2,3] Type B lactic acidosis is only reported after massive acetaminophen overdoses. It is caused by imbalance of lactic acid production and utilization without hypoperfusion.[1] Both acetaminophen and its toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI) inhibit mitochondrial respiration, resulting in increased lactic acid production.[4] Our patient had a significantly elevated lactic acid level. Increased production of pyroglutamic acid is also reported to cause metabolic acidosis with acetaminophen, but usually in the setting of chronic therapeutic dosing rather than acute overdose. Those cases demonstrated an elevated anion gap, an elevated pyroglutamic acid level, and an elevated or normal lactic acid level. However, gap acidosis did not resolve despite lactate level returning to normal.[5] Although we did not test for pyroglutamic acid, the clinical course was consistent with lactic acidosis rather than pyroglutamic acidosis.

Table 1. Laboratory values

Blood pH	7.33
HCO_3 (mEq/L)	16
Anion Gap (mEq/L)	18
APAP Level (mcg/mL)	488.1
AST (U/L)	27
ALT (U/L)	Not available
Salicylate (mg/dL)	<2
Lactic acid (mmol/L)	7.4

64. Toxicity of Long-Acting Methylphenidate Formulations

Hermanns-Clausen M,[1] Koch IE.[2]
[1]Poisons Information Centre VIZ-Freiburg, Centre for Pediatrics and Adolescent Medicine, Freiburg; [2]Institute for Toxicology/Clinical Toxicology and Poisons Information Center (BBGes Berlin), Berlin, Germany

Objective: While immediate-release methylphenidate ingestions up to 1mg/kg are generally associated with no or minor symptoms[1,2] the acute toxicity of long-acting methylphenidate preparations is less clear. Ingestions of long-acting formulations <4mg/kg were associated with minor or no symptoms in 58 patients.[3] *Methods:* Retrospective analysis of acute ingestions was done in a cooperation of the poison centers GIZ-Berlin (2001–6/2008) and VIZ-Freiburg (2001–10/2008). Inclusion criteria were: known dose, follow-up information available. Ingestions were only included if ingestion was witnessed. Severity of poisoning was rated according to PSS.[4] *Results:* 80 exposures, age 1–33 years (median 12) were included. Ingested dose was 0.42–20 mg/kg BW (median 2.5). Patients were observed in health care facility (56) or at home (24). Reason for exposure: unintentional (55), intentional (abuse 6, suicidal 19). Severity of poisoning: moderate (6), minor (51), asymptomatic (23). Moderate symptoms were reported after ingestion of 2.5–13.5 mg/kg (median 2.6). After administration of activated charcoal 6 of 18 patients developed symptoms, while 51 of 62 patients were symptomatic without administration of activated charcoal. Pretreated patients developed symptoms in 71%. *Conclusion:* Patients with ingestions of less than 2.5 mg/kg can be observed at home. Acute-on-chronic ingestions were not associated with a lower frequency of symptomatic poisoning than acute ingestions. Activated charcoal may be of benefit in case of long-acting methylphenidate formulations, but prospective data are missing. *References:* 1. Klein-Schwartz W. Pediatric Methylphenidate Exposures: 7-Year Experience of Poison Centers in the United States. Clin Pediatr 2003; 42:159–164. 2. Foley R, Mrvos R, Krenzelok EP. A profile of methylphenidate exposures. J Toxicol Clin Toxicol 2000; 38:625–630. 3. Marquardt KA, Alsop JA, Lamb JP, et al. Methylphenidate ingestions: comparison of Drug formulations. J Toxicol Clin Toxicol 2004; 42:728. 4. Persson H, Sjöberg GK, Haines JA, et al. Poisoning Severity Score. Grade of acute poisoning. J Toxicol Clin Toxicol 1998; 36:205–213.

65. The Fetal Effects of Aspirin Overdose During Pregnancy

Stephens S, Jones D, Wilson G, Gilfillan C, McElhatton P, Thomas S.
National Teratology Information Service, Regional Drug Therapeutic Centre, Newcastle upon Tyne, UK

Objective: There are limited published data on fetal outcome following aspirin overdose during human pregnancy. The available published data comes from retrospective case reports and case series which are subject to reporting bias. Metabolic acidosis, which is more severe in the fetus than in the mother, has been reported and in a few cases, an increased incidence of intrauterine death (IUD) has also been recorded following maternal salicylate poisoning. This on-going prospective case series aims to collect data and assess the potential fetotoxic effects of aspirin overdose during pregnancy. *Methods:* Using standardised procedures, NTIS has provided fetal risk assessment and collected outcome data on a prospective case series of 90 women exposed to aspirin in overdose during pregnancy. For this data series, overdose was defined as documented ingestion of more than the maximum daily therapeutic amount (4g). *Results:* Of the 90 confirmed cases of aspirin overdose, 26 were not exposed to other medications. The total amount of aspirin ingested varied substantially (range 4.2 – 32g), as did the co-ingestants, where applicable. The frequency of congenital malformations in live born infants (2/71, 2.8%, 95% CI 0.5–10.7) was not significantly higher than the background rate of 2–3% in the general population and no specific pattern

of malformations was detected. *Conclusion:* The published data, combined with the follow up data provided by NTIS, does not indicate an increased risk of congenital malformations or of any specific type of defect. However, because of the limited data available, small increases in overall risk or in the risks of specific malformations cannot be excluded. In the absence of severe maternal toxicity, there is no evidence of an increased risk of other forms of fetal toxicity such as spontaneous abortion and IUD.

66. A Case of Propafenone Overdose Treated with Sodium Bicarbonate Infusion

D'Orazio JL, Curtis JA.
Department of Emergency Medicine & Division of Medical Toxicology, Drexel University College of Medicine, Philadelphia, US

Objective: Propafenone is a class IC antidysrhythmic with sodium channel blocking properties. There are few literature reports of the use of sodium bicarbonate treatment in propafenone overdose. We report a case of propafenone overdose presenting after a generalized tonic-clonic seizure with a widened QRS complex treated with sodium bicarbonate. *Case report:* A 17-year-old male presented to the emergency department (ED) after a witnessed seizure lasting 2 minutes. The patient admitted to ingesting six "percocet" tablets that were purchased from a classmate. The patient noted feeling weak and dizzy approximately three hours after the ingestion, just prior to seizure. On arrival to the ED, the patient was awake, alert, and in no distress. The initial vitals signs were temperature 36.7 degrees Celsius, heart rate 88, blood pressure 118/78, respiratory rate 16, pulse oximetry 100% and blood glucose 101 mg/dl. Physical exam was normal except for abrasions consistent with seizure activity. The electrocardiogram on arrival revealed a normal sinus rhythm at 91 bpm, with a QRS of 168 ms, terminal R in aVR >4 mm, and a QTc of 543 ms. Laboratory findings were significant for a normal chemistry profile, acetaminophen level less than 10 mg/dL, and a negative urine drug screen including tricyclic antidepressants. After initiation of treatment, the pills were identified as propafenone 225 mg tablets (1350 mg total dose, or three times the starting total daily dose). Intravenous sodium bicarbonate was given in two boluses of 1 meq/kg followed by a continuous infusion at a rate of 0.5 meq/kg/hr. The QRS decreased to 90 ms and remained normal for the next eight hours on continuous sodium bicarbonate infusion. The QRS remained normal upon discharge, eight hours after the cessation of the sodium bicarbonate infusion. *Discussion:* Propafenone has sodium channel blocking properties as well as weak beta-adrenergic and calcium channel blocking capabilities. Toxicity from propafenone may resemble cyclic antidepressant toxicity because of a wide QRS. However, few reports have described the use of sodium bicarbonate in the treatment of propafenone overdoses. *Conclusion:* We report a case of a widened QRS complex and generalized tonic-clonic seizure due to propafenone overdose successfully treated with sodium bicarbonate continuous infusion.

67. Recurrent Respiratory Depression in Fentanyl Transdermal Patch Gel Reservoir Ingestion

D'Orazio JL, Curtis JA.
Department of Emergency Medicine & Division of Medical Toxicology, Drexel University College of Medicine, Philadelphia, US

Objective: Fentanyl transdermal patch (FTP) abuse is widespread in the U.S. We report three recent cases of FTP abuse in Philadelphia, PA (U.S.A.) that required continuous naloxone infusion for recurrent symptoms. *Case series:* 1: A 22 year-old female was found unconscious and cyanotic after ingesting the contents of a FTP. Naloxone 1 mg IV was effective, but the patient experienced recurrence of symptoms (ROS) within two hours of the emergency department (ED) observation period. The patient required repeated doses of naloxone and a continuous infusion for ten hours. 2: A 38 year-old male developed CNS and respiratory depression after ingesting the contents of a 100 mcg FTP despite being a self-reported tolerant opioid abuser. The patient received 1 mg of naloxone IV with adequate response. The patient experienced a ROS within the first two hours of the ED observation period requiring repeat doses of naloxone and a twelve-hour continuous infusion. 3: A 22 year-old female presented with respiratory depression after chewing on and swallowing the gel matrix from two FTPs. The patient's respiratory depression responded to 0.8 mg naloxone IV, but there was a prompt ROS upon arrival to the ED. The patient's respiratory compromise required a continuous infusion of naloxone for four hours without ROS after cessation. *Discussion:* There have been many published case reports on various methods of abuse of FTPs, including excessive transdermal application, use of heating pads to increase cutaneous absorption, application to the oral, rectal, and vaginal mucosa, mastication of patches, ingestion of gel reservoir, intravenous injection of patch contents, inhalation of gel reservoir, and ingestion of FTP "tea". In this case series, our patients ingested the gel and experienced recurrent symptoms necessitating continuous naloxone infusions. Explanations for this finding include inadequate naloxone dosing, the opioid effect of fentanyl exceeding the half-life of naloxone, or a delayed release effect of the gel matrix in the gastrointestinal tract. *Conclusion:* FTP abuse is an increasing problem in the US and physicians should be aware of the potential threat for recurrent respiratory depression after the ingestion of the FTP gel reservoir.

68. Effect of Lamotrigine Overdose on the QT Interval

Hodson K,[1] Hill S,[1] Thomas SHL.[1,2]
[1]Newcastle Hospitals NHS Foundation Trust; [2]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK

Objective: Lamotrigine is frequently used to treat epilepsy in younger people. High concentrations of lamotrigine can block the delayed rectifier potassium channel (Ikr)[1] and this might result in QT interval prolongation. Although no effect on the QT interval has been found in thorough studies in humans using therapeutic doses,[2] QT prolongation has been reported after mixed overdose involving lamotrigine.[3] This study was therefore performed to determine the effects of lamotrigine overdose on the electrocardiograph (ECG). *Methods:* Patients were included if they were admitted with a history of lamotrigine overdose between the years 2000 and 2008. Control patients matched for sex and heart rate were selected at random from our database following ingestion of agents not known to prolong QT interval (e.g. paracetamol). Details were recorded from medical notes and 12 lead ECGs analysed for RR, QRS and QT intervals using a CalComp 9000 digitiser. *Results:* Eighteen patients (83% female, median age 39 years [range 19–60]) presented with lamotrigine overdose during the period of study. The median lamotrigine reported dose ingested was 750 mg (range 200 – 5600 mg) and the median time from overdose to the initial ECG was 123 minutes (range 8–1183 min). The mean heart rate (± standard deviation) was 102±23 b.p.m. in the lamotrigine group and 102±21 b.p.m. in the in the control group. There was no difference in QRS duration between the cases and the controls. QTc was slightly longer in the patients who had ingested lamotrigine than in the control group (463±36ms vs 448±22ms, mean difference 15.3 ms; 95% CI 4.1, 34.7; P = 0.137). *Conclusion:* QT interval may be prolonged in patients who have taken lamotrigine overdoses, although severe prolongation appears unlikely. A larger sample size is needed to further investigate this issue. *References:* 1. Danielsson BR, Lansdell K, Patmore L, et al. Effects of the antiepileptic drugs lamotrigine, topiramate and gabapentin on hERG potassium currents. Epilepsy Res 2005; 63:17–25. 2. Dixon R, Job S, Oliver R, et al. Lamotrigine does not prolong Qtc in a thorough QT/QTc study in healthy subjects. Br J Clin Pharmacol 2008; 66:396–404. 3. Venkatraman N, O'Neil D, Hall AP. Life-threatening overdose with lamotrigine, citalopram and chlorpheniramine. J Postgrad Med 2008; 54:316–317.

69. Acute Clozapine Poisoning

Jovic-Stosic J, Babic G, Srnic D, Kilibarda V, Zlatkovic M.
National Poison Control Centre, Military Medical Academy, Belgrade, Serbia

Background: Clozapine, a dibenzodiazepine derivative, is an atypical neuroleptic drug without extrapyramidal side-effects. For this reason it is increasingly prescribed for schizophrenia treatment and the incidence of poisonings is rising.[1] This study evaluates the characteristics of acute clozapine poisoning and their correlation with drug plasma concentration. *Methods:* A two-year retrospective analysis of 32 patients admitted due to clozapine self-poisoning. *Results:* Manifestation of CNS toxicity were noted in 30 patients and primarily included somnolence, sometimes with episodes of agitation (14 patients), stupor (4 patients) and coma (11 patients), or rarely delirium (1 patient). Two patients with normal mental status were admitted because of tachycardia. The incidence of tachycardia was 93.75%. Heart rate was 94–160 (mean 116±17). ECG revealed sinus tachycardia, occasionally with ventricular extrasystoles (6%) and mild conduction or repolarization changes (22%). Hypotension was noted in 4 patients (12.5%), 2 of them needed dopamine stimulation. Respiratory failure developed also in 2 cases. Seizures occurred in a single patient with fatal outcome. He was admitted more than 24 hours post-ingestion, comatose, with generalized seizures, acute respiratory and cardiocirculatory failure. The remainder of the patients recovered without any sequelae, though with sustained tachycardia in 2 cases. Poisoning was complicated by aspiration pneumonia in 4 comatose patients and by venous thrombosis in a single case. Biochemistry revealed mild rhabdomyolysis in 4 cases, and slight transitory elevation of transaminase activities in 3 cases. Leucocytosis was noted in 5 patients. Clozapine plasma concentrations (HPLC assay) ranged from 0.1mg/L to 2.91mg/L. The patient with the highest concentration presented with somnolence and episodes of agitation. Clozapine concentration in comatose patients ranged from 0.67mg/L to 2.61mg/L (mean 1.26mg/L). Treatment included symptomatic and supportive measures. Flumazenil is reported to be effective,[2] so it was administrated in 2 patients, but the effects were minimal. *Conclusion:* The most frequent manifestations of clozapine overdose were CNS depression and tachycardia. The occurrence of tachycardia was not connected with hypotension, so it may be considered as an anticholinergic effect. The other anticholinergic effects were minimal. Severe poisonings were characterized by respiratory and circulatory failure and seizures. The severity of the poisoning was not related to plasma clozapine concentration, but an active metabolite norclozapine was not quantified. *References:* 1. Griffiths C, Flanagan RJ. Fatal poisoning with antipsychotic drugs, England and Wales 1993–2002. J Psychopharmacol 2005; 19:667–674. 2. Peetoom JJ, Schulte PFJ. Flumazenil possibly efficacious in patients in a coma caused by clozapine in combination with benzodiazepines. Dutch J Psy 2004; 3:185–190.

70. Cardiotoxicity in Acute Valproate Poisoning

Letonja M,[1] Petrovic D,[2] Brvar M,[2,3] Bunc M.[2,4]
[1]Department of Internal Medicine, General Hospital, Ptuj; [2]School of Medicine, University of Ljubljana; [3]Poison Control Centre, University Medical Centre; [4]Department of Cardiology, University Medical Centre, Ljubljana, Slovenia

Objective: Valproic acid (VPA) is used for epilepsy, schizoaffective disorder, schizophrenia, migraine and bipolar affective disorder treatment. Searching Medline, we have found no reports of severe cardiotoxicity in VPA poisoning. We present a patient with cardiotoxicity in acute VPA poisoning. *Case report:* A 19-year-old woman with a non-contributory medical history

ingested 40 g of VPA up to 8 hours before admission. On arrival at the Emergency Department she was somnolent with pulse 120 counts/min, blood pressure 90/55 mmHg and respiratory rate 32 counts/min. Her remaining physical examination was otherwise unremarkable. Serum VPA level was 747 microg/mL on admission. Whole blood count, serum electrolytes, creatinine, liver tests, myoglobin and troponin were normal. Initial treatment included gastric lavage, activated charcoal, infusion of crystalloids and oxygen. On the second day she became stuporous and a CT scan confirmed cerebral edema. Laboratory tests revealed increased levels of ammonia, aminotransferases, lipase, creatine kinase and myoglobin, prolongation of prothrombin time and pancytopenia, reflecting multi-organ failure. The patient additionally developed signs of cardiotoxicity with elevated troponin T level (0.7 mg/l) and ECG revealed numerous paroxysms of atrial fibrillation with rapid ventricular rate around 180/minute, inversion of T wave in leads V3 - V6, II, III and aVF and prolongation of QTc interval up to 0.462 second. A transient hypotension was rapidly reversed with infusion of 0.9%NaCl and afterwards systolic arterial pressure remained above 90mmHg with adequate hourly urine flow. At the end of the second day a 5-hour-long bicarbonate haemodialysis using a haemodialysis machine with a polyamide was performed during which the serum VPA decreased from 470 microg/mL at the beginning to 175 microg/mL at the end of the haemodialysis. During subsequent days signs of VPA toxicity gradual resolved and the patient was discharged totally recovered without any electrocardiographic and echocardiographic changes on the seventh day. *Conclusion:* Acute VPA poisoning can result in myocardial necrosis, tachyarrhythmias and QT interval prolongation due to direct VPA cardiotoxicity and multi-organ failure with hypotension and hypoxia.

71. Serotonin Syndrome Following Sibutramine Poisoning in a Child

Bucaretchi F,[1] Fernandes LCR,[1] De Capitani EM,[1] Lanaro R,[1] Barros RF,[2] Costa JL.[3]
[1]Campinas Poison Control Center, University Hospital, Campinas; [2]Pediatric Intensive Care Unit, University Hospital, Campinas; [3]Instrumental Analysis Laboratory, Criminalistic Institute of São Paulo, São Paulo, Brazil

Objective: To report a case of serotonin syndrome after sibutramine overdose in a child. *Case report:* A 4 year-old-girl was admitted with clinical features compatible with serotonin syndrome (diaphoresis, tachycardia, hypertension, agitation, insomnia, motor incoordination, hypertonia and hallucinations), 25h after accidental ingestion of at least 27 capsules of sibutramine 15mg (~23 mg/kg). ECG (admission) revealed sinus tachycardia and QTc = 401ms. Treatment was only supportive, and no cyproheptadine or urine alkalinization were employed. The table below summarizes the main clinical and laboratory features according to number of days post-ingestion, including the monitoring (LC-MS) of sibutramine and its active metabolites (M1/M2) serum levels.[1] Increase creatine kinase (CK) consistent with rhabdomyolysis was also observed. The patient was discharged at D6 in good clinical conditions and returned at D12 without any sequelae. *Conclusion:* Sibutramine is a serotonin-norepinephrine reuptake-inhibitor that has been used as adjunctive therapy for obesity. Sibutramine had been prescribed to the child's father five months earlier without other treatment modalities. In addition, her mother also employed it as self-medication. The child confirmed the ingestion of sibutramine (not safely stored) to her mother, confounding it with candies, closing a cycle of serious mistakes that ended in a severe poisoning. To our knowledge this is the first reported case of serotonin syndrome associated with confirmed sibutramine overdose in a toddler, including sequential monitoring of the drug and its active metabolites. *References:* 1. Jain DS, Subbaiah G, Sanyal M, et al. Liquid chromatography/electrospray ionization tandem mass spectrometry validated method for the simultaneous quantification of sibutramine and its primary and secondary amine metabolites in human plasma and its application to a bioequivalence study. Rapid Commun Mass Spectrom 2006; 20:3509–3521.

Table. Clinical and laboratory features according to number of days post-ingestion

Clinical and laboratory features	Days from ingestion	D1	D2	D3	D4	D5	D6	D12
Tachycardia		+	+	+	+	+	-	-
Hypertension		+	+	+	-	-	-	-
Hallucinations		+	+	+	-	-	-	-
CK serum levels (U/L; RV<145)		689	950	2,577	1,378	587	394	151
Sibutramine serum levels (ng/mL)(C_{max}= 6.6; t½= 5.9h) (1)		2.9*	1.2	0.49	0.42	0.31	0.23	ND
M1 metabolite serum levels (ng/mL)(C_{max}= 4.8; t½= 14.5h) (1)		2.3*	1.8	1.7	0.98	0,94	0,91	0.43
M2 metabolite serum levels (ng/mL)(C_{max}= 10.8; t½= 13.6) (1)		4.7*	2.4	1.7	1.3	1.1	0.94	0.28

*= 26h post-ingestion

72. Early Presentation Following Massive Ingestion of Sustained-Release Paracetamol with Biphasic, Delayed Paracetamol Absorption and Prolonged Treatment with N-Acetylcysteine

Graudins A,[1] Pham HN,[1] Day P,[2] Naidoo D,[2] Chan BS.[1]
[1]Clinical and Experimental Toxicology Unit, Prince of Wales Hospital; [2]South Eastern Area Laboratory Services, Prince of Wales Hospital, Randwick, Australia

Background: Panadol Extend® (GlaxoSmithKline, Australia) is a slow-release paracetamol formulation, comprising 33% immediate and 66% sustained-release fractions. In overdose, absorption may be delayed and the paracetamol treatment nomogram can miss potentially toxic paracetamol concentrations if only one serum estimate is taken.[1] We report a massive ingestion of Panadol Extend® with prolonged absorption requiring extended treatment with N-acetylcysteine (N-ac). *Case report:* A 72 yo female presented 2 hours following ingesting 119×665 mg (1000 mg/kg) tablets of Panadol Extend® and 5×30 mg mirtazepine. The patient was drowsy (GCS14). Activated charcoal was not administered. Pulse 70 bpm, BP 149/63 mmHg, unremarkable physical examination. Two-hour serum paracetamol was 2628 micromol/L falling to 2216 micromol/L, 4 hours post-ingestion. Admission acid-base status and liver function were normal. N-ac was commenced immediately using the 20-hour (300 mg/kg) intravenous protocol and continued for 5 days (total dose 700 mg/kg) until paracetamol concentrations were undetectable. Serum paracetamol peaked a second time 12 hours (3040 micromol/L) and paracetamol absorption continued for 35 hours. Serum AST/ALT peaked on day 3 at 384 and 541 IU/L with normal coagulation profile. Elimination half-life of paracetamol was calculated at 6.84 hrs. Serum glucuronide, sulphate and cysteine metabolites were assayed, revealing higher a glucuronide metabolite fraction (88.6%) based on AUC comparisons, than described after therapeutic dosing. Sulphate and cysteine metabolites represented 9.1% and 2.3% of measured metabolite fractions. *Conclusion:* Massive ingestion of Panadol Extend® may result in biphasic and prolonged paracetamol absorption requiring extended administration of N-ac. Current dosing regimens for N-ac may not provide enough molar equivalents to effectively metabolise paracetamol to non-toxic adducts. This is suggested by the mild hepatic impairment in our case. Commonly, patients with a paracetamol ingestion of 250 mg/kg receive at least a 1:1 molar ratio of N-ac while our patient had only 0.64:1 N-ac to paracetamol ratio. Higher doses of N-ac could be considered in massive paracetamol ingestions. Higher than expected glucuronide metabolite production may result from induction of this pathway after prolonged hepatic exposure to paracetamol.[2] *References:* 1. Graudins A, Najafi J, Rur-SC MP. Treatment of experimental verapamil poisoning with levosimendan utilizing a rodent model of drug toxicity. Clin Toxicol (Phila) 2008; 46:365. 2. Gelotte CK, Auiler JF, Lynch JM, et al. Disposition of acetaminophen at 4, 6, and 8 g/day for 3 days in healthy young adults. Clin Pharmacol Ther 2007; 81:840–848.

73. Difficulties in Baclofen Poisoning

Kutz S,[1] Deters M,[1] Pfeiffer L,[2] Hentschel H.[1]
[1]Poisons Information Centre, c/o HELIOS Klinikum Erfurt GmbH, Erfurt; [2]Hospital Hufeland Klinikum, Mühlhausen, Germany

Objective: Baclofen is a derivative of gamma aminobutyric acid (GABA) and acts specifically at the spinal end of the upper motor neurons to cause muscle relaxation. It is used in the treatment of intractable spasticity due to spinal cord injury, multiple sclerosis, cerebral palsy, and other spinal diseases. We report an illustrative case of baclofen overdose. *Case report:* A 49-year-old woman was found comatose at home. On site, drug ingestion was not suspected in the patient. Clinical findings were massive hypersalivation, miosis, bradycardia, and pronounced hypotonia. Initially, neither monosynaptic nor brainstem reflexes could be induced. Poisoning with clomethiazole, opioids or organophosphates was considered at the first consultation with the PIC. Later, myoclonia induced by tactile stimuli and questionable seizures were observed. Only taking a detailed collateral history revealed self-medication with baclofen because of myogelosis, where upon the clinical features of an overdose were checked at the second consultation with the PIC. The suspicion of baclofen poisoning was confirmed by the measured serum concentration of 3734 µg/L (toxic > 1000 µg/L), which decreased to 103 µg/L within 48 hours (calculated elimination half-life 9.3 h). Weaning was tried without success at sixth and eighth day after admission. At the ninth day, however, the patient was extubated successfully but showed symptoms of psycho-organic syndrome with psychomotor agitation, changing cooperativeness, and thought disorder. Therefore, after 19 days on ICU further treatment was necessary in a mental hospital. *Conclusion:* Symptoms of baclofen overdose may simulate severe cerebral disorders as well as other poisonings.[1] Diagnosis, however, may be difficult if neither additional information nor the possibility of baclofen determination is available. CNS disturbances could persist much longer than would be suspected from the elimination half-life of baclofen. As sequelae hypoxia or seizure-induced brain syndromes may occur. *References:* 1. Ostermann ME, Young B, Sibbald WJ, et al. Coma mimicking brain death following baclofen overdose. Intensive Care Med 2000; 26:1144–1146.

74. Fatality After Intrathecal Application of Methylene Blue

Kutz S,[1] Deters M,[1] Desel H,[2] Hentschel H.[1]
[1]Poisons Information Centre, c/o HELIOS Klinikum GmbH, Erfurt; [2] GIZ-Nord Poisons Centre, University Medical Centre, Göttingen, Germany

Objective: Methylene blue is used as an antidote in the treatment of poisonings with methaemoglobinemia-inducing substances. It should be administered only intravenously. In the previous century, however, it was used also as diagnostic tool to detect spinal *dura fistulae* or defects, despite neurotoxic effects with severe sequelae (meningeal irritation, paraplegia, radiculopathy, encephalopathy).[1,2] We report an intrathecal methylene blue injection from last year. *Case report:* A

sixty-year-old woman was operated on for a severe stenosis of the spinal canal in a small hospital in December 2007. A surgical revision of stenosed segments was necessary eight weeks later, and again after a further two weeks. At that time methylene blue was injected intrathecally to explore a spinal dura defect. The patient developed paraplegia, progressing to tetraplegia a few hours after the injection. She had to be intubated because of respiratory failure and was transferred for further treatment to a department of neurosurgery. Investigation by nuclear magnetic resonance (NMR) showed an extended intramedullary signal enhancement in the whole spinal cord up to the medulla oblongata. This myelopathy was considered as methylene blue induced aseptic myelitis after intrathecal methylene blue administration. The patient was given highdose methylprednisolone and finally the lumbar liquor was drained. The liquor was blue-coloured and its protein concentration was massively elevated. In due course, all brainstem reflexes were absent and the patient died six days later. *Conclusion:* The presented case impressively demonstrates the neurotoxic effects of methylene blue after intrathecal administration. No specific treatment or antidote is available to reverse this professional error. Therefore, it is strictly contraindicated to use methylene blue intrathecally. *References:* 1. Evans JP, Keegan HR. Danger in the use of intrathecal methylene blue. JAMA 1960; 174:856–859. 2. Schultz P, Schwarz GA. Radiculomyelopathy following intrathecal instillation of methylene blue. A hazard reaffirmed. Arch Neurol 1970; 22:240–244.

75. Acute Drotaverine Poisoning

Sentsov VG, Brusin KM, Venichenko NI, Novikova OV.
Department of Toxicology, The Ural State Medical Academy, Ekaterinburg, Russia

Objective: Drotaverine, a benzylisoquinoline derivative, is an analogue of papaverine with smooth muscle relaxant properties. It causes smooth muscle relaxation by increasing intracellular levels of cyclic adenosine monophosphate (cAMP) secondary to inhibition of phosphodiesterase.[1,2] Drotaverine is a very popular medicine in Russia. This is the reason why the drotaverine poisonings are relatively common (2.3% of all poisonings). *Methods:* We have observed 86 cases of acute drotaverine poisoning. The average dosage of drotaverine was 46.3+/–3.2 mg/kg. All of the cases were suicide attempts. Blood pressure, cardiac output (using impedance rheography) and ECG were performed in all patients after admission to the centre and during the treatment. *Results:* According to the PSS scale there were no symptoms in 17 cases (19.8%), mild in 44 (51%), moderate in 23 (26.7%) and severe in 2 (2.3%). The symptoms were weakness in 68 cases (79.1%), sickness in 55 (64%), dizziness in 43 (50%), slow heart rate in 25 (29.1%), vomiting in 15 (17.4%), headache in 14 (16.3%), hypotension in 3 (3.5%) and somnolence in 2 (2.3%). The heart rhythm and conduction disturbances were determined in 39 of 86 cases. Slow heart rate (less than 60 per minute) was registered in 25 cases (29.1%), sinus arrhythmia in 4 and second degree synoatrial block in 4 cases (4.7%), first degree atrioventricular block in 3 cases (3.5%). An incomplete right branch bundle block occurred in one case, complete right branch bundle block was in another case and an incomplete left branch bundle block in a further case. On average in comparison with the control group (22 healthy persons) the median blood pressure was 7% lower, the cardiac output was 21.5% lower. Management included gastric lavage, infusion, atropine injections (dose 0.02 mg/kg) in cases of slow heart rate (17 cases) and dobutamine infusion at the rate of 5 – 10 microg/kg per minute in cases of a repeated bradycardia or shock (15 cases). After atropine injection there was no bradycardia nor atrioventricular block, median blood pressure did not change, cardiac output decreased on average by 22.5%. However, bradycardia recurred in 2 hours in 15 cases. During dobutamine infusion we did not observe any slow heart rate, median blood pressure increased on average by 16.5%, cardiac output increased by 11.3%. *Conclusion:* Drotaverine poisoning commonly induces heart rhythm and conduction disturbances. These patients need cardiac monitoring. Atropine or dobutamine administration can be useful in some cases. *References:* 1. Kapui Z, Petervari J, Boer K, et al. Phosphodiesterase inhibitors as platelet activating factor antagonist in vitro. Throm Res 1992; 65:150. 2. Bolaji O, Onyeji C, Ogundaini A, et al. Pharmacokinetics and bioavailability of drotaverine in humans. Eur J Drug Metab Parmacokinet 1996; 21:217–221.

76. Acute Clonidine Poisoning in the Elderly

Brusin KM, Kolesnichenko LV, Sentsov VG.
Department of Toxicology, The Ural State Medical Academy, Ekaterinburg, Russia

Objective: According to the data of the Sverdlovsk Regional Centre of Clinical Toxicology 3.3% of acute poisonings are caused by clonidine. Patients aged more then 60 years constitute 32% of all patients with acute clonidine poisoning; the mortality rate with older patients reaches 9.4%. *Methods:* We examined 51 patients aged 60 – 87, average age 71.9 ± 1.3. The dosage of clonidine was on average 4.5 ± 0.6 mg (0.75 - 15 mg). The comparison group involved 62 patients aged 15 - 56, average 27.5 ± 1.8. *Results:* According to the PSS scale there was moderate poisoning in 22 cases (43.1%), severe – 26 (51%) and fatal - 3 (5.9%). 47.1% of patients were unconscious, in 19.6% of cases they needed ventilation, in 60% of cases hypothermia appeared (12.4%, 3.4% and 35% in the comparison group respectively). Three patients died (nobody died in the comparison group). Slow heart rate (less than 60 per minute) was registered in 54.9%, atrial fibrillation - in 21.6%, sinus node arrest in 3 cases, atrio-ventricular block of the first degree in 3 cases, intraventricular block in 5 cases, ventricular extrasystole in 3 cases. Blood pressure was high just after admission in 41.2% of cases. In the comparison group slow heart rate was registered in 95.2% of patients, atrial fibrillation in 1.6%. There were no any other disturbances; hypertension was registered in 25.8%. 41 patients were injected with atropine, two of them developed supraventricular extrasystole and tachycardia after the injection, one more patient developed first degree atrio-ventricular block. Dopamine was infused in 11 patients; one of them developed ventricular extrasystole during infusion. *Conclusion:* Acute clonidine poisonings in elderly patients have distinguishing features, such as deeper coma and respiratory disorders. Bradycardia was registered less often than in middle aged persons. There is a possibility of developing heart rhythm disorders in response to atropine and dopamine administration.

77. Trends in the Management of Pure Benzodiazepine Overdoses. The Role of the Clinical Toxicology Unit in Improving Treatment Procedures

Ferrer-Dufol A, Menao Guillen S, Latorre Garces V, Ramos M, Civeira Murillo E.
Clinical Toxicology Unit, Clinical University Hospital, Zaragoza, Spain

Objective: Benzodiazepines (Bzd) are the main family of medications involved in acute poisoning in Spain. Although they are often associated with other substances, in a significant number of cases they are the only agent. The standard treatment for benzodiazepine overdoses is based on decontamination measures and antidote therapy with the antagonist flumazenil. The huge experience amassed over the last 20 years demonstrates the minimum risk of these overdoses, which in most cases do not require any kind of treatment. The Unit of Clinical Toxicology has been taking steps to convince emergency medical personnel, both mobile and emergency room staff, to apply a sound risk-benefit balance to avoid the use of unnecessary measures that in some cases have proven to be able even to worsen the otherwise excellent prognosis. We are showing the evolution of the trends in the management of pure Bzd overdoses following a revision of the Guidelines for treatment from our Unit of Clinical Toxicology, and the measures adopted for spreading them. *Method:* We have reviewed the 490 cases of pure benzodiazepine overdoses presenting to our ED between 2000 and 2007, looking at the clinical symptoms, treatment and evolution. *Results:* Cases of pure Bzd overdoses account for 20.75% of total acute poisonings by medication; 86% were due to suicide attempts, 7% to abuse and 7% to accidents. 66.5% of cases present some symptoms, mainly slight depression of CNS. Some treatment has been used in 60.5% of cases. Among the asymptomatic cases in 40% decontamination procedures were used and in 23% flumazenil was administered. Among symptomatic ones in 31% decontamination procedures was used and in 44% flumazenil was administered. The use of some decontamination procedure by years is 54%, 42%, 46%, 35%, 39%, 46%, 28% and 15% of total cases respectively and flumazenil was administered in 57%, 44%, 30%, 48%, 35%, 54%, 30% and 38% of total cases. *Conclusion:* A slight reduction in the specific treatment of pure overdoses by benzodiazepines following guideline revision was observed. More efforts are needed to reach optimum standards of treatment.

78. Whole Bowel Irrigation in a Newborn Poisoned with Iron Tablets

Bacis G, Panzeri C, Guidetti V, Carrara M, Lorenzi F, Eleftheriou G.
Bergamo Poison Control Center, Ospedali Riuniti, Bergamo, Italy

Introduction: We submit the first case of whole bowel irrigation (WBI) used in a one-month-old preterm newborn for iron tablets poisoning. *Case report:* A 42-day-old male baby (weight 3420 g), born prematurely at the 35th gestational week, vomited spontaneously an iron tablet (1 cm diameter) during lactation. He was admitted to the hospital 30 minutes later. The parents said that the 5-year-old sister administrated him four tablets of iron (525 mg ferrous sulfate with 105 mg elemental iron). An abdomen X-ray showed the other three tablets in the stomach. The total amount of elemental iron ingested was 315 mg (92 mg/kg). For this reason WBI with PEG solution was started at 60 ml/hour and, in the same time, balanced saline solution with omeprazole was infused. One tablet was vomited with a very short episode of laryngospasm, while the other two passed the gastrointestinal tract within five hours. Iron blood level at admission was 299 mcg/dl (normal value 70 – 160 mcg/dl) and decreased to 279, 194, 123 and 73 mcg/dl at 5, 9, 16 and 25 hours after admission respectively. The newborn didn't show any systemic iron toxic effects and was discharged after 48 hours. *Conclusion:* Iron ingestions of doses between 20 and 60 mg/kg are potentially toxic and doses over 60 mg/kg are toxic. Poisoning effects include nausea, vomiting, gastric hemorrhages, intestinal infarction, hepatic damage with release of ferritin, vasodilatation, hypoprothrombinaemia, hypoglycemia, acidosis, hemorrhagic bronchopneumonia, shock and death. WBI with polyethylene glycol solution is recognized as the best method for gastrointestinal decontamination after iron tablets ingestion.[1] PEG solution is used in pediatric patients, usually older than three months, for bowel preparation for elective colonic procedures and for treating constipation. This case-report show the high efficacy of whole bowel irrigation for treating iron tablets ingestion also in a 42-day-old premature baby. *References:* 1. AACT/EAPCCT. Position paper: whole bowel irrigation. J Toxicol Clin Toxicol 2004; 42:843–854.

79. Cardiotoxicity from Promethazine Ingestion

Patil N,[1,2] Ganetsky M.[2]
[1]*Program of Medical Toxicology & Division of Emergency Medicine, Children's Hospital Boston;* [2]*Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, US*

Objective: With the exception of diphenhydramine, first generation antihistamines are not known to cause cardiotoxicity. Several second generation antihistamines such as terfenadine are known to cause polymorphic ventricular tachycardia (Torsades) secondary to blockade of

potassium rectifier channels.[1–4] We report a case of QRS prolongation and cardiac arrest secondary to promethazine ingestion. No reports exist in the literature of promethazine, a first generation antihistamine, causing depolarization abnormalities and cardiac arrest. *Case report*: A 46 year old female with a past medical history significant for dissociative disorder and *pseudotumor cerebri* was brought into the emergency department cyanotic, unresponsive, and in pulseless electrical arrest. The cardiac monitor displayed a monomorphic wide-complex tachycardia. After resuscitation with epinephrine and sodium bicarbonate, an electrocardiogram indicated sinus tachycardia at 145 bpm, QRS of 122 milliseconds, QTc of 507 milliseconds and a terminal R wave in aVR of 2 mm. After receiving 2 ampoules of sodium bicarbonate and being placed on a sodium bicarbonate infusion, a repeat electrocardiogram illustrated sinus tachycardia at 108 bpm, QRS of 86 milliseconds, QTc of 536 milliseconds, and no apparent R wave in aVR. Her serum potassium was within normal limits. A GC/MS comprehensive toxicology panel indicated promethazine, venlafaxine, trimethoprim, and caffeine. During this patient's hospital course, she was successfully extubated, taken off the sodium bicarbonate infusion, and ultimately discharged to a psychiatry facility. Prior to discharge, this patient told staff she had ingested solely promethazine tablets. *Conclusion:* In overdose, promethazine can produce a depolarization cardiac toxicity similar to tricyclic antidepressants (4). Promethazine share a three-ring structure similar to tricyclic antidepressants, potentially explaining the cause of the depolarization abnormality. *References:* 1. Simons FE. Advances in H1-Antihistamines. N Engl J Med 2004; 351:2203–2217. 2. Llenas J, Cardelus I, Heredia A, et al. Cardiotoxicity of Histamines and Possible Role of Histamine in the Arrythmogenesis Produced by Certain Antihistamines. Drug Saf 1999; 21:33–38. 3. Nine J, Rund C. Fatality from Diphenhydramine Monotintoxication. Am J Forensic Med Pathol 2006; 27:36–41. 4. Shannon M, Borron S, Burns M. Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose. 4th ed. Philadelphia, PA: Saunders Elsevier Inc. 2007: 721–735.

80. Usefulness of 13C-Methacetin Breath Test in Liver Injury Evaluation in the Course of Acute Acetaminophen Poisoning. Comparison with King's College Criteria

Hydzik P,[1] Bielanski W,[2] Plonka M.[3]
[1]Department of Toxicology, Jagiellonian University Medical College; [2]Department of Physiology, Jagiellonian University Medical College, Krakow; [3]Department of Anatomy, Academy of Physical Education, Krakow, Poland

Objective: Stabile isotope breath tests have been developed for the non-invasive assessment of microsomal liver function in patients with chronic liver injury. There are not so many publications in which breath tests are used for acute liver injury assessment. In clinical practice acetaminophen blood concentration and calculation with nomogram of Rumack-Matthew are useful for evaluating the possibility of the serious liver injury. In the case of acute liver failure prognostic King's College Criteria (KCC) are commonly used. The aim of this study is to assess the role of 13C-methacetin breath test (MBT) for diagnosing the degree of liver injury in patients with acute acetaminophen overdose and to compare MBT outcomes with KCC. *Methods:* Nine patients (age 17–41) with hepatotoxic acetaminophen overdose (10–20 grams) underwent a MBT following oral ingestion of 75 mg 13C-methacetin. MBT was performed between 1–7 days after acetaminophen overdose. The results of MBT were compared with data obtained in 21 healthy controls (age 20–45). Measurements of 13C content ($13CO_2$/$12CO_2$) in collected breath samples were done using an isotope ratio mass spectrometer. Final results were calculated and expressed in percentage of administered dose of 13C recovered per hour (%13C dose/h) and finally in cumulative percentage of administered dose of 13C recovered over time (%13C cumulative dose). We examined the correlation between percentage dose recovered and cumulative 60 minutes after ingestion of 13C-methacetin, respectively and age, body mass index. *Results:* All patients were admitted to the hospital during the first 24 hours after acetaminophen overdose and were evaluated using the Rumack-Matthew nomogram as probable risk of hepatotoxicity. All of them received N-acetylcysteine in protective dose. None of the examined patients fulfilled KCC. Combining data derived from %13C dose/h > 18% and %13C cumulative dose >13% at 60 minutes after ingestion 13C-methacetin identified patients with liver injury (also with normal or near-normal transaminase activity) and good outcome. *Conclusion:* MBT is a simple, non-invasive diagnostic tool which can be useful as a predictor of outcome, and a discriminating marker of the liver damage severity.

81. Risperidone Overdose: Much to do About Nothing

Page CB, Calver LA, Isbister GK.
Department of Clinical Toxicology and Pharmacology, Calvary Mater Hospital, Newcastle, Australia

Objective: To describe in detail the clinical and electrocardiographic (ECG) features of risperidone overdose, including the frequency of dystonic reactions. *Methods:* A consecutive series of admissions for risperidone overdose were identified from a prospective database of poisoning admissions to a regional toxicology service. Data extracted included patient demographics, details of ingestion, clinical features including neurological findings and evidence of dystonias, ECG parameters (HR, QRS and QT intervals), complications and medical outcomes including intensive care unit (ICU) admission. In addition to descriptive statistics, visual inspection of plots of QT-HR pairs compared to the QT nomogram. *Results:* There were 128 patients with 192 presentations, including 42 patients with 53 risperidone alone overdoses. Of these 42 patients who ingested risperidone alone the median age was 25yrs (interquartile range [IQR]: 16–31) and 23 were female (55%). The median dose ingested was 26mg (IQR: 11–60mg, range: 3–248mg). Median length of stay was 13 hours (IQR: 4–17 hours), and none were ventilated or admitted to ICU. There were eight dystonic reactions (15%), tachycardia (HR>100) occurred in 27 patients (51%) and there were no episodes of hypotension (BP <90mmHg). Only one patient (2%) recorded a GCS <15, of 14, and there were no seizures or deaths. On review of ECGs in 167 of the 192 cases, pre-existing conduction defects were found in two, pre-existing atrial fibrillation in one. In ten ECGs (6%) there was an abnormal QT-HR pair, but all bar one were associated with HR>100bpm. The median maximum QRS width was 80msec (IQR: 73–80msec, range: 40–120msec). *Conclusion:* Risperidone overdose caused minimal effects. Tachycardia and dystonic reactions were the main features of its toxicity. Significant cardiovascular and other neurological features appear to not occur.

82. Methylphenidate: Harmless Intoxication but Severe Side Effects?

Acquarone-Greiwe D,[1] Koch IE,[1] Hermanns-Clausen M,[2] Binscheck T.[1]
[1]Institute of Toxicology/ Clinical Toxicology and Poison Information Centre, BBGes, Berlin; [2]Poisons Information Center VIZ, University Hospital Freiburg, Germany

Objective: The prevalence of attention deficiency hyperactivity disorder (ADHD) varies a lot between different nations. In Germany 4.8% of children and adolescents are diagnosed with attention deficit hyperactivity disorders. The most used medication for the treatment of ADHD is methylphenidate. Between the years 1997 and 2006 the number of prescribed daily defined doses of methylphenidate in Germany has increased tenfold. To estimate the risk of severe symptoms after exposure to non-retarded methylphenidate a retrospective analysis of 179 intoxications with only methylphenidate in children and adolescents were analyzed for the incidence and severity of symptoms. *Methods:* A total of 179 intoxications with only methylphenidate were analyzed retrospectively: 11.2% of the patients were babies <1 year, 29.6% infants of 1–5 years, 34.1% schoolchildren of 6–12 years, and 25.1% adolescents of 13–19 years of age. The ingested dose ranged from 0.3–16 mg methylphenidate/kg body weight. *Results:* The most frequently occurring mild symptoms were restlessness, somnolence, and gastrointestinal symptoms; with moderate intoxication additional symptoms such as moderate tachycardia, agitation, and hallucinations occur. 42% of the children had no, 48.6% mild, and 8.9% moderate symptoms; no incident with severe symptoms occurred. All together, 91% of the patients had no or just mild symptoms. An ingested dose up to 1 mg/kg never caused symptoms. Moderate symptoms occurred with doses exceeding 3 mg/kg body weight. In contrast, a few children treated with methylphenidate developed severe unwanted effects without apparent overdose, therefore being excluded from the analysis. Two children of seven years suffered seizures, in one case recurring. A 13 year old boy revealed an increase of serum creatine kinase after six months therapy. A 15 year old girl developed persistent EPMS due to co-medication with metoclopramide. An 11 year old boy developed a serious psychosis with phobia. Four children in the age of 6 to 9 years became comatose, in two cases probably due to dose progression; all four recovered within few hours, in two cases with complete amnesia. *Conclusion:* Methylphenidate intoxications commonly cause no serious symptoms. However, sudden dose escalation, concurrent medications, or other yet unclear factors may elicit severe side effects.

83. Dystonic Effects and False Increase in Lactate Levels After Lamotrigine Poisoning

Eleftheriou G,[1] Butera R,[1,2] Zavaritt A,[1] Varesio V,[3] Bonomi MT,[3] Manzo L,[2] Del Curto S.[3]
[1]Bergamo Poison Control Center, Ospedali Riuniti, Bergamo; [2]Poison Control Center, IRCCS Maugeri Foundation and University of Pavia, Pavia; [3]S.C. Anestesia e Rianimazione, Azienda Ospedaliera della Valtellina e Valchiavenna, Sondrio, Italy

Objective: Lamotrigine is a commonly prescribed anticonvulsant medication and adjunctive therapy for depression and bipolar disorder. Lamotrigine-induced dystonic reactions are a very rare adverse effect and few cases have been described. Increased lactate levels after lamotrigine poisoning have never been reported. We report a case of acute dystonia and hyperlactatemia secondary to lamotrigine overdose. *Case report:* A 45-year-old man with a history of bipolar disorder was brought to the emergency department after ingestion of lamotrigine (8400 mg). He was drowsy, with involuntary tongue protrusion, masticatory muscle contractions and abnormal upper limb movements without seizure activity. The patient was intubated and activated charcoal was administered. ECG and routine laboratory tests were within normal limits. Arterial blood gases revealed pH 7.375, pCO_2 39.9 mmHg, pO_2 61 mmHg; lactate levels were increased (6.9 mmol/L, normal range 0.5-1.6 mmol/L). Lamotrigine serum concentrations were 40 µg/ml at admission (usual levels during therapy 3 to 4 µg/ml), 15 µg/ml on the 2nd day and 11.7 µg/ml on the 3rd day after admission. Lactate arterial blood levels decreased as lamotrigine levels decreased: 5.9 mmol/L at the 2nd day and 0.3 mmol/L at the 3rd day after admission. Acidosis was never observed in the patient, in spite of hyperlactatemia. The patient was discharged 4 days after admission with no symptoms and normal laboratory values. *Conclusion:* Dystonic side effects have been reported after lamotrigine overdose.[1] It has been postulated that the drug at high doses blocks the serotonin reuptake or alternatively fails to regulate the presynaptic release of excitatory aminoacids. The finding of hyperlactatemia remains unclear: to our knowledge this is the first report of hyperlactatemia associated with lamotrigine poisoning and no mechanistic data are available to explain this observation. In the medicinal product ingested by the patient, each pill of lamotrigine contains sodium starch glycolate (10% of the active principle): thereby 840 mg of this compound were ingested. Glycolate is very similar in structure to lactate and interferes with the measurement of blood lactate levels,[2] which can result falsely elevated as happened in

the case described here. *References:* 1. Miller MA, Levsky ME. Choreiform dyskinesia following isolated lamotrigine overdose. J Child Neurol 2008; 23: 243. 2. Morgan TJ, Clark C, Clague A. Artifactual elevation of measured plasma L-lactate concentration in the presence of glycolate. Crit Care Med 1999; 27:2177–2179.

84. A Case of Fatal Caffeine Poisoning

Rudolph T, Knudsen K.
Department of Anesthesia and Intensive Care, Sahlgrenska University Hospital, Gothenburg, Sweden

Objective: Despite its widespread use, fatal caffeine poisoning is rare.[1,2] We would like to report a case with repeated ventricular fibrillation, profound hypokalemia, extensive diuresis and severe lactic acidosis. *Case report:* A 21-year-old woman called for the ambulance herself after ingestion of about 100 caffeine tablets, resulting in a total amount of 10,000 mg. At the arrival of the ambulance she was awake but developed ventricular fibrillation soon after and went into cardiac arrest. CPR was immediately commenced with endotracheal intubation and external heart compressions. Ventricular fibrillation (VF) was initially resistant against defibrillations. After a protracted resuscitation period the patient was transferred to hospital. Shortly before arrival she went into VF again and was first stabilized after one more defibrillation and intravenous administration of amiodarone, sodium bicarbonate and epinephrine. The arterial blood gas at arrival was severely deranged with pH values at 6.47 and lactate 33 mmol/L. Despite metabolic acidosis the potassium level was remarkably low at 2.3 mmol/L. The patient was transferred to the ICU where haemodialysis was installed to remove caffeine. Circulation was stabilized using phenylephrine and no further arrhythmias appeared with the continuous infusion of amiodarone and potassium. On the second day the amount of urinary production increased to more than 18 litres. Potassium replacement was given with 370 mmoles during the first day, electrolytes and blood gases then were normalized. Unfortunately, a neurological examination revealed irreversible anoxic brain damage and the patient died of pneumonia 11 days after the primary caffeine poisoning. *Conclusion:* Stabilisation of heart rhythm in this case of severe caffeine poisoning was achieved only after administration of amiodarone and potassium. This patient needed huge amounts of potassium to establish normal potassium values in spite of severe acidosis. Epinephrine and buffer solutions may further decrease blood potassium levels and should be administrated cautiously. *References:* 1. Mrvos RM, Reilly PE, Dean BS, et al. Massive caffeine ingestion resulting in death. Vet Hum Toxicol 1989; 31:571–572. 2. Holmgren P, Nordén-Pettersson L, Ahlner J. Caffeine fatalities - four case reports. Forensic Sci Int 2004; 139:71–73.

85. Favourable Outcome after Long Term Resuscitation of a Patient with Propranolol-Induced Cardiac Arrest

Carlvik B, Höjer J.
Swedish Poisons Information Centre, Karolinska Institute, Stockholm, Sweden

Objective: Several previous case reports of successful long term resuscitation after beta blocker-induced circulatory arrest have been published.[1–4] We further emphasize the importance of this by presenting a case report in which the patient was declared dead for a few minutes, but nevertheless finally had a favourable outcome. *Case report:* A 50-year-old female ingested 5.2 g propranolol together with an unknown amount of benzodiazepine tablets. Within two hours after exposure she was found deeply unconscious. When the ambulance arrived she was breathing spontaneously but her pulses were not palpable. On admission to hospital oxygen saturation was 97% and ECG showed a sinus bradycardia of 40 bpm. Atropine and fluids were given intravenously and the patient was immediately transferred to the ICU. Her condition rapidly deteriorated with respiratory failure necessitating intubation and ventilatory support. Heart rate declined to 20 bpm despite repeated doses of epinephrine and infusions of adrenergic drugs. The poison centre was consulted at this point and recommended glucagon iv and insertion of a transvenous pacemaker. However, before these interventions were performed the patient had a cardiac arrest. Cardiopulmonary resuscitation was started and continued for approximately two hours without return of spontaneous circulation, despite intravenous administration of epinephrine, glucagon, sodium bicarbonate and calcium. It was therefore decided to refrain from further resuscitation efforts and the patient was declared dead. Shortly after extubation, the patient surprisingly started to breathe spontaneously, which is why resuscitation was restarted. The patient was again intubated and connected to the ventilator and cardiac monitor. Adrenergic drugs and glucagon were reinserted and a pacemaker was put in place, although the heart rate was now around 70 bpm and the blood pressure measurable for the first time. Twelve hours later the patient started to wake up and on the second day she was able to speak. At follow up one year later she was back at work and had no signs of sequelae. *Conclusion:* Prolonged CPR is imperative after cardiac arrest due to overdose of betablockers. *References:* 1. Freysz M, Honnart D, Besancon A, et al. Cardiac arrest after beta-blocker poisoning. Crit Care Med 1986; 14:837–838. 2. Kenyon CJ, Aldinger GE, Joshipura P, et al. Successful resuscitation using external cardiac pacing in beta adrenergic antagonist-induced bradyasystolic arrest. Ann Emerg Med 1988; 17:711–713. 3. Tai YT, Lo CW, Chow WH, et al. Successful resuscitation and survival following massive overdose of metoprolol. Br J Clin Pract 1990; 44:746–747. 4. McVey FK, Corke CF. Extracorporeal circulation in the management of massive propranolol overdose. Anaesthesia 1991; 46:744–746.

86. Hypotension and Bradycardia Following Varenicline Overdose

Jones SSD, Thompson JP.
National Poisons Information Service (Cardiff), University Hospital Llandough, Cardiff, UK

Objective: To report a case of symptomatic varenicline overdose in an adult. *Case report:* Varenicline is a new drug for smoking cessation. It is both a partial agonist and antagonist to the nicotine receptor. Trials have shown safety and efficacy at doses of 1 mg BD.[1] Adverse effects have included nausea, vomiting, headache, fatigue and drowsiness.[2] There are few reports of overdoses involving varenicline. A 14 year old female developed lethargy after ingesting 21 milligrams.[3] Hypotension, tachycardia and coma have occurred when varenicline has been ingested in combination with unknown amounts of valproic acid and quetiapine.[4] We report the case of a 48 year old male who ingested 12.5 milligrams of varenicline. Alcohol was co-ingested. The patient presented to hospital four hours after ingestion. On admission he was drowsy, hypotensive and experiencing hyperhidrosis. In accordance with TOXBASE (the primary clinical toxicology database of the National Poisons Information Service), the management plan for the patient included monitoring blood pressure, pulse, respiratory rate and temperature. A twelve lead ECG was recommended. Subsequently the patient become bradycardic and was given atropine and ephedrine. IV fluids were administered. Over a six hour period his condition improved and he made a complete recovery. *Conclusion:* Varenicline is a new drug and very little is known about its effects in overdose. This case suggests that toxicity may be seen at a dose which is relatively small compared to previously reported cases. *References:* 1. Faessel HM, Gibbs MA, Clark DJ, et al. Multiple-dose pharmacokinetics of the selective nicotinic receptor partial agonist, varenicline, in healthy smokers. J Clin Pharmacol 2006; 46:1439–1448. 2. SPC for Champix, Pfizer Limited. From http://emc.medicines.org.uk. Cited 10th November 2008. 3. Feng S, Goto CS, Velez LI, et al. Varenicline (Chantix) overdose in an adolescent female (abstract). Clin Toxicol 2008; 46:362. 4. Goto CS, Feng S, Velez LI, et al. Spectrum of toxicity due to varenicline (Chantix) exposure (abstract). Clin Toxicol 2008; 46:365.

87. Final Year Medical Student's Knowledge of the Paracetamol Content of Over the Counter Analgesics, Cough-Cold Remedies and Prescription Medications

English E,[1] Dargan PI,[2] Wood DM.[2]
[1]School of Medicine, King's College London; [2]Guy's and St Thomas' Poisons Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK

Objective: Paracetamol is widely available both over-the-counter (OTC) and on prescription in the UK. Supratherapeutic/toxic ingestion of paracetamol is common and can result from poor knowledge of the maximum dose of paracetamol or using multiple paracetamol containing products inadvertently. Studies in the US have shown that patients have variable knowledge of which products contain paracetamol.[1] Medical staff maybe asked by patients about the safe combination of paracetamol-containing medications. Previous studies have shown that final-year medical students feel underprepared to prescribe on graduation.[2] As this is likely to be one of the medications that they are most likely to prescribe and/or be asked about following graduation, we surveyed final year medical students' to assess their knowledge concerning paracetamol-content of medications. *Methods:* A single-page questionnaire listing 15 common OTC analgesics, cough-and-cold remedies and prescription medications (10 paracetamol or paracetamol-combination preparations; 5 non-paracetamol preparations) was designed. 200 final-year medical students attending a revision lecture were surveyed; students scored 1 for each product they correctly identified as containing paracetamol or not (maximum score 15). They were also asked the maximum recommended daily paracetamol dose. *Results:* Completed questionnaires were returned by 110 (55%) students. The mean total correct score was 8.4±2.4. Only 9 students correctly identified all the paracetamol containing drugs and 3 correctly identified that there was no paracetamol in the non-paracetamol containing products. 89 (80.9%) of participants knew the correct maximum daily paracetamol dose. 16 (14.5%) students stated supra-therapeutic or potentially toxic daily paracetamol dose. *Conclusion:* The majority of medical students were aware of the maximum daily paracetamol dose, but there is variable knowledge of the preparations that contain paracetamol. Of particular concern is that a significant minority stated potentially toxic daily paracetamol doses, which could be associated with significant morbidity and mortality. *References:* 1. Fosnocht D, Taylor JR, Caravati EM. Emergency department patient knowledge concerning acetaminophen (paracetamol) in over-the-counter and prescription analgesics. Emerg Med J 2008; 25:213–216. 2. Han WH, Maxwell SR. Are medical students adequately trained to prescribe at the point of graduation? Views of first year foundation doctors. Scot Med J 2006; 51:27–32.

88. Analysis of Poisoning Severity Score and Association Between Severity Grade and Length of Stay of Poisoned Patients Admitted in one Emergency Department of Manaus, Amazonas, Brazil from 2005 to 2007

Galvão TF,[1] Silva MT,[2] Silva CD,[1] Barotto AM,[3] Gavioli IL,[4] Bucaretchi F,[5] Atallah AN.[6]
[1]Amazonas Poison Centre, Getúlio Vargas University Hospital, Manaus; [2]Department of Science and Technology, Ministry of Health, Brasília; [3]Santa Catarina Poison Centre, University Hospital/Federal University of Santa Catarina, Florianópolis; [4]Rio Grande do Sul Poison Centre, State Foundation of Production and Research, Porto Alegre; [5]Campinas Poison Control Center, University Hospital, Campinas; [6]Medicine Department, Federal University of São Paulo, São Paulo, Brazil

Objective: To assess the severity grade agreement and the association between severity grade and length of stay (LOS) of poisoned patients admitted to one emergency department (ED) of Manaus, Amazonas. *Methods:* From a retrospective cohort study performed in a Manaus public ED (Hospital e Pronto Socorro 28 de agosto), that included all patients

with poisoning diagnosis admitted to the ED from 2005 to 2007. Inclusion criteria: confirmed xenobiotic, time of exposure less than 12h, and no severe co-morbidities. Collected data included sex, age, admission and discharge date, length of stay, xenobiotic, clinical history, outcome and clinical effects. Medical records were sent using a free online platform to two independent reviewers, physicians experienced in clinical toxicology. Reviewers used the Poisoning Severity Score[1] which has 5 severity grades: none, minor, moderate, severe and fatal poisoning. A consensus analysis to conflicting classification was performed by a third reviewer. Data was tabulated and then analysed with Epidat 3.1 to obtain descriptive statistics, Kappa statistic, chi square test and Analysis of Variance (ANOVA). *Results:* Ninety patients were included, there was no predominance in gender and mean age was 30.46 ± 14.24 years. Kappa statistic was 0.6811 (0.5708–0.7915, CI 95%), pointing to substantial agreement. Patients with discordant grades (n = 34) had significant differences from the others in terms of age, sex, poor outcomes and admission to ICU ($p < 0.05$). Association between severity grade and LOS was statistically significant by ANOVA ($p<0.0001$). Distribution of severity grade and LOS were (n of severity, mean±SD): none (n=2, 4.0 ± 1.41); minor (n = 15, 2.53 ± 0.64); moderate (n=53, 3.87 ± 2.46); severe (n=18, 8.72 ± 5.25) and fatal (n=2, 34. 5 ± 16.26). *Conclusion:* For PSS there was substantial agreement between the two specialists, showing it to be a useful instrument which should be standardized in Brazilian Poison Centres, however, some variables should be better evaluated for more accurate future analysis. In addition, the present data confirm that the association between severity grade and LOS is statistically significant, leading to the conclusion that the more severe the case, the higher the LOS. *References:* 1. Persson HE, Sjöberg GK, Haines JA, et al. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol 1998; 36:205–213.

89. Liquitabs – A Thorough and Comprehensive Review of the UK National Data

Wood KL, Thompson JP.
National Poisons Information Service (Cardiff), Llandough Hospital, Penarth, UK

Objective: To analyse the number of calls and symptoms observed in enquiries regarding liquitabs to the UK National Poisons Information Service (NPIS). *Discussion:* Liquitabs are liquid detergent sachets that are added to your washing machine. There are several types of detergent including cationic, anionic and non-ionic. These liquid detergent sachets are classed as irritant (Xi, R36) according to the EU directive 1999/45/EC. The following table (Table 1) lists the surfactants contained in various types of liquitabs. *Methods:* UK national data was extracted and analysed for the year end of October 2007 to the end of October 2008. *Results:* There were 472 enquiries nationally on liquitab exposures with 10 cases (2.1%) exhibiting central nervous system (CNS) features. The age range of those patients exhibiting CNS features were age ≤2yrs. Of these patients the main features listed were drowsiness, hypo-responsiveness, lethargy and falling Glasgow Coma Scale (GCS). *Conclusion:* The NPIS currently classes these products as low systemic toxicity. In view of the symptoms reported in 10 cases this year, further investigation may be warranted regarding the potential systemic toxicity of these detergents and whether those at the extremes of age are more susceptible to developing CNS effects.

Table 1. Surfactants contained in various types of liquitabs

	Anionic Surfactants 10–30%	Non-ionic Surfactants 1–5%
Bold 2 in 1 Lavender & Camomile Liquitabs	+	
Daz Liquitabs	+	
Ariel Colour Liquitabs	+	+
Ariel Non Biological Liquitabs	+	+

90. Complications from (EWALD) Gastric Tube Placement

Durback-Morris L,[1] Scharman E,[1] Brooks DE.[2]
[1]West Virginia Poison Center, West Virginia University Charleston Division Campus, Charleston; [2]Banner Poison Control Center, Banner Good Samaritan Medical Center, Phoenix, US

Background: Gastro-intestinal decontamination (GID), including gastric lavage (GL), has fallen out of favor in terms of the initial management of potentially toxic ingestions. Our poison center strongly recommended against GL, having recommended its use in only five times (0.8%) in four years. Despite this, 626 cases of GL were performed by health care facilities over this same period. We report two major iatrogenic complications associated with GL, specifically, the use of 36 French gastric (Ewald) tubes. *Case series:* Patient one was a 51 year old man who presented 20 minutes after a witnessed ingestion of unknown amounts of tizanidine and acetaminophen/hydrocodone tablets. Immediately after an Ewald tube was placed (we suspect endotracheally) he de-saturated and had a cardiac arrest. The Ewald tube was removed, he was intubated and successfully resuscitated; the patient was discharged on hospital day three. Patient two was a 44 year old man who presented 45 minutes after ingesting unknown amounts of clonazepam and ethanol. He was intubated for airway protection but suffered an esophageal tear from attempted Ewald placement. This tear was endoscopically repaired and he was extubated and ambulating on hospital day seven. *Conclusion:* GID continues to be employed in the initial management of (potentially) toxic ingestions despite established guidelines that recommend against its routine use. Gastric lavage is associated with adverse effects, including esophageal rupture and respiratory arrest.

91. Aspiration of Polyethylene Glycol Following Inadvertent Bronchial Intubation with a Naso-gastric Tube

Orletsky P, LoVecchio F, Brooks DE.
Banner Poison Control Center, Banner Good Samaritan Medical Center, Phoenix, US

Background: Polyethylene glycol (PEG) is commonly used in all patient populations, often for bowel preparation or dys-impaction. The administration of PEG via a naso-gastric tube (NGT) is considered safe with few reported adverse effects. *Case report:* A 7 year old girl had a NGT placed for the administration of PEG to alleviate chronic constipation. Her initial examination, vital signs and oxygenation were normal, but she was reported to be "combative" during the NGT placement. After the initiation of PEG at 280 mL/hr she developed nausea and emesis. Four hours later, after greater than 1000 ml of PEG administration, she developed cough, tachypnea (RR > 30) and her room air oxygen saturation decreased to 77%. A chest x-ray revealed that the NGT was in her left mainstem bronchus and a left lower lobe aspiration had resulted. The NGT was removed, she received 100% oxygen, albuterol and IV ampicillin/sulbactam, and then transferred to a children's hospital where our poison center was contacted. On hospital day (HD) two she developed a fever (38.7 F) but quickly defervested without leukocytosis, re-current fever or productive cough. She was receiving appropriate supportive care and we recommended against the use of steroids or antibiotics. On HD four she was asymptomatic, oxygen saturation of 97% on 1LPM with minimal left sided rhonchi. She was discharged on HD six with a normal examination and normal oxygenation. *Conclusion:* PEG administration via NGT can result in aspiration with a resulting chemical pneumonitis. Empiric steroids and antibiotics following PEG aspiration are not recommended.

92. Preliminary Data on Exposure to Trichloroethylene During Pregnancy

Wilson G, Jones D, Stephens S, Bradley S, McElhatton P, Thomas SHL.
National Teratology Information Service, Regional Drug and Therapeutics Centre, Newcastle upon Tyne, UK

Objective: Trichloroethylene (TCE) is a halogenated hydrocarbon solvent used as a degreasing agent, a component in paints, lubricants, pesticides, varnishes and as a dry cleaning agent. Historically it has been used as an anaesthetic agent. TCE is also a common drinking water contaminant.[1] While some animal studies have suggested that TCE is a specific cardiac teratogen,[2,3] this has not been proven. This on-going prospective case series aims to collect data and assess the potential fetotoxic effects of TCE during human pregnancy. *Methods:* Using standardised procedures, NTIS has provided fetal risk assessment and collected outcome data on a prospective case series of 18 women exposed to trichloroethylene during pregnancy. *Results:* Of the 18 pregnancies, nine were not exposed to any other chemicals or other therapeutic agents. Fifteen exposures occurred in the 1st trimester, four of which continued into the 2nd trimester. Three malformations were reported: a cleft palate (family history), possible VACTERL association with IUGR and hydronephrosis. The frequency of congenital malformations in the live born infants (3/17, 17.6% 95% CI 4.7–44.2) was significantly higher than the expected background rate of 2–3% in the general population. However, this is based on a small number of cases, with considerable co-exposures in some cases. No specific pattern of malformations was seen and no cardiac malformations were detected. *Conclusion:* The published data, alongside the follow up data provided by NTIS, do not prove a causative association between TCE exposure and increased incidence of CHD or other specific malformations. However, it is also not possible to exclude this. The data are confounded by a number of variables, making interpretation difficult. More data are required for this ongoing series. *References:* 1. World Health Organization. Trichloroethylene. http://www.euro.who.int/document/aiq/5_15trichloroethylene.pdf. 2. Johnson PD, Dawson BV, Goldberg SJ. Cardiac teratogenicity of trichloroethylene metabolites. J Am Coll Cardiol 1998; 32:540–545. 3. Fisher JW, Channel SR, Eggers JS, et al. Trichloroethylene, trichloroacetic acid and dichloroacetic acid: do they affect fetal rat heart development? Int J Toxicol 2001; 20:257–267.

93. Aspiration of Baby Powder. Observations of Poison Centers in Austria, Germany and Switzerland

Stedtler U,[1] Genser D,[2] Hueller G,[3] Merx C,[4] Sauer O,[5] Seidel C,[6] Stürer A.[7]
[1]Poison Center, Freiburg, Germany; [2]Poison Center, Wien, Austria; [3]Poison Center, Erfurt, Germany; [4]Poison Center, Berlin, Germany; [5]Poison Center, Mainz, Germany; [6]Poison Center, Bonn, Germany; [7]Poison Center, Zurich, Switzerland

Objective: Powder aspiration may result in severe pulmonary injury especially in young children. Thus interventional treatment with bronchoscopy or bronchoalveolar lavage have been recommended. We aimed to examine if powder aspiration constitutes a medical problem in Austria, Germany and Switzerland and how often interventional treatment is applied. *Methods:* The databases of 7 poison centers were searched for cases of aspiration of baby powder with initial respiratory symptoms and follow up information. *Results:* A total of 113 cases were reported which met the inclusion criteria. Mostly children in the age of 0.5 to 2 years of age were affected. Initial symptoms were considered minor in 92 cases and moderate in 21 cases. Bronchoscopy was performed in 55 cases (47% of the minor 71% of the moderate severe cases), in some cases with lavage, in other with selective suction. In 5 cases the clinical course worsened compared to the initially reported severity, 4 of these 5 patients underwent bronchoscopy. 2 patients deteriorated to severe symptoms. In both cases bronchoscopy was performed. *Conclusion:* This case series indicates

that most patients reported to the poison centers because of powder aspiration showed a minor or moderate-severe course. Bronchoscopy was a procedure frequently performed in patients with powder aspiration. Severe course was observed in only 2 patients and could not be prevented by bronchoscopy. Hence recommendation of interventional treatment should be considered carefully and individually in each case of powder aspiration.

94. Preparedness for Chemical Emergencies: Organizational and Training Needs in Italian Emergency Departments

Petrolini V,[1] Locatelli C,[1] Bigi S,[1] Lonati D,[1] Giampreti A,[1] Vecchio S,[1] Manzo L,[1] Volpini A.[2]
[1]Poison Control Centre and National Toxicology Information Centre, IRCCS Maugeri Foundation and University of Pavia, Pavia; [2]Italian Civil Protection Department, Rome, Italy

Objective: Medical response to major chemical emergencies (MCE), conventional and otherwise, needs specifically organized emergency departments (EDs), with adequate equipment and appropriately trained medical staff. Italian EDs do not have a single standard operating plan, and preparedness for MCE has not yet been investigated. In 2008 we conducted a survey for better identification of organizational and training needs in Italian EDs. We report some of the data collected. *Methods:* All Italian EDs, including general Intensive Care Units (ICU) and Emergency-Medical-Service-Centres (CO118), received a questionnaire. Availability of decontamination areas and of procedures for MCE, training (during the last 4 years) on toxicology and NBCR emergencies, chief's opinion on the adequacy of each ED to face a MCE were investigated. *Results:* 1180 questionnaires were sent: 120 answers from EDs (16% of the existing EDs), 40 from CO118 (38.4% of total) and 36 from ICU were received. Among the emergency disciplines, the lower number of days of training in 2004–2008 were dedicated to NBCR emergencies and clinical toxicology: 51.6% of EDs, 72.2% of ICU, 20% of CO118 had no training on NBCR emergencies. Twenty-nine EDs have a written procedure for MCE, but only in a few cases (14, 48.2%) were medical staff aware, and 3 services (10%) also do regular simulations. 67% of EDs have a written procedure for a massive patient flow; in 82% medical staff are informed about this, and 18 services do training. 40% of CO118 have a written procedure for MCE which is known by 75% of medical staff, and 31.2% of the CO118 do regular simulations. 75% of chiefs of services consider their ED is not appropriately equipped to manage an MCE, and 68% think their medical staff would not be adequately prepared for this kind of emergency; 83% consider that a specific training program would be appropriate. *Conclusions:* The data collected show an important lack in organization and training in all EDs concerning intervention in MCE. Acknowledgements: Study carried out with the support of Italian Civil Protection Department.

95. Diphoterine®: Review of the Dermal Toxicological Data

Hall AH,[1] Cavallini M,[2] Mathieu L,[3] Burgher F,[3] Fosse C,[3] Maibach H.[4]
[1]School of Public Health, University of Colorado, Denver, US; [2]Department of Plastic Surgery, Galeazzi Hospital, Milan, Italy; [3]Prevor, Valmondois, France; [4]Department of Dermatology, University of California San Francisco School of Medicine, San Francisco, US

Objective: To increase the knowledge about toxicological effects of Diphoterine® for immediate skin chemical splash decontamination and to determine whether or not it could be safely used for delayed management. *Methods:* All available reports are reviewed and recently, new studies have been performed to determine the safety of Diphoterine® on both normal and damaged skin, blood, as well as non-occlusive, semi-occlusive or occlusive application. *Results:* Acute dermal LD50, showed no deaths, no toxic effects (LD50 > 2000 mg/Kg). *In vitro* irritation test: non-irritant. An MTT test on cytotoxicity of Diphoterine® in murine fibroblasts, compared to sodium lauryl sulphate as positive control, did not show any cytotoxic effects up to 24 hours (IC50 > 5mg/l versus 0.08mg/l for SLS). Local tolerance (single, semi-occluded or non-occluded application to scarified / non-scarified skin in the rabbit):[1] non-irritant and no toxic effects. A skin sensitization study in the guinea pig (Magnusson-Kligman method) showed no sensitizing effects.[2] Diphoterine® can also be considered as non-irritant after an application of 4 consecutive hours on 55 human volunteers and hypoallergenic (Marzulli-Maibach method on 150 human volunteers with normal skin). High tolerability is showed, even after 6 hours (MTT test – 87.6% cell viability –) and its percutaneous diffusion is very weak (Diphoterine® through the epidermis <0.0035%). Diphoterine® is also haemocompatible when compared with saline solution (from 80% to 26.7% in water - Optical Density between 0.018 and 0.003). It is also non-mutagenic (Ames test) and not irritating to the eye (on rabbits). *Conclusion:* Diphoterine® showed no irritating, skin sensitizing, or toxic effects to normal or damaged skin. These results are in accordance with the lack of adverse effects observed in workers after immediate use of Diphoterine®. Further clinical comparative studies will be conducted in order to clearly show any interest of its delayed use on the skin. *References:* 1. Mathieu et al. Diphoterine®: local tolerance after single application on the skin in the rabbit (abstract). Presented at the EUROTOX 2007 Congress, Amsterdam, The Netherlands. 2. Mathieu L, Burger F, Hall AH. Diphoterine® chemical splash decontamination solution: Skin sensitization study in the guinea pig. Cutaneous Ocular Toxicol 2007; 26:181–187.

96. Lipid Emulsion Therapy in Massive Imipramine Overdose

Al-Duaij N,[1] George M,[2] O'Donnell K,[1] Burns Ewald M.[1]
[1]Emergency Medicine, Children's Hospital Boston, Boston; [2]Crystalrun Healthcare LLP, Middletown, US

Objective: To report the first case of a massive imipramine overdose successfully resuscitated with 20% lipid emulsion therapy. *Case report:* A 52-year-old female ingested 120 tablets of the tricyclic antidepressant (TCA) imipramine (6000 mg) in a suicide attempt and developed pronounced cardiotoxicity. She was found unresponsive with agonal respirations and, following endotracheal intubation, was taken to a nearby emergency department (ED) where her initial QRS interval was 140 milliseconds. In the ED, while receiving standard sodium bicarbonate therapy, her pH rapidly rose to 7.55, she became hypotensive, and developed ventricular tachycardia. In addition to standard ACLS protocol and vasopressor therapy, a 200 mL infusion of 3% hypertonic saline transiently stabilized her condition. However, in the intensive care unit (ICU), she developed seizures, recurrent ventricular tachycardia requiring defibrillation, and ultimately progressed to intermittent complete heart block. Her serum sodium had reached 166 mmol/L. Recommendations were made to initiate 20% lipid emulsion therapy for her persistent hemodynamic instability. She received a total of two bolus doses of 100 mL Intralipid® followed by an infusion of 0.25 mL/kg/minute over 30 minutes. This stabilized her heart rate and the vasopressors were weaned. Although she suffered additional bouts of ventricular dysrhythmias, her episodes became less frequent and, over the subsequent 4–6 hours, eventually resolved. Following a 17-day hospital stay, the patient was discharged to psychiatry having sustained no neurological sequelae. *Conclusion:* The use of lipid emulsion therapy in the resuscitation of critically ill patients suffering the effects of fat-soluble cardiotoxic agents stems from its presumed adsorptive properties which appear to transiently relieve the burden of toxin through intravascular sequestration. Recent animal studies and human case reports suggest that the spectrum of therapeutic indications could be expanded beyond local anesthetics to include calcium channel blockers and, possibly, tricyclic antidepressants.[1,2] Our case illustrates its utility in the setting of a substantial TCA overdose unresponsive to conventional therapy. *References:* 1. Harvey M, Cave G. Intralipid outperforms sodium bicarbonate in a rabbit model of clomipramine toxicity. Ann Emerg Med 2007; 49:178–185. 2. Turner-Lawrence DE, Kerns II W. Intravenous fat emulsion: a potential novel antidote. J Med Toxicol 2008; 4:109–114.

97. A Potential Way to Increase the Efficiency of Pralidoxime

Kayouka M, Houzé P, Baud FJ.
Toxicological Laboratory, Paris Descartes University, Paris, France

Objective: Pralidoxime (PRX) is used as an antidote to treat organophosphate poisoning. PRX elimination is characterized by fast renal excretion considered the main determinant of PRX pharmacokinetics. We studied the role of organic cation transporters (OCT) in the renal secretion of PRX using specific OCT substrates (TEA) and Knock-out mice (OCT1/2-/- ; OCT3-/-). We then studied the effect of TEA pretreatment on pralidoxime antidotal activity using paraoxon-poisoned rats. *Methods:* To determine pralidoxime renal clearance, Sprague-Dawley rats received a loading dose of PRX (31 mg/Kg) followed by a continuous infusion to achieve a plasma PRX concentration of 10 mg/l during 180 min. Then, blood and urine were collected. In rats, the pharmacokinetics of PRX (50 mg/Kg, 30 min perfusion) was determined 15 min after TEA treatment (75 mg/kg, IM). Knock-out and wild type mice received a PRX injection (50 mg/Kg, IM), blood samples were taken at 45 and 90 min post-injection. Ventilation at rest was chosen to evaluate the antidotal activity of pralidoxime using whole-body plethysmography over 4 h paraoxon-poisoned rats (50% of the LD50). TEA (75 mg/kg) and pralidoxime were injected 15 min and 30 min, respectively after the paraoxon injection. *Results:* The renal clearance of pralidoxime (30.1±1.8 ml/min/kg) was significantly higher ($p < 0.001$) than creatinine clearance (9.6±0.9 ml/min/kg) evidencing its renal secretion. Pretreatment by TEA significantly increases the plasma pralidoxime concentrations by reducing its clearance (Cl PRX under TEA 14.3 ± 2.1 ml/min/kg versus Cl PRX 30.1±1.8 ml/min/kg, $p<0.01$). The deficiency in organic cation transporters 1 and 2 in mice (OCT1/2-/-) resulted in a significant increase ($p < 0.001$) in plasma pralidoxime concentrations at 45 min (6.40 ± 0.46 versus 2.37± 0.13 mg/l) and 90 min (2.83±0.17 versus 1.47 ± 0.07 mg/l). Lack in OCT3 did not change the plasma PRX concentrations. The antidotal activity of one dose of pralidoxime (50 mg/kg) has significant effects (longer and greater) when administered to rats where the plasma concentrations of pralidoxime are higher due to a pretreatment with tetraethylammonium. *Conclusion:* Our data show that PRX is secreted in urine by an active process involving organic cation transporters 1 and 2 (but not 3). The efficiency of the pralidoxime depends on the circulating concentration that can be increased by a concomitant use of pralidoxime with an OCT inhibitor/substrate.

98. Acute Renal Failure Enhances the Antidotal Activity of Pralidoxime Towards Paraoxon-Induced Respiratory Toxicity

Kayouka M, Houzé P, Baud FJ.
Toxicological Laboratory, Paris Descartes University, Paris, France

Objective: Pralidoxime is an antidote to organophosphate intoxications. An experimental study showed the efficiency of pralidoxime depended on its plasma concentrations that should be above 4 mg/l; while the clinical efficiency of high but not of low doses of pralidoxime in human organophosphate poisonings supports this assumption. Pralidoxime is rapidly eliminated unchanged primarily by the renal route rapidly resulting in low plasma concentrations. We recently showed in a rat model of dichromate-induced acute renal failure (ARF) that the elimination but not the distribution of pralidoxime was altered resulting in sustained plasma

pralidoxime concentrations. We hypothesized increased plasma pralidoxime concentrations should be associated with increased antidotal efficiency. *Methods:* In paraoxon-poisoned rats, ventilation at rest was assessed using whole-body plethysmography over 4 hours after intoxicating the rat (Sprague-Dawley) with paraoxon (50% of the LD_{50}). Whole body plethysmography allowed the measurement of the following parameters: the tidal volume (V_T), the inspiratory time (T_I), the expiratory time (T_E), the total respiratory time ($T_{TOT}=T_I+T_E$), the respiratory frequency (f), and the minute ventilation ($V_E=V_T \times f$). There were 8 animals in each group. Data were compared using two-way ANOVA for repeated measurements. Results of statistical analyses are expressed as the level of significance of the time x treatment interaction. *Results:* A single dose (50 mg/kg, IM) of pralidoxime had transient effect towards paraoxon respiratory toxicity regarding TTOT ($p < 0.05$), TE ($p < 0.05$), and VT ($p < 0.05$). In the ARF model, the same dose of pralidoxime decreased significantly the TTOT ($p < 0.01$), TE ($p < 0.01$), TI ($p < 0.05$), and VT ($p < 0.01$) and increased the f ($p < 0.01$) towards control values during 120 minutes in comparison with paraoxon-induced respiratory toxicity. *Conclusion:* These results show that the efficiency of pralidoxime is enhanced in paraoxon-poisoned rats when plasma pralidoxime concentrations are sustained.

99. A Metaanalysis of the Effect of Activated Charcoal on the Elimination of Intravenously Administered Drugs

Jürgens G,[1] Graudal NA.[2]
[1]*Danish Poison Information Centre, Bispebjerg Hospital, Copenhagen;* [2]*Department of Rheumatology, National University Hospital, Copenhagen, Denmark*

Objective: To estimate the effect of activated charcoal (AC) on the elimination of intravenously administered drugs and evaluate the influence of pharmacokinetic drug properties and the given amount of AC on the percentage reduction of drug exposure. *Methods:* 16 randomised controlled trials (21 comparisons, 148 participants) were included in the metaanalysis. Standardized mean difference (SMD) of AUC of AC treated subjects compared to non-treated subjects was calculated using a random effect model. Furthermore, the percentage reduction of AUC was calculated. Meta-regression analyses were performed to estimate the influence of Vd and cumulated AC dose by means of a multiple linear regression. *Results:* SMD between AC treated and non-treated subjects was –2,02 ($p < 0.00001$). The median percentage reduction of AUC was 40% (25–75% percentile: 27–53). The correlation coefficient for this multiple linear regression was 0.56 ($p < 0.05$). The contribution cumulated AC dose was statistically significant ($p < 0.05$) while the contribution of Vd only was borderline significant ($p = 0.09$). *Conclusion:* Increased elimination contributes significantly to the effect of AC. The effect is correlated to the cumulative AC dose and possibly Vd of the individual drugs.

100. Free and Total Digoxin in Serum During Treatment with Fab-Fragments in Acute Digoxin Poisoning

Eyer F,[1] Steimer W,[2] Müller C,[2] Zilker T.[1]
[1]*Toxicological Department, Klinikum rechts der Isar, München, Germany;* [2]*Institute for Clinical Chemistry and Pathobiochemistry, Klinikum rechts der Isar, München, Germany*

Objective: Treatment of severe intentional digoxin overdose with Fab antibody fragments (Fab) has been shown to be both effective and safe. However, this therapy is extremely expensive and the dosing of Fab is mostly based on the calculation of equimolar doses of anti-digoxin fragments. It has been debated that this dose may be unnecessary high. *Case report:* A woman ingested a large dose of 10 mg methyldigoxin in a suicide attempt. On admission she showed signs of relevant glycoside intoxication. The digoxin concentration peaked at 7.4 ng/mL and antidotal therapy using DigiFab™ was initiated. A bolus dose of 80 mg DigiFab™ was given within 15 minutes intravenously followed by a continuous infusion of 30 mg/hour. This resulted in a cumulative dose of DigiFab™ of 395 mg given within 10.75 hours. Total digoxin in serum increased intensely after initiation of Fab-therapy, peaked at 125 ng/mL at t = 23h and decreased with a calculated terminal half-life of 34 hours. Free digoxin in serum immediately dropped to the nontoxic range, reappeared not before t = 34 hours and peaked at t = 55 hours, staying fairly within the therapeutic range (0.8–2.0 ng/mL). This recurrence was not accompanied by any clinical nor electrocardiographic disturbance. The cumulative amount of free and bound digoxin in urine was 900 µg and 1600 µg, respectively. Half-life of bound digoxin in urine was calculated to be 9.9 hours with a mean clearance of bound digoxin in urine being 7.3 ml/min. *Conclusion:* On the basis of these kinetic data of pharmacologically active unbound free and total digoxin during therapy, a smaller initial bolus dose of Fab followed by a continuous infusion may be a more tailored, affordable and relatively safe therapy in overdoses with cardiac glycosides. However, the exact dosing scheme remains to be determined.

101. Venomous Exotic Snakes: Global Overview

Warrell DA.
Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK

Venomous snake bites are predominantly an occupational and environmental hazard of indigenous people living in rural areas of tropical developing countries. Tens of thousands of deaths result each year with at least as many cases of disabling sequelae. Western travellers can on rare occasions become victims and even fatalities and since there are increasing numbers of dangerous snakes being kept, often illegally, as pets in developed countries, poisons centres may be asked to advise on the treatment of bites by exotic species. Global hot spots for snake bite include the savannas, plantations and rain forests of West African, South Asia, the Amazon basin and New Guinea. Medically important venomous snakes belong to the *Elapidae* (cobras, kraits, mambas, coral snakes, Australasian terrestrial snakes, sea snakes), *Viperidae* (vipers, adders, rattlesnakes, moccasins and pit vipers), *Atractaspididae* (burrowing asps or stiletto snakes) and *Colubridae*. Snake venoms are complex, containing more than 100 enzymes and peptides. Cytolytic (digestive) hydrolases cause tissue necrosis. Anti-haemostatic components include procoagulant enzymes, metalloproteinase "haemorrhagins" that damage vascular endothelium, platelet activators/inhibitors and anticoagulants. Peripheral neuromuscular blockade results from presynaptic phospholipases A2, some with myolytic activity, and post-synaptic polypeptide toxins. Oligopeptide vasoactive agents include endothelin-like sarafotoxins and ACE-inhibitors/bradykinin potentiating peptides. Clinical effects include local swelling, bleeding, bruising, lymphangitis, blistering, necrosis, painfully enlarged regional lymph nodes and systemic bleeding, shock, acute renal failure, descending paralysis and generalised rhabdomyolysis. Among *Elapidae:* kraits, coral snakes, Australian death adders, some cobras and sea snakes are almost purely neurotoxic whereas African spitting cobras and Asian cobras cause local tissue destruction. Australasian terrestrial snakes cause neuromyotoxicity, haemostatic abnormalities and renal failure. *Viperidae* usually cause severe local effects with haemostatic disturbances and shock. A small minority of species cause acute renal failure and neurotoxicity. Fortunately, in 10–70% of bites by venomous snakes, the amount of venom injected is insufficient to cause any clinical evidence of envenoming ("dry bites"). African and Asian spitting cobras can eject venom defensively from the tips of their fangs into the eyes of aggressors, causing painful chemical conjunctivitis that may be complicated by corneal ulceration, infection and blindness. First aid treatment involves reassurance, immobilization of the whole patient and especially the bitten limb with a splint or sling to minimise spread of venom and rapid transport to hospital. "Pressure immobilisation" may restrict venom to the occluded limb but is technically difficult. Where practicable, it is recommended for all bites in which a dangerous elapid cannot be excluded. Snake bite can become an extreme medical emergency. Hospital treatment: resuscitation is followed by rapid clinical assessment and species diagnosis. It is important to decide whether antivenom is indicated. Antivenoms (hyperimmune equine or ovine IgG, F(ab´)2 or Fab fragments), the only specific antidote, may be monospecific (neutralising the venom of one species only) or polyspecific (neutralising venoms of the most important species found in a particular geographical area). Indications for antivenom treatment include haemostatic abnormalities or spontaneous systemic bleeding, shock, neurotoxicity, myotoxicity, nephrotoxicity and severe local envenoming. Administration is by slow intravenous injection or infusion. Early anaphylactic reactions are common and so 0.1% adrenaline (im) is drawn up beforehand. Prophylaxis with adrenaline, hydrocortisone or H1 histamine blockers alone or in combination have not proved effective. Antivenom reactions are very rarely IgE-mediated, type I hypersensitivity reactions. They are caused by direct complement activation and so are not predictable by hypersensitivity testing. Late serum sickness reactions should be treated with antihistamines or corticosteroids. More antivenom may be may be needed if coagulopathy persists for six hours or if other signs of envenoming deteriorate, appear or reappear. Recurrent envenoming, results from continued absorption or redistribution of venom, especially with rapidly eliminated Fab antivenoms (e.g. "CroFab" used for North American rattlesnake bites). Supportive treatment is essential for respiratory, circulatory or renal failure. Surgical intervention is absolutely contraindicated until normal haemostasis has been restored with antivenom ± clotting factors. Early surgical drainage of abscesses and debridement of necrotic tissue is appropriate but fasciotomy has been used excessively. It is indicated only if there is objective evidence that intracompartmental pressure is raised (>40 mmHg). Prevention is by education about avoiding high risk activities; using protective clothing, especially footwear; use of lights when walking after dark and by avoiding sleeping on the ground (danger of bites by spitting cobras in Africa or kraits in Asia) unless under a mosquito net, on a camp bed, hammock or in a tent with sewn in ground sheet. *References:* 1. Anokbongo W, et al. Guidelines for the prevention & clinical management of Snake bites in the WHO African Region. Brazzaville, WHO 2009. 2. Gutiérrez JM, Theakston RD, Warrell DA. Confronting the neglected problem of snake bite envenoming: the need for a global partnership. PloS Med 2006; 3:e150. 3. Meier J, White J, eds. Clinical toxicology of animal venoms. Boca Raton, USA: CRC Press, 1995. 4. Sutherland SK, Tibballs J. Australian animal toxins. The creatures, their toxins and care of the poisoned patient. 2nd ed. Melbourne, Australia: Oxford University Press, 2001. 5. Warrell DA. 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102. Exotic Snakes – Supply of Antivenoms in Europe and the Swedish Experience

Karlson-Stiber C, Salmonson H, Persson H.
Swedish Poisons Information Centre, Stockholm, Sweden

Objective: Over the last years enhanced attention has been paid to the problem of exotic snakes, kept as pets in European countries.[1–6] In severe envenomation administration of a specific antivenom may prove crucial for the outcome, and this is why availability of appropriate antivenoms is urgent. A survey has been undertaken of the current European supply of antivenoms against non-indigenous snakes. *Methods:* A questionnaire, designed to map out the actual situation concerning storage and distribution of "exotic" antivenoms, was sent to all European Poisons Centres. To illustrate the current problems related to treatment of exotic snake bites, data concerning such bites in Sweden during the period 2000–2007 were also compiled by the Swedish Poisons Centre. *Results:* The European questionnaire was completed by 23 centres located in 16 countries altogether. The number of consultations concerning bites by non-European snakes varied greatly between the centres; six centres had none at all, ten centres had one to five inquiries annually, four got nine to fifteen and another four centres received 29 - 43 questions every year. The latter four centres are located to Germany, Sweden and UK. Formal, legal directives addressing a responsibility to supply hospitals with appropriate antivenoms are lacking in 11 out of 16 countries. Moreover, in three of the five countries where directives do exist, the compliance with these is low. This shortcoming is presumably due, either to contradictory instructions or to the fact that the snake-keepers themselves have been declared responsible for purchase and storage of the actual antivenoms and this does not seem to work at all. Stocks of several different antivenoms in amounts sufficient enough to treat severely envenomed patients are held in five of the responding countries (France, Germany, the Netherlands, Sweden, Switzerland). Seven centres in four countries (Austria, Brussels, Italy and Germany) regularly use the Munich Antivenom Index (MAVIN). National zoos, museums and vivariums were mentioned as possible providers of antivenom by a few centres. Nine countries have a 24 hours service for emergency dispatch of antivenoms. However, in five of these countries antivenoms for treatment of bites by exotic snakes are always or occasionally lacking. Obviously, there are difficulties in matching ambitions and practice. Common concerns pointed out by several centres were: the actual snake species may be unknown; practical difficulties to get hold of the antivenom and arrange an immediate delivery; insufficient efficacy and safety data of the products; short term expiry and high costs given the infrequent use of the products; shortage of antivenoms available to purchase; the products are not approved by national authorities which is why special procedures are required before use; reluctant governments (one government has even come to a formal decision to stock antivenom only for indigenous snakes). Swedish experience: During the period 2000–2007 the Swedish Poisons Information Centre was yearly consulted concerning 15–20 bites (generating *ca* 40 inquiries yearly) by non-European venomous snakes and 50–70 non-venomous exotic snakes. During the same period 44 hospital case records on patients bitten by venomous non-indigenous snakes were studied in detail by the centre. All but one of these patients were men and the bite had struck the hand in 38 cases. At least fourteen were drunk. Grading according to the Poisoning Severity Score[7] was done and the severity of envenoming was distributed as follows: none 23 % (10 cases), minor 27 % (12 cases), moderate 32 % (14 cases), severe 18% (8 cases). Antivenom was used in 21 out of 44 cases. Fasciotomy was performed in three patients. The bitten person was able to specify the species of the snake in all cases and, hence, there were no problems to decide upon which antivenom to be given. Bites by venomous snakes from all continents did occur. The current system for 24-hours dispatching of antivenoms worked well in all but one case. At the time for that bite we were not aware of the presence of the actual snake (*Hoplocephalus bungaroides*) in our country but proper treatment could be given thanks to the MAVIN system in Munich. *Conclusion:* The enchantment of keeping dangerous reptiles as pets is increasing and, accordingly, this is true also for the number of bites. Experience from many countries indicate that the typical victim is a male amateur, aged around 30, bitten in the hand and inebriated by ethanol. Access to the ultimate treatment in severe envenomation - immunotherapy – is utterly variable throughout Europe. Collaboration within countries as well as over national borders seems necessary to improve the availability of a wide range of antivenoms. In such a strategy also the global shortage of antivenoms must be taken into account.

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103. Long-Term Sequelae after Bites by *Vipera Berus*

Felgenhauer N, Hohe M, Ganzert M, Zilker T.
Toxikologische Abteilung, Technische Universität München, Munich, Germany

Objective: Initial clinical presentation and acute management of bites by *Vipera berus* are well established. However, data about long-term sequelae after these bites are rare. *Methods:* A retrospective study was performed of all bites by *Vipera berus* treated at our department in Munich between 1995 and 2006. A clinical gradation scale is used for determining the initial degree of severity distinguishing none (grade 0), minor (grade 1), moderate (grade 2) and severe (grade 3) envenomations. All patients received a mail questionnaire concerning the circumstances of the snake bite and the development of long-term sequelae. The latter are defined as symptoms which either reappeared after full recovery or lasted more than 6 months. *Results:* 78 patients with bites by *Vipera berus* were treated in the period of investigation. 52 patients answered the questionnaire and were included in the study. 15 patients (28.8%) developed long-term sequelae, including 12 with paraesthesiae, 7 with oedema and 6 with persistent pain in the area of the snake bite; 4 patients reported restricted mobility of the affected limb. Grade 1 envenomations developed long-term sequelae in 25% (6/24), grade 2 envenomations in 31.8% (7/22) and grade 3 envenomations in 66.7% (2/3). Long-term oedema occurred at lower extremity in 25% (5/20), at upper extremity in 6.25% (2/32). Patients with Grade 2 envenomation receiving specific Fab antivenin developed long-term sequelae in 21.4% (3/14), those without antivenin administration revealed these consequences in 50% (4/8). Patients with grade 1 envenomation treated as outpatients developed long-term sequelae in 50% (4/8), those with hospital treatment ≤3 days showed these effects in 20% (2/10); none (0/6) of these patients treated in hospital for one week had any long-term sequelae. Grade 1 envenomations treated with immobilization revealed in 15.8% (3/19) long-term sequelae, whereas patients with the same severity score treated without immobilization showed long-term effects in 60% (3/5). *Conclusion:* Long-term sequelae after bites by *Vipera berus* are no rarity. Risk factors for long-term sequelae are high severity score after the snake bite, absence of specific Fab antivenin administration in grade 2 envenomations, outpatient treatment and absence of immobilization in grade 1 envenomations.

104. Coagulation Factor Deficiencies Associated with Venom Induced Consumption Coagulopathy in Australian Snake Envenoming

Isbister GK,[1,2] Scorgie F,[3] Brown SGA,[4] O'Leary MA,[1] Seldon M,[3] Lincz L.[3]
[1]Department of Clinical Toxicology, Calvary Mater Hospital, Newcastle; [2]Menzies School of Health Research, Darwin; [3]Hunter Haematology Research Group, Calvary Mater Hospital, Newcastle; [4]Centre for Clinical Research in Emergency Medicine, Western Australian Institute for Medical Research and University of Western Australia, Perth, Australia

Objective: There is limited information on individual coagulation factor plasma concentrations and their recovery in patients with venom induced consumption coagulopathy (VICC). We measured coagulation factor concentrations in blood samples from patients with VICC to better understand the time course of the coagulopathy, the range of severity and difference between snake groups. *Methods:* 137 patients recruited to the Australian Snakebite Project were used including; 112 patients with severe VICC (62 brown snake, 48 tiger snake group, and 2 taipan envenomings), 16 patients with mild VICC and 9 non-envenomed comparisons. Severe VICC was defined as INR >3 and an unrecordable fibrinogen; mild VICC was defined as an INR between 1 and 3, with low but recordable fibrinogen. Citrated blood and sera were collected up to 6 days after the snake bite, with a total of 677 samples. Citrate samples were double centrifuged and platelet poor plasma stored. Prothrombin time (PT), activated partial thromboplastin time (aPTT), concentrations of fibrinogen, factors II,V,VII,VIII,IX, X,vWF antigen and D-dimer were measured by automated coagulation analysers. Venom concentrations were measured by Enzyme-Linked ImmunoSorbent Assay. *Results:* Patients with severe VICC exhibited an almost complete absence of fibrinogen, factor V and factor VIII within the first 4 to 12 hours after the snake bite, with modest reductions in factors II, VII, IX and X. In patients with mild VICC, there were less severe reductions in factor concentrations. D-dimers were exceedingly high in severe VICC with many of the cases above the limit of quantification (900mg/L), compared to patients with mild VICC. There were no differences between VICC caused by brown snakes or the tiger snake group. Fibrinogen recovered the slowest returning to concentrations >1g/L only after 20 to 40 hours, while factor V and VIII reached >50% within 5 to 15 hours in the majority of cases. Improvement in the INR (to less than 2.0) and the aPTT appeared to correlate best with the recovery of factors V and VIII. *Conclusion:* VICC in Australian elapid envenoming is characterized by rapid development of almost complete deficiencies in fibrinogen, factor V and factor VIII concentrations, and a partial deficiency of prothrombin; similar for all snake types. The time course of coagulation recovery is similar in all cases of VICC and appears consistent with re-synthesis of the factors.

105. Diphenhydramine Decreases Survival Time in a Porcine Model of Intravenous Rattlesnake Envenomation

Meggs WJ,[1] Sekhon N,[1] Fish L,[1] Brewer KL,[1] O'Rourke D,[2] Lust RM.[3]
[1]Department of Emergency Medicine, Brody School of Medicine at East Carolina University; [2]Department of Comparative Medicine, Brody School of Medicine at East Carolina University; [3]Department of Physiology, Brody School of Medicine at East Carolina University, Greenville, US

Objective: Rapid onset of cardiovascular collapse seen in rattlesnake envenomations is attributed to intravenous injection of venom.[1] To further elucidate this process, a porcine model of intravenous rattlesnake envenomation was developed with hemodynamic

parameters determined by ultrasound. Subjects rapidly developed hypotension, tachycardia, and poor ventricular filling, with unimpaired cardiac output. All subjects recovered without treatment by 4 hours. Diffuse erythroderma was observed. This result suggested the possibility of a histamine effect, perhaps through cytotoxic effects on circulating basophils. The objective of this study was to determine if the H1 antihistamine diphenhydramine would mitigate shock induced by intravenous rattlesnake venom. *Methods:* Six domestic swine weighing 10.77±1.12 kg received Xylazine, 1 mg/kg and Telazol, 5–6 mg/kg intramuscularly for anesthesia induction. Pigs were intubated and anesthetized with isoflurane. Intravenous access was obtained via peripheral veins. An arterial line was inserted into the femoral artery via cut-down for continuous blood pressure monitoring and arterial blood sampling. Blood pressure, heart rate and rhythm, central venous pressure, and oxygen saturation by pulse oximetry were obtained at baseline and every two minutes for the first thirty minutes followed by measurements every hour. Three pigs were pre-medicated with diphenhydramine 1 mg/kg. Freeze-dried *Crotalus atrox* (Western diamondback rattlesnake) venom at a dose of 25 mg resuspended in 1 ml of sterile water was injected intravenously in a peripheral vein. At the end of the treatment period, animals were euthanized without gaining consciousness. Chi-square analysis was used to compare survival time. The institutional animal care and use committee approved the protocol. *Results:* The three untreated pigs developed hypotension, shock, diffuse erythroderma, and tachycardia, but survived the four hour study period and made a full recovery without treatment. Pigs pre-medicated with diphenhydramine expired in 8.33 ± 3.88 minutes (range 4 to 11.5 minutes). Chi-square p value was 0.03, which was statistically significant. *Conclusion:* Diphenhydramine had a deleterious effect on survival after intravenous rattlesnake envenomation in this experiment. Further study is needed to determine the mechanism. *References:* 1. Davidson TM. Intravenous Rattlesnake Envenomation. West J Med 1988; 148:45–47.

106. Exotic Venomous Animals in Europe; an Overview of Issues and Solutions

White J.
Toxinology Department, Women's & Children's Hospital, Adelaide, Australia

Compared to the rest of the World, Europe has a paucity of native venomous animals capable of causing injury in humans,[1] but a wide range of exotic venomous fauna is becoming available for public and private collections[2] and opportunities for accidental introduction of exotics in the wild are potentially increasing. European PICs and toxicologists will likely be faced with managing increasingly diverse exotic envenomings in the future. These will include a greater range of snakes, plus scorpions, spiders, centipedes, and many types of marine venomous/poisonous animals. Developing systems for effectively managing this diversity of presentations, including information access, expertise development, and availability of appropriate antivenoms/antidotes will be crucial in securing optimal outcomes for patients.[3] Internet-based and other resources covering clinical toxinology are already available (e.g. www.toxinology.com and other sites), and expanding, as is specific training in clinical toxinology, with a growing number of experts in this field available for consultation. While the focus in the past has largely been venomous snakes[4,5] scorpions, spiders, other arthropods and marine animals are all already in collections in Europe[2,6–9] and some species can cause major morbidity and can be rapidly lethal,[1] more so than most venomous snakes. Arthropods, in particular, notably spiders and scorpions, have a far higher potential than snakes for establishment as wild pest species in Europe. Should this occur, it will further complicate the diagnostic process, until such wild populations are recognised and defined. The Australian redback spider (a widow spider; *Latrodectus*) has already seeded successfully to Japan (10), probably Dubai, and has also escaped in Europe. Banana spiders (*Phoneutria*) regularly arrive unwanted in the UK from Brazil. The role of antivenom in managing envenoming by widow and banana spiders remains controversial, but these envenomings, though distressing, are rarely fatal.[11] The only truly deadly spiders, the funnel webs from Australia (*Atrax* & *Hadronyche*),[12] are less likely to successfully travel accidentally, but could be purposely transported by collectors. Without specific antivenom, major bites by these spiders can often result in fatality. Envenoming causes a severe catecholamine storm, with death recorded within 30 minutes of a bite, and survival in a severe case requires antivenom treatment. The notoriety of these spiders may make them attractive to keepers, but antivenom supply is limited. Even more concerning are dangerous exotic scorpions, already kept and bred by enthusiasts in Europe, because some medically important species are well adapted to survive in urban environments, including one parthenogenetic species from Brazil. Again, antivenom is the key therapy in reducing morbidity and mortality, yet needs to be given early for effectiveness, which is unlikely to be possible as an exotic species in Europe, unless appropriate antivenoms are widely distributed amongst PICs/toxicology units.[11] Most of these scorpions also cause a catecholamine storm-like envenoming, developing rapidly, with children and the infirm at greatest risk.[1] However, one group of scorpions, from Iran, cause quite different envenoming, resulting in both local necrosis and systemic envenoming, including haemolysis and renal failure.[13] In Kuzestan, Iran, these scorpions are the leading cause of envenoming fatalities. While an antivenom is available in Iran, current data do not unambiguously support its effectiveness. There is a clear need to start documenting incidents involving exotic envenoming in Europe, so that the extent of real risk can be tracked and appropriate responses developed, including rational antivenom stocking policies and effective medical expert consultation networks that ensure patients receive optimal care. *References:* 1. Meier J, White J, eds. Handbook of Clinical Toxicology of Animal Venoms and Poisons. Boca Raton, USA: CRC Press, 1995. 2. Schaper A, Desel H, Ebbecke M, et al. Bites and stings by exotic pets in Europe: an 11 year analysis of 404 cases from Northeastern Germany and Southeastern France. Clin Toxicol (Phila) 2009; 47:39–43. 3. Leclerc T, Debien B, Perez JP, et al. [Mamba envenomation in mainland France: management of exotic envenomations needs rethinking] Ann Fr Anesth Reanim 2008; 27:323–325. 4. Malina T, Krecsák L, Korsós Z, et al. Snakebites in Hungary--epidemiological and clinical aspects over the past 36 years. Toxicon 2008; 51:943–951. 5. 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107. Marine Toxinology: Antivenom in Hot Water and Other Treatment Controversies

Isbister GK.
Department of Clinical Toxicology and Pharmacology, Calvary Mater Newcastle Hospital, Darwin, Australia

Although marine stings and injuries are common, the majority are minor, rarely present to healthcare services for treatment, or call poison centres. Venomous marine injuries are divided into contact injuries from jellyfish and penetrating injuries from stingrays, spiny fish and sea urchins. Treatment for marine stings mainly consists of first aid. Specific treatments such as antivenom are only available for particular envenoming syndromes and usually only in severe cases.[1] First aid for jellyfish stings includes removal of the tentacles, hot water immersion for *Physalia* stings[2] and vinegar for major box jellyfish. Numerous other topical first aid treatments are suggested but little evidence exists to support their use. Box jellyfish are the most dangerous from an envenoming perspective and may cause severe and potentially life-threatening effects. *Chironex fleckeri* stings in northern Australia require early resuscitation in the rare severe cases. Antivenom is available but it is unclear whether it is effective.[3] Spiny fish and stingrays cause a combination of traumatic injury and venom-mediated effects. First aid is hot water immersion, but may only provide transient symptomatic relief. Treatment includes analgesia, thorough wound cleaning and close review for secondary infection. The use of prophylactic antibiotics remains controversial.[1] Antivenom exists for stonefish stings.[4] Stingray injuries are associated with more significant trauma and can rarely result in penetrating abdominal or thoracic injury. Marine poisoning differs in epidemiology, location and clinical manifestations to marine envenoming.[5] There are four major clinical syndromes of marine poisoning, three that have important neurological manifestations – ciguatera, tetrodotoxin poisoning and paralytic shellfish poisoning – and the fourth, scrombroid which has similar effects to an allergic reaction. Ciguatera is the most common, but is rarely life-threatening causing gastrointestinal effects (vomiting, diarrhoea and abdominal cramps) and neurological effects (myalgia, paresthesiae, cold allodynia and ataxia). Tetrodotoxin poisoning and paralytic shellfish poisoning are rare but have a higher fatality rate. They are characterised by mild gastrointestinal effects and a descending paralysis that rapidly progresses to respiratory failure in severe cases.[5] The mainstay of care is supportive and no antidotes currently exist. Numerous specific treatments have been suggested and used anecdotally for ciguatera poisoning. In particular, mannitol has not been shown to be effective in a controlled trial.[6] *References:* 1. Isbister GK. Managing injuries by venomous marine creatures in Australia. Aust Prescrib 2007; 30:117–121. 2. Loten C, Stokes B, Worsley D, et al. A randomised controlled trial of hot water (45 degrees C) immersion versus ice packs for pain relief in bluebottle stings. Med J Aust 2006; 184:329–333. 3. Winter KL, Isbister GK, Jacoby T, et al. An in vivo comparison of the efficacy of CSL box jellyfish antivenom with antibodies raised against nematocyst-derived Chironex fleckeri venom. Toxicol Lett 2009; (in press). 4. Currie BJ. Marine antivenoms. J Toxicol Clin Toxicol 2003; 41:301–308. 5. Isbister GK, Kiernan MC. Neurotoxic marine poisoning. Lancet Neurol 2005; 4:219–228. 6. Schnorf H, Taurarii M, Cundy T. Ciguatera fish poisoning: a double-blind randomized trial of mannitol therapy. Neurology 2002; 58:873–880.

108. Marine Toxinology: A European Perspective

de Haro L.
Poison Centre, Marseille, France

Introduction: Natural toxins are numerous in tropical seas where various venomous and poisonous species can cause severe human health troubles. In temperate seas, marine toxinology seems to represent a less important problem, but according to recent data, the situation is changing for two main raisons: firstly climate modifications allow the development of several toxic indigenous species like dinoflagellates or jellyfish; secondly the establishment of introduced tropical species including toxic algae or fish is now possible with the milder weather. *Discussion:* In the activity of poison centres located near the European coastlines, several emerging toxicological marine problems are at the origin of unusual case reports. Some examples can be mentioned like the case series of envenomations by Portuguese man-of-war (*Physalia sp.*) on the same day during summer 2008 at Biscarosse in the French Atlantic coast

(data from the Bordeaux Poison Centre); or like poisonings and stings by the Lessepsian rabbitfish (*Siganus luridus* which is poisonous and venomous) originally from the Red Sea but now present throughout the Mediterranean Sea.[1] However, the most important public health problems are the consequences of the more and more frequent blooms of toxic species involving indigenous species[2] (dinoflagellates as the origin of different kinds of shellfish poisoning, cyanobacteria mostly in freshwater but also in saltwater, jellyfish) and exotic introduced species (with the major problem of the tropical microalgae *Ostreopsis ovata*). The situation in the Mediterranean Sea of *O. ovata* is really worrying because its development is very rapid and the toxins produced (palytoxin-like toxins with an important vaso-constricting power) are able to induce severe human poisonings. *O. ovata* is, since 2006, a serious problem with summer blooms leading to numerous hospitalizations in Italy, Spain and France where humans are contaminated by the respiratory route.[1] The food chain contamination by the toxins of *O.ovata* in the Mediterranean Sea is not proven for the moment, but it may soon be a real hazard: palytoxin-like toxins are able, in tropical areas, to turn edible shells, crustaceans and some fish into very toxic food with several deaths reported in the literature. *Conclusion:* The situation of marine toxinology in Europe is quickly evolving, with new toxins and more cases of intoxication.[1] Clinical toxicologists are now confronted with new possibilities for poisonings and envenomations while they are not really trained to manage such emerging illnesses. European Poison Centres have a major role to play in the new challenge of increasing the knowledge concerning emerging marine toxinology. *References:* 1. De Haro, L. Intoxications par organismes aquatiques. Med Trop 2008; 68:367–374. 2. Ciminiello P, Fattorusso E. Bivalve molluscs as vectors of marine biotoxins involved in seafood poisoning. Prog Mol Subcell Biol 2006; 43:53–82.

109. Strategies for Establishing and Sustaining a Poison Centre

Tempowski J.
International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Objective: To describe strategies for establishing a poisons centre. *Methods:* The stimulus to start a poisons centre is usually the recognition that poisoning causes significant morbidity and mortality and that it is not being optimally managed in healthcare facilities. The rationale is that the toxicology content of medical training is limited, moreover, medical staff cannot know about all of the possible substances that could give rise to poisoning, and therefore the provision of a specialized information service will improve management and result in better outcomes. The initiator of the poisons centre may be an interested individual or group, an institution or a government body. Usually the initiator comes from within the health sector; in developing countries, however, the initiative, as well as support, may come from the environment sector. A proposal for establishing a poisons centre should start with a justification of need, including background information about the poisoning incidence in the country and identification of data gaps. It should describe the planned tasks and activities of the centre (is it an information service only, will it include treatment and/or laboratory facilities?) and how these will benefit the population served, perhaps citing evidence from other countries. It should describe the staff, equipment, information-resource and location needs, and provide a budget for setting up the centre and for running costs. It should also describe the recruitment and training plan (both initial and continuing education), and make a commitment to a quality assurance procedure. The proposal should identify who will be responsible for its implementation, and it should suggest time lines and milestones. Obtaining political support for a new poisons centre is very important, particularly in developing countries, and international organizations and professional associations such as WHO, EAPCCT and AAPCC can help with advocacy. These bodies also provide guideline documents that can serve as reference material for the proposal. In addition, it is useful to refer to priority needs agreed at intergovernmental fora such as the Intergovernmental Forum on Chemical Safety, Conferences of the Parties for chemical safety conventions, and the International Conference on Chemicals Management. These priority needs are also taken into account by donors. Once a poisons centre has started operations it gives rise to certain expectations. The most important of these is that it will provide a high quality, accessible, authoritative and reliable service to its users. This is an expectation that the poisons centre must endeavour to meet, since, from the beginning, it will have to convince potentially sceptical users that it does have something of value to offer. It is essential, therefore, that staff are given adequate training, that adequate information resources are available, that the telephone lines are reliable, that the stated operating hours are kept to, and that procedures are in place for handling poisons enquiries, before the centre starts to promote its services. There will be other expectations, for example that the poisons centre will reduce morbidity and mortality from poisoning, that it will save healthcare costs, that it will provide epidemiological data on poisoning in the community, that it will reduce the incidence of poisoning. It takes time for a poisons centre to make such impacts: the poisons centre must first establish itself and develop a solid user base; indeed it may have to induce a cultural change among its target users before they will call the centre routinely. Demonstrating these impacts requires good health data systems, which are frequently not available in developing countries. Data on poisoning cases collected by the centre may, therefore, become an important contribution to national health statistics and the poisons centre should give some priority to implementing a good documentation system for its enquiries. This will benefit the centre in other ways, e.g. by enabling it to report to its sponsoring organization(s) on progress and achievements. Promotion of the poisons centre and its activities is important to ensuring its sustainability. This is a continuous activity and requires some resources. Methods of promotion include dissemination of leaflets and posters about poisoning, participation in medical and nursing education programmes, use of the mass media to provide poisons prevention and first aid information, and publication in professional journals. Providing a 24 hour service on a toll-free telephone number also helps to promote use of the service. Poisons centres in developing countries face particular challenges since they are competing for limited health funds and must operate on a very small budget. There may in addition, be serious infrastructural deficiencies, particularly with regard to telecommunications (including Internet access) and power supply. Access to the poisons centre from rural primary health care facilities may be restricted or impossible. Outreach strategies are very important therefore, particularly educational outreach. Financial support for such activities can sometimes be obtained from donors and from international organizations. Ensuring sustained, adequate funding is a problem for most poisons centres. Gaining political support for the centre helps to guarantee a level of funding, as does the granting of legal status to the centre. It is also essential to keep the profile of the centre high, for example through regular outreach activities, regular reporting on activities to funding bodies, and seizing opportunities to promote the role of the poisons centre in new areas. An example of the latter is the need faced by countries to improve health surveillance for the early detection of disease outbreaks, including those caused by chemicals, as required by the International Health Regulations (2005). This is certainly something that fits within the remit of poisons centre work. In fact, many well-established poisons centres have diverse sources of funding through a range of income-generating activities. These activities usually require the centre to have a good data collection and documentation system in place. Opportunities for income generation are likely to increase as the poisons centre becomes better recognized. *Conclusion:* History has demonstrated the value of poisons centres. Assistance in provision of resources and training is available through WHO, the EU, the European Council, the ESF, professional associations, and, indeed, the poisons centre community at large.

110. National Integration of Poison Control Centres: The Italian Experience

Locatelli CA.
Poison Control Centre and National Toxicology Information Centre, IRCCS Maugeri Foundation and University of Pavia, Pavia, Italy

Objective: National health systems have organizational characteristics that differ amongst countries: similarly, Poison Control Centres (PCCs) in the different European and extra-European countries, even if assuring the same basic activities (e.g. consultation for diagnosis and treatment of poisonings, toxicovigilance),[1] differ one from the other for several functional aspects. Guidelines from WHO-IPCS and scientific societies (e.g. EAPCCT, AAPCC) have pointed out and underlined the key roles, functions and activities of PCCs, promoting the accomplishment of operational standards and providing general indications for the implementation of PCCs in developing countries. Nevertheless, while a relative abundance of "scientific evidence" on functions and activities, health benefits and cost-benefit relationships is already available, only few normative acts exist in the legislation of the European countries meant to define the role of the PCCs in each health system. The opportunity, the importance or even the necessity of a "legal status" of the PCCs probably differ from country to country. Nonetheless there is a diffuse increase of the need of expertise, the acquisition of new skills in toxicology, methodology and quality assurance. *Methods:* Establishment of a specific commission (representatives of Italian Ministry of Health, of the National Institute of Health, of the Health Offices of the Regional Governments, of the Italian Society of Toxicology representing the Poison Control Centres) working on (i) the definition of the role, functions and activities of the Italian PCCs, (ii) the minimum data set for the PCCs data sharing, and (iii) toxicological syndromes that have to be included in the national surveillance system. *Results:* The act that on February 2008 has been defined in Italy is a "State-Regions agreement regarding the definition of activities and the fundamental requirements for PCCs" and probably represents an example of improvement of PCCs' status in a European country. Several reasons have induced the Health Offices of national and regional Governments and the Italian Society of Toxicology (that represented the Italian PCCs of Pavia, Bergamo, Milano, Genova, Firenze, Roma (two centres) and Napoli - in the State-Regions Conference), to define role and functions of the PCCs. The main reason consists of the need to guarantee a network of stable and well consolidated PCCs in the country, equipped with the necessary resources to adequately operate in the national health system and to assure the required public health activities (e.g. syndromic surveillance) with no risk of disappearing, for instance, due to local actions of cost containment. Moreover the medical activities and functions guaranteed by the Italian PCCs, similarly to other European and extra-European countries, are considered essential and unique, necessary for the national health service, as "specific and not referable to other medical services". Functions and roles identified for the Italian PCCs include: (i) specialized toxicological consultation for population, medical doctors and health care professionals in order to screen toxic exposures and to manage poisoned patients (ii) direct and specialized activity in the clinical departments of the hospital in which PCC is in force (iii) implementation of a national analytical toxicology network for a rationalization and better availability of the existing resources (iv) implementation and continuous updating of toxicological data-bases (v) collection of epidemiological data of poisonings (vi) participation to the national activities of surveillance, vigilance and alert (vii) stocking and supplying of antidotes in emergency (viii) evaluation of effectiveness and safety of the antidotes (ix) participation to the planning for the management of possible chemical emergencies (including a terrorist attack) (x) educational activities for medical doctors, health care

professionals, medical students, and population in the management and prevention of poisonings and toxicological exposures (xi) clinical research activity, with particular reference to diagnosis, treatment and prevention of poisonings (xii) realization and maintenance of a national network operating with both emergency and prevention services, possibly interfaced with European PCCs. The act establishes also (i) a minimum data set in order to share the data of all the Italian PCCs, and (ii) some syndromes that have to be included in the national surveillance system. Moreover, the act also underlines that, for their particular functions, the PCCs need to be autonomous services in which the activity is accomplished by physicians specialized in medical toxicology (this medical specialization is active in Italy). An accreditation process is needed for the PCCs that wish to be part of the network. Three major results are expected: (i) a better management of poisoned patients and of appropriateness of care; (ii) reduction of the improper accesses to the emergency departments, of the unnecessary hospital admissions and of the inappropriate diagnostic investigations, and (c) a valid specialized support to the Governmental Institutions in the management of chemical-toxicological emergencies, and in the surveillance and prevention activities. This important recognition of the functions and activities of the PCCs implies a development and the making of the existing Italian services adequate in a brief period of time, in order not only to effectively face the emergency consultations, but also to give answer to the increasing request for documentation and for epidemiological evaluation coming from local, regional, national and supranational Institutions and Organizations. *Conclusion:* The Italian act, even if with possible adaptations, may nowadays represent a valid indication for European countries that still need an appropriate legal referral. *References:* 1. Andrew E. Comparison between eight poisons information centres in Europe. Clin Toxicol 2006; 44:345–350.

111. Setting Up a Poison Control Centre – The Lithuanian Experience

Surkus J, Rutkauskaite R, Gailius V.
Poisons Control and Information Bureau, Health Emergency Situations Centre, Vilnius, Republic of Lithuania

Introduction: This review has been prepared in order to exchange experience and to discuss the main problems in setting up a Poison Control Centre. *Methods:* Establishment of a Poisons Control and Information Bureau (PCIB) in Lithuania was evaluated by analysing data and internal documents of PCIB, official documents of the Ministry of Health, statistic data of the State Patients Fund and publications. *Discussion:* The number of poisonings in our country is increasing with every year (from 28,565 patients treated in 2002 to 32,278 patients treated in 2007), despite the fact that the number of inhabitants was decreasing at the same time. More than half of the patients (in 2007 - 17,576 patients or 54.5 percent) were treated in hospitals. Mortality of in-patients differs in different hospitals. In the Department of Acute Poisonings located in Vilnius University Emergency Hospital, where poisoned adults from Vilnius and the most severe cases from other areas are treated, mortality varied from 1.6 percent in 1999 to 7.5 percent in 1993;[1] in 2007 it was 2.48 percent; and general mortality of all poisoned patients overall in the country in 2007 was 0.5 percent (168 cases). It is possible to obtain the speciality of clinical toxicology during 3 years studies in residency in Vilnius University and Kaunas Medical University. At this moment 22 licensed clinical toxicologists are working in different health care institutions. In this context official activities of PCIB started on the 1st of January 2002, but before this the work was already carried out by clinical toxicologists. Before independence in 1990, the Department of Acute Poisonings in Vilnius was the only specialized department in the country. Physicians who were on duty consulted colleagues from other hospitals as necessary and in the most severe cases visited other health care institutions. In 1991 it became obvious that it is necessary to organize a Poison Information Centre but this idea did not get any support from the health care authorities. At that time in the Department of Acute Poisonings in Vilnius University Emergency Hospital one consulting-room was transformed into a library from which started the first activities of the future PCIB. It was possible to perform these activities only due to help from Western colleagues. The main assistance was from the Nordic Association of Poison Information Centres (NAPC) and especially Swedish Poisons Information Centre: training of staff, medical literature, data bases, and support for participation in EAPCCT and NAPC meetings. During this period it became clear that even the best sources of information cannot give answers to all questions and in the beginning the most useful staff were physicians experienced in the treatment of poisonings because for them it was easier to solve clinical problems in the absence of guidelines adapted to the local situation. Official authorities paid more attention to PCIB only during the process of negotiation with the European Union and for economic reasons it was established as a part of State Environmental Health Centre (SEHC). That caused some serious problems. Obligatory presentation of information (this is common for public health institutions in our country) about poisonings was not effective and SEHC is not licensed for health care, also. This restricted activities of PCIB and on the 1st of September 2005 PCIB was transferred to the Health Emergency Situations Centre. Now activities of PCIB are organized according to the Guidelines for Poison Control provided by WHO. For the reason that it is impossible from the beginning to operate equally in all spheres, the main areas of Lithuanian PCIB are: 24 hours telephone service assisting in prevention, diagnosis and management of poisonings; policy for antidotes; preparation and publishing of local guidelines for the most dangerous and frequent poisonings; dissemination of important information for health care professionals and for society (lectures, articles, interviews, etc); participation in international projects. The telephone service is open both for health care professionals and for members of the public. The number of calls is increasing quite slowly but constantly (726 in 2002, 693 in 2003, 1124 in 2004, 1343 in 2005, 1378 in 2006 and 1386 in 2007). Whether to answer consultations on animal poisonings still remains undecided, this depends only on the free will of staff on duty. Another unresolved problem is the division of interest spheres with other institutions that have partially similar functions, such as the Drug Control Department, SEHC. The only example of absolutely successful collaboration is the joint activities of PCIB and Lithuanian Society of Clinical Toxicology, especially in preparation of guidelines. *Conclusion:* 1. From statistical data we can estimate that the number of poisonings in Lithuania is at least 2–3 times greater but at least half of the patients do not need or do not apply for medical aid. These data emphasize the necessity to enlarge the activities of Lithuanian PCIB. 2. In the initial period of Poison Control Centre activities the most useful staff are the physicians with experience in treatment of poisonings – clinical toxicologists, intensive care specialists, etc. 3. The Poison Control Centre must be an independent institution or part of other institutions with the right to provide health care services. 4. In the beginning the optimal way of functioning is concentration of activities on the most important functions. *References:* 1. Groszek B, Pach J, Targosz D, et al. Key Activities of Selected Poison Centers in Poland and Baltic States – Pilot Study. Clin Toxicol 2005; 43:395–396.

112. A Knowledge-Based Consultant for Human Toxic Exposures

Schipper JD,[1] Schauben JL,[2,3] Dankel DD,[3] Arroyo AA,[3] Sollee DR.[2]
[1]Bradley University, Peoria; [2]Florida/USVI Poison Information Center, Jacksonville; [3]University of Florida, Gainesville, US

Objective: We sought to create a knowledge-based system capable of generating differential diagnoses for human exposures involving unknown toxins. Knowledge-based systems use computerized data analysis to provide relevant advice and potential solutions within a specific domain, such as toxicology. Although a few systems for clinical toxicology have been created,[1–3] no similar systems are currently in use in the United States. Additionally, these existing systems either do not use established medical mathematics or require a significant commitment of expert toxicologists to create rules and scores. Conversely, our system makes use of likelihood ratios and implements data mining techniques to generate rules automatically. The creation of the American Association of Poison Control Centers' National Poison Data System (NPDS),[4] and its predecessor, the Toxic Exposure Surveillance System (TESS),[5] has provided a common set of fields collected by all United States poison centers. This produced an opportunity to implement a knowledge-based system useful to poison control centers around the United States, regardless of their data collection software. Leveraging human patient exposure data collected by the Florida Poison Information Center Network, a prototype medical decision support system was developed. By analyzing an existing database of toxic exposures, such a system can provide medical practitioners with valuable case-based information to aid in providing a narrowed differential diagnostic list. *Methods:* Data mining techniques were used to extract human exposure case data from cases managed by the Florida/USVI Poison Information Center in Jacksonville. The database was filtered to include only those cases flagged as being "followed to a known outcome." This ensured that every case involved at least one clinical effect and that the accuracy of the case's medical outcome had been "documented with reasonable certainty." We have assumed that as the number of exposures grows annually, incorrectly reported outliers should become insignificant contributors to the system's calculations. Based on the filtered data set, likelihood ratios were calculated with each clinical effect being treated as a test for a specific toxic substance. To overcome the limitations of traditional likelihood ratios, the equation employed by the system was adjusted to account for every possible outcome. Using adjusted likelihood ratios facilitated system stability while closely modeling the calculations of traditional likelihood ratios. Combining the likelihood ratios for each toxin with respect to the observed clinical effects and accounting for pre-test probabilities, the system generated a differential diagnosis of toxins. A system diagnosis was considered accurate if the correct diagnosis appears in the top 10% of all possible diagnoses. During evaluation, the system was trained on nine-tenths of exposure cases and then tested against the remaining tenth. The process was repeated ten times, testing on a different set of data each time. Furthermore, system accuracy was determined for various exposure severities as well as at different levels of identification (diagnosis by substance, major and minor categories, and major category alone). *Results:* Trained and tested using 30,152 single exposure cases, the system achieved accuracies as high as 79.8% when diagnosing by substance and 78.9% when diagnosing by major and minor categories. Accuracies for diagnosing by substance were 62.8% for exposures resulting in death, 79.8% when including major severity, 76.6% when adding moderate severity, and 67.4% when adding minor severity cases. Attempts to diagnose multiple toxins involved in multiple exposure cases failed due to the complexity of the problem and lack of data. However, diagnosing the primary contributor in multiple exposure cases using 37,617 single exposure cases and 8,901 multiple exposure cases yielded accuracies of 83.5% when diagnosing by substance and 86.9% when diagnosing by major and minor categories. *Conclusion:* With the exception of exposures resulting in death, as case severity increased, system diagnosis accuracy also increased. This observation indicates that the system was training properly because the more severe the toxic exposure, the more clinical effects are involved. Exposures with multiple clinical effects are generally easier to identify than those involving only a single clinical effect. Exposures resulting in death, however, involve clinical effects caused by multiple organ system derangements or failures. These produce effects not normally associated with a particular substance, hindering the ability of the system to diagnose the exposure correctly. We also observed that the system was capable of providing recommendations on

the primary contributors involved in multiple exposures by training chiefly on single exposure cases. These results indicate that although multiple exposure cases can involve drug interactions, such as synergy and antagonism, the majority of multiple exposure cases are dominated by the clinical effects of a single substance. Since multiple exposure cases account for more than 50% of all toxic exposure deaths in the United States,[5] these results indicate that the system may be a useful tool in saving lives. Lastly, even with the increased complexity involved in diagnosing primary exposures for multiple exposure cases, the larger training data set yielded a higher accuracy. As more cases are added to the training set annually, the accuracy of the system should gradually improve. The findings of this research are modest, yet promising. Plans are underway to fine tune the system and implement it for real time consultation at the Florida/USVI Poison Information Center in Jacksonville. *References:* 1. Althoff K, Bergmann R, Wess S, et al. Case-based reasoning for medical decision support tasks: the Inreca approach. Artif Intell Med 1998; 12:25–41. 2. Darmoni S, Massari P, Droy J, et al. Functional evaluation of Seth: An expert system in clinical toxicology. In: Barahona P, Stefanelli M, Wyatt J, eds. Artificial Intelligence in Medicine. Berlin/Heidelberg, Germany: Springer Verlag, 1995:231–38. 3. Monov A, Iordanova I, Zagorchev P, et al. MEDICOTOX CONSILIUM - An expert system in clinical toxicology. MEDINFO 92:610–614. 4. Bronstein A, Spyker D, Cantilena L, et al. 2006 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS). Clin Toxicol 2007; 45:815–917. 5. Watson W, Litovitz T, Rodgers G, et al. 2004 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. AJEM 2005; 23:589–666.

113. Preparing for the Business World: Early Experiences of Adapting a Poisons Centre Service and Database for Commercial Activity

Campbell A.
Veterinary Poisons Information Service (London), Medical Toxicology Unit, London, UK

Introduction: Since 1992 Guy's & St Thomas' Poisons Unit in London (GSTPU), along with the Medicines Information Service of Leeds General Infirmary, has provided the Veterinary Poisons Information Service (VPIS) to veterinary professionals on a subscription basis.[1] In 2008, following the effective cessation of GSTPU's emergency human poisons information service, the centre and its parent hospital trust's corporate development division has spent time consolidating and developing the unit's existing "non-core" activities into a financially self-supporting viable business, including the VPIS. *Methods:* All aspects of the VPIS activity were subject to thorough internal and external review and SWOT analysis (strengths, weaknesses, opportunities and threats). Initially, major stakeholders and professional bodies and associations representing the VPIS's major users were invited to comment about their perceptions of the service, its continuance and future development. Later consultations over service charges, availability and development were opened to all UK veterinary surgeons/practices by means of regular questionnaire surveys. Feedback has, to date, been overwhelmingly supportive and constructive. *Issues:* there were many facets of the operation that needed assessment. These were a) service availability and guarantee, b) financial, c) professional liabilities and indemnity, d) administrative, e) VPIS' database, f) governance and staffing considerations, g) investment and development, and h) commercial partnerships. *Results:* a) service availability. Current users wished, overwhelmingly, for VPIS to remain a fully-staffed 24 hour telephone-based operation, ideally with capacity increased at busy times of day. b) Financial. It was recognized costs to users would increase. Perhaps surprisingly, current users expressed a preference for charges to incorporate a charge per case/call component in addition to a membership fee allowing them to pass charges on to their clients transparently. Many indicated the levels of charges they thought appropriate, and some indicated the charge should vary dependent on time of day. Several wished the facility to manage their accounts on line. The questionnaires prompted debate about how charges for clients who did not present to surgery might be handled, with some suggesting the VPIS took triage calls from the public. c) Liabilities, insurance and protection. It was recognized the VPIS needed to set out newly drafted and comprehensive terms and conditions for its subscribers, and to indemnify the service appropriately. d) A review of the administration of the service was undertaken to determine how the potential administrative burden of charging per case could be minimized. It was considered that an on-line account system might provide a solution. e) The VPIS database. Hitherto the VPIS has used a variety of sources to answer enquiries, including its electronic database of past case reports and subscription management system. These systems had been developed "in-house" in 1999 and were rapidly becoming unwieldy and stretched to meet service demands. A need for major investment in this area was identified, to enhance and upgrade the database, incorporate new and needed features, including a web-based interface for administration and for some service delivery aspects. This would necessitate steps to ensure robustness and protection from intrusion attacks. Professional advice was sought concerning the registering of intellectual property rights on all databases and other information resources. f) Governance and staffing. It was recognized that the VPIS staff had considerable competence, experience and expertise that needed to be maintained, enhanced and retained. A framework to assure quality of service and operational procedures is to be further developed. The lack of major veterinarian involvement in the service to date was identified as a potential weakness. VPIS is seeking to employ a qualified veterinarian on a part-time consultancy basis to assist with complex enquiries, but also for audit and assurance purposes. In time VPIS will consider the application of a management standard such as ISO (International Organisation for Standardisation). g) Investment and development. In addition to overhaul of database systems and procedures the need for further market research to identify other potential services and markets, and service enhancements such as development of training programmes for service users was realised. These would need appropriate marketing and nurturing. h) Commercial partnerships. It has been recognized that more formalized partnerships with some professional and commercial bodies may bring mutual benefits. Several potential commercial partnerships have been identified and are under early negotiation. *Discussion and conclusions:* The business appraisal of the VPIS has been conducted in a both a comprehensive and diligent manner. It is clear that with some considerable initial investment there is a potentially viable and self-sustaining business opportunity for the VPIS in the commercial world, even considering the current world financial climate. The VPIS already has a long-standing, loyal and extremely supportive client base, but one with capability for expansion. Early experiences of the road towards an existence in a competitive commercial world have been exhausting, enriching and motivational. *References:* 1. Campbell A. Should poisons centres provide veterinary advice? (abstract). Clin Toxicol 2006; 44:427.

114. Transition of a Poisons Centre from a Public Health Domain to a Private Care Domain

de Vries I,[1,2] Leenders MEC,[1,3] Meulenbelt J.[1,2]
[1]*National Poisons Information Centre, National Intitute for Public Health and the Environment, Bilthoven;* [2]*Intensive Care Centre, University Medical Centre, Utrecht;* [3]*Perioperative and Emergency Care, University Medical Centre, Utrecht, The Netherlands*

Introduction: Being established in 1959, the National Poisons Information Centre in the Netherlands is considered the first poisons centre in Europe. At that time it was decided within the National Institute for Public Health (nowadays the National Institute for Public Health and the Environment, RIVM) to start a poisons information service because of the increasing number of requests from physicians how to treat patients with medication overdoses. In order to provide the best possible medical advice it was thought best to locate the poisons centre within the nearby university hospital. This was the beginning of a close cooperation between the poisons information centre of the RIVM and the department of intensive care of the Utrecht University Medical Centre. What started as a small poisons unit with few employees, turned into a centre of 32 full time positions, dealing with the "full package" of poisons information deliverance, surveillance, teaching and training programs, research, and treatment of patients. The poisons information service is offered to health care professionals, with yearly about 40,000 telephone calls, covering over 57,000 human and animal exposures. Nowadays, it is also possible to directly approach the poisons' centre database through a web site. Over the years, stable recurrent funding was a major problem. However, in 2008 the poisons centre is faced with an entirely different issue. In the coalition agreement for the period 2007–2011, the Dutch government decided to decrease the number of public servants. All national agencies, including the RIVM, are forced to decrease their number of employees. The RIVM has adopted a policy of outplacement and intends to outplace the poisons centre to the university hospital. *Discussion:* The first step in a process like this is to develop a systematic approach with the ultimate goal of establishing a stable and financially healthy centre providing long-term poisons information service. The key players in the process are the RIVM, the University Medical Centre, the Ministry of Health, Welfare and Sports, and the poisons centre. In addition, it is obligatory that the work council is closely involved. The RIVM is an agency of the Ministry of Health, and as "owner" of the RIVM, this Ministry has to sign the final agreement. The Ministry of Health also functions as the main commissioner of the poisons centre. Other ministries commissioning the poisons centre need to be involved as well. Obviously, the University Medical Centre has to address the question whether they truly wish to obtain the poisons centre. Working groups within and between the various organizations were formed, as well as a more formal steering committee. A time path was established, aiming at a possible transfer of the poisons centre after one and a half years. The next, very crucial, step is to develop a vision for the future organization, structure and funding of the poisons centre. An inventory of all requirements of the organizations involved needs to be drawn up. There is general agreement that the quality of all current functions of the poisons centre must remain at the same high level. To the ministries and the RIVM, it is essential that the poisons centre maintains its position in the chain of organizations dealing with mass disasters. As some of these disaster organizations are established within the RIVM, clear arrangements need to be made between the RIVM and the University Medical Centre as to how to guarantee this duty of the poisons centre at all times. All parties stress the importance of long term and stable funding. As there is only one poisons information centre in the Netherlands, this centre holds a natural monopoly position. This leads to inevitable questions at the various organizations concerning the stability of the price for poisons information delivery and the importance of financing all current activities of the poisons centre in the near future. Although it is evident that poisons centres have a public health function, and thus public health funding should be normal, there have been numerous debates in the past whether the poisons information directed at the individual patient can be regarded as patient care. The view existed that funding by health insurances would be more appropriate, thus decreasing funding by the ministries. This issue may be raised once again, making negotiations more difficult. The working groups need to come up with a list of structural preconditions from each organization that can be negotiated and finally agreed upon. This will lead to the signing of a declaration of intent. Then, all personal, financial and legal aspects need to be worked out and agreed upon. Thereafter, the final decision can be made whether or not a transition is feasible. *Conclusion:* Although the possible transition of the poisons centre from the RIVM to the University Medical Centre is initiated by a broad governmental coalition agreement, and at first glance it does not seem quite appropriate for a poisons centre, this transition

might offer new opportunities for the centre. For the near future (for example, the next five years) it seems essential that funding by the ministries will be guaranteed at the current level, with inflation correction. In the meantime it can be evaluated whether non-governmental funding is possible, without losing the public function. In addition, the possibilities for non-governmental research funding can be explored. In any case, we envision a poisons centre with high quality service delivery, surveillance, and research, firmly imbedded in both public health and medical care services.

115. Prognosis and Treatment of Amatoxin Poisoning

Zilker TH.
Toxicological Department of 2nd Medical Clinic, Technical University, Munich, Germany

Background: Amatoxins are produced by 3 genera of mushrooms, *Amanita*, *Galerina* and *Lepiota*. Amatoxins are cyclic octapeptides with 3 main derivates: alpha-beta-gamma-amanitin. Amatoxins bind to RNA-polymerase II, a nuclear enzyme that transcribes DNA into m-RNA. Inhibition of the transcription-process leads to a lack of templates for protein synthesis. Amatoxins form a strong but not covalent complex with polymerase II.[1] In hepatocytes the enzyme exists as 40,000 copies per cell, corresponding to a concentration of 5x10-8 M.[2] Due to a pool of m-RNA in every cell, the cell can continue to function for some time and this is responsible for the latency until the onset of symptoms. New research[3] has clarified what is happening after the blockade of transcription. Apoptosis via an extrinsic and an intrinsic pathway is induced. The activation of both signalling pathways is mediated by p53, p63 and p73. This p53 family leads to an expression of death receptors CD95, TNFR1 TRAIL R1 and R2 at the surface of the cells. Amatoxins activate caspases which produce split products of p53 that lead to an enhancement of depolarization of mitochondrial membranes (intrinsic pathway). Treatment of amatoxin poisoning is still not satisfactory. At the start of the last century the mortality was over 50%,[4] it came down to 20% after penicillin was introduced into therapy.[5] The introduction of silibinin+penicillin or penicillin alone brought the mortality down to 5–15% in smaller studies.[6] Many physicians didn't think that this was a success as symptomatic treatment had improved over the years, and there was no possibility to enhance amatoxin elimination.[7] The theory behind the penicillin treatment was the blockade of the now known transporter (OATP) for amatoxins into hepatocytes.[8] This can be reached by several drugs (steroids, cephalosporins). Using silibinin was thought to act in the same way but to be less toxic. Many cases were treated with a combination of penicillin+silibinin, possibly because penicillin was available immediately, and possibly because two "antidotes" were thought to be better than one. *Case series:* We were able to study, together with the firm Madaus, 604 cases with suspected diagnosis of amatoxin poisoning. 367 cases were finally included in the study as diagnosis was certain and treatment was well documented. *Results:* 118 patients had received silibinin alone and 249 silibinin in combination with penicillin. Using ROC a prothrombin time below 20% and creatinine above normal showed a sensitivity of 100% and a specificity of 98% for the outcome death or LTx.[9] Logistic regression analyses were applied to investigate the efficacy of both treatments. A potentially independent influence on outcome of age, sex, year of treatment, latency period of symptoms and start of silibinin therapy was taken into account. In the group who had received the combination therapy 8.8% died or underwent LTx whereas 5.1% died or had LTx in the silibinin-only group (adjusted OR: 0.58; 95% CI: 0.21–1.57; p= 0.28). The difference was not significant. Sufficient power to achieve statistical certainty would have needed 600 cases in each group! A longer latency period (<12 h vs >12 h) showed a significant reduction of risk of death or being transplanted (OR: 6.1; 95% CI: 1.77–21.3; p = 0.004). A delayed start of silibinin therapy (>24 h vs < 24h) was associated with a higher risk (OR: 3.0; 95% CI: 0.96–9.10; p= 0.089). Age, sex, and year of treatment did not significantly influencing the outcome.[10] *Conclusions:* We come to the conclusion that silibinin should be the only treatment besides basic intensive care. It might be an indirect clue to the efficacy of silibinin treatment that an early start leads to a significantly better survival. This is supported by recent research[3] where silibinin has an intracellular effect in hepatocytes lowering the rate of apoptosis significantly showing that silibinin does not only hamper the uptake of amatoxins for which it might be too late when started, but acting on the intrinsic and extrinsic signalling pathways for apoptosis in a later face of a poisoning. *References:* 1. Cochet-Meilac M, Nuret P, Corvalin JL, et al. Animal DNA-dependent RNA Polymerases. 11. Mechanism of the inhibition of RNA Polymerases B by amatoxins. Biochem Biophys Acta 1974; 353:160–184. 2. Cochet-Meilac M, Nuret P, Corvalin JL, et al. Animal DNA-dependent RNA Polymerases 12. Determination of the cellular number of RNA Polymerase B molecules. Biochem Biophys Acta 1974; 353:185–192. 3. Behm V, Müller B, Koch A, et al. Knollenblätterpilzvergiftung und neue Therapieoptionen. 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116. Can Morels (*Morchella SP.*) Induce a Toxic Neurological Syndrome?

Saviuc P,[1] Harry P,[2] Pulce C,[3] Manel J,[4] Garnier R.[5]
[1]*Centre de Toxicovigilance, CHU, Grenoble;* [2]*Centre Antipoison et de Toxicovigilance, CHU, Angers;* [3]*Centre Antipoison et de Toxicovigilance, Hôpital Edouard Herriot, Lyon;* [4]*Centre Antipoison et de Toxicovigilance, CHU, Nancy;* [5]*Centre Antipoison et de Toxicovigilance, Hôpital Fernand Widal, Paris, France*

Objective: Morel-poisoning cases with neurological symptoms were reported in 2006 in France. To confirm the existence of a new mushroom-poisoning syndrome, data from the French poison and toxicovigilance centres (CAPTV) were analysed. *Methods:* Retrospective study based on symptomatic cases involving morel (*Morchella*), collected from 1976 to 2006 in the French CAPTV databases. Cases were classified into: isolated gastrointestinal syndrome (GIS), neurological syndrome (+/– associated with GI signs) (NS) and other signs or symptoms (OS). Time elapsed from ingestion to symptom onset, age, sex, duration of signs or symptoms, eating conditions and quantities ingested were recorded. *Results:* After ingestion of morels, 146 patients presented with GIS (nausea 28%, vomiting 60%, abdominal pain 35% and diarrhea 43%), with a median onset time of 5 hours (25th–75th percentiles: 2-12 h); 129 intoxicated patients presented with NS (tremor 53%, dizziness/inebriation 53%, balance disorders/ataxia 21%), with a median onset time of 12 h (25th–75th percentiles: 10–14 h; significantly different from the GIS onset time: p<0.001); the first case was reported in 1976. In the NS group, GI signs (67%) and other neurological signs (ocular: 25%; paresthesia: 7%) were also observed; all signs improved within a median time of 12 h. Eleven patients presented OS, including 4 cases suggestive of an allergic reaction. No significant differences in age (median: 41 and 50 years, respectively) or sex were observed between the GIS and the NS groups. Morels had been eaten raw or poorly cooked in half of the cases. Ingestion of large quantities of morels were more frequent in the NS group (35.9% vs. 5.8%, p = 0.001). Confusion with *Gyromitra* and contamination with xenobiotic agents (pesticides, metals) were ruled out. *Conclusion:* In 2006, a German 6-case series of cerebellar signs induced by Morchella was reported (1). Isolated cases had been published earlier in mycology journals in 1930 (Algeria), 1962 (Germany) and 1999 (Spain). Existence of a cerebellar-like syndrome after morel ingestion was confirmed in this series. Ingestion of large amounts of morels seems to be the main determining factor. *References:* 1. Pfab R, Haberl B, Kleber J, et al. Cerebellar effects after consumption of edible morels. Clin Toxicol 2008; 46:259–260. *Acknowledgement:* French poisons and toxicolvigilance centres in Bordeaux, Lille, Marseille, Reims, Rennes, Strasbourg and Toulouse, France.

117. Deaths and Organ Transplantations after Mushroom Poisoning in Finland 1937–2006

Mustonen H, Hoppu K.
Poison Information Centre, Helsinki University Central Hospital, Helsinki, Finland

Objective: To study the incidence of death or organ transplantation due to mushroom poisonings in Finland during a 70 year period. *Methods:* Copies of all death certificates of all persons who died due to a mushroom poisoning between 1969 and 2006 were obtained from the Statistics of Finland. Similar data was available from a published study for 1937–1968.[1] The Finnish Official Cause-of-Death Statistics are in practice 100% complete. The accuracy of the death certificates and their cause-of-death codes are verified by medico-legal autopsies performed in all cases suspected to be due to poisoning. Data on transplantations performed in Finland were obtained from the Finnish Transplantation Registry. The annual mid-populations were obtained from the Official Statistics of Finland. *Results:* Fourteen persons died in mushroom poisoning during the 70 years, with a total incidence of 0.004 per 100,000 person-years. In 10-year intervals, the number of deaths varied between 0–5 (0–0.011 per 100,000 person-years), without any clear trend over time. Kidney transplantations started in 1964 and liver transplantations in 1983. Five persons received a kidney, and 3 a liver transplant for a mushroom poisoning. *Amanita virosa* caused 3 of the deaths and all liver transplantations. Additionally 2 deaths were caused by unidentified phalloidin containing mushrooms. *Cortinarius rubellus* caused 3 deaths, all after kidney transplantation, and 4–30 yrs after the poisoning. Two deaths in the 1940s were attributed to *Gyromitra esculenta*, both were children who had eaten raw mushrooms. One death was attributed to *Paxillus involutus* and three deaths in 1941–1950 to unidentified mushrooms. *Conclusion:* Deaths due to mushroom poisonings are rare in Finland. The incidence of mushroom poisoning deaths has remained essentially unchanged over 70 yrs. *Amanita virosa* and *Cortinarius rubellus* were the most common causes of mushroom poisoning leading to death or organ transplantation. Thanks to kidney transplantation, deaths after *Cortinarius rubellus* poisoning followed on the average 18 yrs after the poisoning. *References:* 1. Åkerblom H. [Mushroom poisoning]. Duodecim 1967; 83:809–820.

118. Clinical Features of 60 Consecutive ICU-Treated Patients Envenomed by *Bungarus Multicinctus*

Höjer J,[1] Hung HT,[2] Du NT.[2]
[1]*Swedish Poisons Information Centre, Karolinska Institute, Stockholm, Sweden;* [2]*Vietnam Poison Control Center, Hanoi Medical University, Hanoi, Vietnam*

Objective: In northern Vietnam, *Bungarus multicinctus* (many-banded krait, Chinese krait) is the only krait of medical importance. This snake exists in many Asian countries, but only a few case series have been published.[1,2] *Methods:* We report a retrospective study of 60 consecutive patients admitted to an ICU in

Hanoi during 2000–2003 because of envenoming by *B. multicinctus*. *Results:* Their mean age was 33 years (range 12–67) and 77% were male. The majority were agricultural workers and 69% of the snakebites occurred during the night. The mean length of time until the first symptom developed was 3 hours (range 0.5–24 hours). The only sign at the site of the bite was fang marks, which were noted in 90%. The most common neuromuscular symptoms were ptosis and mydriasis (93%), ophthalmoplegia (82%), jaw weakness (90%), pharyngeal pain (83%), palatal palsy (90%), neck muscle paralysis (85%), limb paralysis (85%), and paralysis of the respiratory muscles (87%). No antivenom was available. Fifty-two patients (87%) needed mechanical ventilation for a mean of 8 days. The most surprising laboratory finding was a high rate of significant hyponatremia (42%). The mean duration of the ICU stay was 12 days and the hospital mortality was 7% (four cases). According to the Poisoning Severity Score criteria, 54 patients (90%) were classified as severe or lethal envenoming. *Conclusion:* This study provides important information on envenoming by *B. multicinctus*. The new finding of a high rate of hyponatremia makes screening and in some cases prompt sodium replacement imperative, and the pronounced neuromuscular symptoms recorded urge for a specific antivenom. *References:* 1. Chan JCN, Cockram CS, Buckley T, et al. Envenoming by Bungarus multicinctus (many-banded krait) in Hong Kong. J Trop Med Hyg 1995; 98:457–460. 2. Pe T, Myint T, Htut A, et al. Envenoming by Chinese krait (*Bungarus multicinctus*) and banded krait (B. fasciatus) in Myanmar. Trans R Soc Trop Med Hyg 1997; 91:686–688.

119. When and Why is Chromium Carcinogenic?

Bradberry S.
National Poisons Information Service (Birmingham Unit), Birmingham, UK

Introduction: Naturally occurring chromium exists predominantly in the trivalent state as chromite ore which is a mixture of chromium, iron, aluminium and magnesium oxides. Trivalent chromium salts have some industrial applications including use as tanning agents, paint pigments and catalysts. Hexavalent chromium is used in chrome plating, leather tanning, chromate dye and pigment manufacture and is formed as a by-product of stainless steel (a combination of iron and ferrochromium) welding and smelting. Chromium is also encountered as metallic chromium and in chromium alloys (including ferrochromium) in which it possesses a valency of zero. Why is chromium carcinogenic? An association between occupational chromium exposure and cancer has been recognized for over a century.[1] Hexavalent chromium is a confirmed carcinogen though there is inadequate evidence in humans for the carcinogenicity of trivalent chromium compounds.[2,3] Important differences in the physicochemical properties of these two oxidation states account for their respective contribution to chromium carcinogenicity. Hexavalent chromium forms strongly oxidizing chromate and dichromate ions which are generally well absorbed and readily cross biological membranes through anion channels. In contrast, trivalent chromium is more stable, less well absorbed and can only cross cell membranes by phagocytosis or complexed with transferrin. However, within cells hexavalent chromium is reduced readily to trivalent chromium. Reactive oxygen species (including hydroxyl radicals and superoxide) generated during this process can cause oxidative damage to DNA.[4] Intracellular trivalent chromium forms stable complexes cross-linking the phosphate backbone of DNA with molecules such as proteins, glutathione and cysteine. The resulting DNA damage results in an increased frequency of gene mutations and thus greater risk of deranged cell division and differentiation. In addition hexavalent chromium alone has been shown in *in vitro* studies to activate mitogenic protein kinases and transcription factors that are involved in inflammation and tumour growth.[4] When is chromium carcinogenic? There is a wealth of epidemiological data showing that occupational exposure to hexavalent chromium results in an increased incidence of lung cancer in chromate and chromate pigment production workers and chrome platers.[2,5] For this reason, OSHA has recently reduced the permissible exposure limit (PEL) of hexavalent chromium in air (8-hour time-weighted average) from 52 micrograms per cubic metre to 5 micrograms per cubic metre.[5] Controversy, however, exists regarding the carcinogenic potential of hexavalent chromium following ingestion. This has been fuelled partly by the successful litigation brought against a Californian energy company in 1993 by the environmental activist Erin Brockovich.[6] Less than 10 per cent of orally administered hexavalent chromium is absorbed from the gastrointestinal tract in man and this is reduced further (to less than 1 per cent) if given with a reducing agent such as ascorbic acid, presumably due to reduction to trivalent chromium before absorption.[7] However, even when administered with ascorbic acid, the urinary half-life of orally administered hexavalent chromium is longer than that for trivalent chromium, suggesting that hexavalent chromium is not completely reduced in the acidic conditions in the stomach.[7] Thus, ingestion may result in systemic uptake of hexavalent chromium. Epidemiological data assessing the cancer risk of hexavalent chromium-contaminated drinking water are limited.[8] A recent re-evaluation of experience in the Liaoning Province of China between 1970 and 1978 which provided nearly 100,000 person-years of mortality follow-up among villagers exposed to drinking water contaminated with waste from a chromium processing plant, showed a substantial association between stomach cancer mortality and exposure to contaminated water.[9] In addition, a meta-analysis of occupational studies of hexavalent chromium-exposed workers revealed a statistically significant increase in stomach cancers which may reflect a degree of chromium ingestion in these occupations.[8] Hence it appears that hexavalent chromium can be carcinogenic by ingestion but the threshold for this effect remains to be clarified. *Conclusions:* Hexavalent chromium is carcinogenic via intracellular mechanisms that involve conversion to trivalent chromium. As hexavalent chromium is such a potent carcinogen, it is essential that occupational exposure is reduced to a minimum which could be achieved by a global reduction in the workplace airborne exposure limit to less than 5 micrograms per cubic metre. It is also imperative that measures are taken to ensure that hexavalent chromium does not contaminate water courses. *References:* 1. Langård S. One hundred years of chromium and cancer: a review of epidemiological evidence and selected case reports. Am J Ind Med 1990; 17:189–215. 2. IARC. Chromium and chromium compounds. IARC Monogr Eval Carcinog Risks Hum 1990; 49:208–14. 3. Gibb HJ, Lees PSJ, Pinsky PF, et al. Lung cancer among workers in chromium chemical production. Am J Ind Med 2000; 38:115–126. 4. Beyersmann D, Hartwig A. Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. Arch Toxicol 2008; 82:493–512. 5. Occupational Safety and Health Administration (OSHA). 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120. Is there Evidence that Treating Mercury-Exposed Individuals with DMPS Alters Outcome?

Felgenhauer N.
Toxicological Department of 2nd Medical Clinic, Technical University, Munich, Germany

The therapeutic effect of DMPS in inorganic mercury poisoning was already demonstrated by G.A. Belonozhko in 1958, who reported an accelerated elimination of mercury from the organism, a normalization of the kidney function and a decreased mortality of animals after treatment with DMPS. Several other investigators confirmed these results. In comparison to many other chelating agents DMPS was the most effective one: DMPS increased urinary mercury excretion leading to a reduction of the mercury content in almost all organs; only in removing mercury from the brain DMPS appeared rather insufficient.[1] Removal of methyl mercury from the body is particularly difficult because of binding of the substance to plasma and cellular proteins. Multiple studies on rodent models have demonstrated that administration of DMPS enhances mercury excretion leading to a marked decrease of mercury body burden. This is particularly obvious for the kidneys. But concerning the brain, which is the target organ of methyl mercury, treatment with DMPS had no significant effect.[2] Only a few reports have been published about DMPS treatment in human mercury poisoning. There are several studies about "chelation challenge tests" for the determination of mercury body burden or chelation in patients with dental amalgams, but reports about DMPS treatment in human mercury poisoning are regrettably anecdotal and uncontrolled so that information about the clinical benefit of DMPS treatment in mercury poisoning is very limited. In human inorganic mercury poisoning the kidney is the main target organ. As long as the renal function is still intact DMPS-treatment leads to an increased urinary mercury excretion[3] followed by a marked decrease in the mercury blood level. Severe acute inorganic mercury poisonings with acute renal failure are successfully treated by DMPS, together with haemodialysis or continuous venovenous haemodiafiltration (CVVHDF). Toet et al reported about a case of severe mercuric chloride poisoning with an initial blood mercury concentration of 14,300 µg/L treated with DMPS in combination with haemodialysis. The recovery was uneventful and complete in spite of the fact that haemodialysis proved to be ineffective with regard to mercury elimination.[4] Dargan et al. reported about a 40-year-old man who ingested 1 g mercuric sulphate and revealed initial blood mercury of 15,580 µg/l. The patient received CVVHDF for 14 days and DMPS for 19 days. When he was discharged from hospital on day 50, he was asymptomatic, with blood mercury of 32 µg/L. The total amount of mercury in the ultrafiltrate was 127 mg.[5] At the occupational level, elemental mercury vapour is the main form of mercury exposure affecting mainly the brain as target organ. A few studies demonstrate a favourable effect of DMPS in enhancing mercury elimination and to some extent in improvement of symptoms too.[6,7] Two clinical studies reported about the effects of DMPS in human subjects exposed to methyl mercury compounds.[8,9] Both studies found an enhanced urinary Hg excretion and a decreased blood mercury level following DMPS treatment. However, an immediate improvement in the condition of the patients was not observed. In summary there is no doubt that DMPS therapy enhances urinary mercury excretion. However, this enhanced excretion is meaningless from a therapeutic point of view if it is not paralleled by a decrease in the metal concentration in the critical organ.[10] According to animal studies and poor results in the few human methyl mercury poisonings there exists no evidence justifying the application of DMPS in methyl mercury poisoning. In elemental mercury vapour inhalation the highly anecdotal data do not allow any final statement regarding the clinical benefit of DMPS treatment. In inorganic mercury poisoning animal studies and partly encouraging clinical experience may recommend the treatment with DMPS. However, also in inorganic mercury poisoning there is still no evidence that DMPS alters patient outcome. *References:* 1. Buchet JP, Lauwerys RR. Influence of 2,3-dimercaptopropane-1-sulfonate and dimercaptosuccinic acid on the mobilization of mercury from tissues of rats pretreated with mercuric chloride, phenylmercury acetate or mercury vapors. Toxicology 1989; 54:323–333. 2. Graziano JH. Role of 2,3-dimercaptosuccinic acid in the treatment of heavy metal poisoning. Med Toxicol 1986; 1:155–162. 3. Garza-Ocanas L, Torres-Alanis O, Pineyro-Lopez A. Urinary mercury in twelve cases of cutaneous mercurous chloride (calomel) exposure: effect of sodium 2,3-dimercaptopropane-1-sulfonate (DMPS) therapy. J Toxicol Clin

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121. Mass Arsenic Poisoning from Drinking Water in Bangladesh

Bond GR.
Cincinnati Drug and Poison Information Center, Cincinnati Children's Hospital, Cincinnati, US

Much of Bangladesh (and some of the Indian state of West Bengal) sits atop the Ganges/Meghna/Brahmaputra river delta, and has a very shallow underground water table. In the 1970s, to fight diarrhea illness and infant mortality, a policy to encourage use of cheap, shallow "tube wells" began. Initially wells were funded by UNICEF, NGOs and the Bangladeshi Department of Public Health Engineering, but by the 1990s, most wells were privately financed. These wells are approximately 5 cm in diameter and go down 10–50 M. Tube wells can be bored manually (and relatively cheaply) to about 100 M.[1] The project was considered a great success in that by the millennium, over 10 million wells were dug, over 100 million persons were provided clean water and, even better, water was generally provided in the home limiting the need to carry water or share public resources. Three quarters of the wells were privately owned. Skin lesions consistent with arsenic exposure and a few wells with high arsenic levels were identified as early as the late 1970s and early 1980s.[2,3] However, these were sporadic and no major follow up occurred. In West Bengal the problem was apparent starting in about 1987, but it was not until 1995 that the problem was widely acknowledged in Bangladesh.[2] It took several more years until it was explored and characterized.[2] Research revealed that the soil layer into which the tube wells were sunk contained a large, easily mobilized burden of arsenic. Arsenic content in the tube wells ranged from <10 ppb to >400 ppb.[1] The WHO acceptable level is 10 ppb (micrograms/L). The acceptable limit in India and Bangladesh is 50 ppb. It is estimated that at least 35 million Bangladeshis are exposed to a water supply that exceeds 50 ppb.[1] A key issue is that of responsibility. Parties include individuals who chose wells for their homes; those who installed the wells; the government which encouraged tube wells and did not test the water or intervene when the problem was recognized; the international community which in many cases encouraged, funded or subsidized the tube wells; or the British government (via the British Geological Survey) which did a preliminary analysis of water in some parts of Bangladesh in 1992 and did not test for arsenic. Against the majority of scientists, some Indian scientists have argued that contamination is actually a result of earlier use of arsenic containing rodenticides, suggesting that those who advocated for and profited from the green revolution (Western governments, NGOs, fertilizer and seed companies) are responsible.[4] Blame has particularly focused on those with the assets to remediate the problem. The British Geological Survey has been sued (unsuccessfully) for negligence for failing to test for arsenic in water testing done in 1992.[4] The consequences of chronic sub-acute arsenic exposure include skin lesions (thickening leading to cracked, painful and infected skin), skin cancer, peripheral neuropathy, hypertension, diabetes and solid organ cancer (3,5,6,7). The nature of the risk and the lag time to onset of specific symptoms depends on the arsenic level in the water. The excess risk of dying of cancer associated with a level as low as 50 ppb has been estimated to be 1 per 100 exposed persons.[5] Accelerated atherosclerosis and diabetes risk have been linked to arsenic exposure in a dose dependent way as well.[6,7] The number of exposed persons has been estimated but the exact number of victims and the specific consequences are unknown. Furthermore, the long lag time to clinical effects, decades in the case of solid organ tumors, means that the cancer epidemic is just beginning.[2,3,4,5,6] Arsenic does not bioaccumulate. Serum or urine arsenic concentrations reflect recent exposure. Apart from symptoms, there are no markers for the extent of individual exposure over time. With cessation of exposure arsenic is renally excreted.[5] No specific treatment for chronic, low dose, inorganic arsenic exposure is used, but risk identification, exposure reduction and longitudinal tracking for disease is important.[5] Only recently have efforts to find and track victims begun.[2] As arsenic falls, skin lesions and neuropathy improve. Risk of atherosclerosis, diabetes and cancer stabilizes (but may not decrease). Options for an arsenic free water supply include return to surface water use, identifying and sharing low arsenic tube wells, deeper wells, post extraction water treatment in bulk or in the home and piped water from a central source.[1,2,4] For the Bangladeshis, most options are cost prohibitive.[2,3] Since 1997 the World Bank has committed $2 per known exposed person to the Bangladesh Arsenic Water Supply Project.[2] This project has focused on education (willingness to pay for remediation correlates with understanding the hazard), identification of victims, identification of at risk wells, and mitigation (particularly in villages where more than 80% of supply is unacceptable).[2] Advocacy websites and academic papers have scathingly reviewed the management efforts of the Bangladeshi government, by some markers one of the most corrupt and inefficient on earth.[2,4] Any long term solution will require will, organization and money, none of which is currently unavailable. In the mean time millions suffer. *References:* 1. Kinniburgh DG, Smedley PL, eds. Arsenic contamination of groundwater in Bangladesh. British Geological Survey Technical Report Vol 2: Final Report February 2001. 2. Atkins P, Hassan M, Dunn C. Poisons, pragmatic governance and deliberative democracy: The arsenic crisis in Bangladesh. Geoforum 2007; 38:155–170. 3. Chowdhury AMR. Arsenic Crisis in Bangladesh. Sci Am 2004; 8:87–91. 4. http://www.sos-arsenic.net accessed 12/5/08 5. Smith AH, Lingas E, Rahman M. Contamination of drinking water by arsenic in Bangladesh: a public health emergency. Bull World Health Organ 2000; 78:1093–1103. 6. Navas-Acien A, Silbergeld EK, Pastor-Barriuso R, et al. Arsenic Exposure and Prevalence of Type 2 Diabetes in US Adults. JAMA 2008; 300:814–822. 7. Wang CH, Jeng JS, Yipet PK, et al. Carotid atherosclerosis is associated with ingested inorganic arsenic, showing a significant biological gradient. Circulation 2002; 105:1804–1809.

122. Strategies to Improve Poison Center Efficiency and to Reduce Workload

Krenzelok EP.
Pittsburgh Poison Center, University of Pittsburgh Medical Center, Pittsburgh, US

Introduction: Poison information centers operate 24/7/365 and are labor-intensive operations. Functional responsibilities include caller consultation, medical record documentation, researching toxicology and patient care issues, and other time-consuming activities. The advent of computerization has facilitated both documentation and toxic exposure assessment and has helped to make poison centers operate more efficiently and effectively. Yet, even with these advancements, poison centers rely most heavily upon human resources, which account for approximately 80% of the poison center operational budget. The needs of each poison center are different and this presentation illustrates two strategies that helped to enhance staff efficiency at the Pittsburgh Poison Center (PPC) and thereby, reduce workload. *Discussion:* In 2003, the American Association of Poison Control Centers National Poison Data System reported 617,414 medication identification requests (MIR): 17.3% of all inquiries directed to poison information centers. In 2007 there were 948,055 MIR: 24.4% of U.S. poison center incoming call volume. The Pittsburgh Poison Center (PPC) experienced similar growth in the volume of MIR as well. MIR were responsible for 24,643 (18.5%) requests in 2003 and 55,473 (42.3%) in 2007; a 225% increase. The MIR occurred in a pattern that was similar to the human exposure call volume and exceeded human exposure call volume between the hours of 14:00–06:00. During 2007 the mean documented MIR daily call volume was 153 and the mean human exposure volume was 134. MIR present a significant call volume and documentation challenge/burden for poison centers. Individual workload related to responding to and documenting the MIR increased dramatically. As an initial response to the increasing MIR volume, the staff were required to collect and document only minimal information on the electronic medical record: date and time (auto-entry), caller postal zip code and the seven digit Poisindex® code of the medication that was identified. This reduced the amount of time that the professional staff spent documenting MIR, but still ensured that adequate information about trends involving the potential abuse of prescription medications was being collected. However, the shear volume of MIR competed with the core responsibility of the specialist in poison information—managing exposure calls. The increased MIR volume was responsible for a substantial amount of overtime compensation for additional staffing during the evening shift which correlated with both the peak human exposure and MIR call volumes. Secondary fallout included staff job dissatisfaction, the inability to work on special projects, participate in continuing education and have adequate work breaks. To address this issue the PPC investigated a number of strategies. The option of no longer providing the service was considered, but not considered to be a viable solution since the data obtained from MIR have a number of important applications. The addition of several staff members was an option, but a funding source could not be identified. As federal financial assistance was identified to assist the PPC enhance surge capacity, funding became available to develop an automated medication identification system that utilized interactive voice response (IVR) system technology. The PPC partnered with an established innovator in the development of self-service IVR applications to develop an all-in-one integrated voice service application to manage MIR: the PPC Medication Identification System®. The application-based system was designed to streamline poison center MIR activities through automated speech recognition and text to speech technologies. While the IVR has the capability of managing and triaging all calls electronically, PPC callers are first screened by a specialist in poison information to identify the emergent poisoning calls and to determine whether the non-emergent MIR calls should be managed by a specialist (e.g. calls that originate from a health care professional, law enforcement personnel, elderly person seeking assistance with their medications) or transferred into the IVR. The appropriate callers with a MIR are transferred to the automated self-service application; thereby, increasing poison center efficiency by freeing specialists to manage exposure calls. Through this application the PPC is able to also collect caller demographic information. In a sequential manner, the system collects, via speech recognition, the caller's postal zip code, gender, age and the medication identification code and then identifies the medication for the caller. Actual MIR-related workload has decreased by approximately 95% with the implementation of the PPC IVR application. The actual one-time development and implementation cost was approximately 50% of the annual cost associated with increasing the staff size to respond to MIR. Access to evidence-based literature in a timely and efficient manner is critical in responding to a call to the poison information center. Searching electronically or manually

retrieving key documents can expend valuable time during time-critical situations. Various electronic document management programs were evaluated and compared based on the cost of implementation and maintenance, ease of use, capabilities, and efficiency. After an evaluation process, it was determined that the Adobe Acrobat Professional® software, fulfilled all of the requirements with minimal expense. The implementation process involved scanning selected literature such as biological, chemical and radiological terrorism publications via a high speed optical scanner which produces high quality documents that are scanned efficiently at high speed (50 pages per minute) into electronic folders. The Adobe Acrobat Professional® software was used to enter the author, title, and keywords for searching. Once the information was entered, the documents were organized into a hierarchy of folders for improved search times. The searching component for SPIs was available through Adobe Acrobat Reader®. This free software, like the fully licensed version, enables the SPIs to search for literature by the date created, author, title, subject, assigned keywords or free-text search. Key papers are accessible rapidly to all specialists whether they are working in the center or remotely and eliminates manual searching of hard copy files. This improves efficiency when surge capacity is compromised, such as in a terrorism incident. *Conclusion:* Poison center budgets are generally inflexible and do not allow the acquisition of additional staff. Technology enhancements may assist SPIs in maximizing patient care by reducing factors that unnecessarily increase their workload.

123. To be Continued: The ASHT II Project

Schaper A,[1] Coleman G,[2] Desel H,[1] Edwards N,[3] Dragelyte G,[4] Duarte-Davidson R,[2] Kupferschmidt H,[5,8] Mathieu-Nolf M,[6] Orford R,[2] Pelclova D,[7] Siemon W,[1] Wyke S.[2]
[1]GIZ-Nord Poisons Centre, University Medical Centre, Göttingen, Germany; [2]Health Protection Agency, Cardiff, UK; [3]Medical Toxicology Unit, Guy's and St. Thomas' NHS Foundation Trust, London, UK; [4]Health Emergency Situations Centre, Vilnius, Lithuania; [5]European Association of Poisons Centres and Clinical Toxicologists, Brussels, Belgium; [6]Centre Hospitalier Universitaire de Lille, Lille, France; [7]General Faculty Hospital, Prague, Czech Republic; [8]Swiss Toxicological Information Centre, Zurich, Switzerland

Objective: Within the European Union there is a mesh of rapid alert systems (RAS) for different hazards, e.g. food and feed (RASFF), dangerous consumer products (RAPEX) and communicable diseases (EWRS = early warning and response system). The abbreviation RAPEX stands for the rapid alert system for all dangerous consumer products, with the exception of food, pharmaceutical and medical devices. These systems link national and European public health authorities. Although the rapid alert system for biological and chemical attacks (RAS-BICHAT) connects national focal points in case of confirmed terror attacks with chemicals, there is still a gap for chemical hazards in cases of mere suspicion: in the future poisons centres and the EAPCCT will play an important role in the process of exchanging warnings concerning these hazards within the European Union. The ASHT research project prepares tools for these important new functions. The scope of the ASHT I projects was the creation of an EU-wide alerting system to detect covert release of chemicals with a criminal or terrorist intent. The acronym "ASHT" stands for "Alerting System and Development of a Health Surveillance System for the Deliberate Release of Chemicals by Terrorists". In ASHT II this task expands to all chemical incidents. *Methods:* Description of political, financial, toxicological and technical aspects of the project. *Results:* In the first phase of the project, ASHT I, two major tasks were accomplished: the feasibility of both a rapid alert system for chemicals (RAS-CHEM) by creating DEV RAS-CHEM, a preliminary "developmental" version, and a European surveillance system between poisons centres. Like ASHT I the second phase of the project is funded by the European Commission, the EAPCCT and the other project members. The duration of the project is 36 months. In ASHT II several tasks will have to be accomplished. Firstly, the DEV RAS-CHEM draft version must be converted into an EU-wide operating rapid alert system for chemicals (RAS-CHEM). The data base must be accessible via the internet. The data base shall carry out the delivery of "chemical event" alerting. The member states' public health surveillance authorities are to be integrated in the process. On the other hand the 'EU PC Forum' as a means of emergency communication between European poisons centres is to be created. This includes the testing of a prototype toxicosurveillance tool using automated data sampling in poisons centres. Toxicological aspects include the refinement of lists of chemicals, symptoms or toxidromes as important bases for mutual data exchange. Concerning the information technology level, several requirements are to be taken into consideration: for the creation of an event and for retrieval functions an appropriate relational data base structure is essential. National Public Health Authorities of the member states of the European Union and the WHO are integrated into the project as associate partners. *Conclusion:* The early warning system for chemicals (RAS-CHEM) will be integrated into the suite of other pre-existing EU early warning systems in the near future. There is a chance that poisons centres and the EAPCCT could upgrade their role for chemical alertness in Europe.

124. The Toxicological Documentation and Information Network in Germany – 2 Years Experience of Automatic Product Data Exchange Between Companies, National Authorities and Poisons Centres

Desel H,[1] Ganzert M,[2] Cordes Tillmann,[3] Butschke A,[4] Hahn A,[5] Hüller G,[6] Stürer A.[7]
[1]GIZ-Nord Poisons Centre, University Medical Center, Göttingen, Germany; [2]Department of Toxicology, Klinikum rechts der Isar der TU München, Munich, Germany; [3]Informatik-Service Tillmann Cordes, Freiburg, Germany; [4]Federal Office of Consumer Protection and Food Safety (BVL), Berlin, Germany; [5]Federal Institute for Risk Assessment (BfR), Berlin, Germany; [6]Poisons Information Centre, Erfurt, Germany; [7]Swiss Toxicological Information Centre, Zurich, Switzerland

Objective: More than a million different commercial products are marketed in Europe today. Access to product data is essential for efficient poisons centre (PCs) service. European and national laws regulate notification of data on dangerous products and biocides. Data notification of other products is regulated by national law only or is performed in a voluntary way. A necessity for advanced information technique for data management of product data was anticipated in the 1990. *Methods:* All German PCs and two German federal agencies were actively involved in the 'The Toxicological Documentation And Information Network (TDI) Research Project' between 1999 and 2006.[1] A product data format, a sophisticated data exchange protocol and a database system were developed in several continuously improved versions, each. Local TDI database systems were installed in German poison centres and tested comprehensively. At the end of the research project a reliable TDI network was established: two federal agencies, BfR and BVL, collect data notified by companies on dangerous products, biocides, detergents or cosmetics (and in the future tattoo colouring agents). Data packages containing recently notified data are distributed using the TDI 'file transfer protocol' (ftp) server or using CD-ROM media monthly. Product data that is notified voluntarily to PCs are also distributed via ftp server on demand. All data are formatted using product type specific formats described by Rosetta Markup Language (RML, 2) and are encrypted by Chiasmus procedure supplied by the German Federal Office for Information Security (BSI). Data download via ftp, decryption and import into the PCs' local TDI databases are facilitated by an automated procedure of TDI database software (one click only). Flexible database retrieval and data display in a product type dependent manner can than be performed consecutively using the same software tool. *Results:* Up to November 2008, about 270,000 product documents were automatically distributed to 9 PCs via TDI. About 10,000 new or altered documents are exchanged monthly. *Conclusion:* TDI database system has become an reliable tool for product data retrieval in the daily work of 9 PCs in Germany. TDI experience may be helpful in developing a Europe-wide product data exchange. *References:* 1. www.tdi-network.org, 2. www.toxinfo.org/Rml

125. A Systematic Evaluation of Medication Errors Reported to the Poison Center

Farmer BM,[1,2] Nelson LS,[1,2] Hoffman RS.[1,2]
[1]Dept. of Emergency Medicine, New York University School of Medicine; [2]New York City Poison Control Center, New York, US

Objective: Medication errors potentially result in patient harm. This study evaluated medication errors reported to the poison center (PC) that lead to significant patient harm including death, cardiac arrest or respiratory arrest. *Methods:* The PC database was searched from 1/1/2000-8/31/2008 for unintentional therapeutic errors that occurred in a healthcare facility (HCF). Cases were excluded if they resulted in no harm, an unrelated effect, or were not followed due to no or minimal expected patient harm. The number of outcomes, types of events, and common medications implicated were cataloged. *Results:* A total of 530 cases were identified, 267 of which were excluded (66, not followed; 189, resulted in no harm; 12, were coded as unrelated). Among the remaining 263 (49%) cases leading to clinical effects there were 8 deaths, 5 of which were directly related to the medication error. Three deaths were coded as unknown if related, although a medication error resulted in the initial call to the PC. These patients likely died from their underlying condition and not their medication error. Errors that resulted in fatality involved anticoagulation (heparin runaway infusion), antihypertensives (crushed sustained release calcium channel blocker), opioids (morphine dosed too frequently), sedatives (propofol used during intubation), and anticonvulsants (fosphenytoin – 10× dosing error in an infant). Three cardiac arrests (dosing error of a local anesthetic, runaway diltiazem infusion, and high dose antihypertensives given to wrong patient) and 3 respiratory arrests (carbamazepine - 10× dosing error in a neonate, methadone given to the wrong patient, and parenteral opioid given in too high of a dose) were reported in which the patients survived. *Conclusion:* Nearly half (49%) of medication errors reported to the PC resulted in known effects to the patient. Of these, 3% resulted in death, an additional 1% in cardiac arrest, and an additional 1% in respiratory arrest. Malfunctioning pumps, high risk populations, opioids, anticoagulation, antihypertensives, and anticonvulsants were common to many of the cases. Systems must be in place to protect patients in high risk populations from common medications involved in errors reported to the PC.

126. Plant Poisoning in Children

Vivisenco CI, Babaca DA.
Department of Toxicology, Emergency Hospital for Children Grigore Alexandrescu, Bucharest, Romania

Objective: The aim of the study is to evaluate the spectrum of potentially poisonous plants exposures dealt with by the Department of Toxicology of our hospital. *Methods:* We reviewed retrospectively the medical records of the children admitted with the diagnosis of acute plant poisoning between November 1st, 2003 and October 31st, 2008. We recorded demographic characteristics, seasonal distribution, plant species involved, clinical presentation and outcome. *Results:* During the 5 years period of study, 28 cases of acute plant poisoning were recorded. This represents 0.49% of all cases admitted with acute poisoning in our department. The children were aged 9 months to 16 years old, with a peak of incidence in the 1–3 years group (n = 15, 53%). There were many more boys (n=19, 68%) than girls (n=9, 32%). 60% of patients came from rural environment. The seasonal distribution showed a higher incidence in summer-fall months (70%). The toxic plants involved were house ornamental plants in 9 cases – *Colocasia spp*

(n = 7) and wild plants in 19 cases - *Atropa belladonna* (n = 6), *Ricinus communis* (n = 3), *Datura stramonium* (n = 2), *Conium maculatum* (n = 1) and *Sambucus ebulus* (n = 4). 5 plants were not identified. All cases were due to accidental ingestion. The ingestion of *Colocasia spp* was followed by lips and tongue oedema and sialorrhea (all cases), dysphonia (1 case), gastroenteritis (3 cases). *Atropa belladonna* and *Datura stramonium* caused atropinic syndrome: mydriasis, tachycardia, dry mucous membranes (all cases), hallucinations (5 cases), hyperthermia (1 case). *Conium maculatum* caused nausea and vomiting. *Ricinus communis* caused choleriform enterocolitis. *Sambucus ebulus* didn't cause any symptoms. All the patients were discharged home without complications after an average hospitalisation period of 1.39 days. *Conclusion:* Compared to drug overdosage and exposure to household and agricultural poisonous chemicals, the incidence of plant poisoning is low. The amount of plant ingested by children is usually small, thus the incidence of serious systemic toxicity is low. The most serious clinical manifestations are associated with plants containing atropine-like alkaloids. *References:* 1. In: Shannon M, Borron S, Burns M., eds. Haddad and Winchester's Clinical Management of Poisoning and Drug Overdosage, 4th ed. Saunders Elsevier, 2007:473–506. 2. Bruneton J. Toxic Plants Dangerous to Humans and Animals, Lauvoisier Publishing, 1999.

127. Life-Threatening Systemic Toxicity and Airway Compromise from a Common Adder Bite to the Tongue

Jessen C,[1] Hoegberg LCG,[3] Rasmussen AC,[3] Lambertsen K,[2] Stensballe J.[3]
[1]Department of Anaesthesiology and Intensive Care Medicine, Aarhus University Hospital, Aarhus; [2]Department of Otorhinolaryngology, Aarhus University Hospital, Aarhus; [3]The Danish Poisons Information Centre, Bispebjerg University Hospital, Copenhagen, Denmark

Objective: The tongue is a highly vascular organ taking part in the upper airway integrity, where envenomation may lead to severe reactions. Envenomation by the common adder (*Vipera berus*) is rarely fatal, however we present a case with life-threatening airway compromise and severe systemic toxicity after envenomation to the tongue. *Case report:* 24-year old man attempted to kiss a common adder, which bit him on the tongue. Within 15 minutes of envenomation, he experienced tongue swelling and hypotension (BP 75/45 mmHg, HR 110 beats/min). Antihistamine, corticosteroid and crystalloids were administered. The patient arrived in hospital within two hours of envenomation, where fang marks at the anterior part of the tongue was identified. The patient experienced increasing oral, pharyngeal and facial oedema, not allowing for oral airway access, and was still in a hypotensive state (BP 85/45 mmHg, HR 130–145 beats/min). Fiberoptic nasopharyngeal intubation failed due to complete upper airway obstruction. Acute tracheotomy was successfully performed and stabilised the saturation from 30% to 97%. Ovine Fab antivenom, ViperaTab®, was administered as a infusion of 200 mg in 30 min, but had to be paused due to circulatory collapse (BP 65/35 mmHg). Infusion of inotropes stabilised the circulatory failure, and the patient was transferred to the ICU. The ViperaTab® was continued without further complications, but along with inotropes and volume resuscitation. Due to continued circulatory failure, ViperaTab® was uncomplicatedly re-dosed 14 hours after arrival. The re-dosing was successful in the treatment of the systemic, toxic effects, but the patient stayed until day 8 in the ICU due to prolonged airway compromise. He was discharged eleven days after envenomation. Arrival laboratory analyses revealed severe leucocytosis (29 × 109/l), elevated C-reactive protein, non-overt DIC, and slightly elevated kidney, muscle damage, and cardiac parameters. *Conclusion:* We present a severe local and systemic toxic reaction due to envenomation from the common adder, a relative low-venomous venom. The reaction was severe and sustained due to rapid and suspected high-dose uptake of venom. The possible cause of the reaction to the first ViperaTab® dose is unclear. A repeated dose of ViperaTab® and advanced symptomatic treatment supported our patients full recovery.

128. Recovery After Life Threatening *Taxus Baccata* Poisoning

Pap C.
Department of Clinical Toxicology, Péterfy Hospital, Budapest, Hungary

Objective: The mortality rate of intoxication caused by *Taxus baccata* is very high and we have no antidote for it. *Case report:* A 42-y-o woman ingested a cup of tea made from yew leaves. After an hour she appeared at our department. On admission she had stable vital parameters. The 12-lead surface ECG showed diffuse ST-segment depression and mildly widened QRS-complexes. Echocardiography examination revealed hypokinesis of the apex and that of the distal segment of lateral and anterior wall. After the bedside echocardiography she suddenly developed a polymorphic ventricular tachycardia followed by ventricular fibrillation. Electrical defibrillation was performed 18 times. After giving her an intravenous bolus of 480 mg digitalis Fab fragment the VF was terminated. One day after a controlled examination of echocardiography showed no wall motion abnormalities. Five days after she discharged without sequelae. *Conclusion: Taxus baccata* poisoning can cause myocardial wall motion abnormality. As for therapy, although the exact mechanism of taxin alkaloids is not perfectly understood, digitalis Fab fragment may be a useful therapy of choice for patients poisoned by *Taxus baccata*.

129. An Occupational Scorpion Sting in Philadelphia from a Nonindigenous Species

Madsen JM, Greenberg MI.
Department of Emergency Medicine, Drexel University College of Medicine, Philadelphia, US

Objective: Scorpion stings can occur in parts of the world where scorpions are not normally found. This report describes such a case and illustrates the importance of not considering the possibility of such envenomations regardless of geographical location. The case also resulted in unusual long-term sequelae. *Case report:* A 72-year-old warehouseman in Philadelphia, Pennsylvania (USA) was unpacking basil in a shipment from Florida when he experienced intense pain in his right thumb. Approximately an hour later, he began to exhibit hypersalivation, coughing, and difficulty breathing. He became agitated and confused and was admitted to a hospital, where his course was remarkable for hypertension. Six months after his discharge, he reported persistent numbness in his right thumb as well as pronounced anxiety and restlessness. Although hospital staff initially discounted the possibility of a scorpion bite, the scorpion that stung the patient was in fact recovered from the warehouse. We determined that it was a *Centruroides* species, either *C. vittatus* or *C. hentzi*. The range of these two species does not include Pennsylvania. Both of these species are unusual in exhibiting climbing rather than burrowing behavior in response to threats, and this specimen appears to have climbed the basil that ended up being shipped from Florida. However, basil is shipped from a wide variety of sites throughout the world, and the proximate port need not be the ultimate origin of inadvertently imported scorpions. *Conclusion:* It is important to realize that because of international trade scorpion bites can occur in geographical areas remote from the known distribution of scorpion species. Scorpions must not be discounted as potential causes of occupational envenomations, and it must be realized that even seemingly innocuous species can produce long-term toxicological sequelae. *References:* 1. Shelley RM, Sissom WD. Distributions of the scorpions Centruroides vittatus (Say) and Centruroides hentzi (Banks) in the United States and Mexico. J Arachnol 1995; 23:100–110. 2. Brown CA, O'Connell DJ. Plant climbing behavior in the scorpion Centruroides vittatus. Am Midl Nat 2000; 144:406–418. 3. Ismail M. The scorpion envenoming syndrome. Toxicon 1995; 33:825–858.

130. Pantherina Syndrome Related to *Amanita Abietum*

Payen C,[1] Saviuc P,[2] Moreau P-A,[3] Zamour-Tissot C,[4] Pulce C,[1] Hayek M,[5] Descotes Jacques.[1]
[1]Poison Centre, University Hospitals, Lyon; [2]Toxicovigilance Centre, University Hospitals, Grenoble; [3]Laboratory of Botanics, School of Pharmacy, Lille; [4]Mobile Emergency Care Services, Valence; [5]Poison Centre, University Hospitals, Marseille, France

Introduction: Amanita abietum is a mushroom species very close to *Amanita pantherina*, whose toxicity is rarely mentioned and considered to be similar to *A. pantherina*. To date, no cases have been described. We report a case of collective poisoning. *Case report:* In June 2008, a man (64 years old) and two women (65 and 76) each ate 3 spoonfuls of a potato-mushroom dish. The mushrooms had been picked the day before and were thought to be *Amanita rubescens*. They did not eat the whole dish because of a lack of organoleptic properties. Shortly after the meal, the man presented with vomiting and the women with nausea and dizziness. The 65-year-old woman called the poison centre 1.5 hours after the meal. The interview was confused and frequently interrupted by her efforts to vomit. Yet she never remembered having this interview. Because of her cognitive disorders and phone contact becoming lost within the next hour, the mobile emergency medical care unit decided to intervene. Her Glasgow Coma Scale score was 8 and she had probably convulsed (presence of a lateral tongue biting). The two other poisoned patients had impaired consciousness (Glasgow Coma Scale score at 10). At hospital admission, the two women were still very sleepy and they presented with agitation associated with hallucinations, myoclonias, tachycardia and bilateral mydriasis. The clinical setting of the man was less severe (due to early vomiting?). Symptoms receded within less than 24 hours for the 3 patients. *Conclusion:* The poisoned patients presented a severe pantherina syndrome. *Amanita abietum* was clearly identified by an experienced mycologist among mushrooms gathered a few days later at the original picking location. This species is likely to be mixed up with *Amanita rubescens* (edible and tasty) and overall with *Amanita spissa* (edible but poor-tasting).

131. Death After Ingestion of a Topical Aphrodisiac Containing Toad Venom

Soghoian S,[1,2] Ravikumar P,[3] Nelson LS,[1,2] Hoffman RS.[1,2,3]
[1]New York City Poison Control Center; [2]New York University; [3]New York City Department of Health and Mental Hygiene, New York, US

Objective: Toad venom, a constituent of some "herbal" aphrodisiacs, contains potent bufodienolides that cause digoxin-like toxicity. Treatment with empiric doses of digoxin specific Fab fragments (Fab) was life-saving in several cases of toad venom ingestion.[1] We report a patient who developed a fatal dysrhythmia 32 hours after ingestion of a topical aphrodisiac called "piedra"', despite administration of 35 vials of Fab (DigiFab™). *Case report:* A 35 year old healthy Mexican laborer presented to the ED with vomiting and chest pain that developed four hours after ingesting an aphrodisiac "pill" given to him by a friend. Paramedics found him *in extremis*, with a barely palpable pulse of 40/min. Atropine 1 mg and 1L saline were infused intravenously. On arrival the vital signs were: BP 118/68 mmHg; HR 110/min; RR 18/min; oxygen saturation 100% on room air, and capillary glucose 9.4 mmol/L (170 mg/dL). The patient was alert, diaphoretic, and pale. Examination was otherwise remarkable only for mild epigastric tenderness. An electrocardiogram demonstrated junctional tachycardia. Twenty minutes later he again became bradycardic, and again responded briefly to another 1 mg dose of atropine. He was treated empirically with 10 vials of Fab and improved clinically. His serum potassium was 7.0 mEq/L, and a serum digoxin concentration was 2.9 ng/mL. Multidose activated charcoal was instituted, and an additional 10 vials of Fab were administered as an infusion over 12 hours. During the infusion

the patient developed varying degrees of heart block and dysrhythmias that were responsive to additional boluses of Fab. Thirty-two hours after ingestion he developed ventricular fibrillation and could not be resuscitated. Autopsy revealed a friable cube of drug-impregnated resin bathed in charcoal slurry in the stomach. Thin layer chromatography against known toad venom and standards of bufodienolides known to be present in toad venom confirmed both the identity of piedra and the absence of digoxin. *Conclusion:* Although toad venom toxicity may respond to treatment with Fab, clinicians should be aware of the potential for cyclical symptoms after ingestion of resin-based drugs since absorption can be prolonged or intermittent or the effects of Fab transient. *References:* 1. Brubacher JR, Heller MB, Padinjarekuttu RR, et al. Treatment of toad venom poisoning with digoxin-specific Fab fragments. Chest 1996; 110:1282–1288.

132. Severe Poisoning by Snakebite – A Case Report

Sarc L,[1] Priman T.[2]
[1]Poison Control Center, University Medical Center Ljubljana; [2]Izola General Hospital, Izola, Slovenia

Objectives: An increase in the incidence of snakebites was registered by national PCC in the last three years in Slovenia. In most cases the bites are considered to be caused by non-venomous snakes or as "dry" bites of venomous snakes. In Slovenia there are two species of venomous snakes *Vipera ammodytes* and *Vipera berus*. *Case report:* We present a case of a 53 year old female bitten by a horned viper. Two hours after the bite in the finger of her right hand she was admitted to the General Hospital. At admission local signs only were present: a small wound on the right thumb and arm oedema. First laboratory findings (2 hours after bite) showed thrombocytopenia 3x109/L, INR 1.52. She was treated by methylprednisolone, clemastine and epinephrine without benefit. In the following few hours she developed widely extended oedema and haematoma of the right arm and progressive systemic reaction: nausea, abdominal cramping, leukocytosis, thrombocytopenia, disseminated intravascular coagulation, hypotension, metabolic acidosis and shock, resistant to treatment with intravenous fluids and pressor drugs. She was not fit for the transport to our PCC. At the last minute (8 hours after bite) we provided her with European Viper Venom Antiserum. 10 ml of the antiserum were successfully and efficiently administered intravenously over 10 min. Sensitivity pre-testing was not accomplished due to the emergency. The dose was repeated twice: after 2 and 24 hours because of renewed decrease in blood pressure. After the third dose of the antiserum, only local symptoms were present. She did not develop any adverse reaction to the antivenom and was discharged in the next few days. *Conclusion:* Severe poisoning by snakebite has been rare, and treatment with the venom antiserum has not been used for more then 15 years in Slovenia. Climate changes could contribute to the increase in the *Vipera ammodytes* population as well as to their venom changes. This could be a reason for more frequent and severe poisonings by snakebite. The course of such poisoning may be quite rapid and therefore many hospitals have to be provided with viper venom antiserum.

133. Poisoning from *Latrodectus Tredecimguttatus*: Two Clinical Cases

Vecchio S,[1] Petrolini V,[1] Bigi S,[1] Lonati D,[1] Giampreti A,[1] Sesti E,[2] Locatelli C.[1]
[1]Poison Control Center and National Toxicology Information Centre, IRCCS Maugeri Foundation and University of Pavia, Pavia, Italy; [2]Emergency Department, G. Giglio Hospital, Cefalù, Italy

Objective: Latrodectus tredecimguttatus is an arachnid of the black widow spider family, recognizable for its 13 red spots on the black dorsum. Its venom may cause local effects and systemic symptoms. We describe two cases of poisoning with severe clinical course. *Case report 1:* A 28 year-old patient presented to the Emergency Department (ED) with profuse sweating, accompanied by chest, abdominal and back pain, dyspnoea, abdominal distension, urinary retention, hyperthermia. Suspecting an aortic dissection or pulmonary embolism, diagnostic exams were performed with negative results. Later, the patient referred to the fact that he had felt a sting on his calf and seen a black red-spotted spider. The bitten area was mildly hyperaemic. Latrodectus bite was suspected and symptomatic treatment was started. During the following hours a diffuse cutaneous rash appeared. The following day the patient still presented diffuse muscular and abdominal pain, angor, hypertension, leukocytosis, mild increase of troponin I, normal ECG and cardiac ultrasound. He completely recovered on day 5 after symptomatic treatment. *Case report 2:* A 62 year-old patient presented to ED with a sting on his hand. At admission he presented sudden chest, dorsal and abdominal pain, sweating and transient loss of consciousness. Chest X-ray, ECG, routine haematochemical and cardiac enzymes were normal. Subsequently, the patient twice developed sweating and syncope. After regaining consciousness, he presented mild dysarthria, deficit of VII cranial nerve, hyposthenic omolateral arm, hypotension. Encephalic and chest CT-scan were performed to exclude an aortic dissection or stroke, with negative results. In correspondence with the sting an ecchymotic-oedematous lesion, lymphangitis up to the axilla appeared, with leukocytosis and D-dimer increase. Latrodectus bite was suspected and crystalloids, steroids, antihistaminics and antibiotic prophylaxis were administered with improvement until discharge on day 17. *Conclusion: Latrodectus* venom contains proteins and enzymes that bind to specific receptors, increasing cell membrane permeability and releasing acetylcholine. Local lesions (cyanotic-whitish, oedematous) can be accompanied by muscular, chest and abdominal pain, altered consciousness, vomiting, respiratory and cardiac failure and cutaneous rash. Persistence of symptoms varies depending on quantity of venom inoculated. Serum antilatrodectus could be efficacious, but was not available in Italy.

134. Treatment of *Digitalis Purpurea* Poisoning with Digoxin Specific Fab Fragments

Pistelli A, Botti P, Galli V, Gambassi F, Ieri A, Missanelli A, Mannaioni G.
Toxicology Unit, Azienda Ospedaliero Universitaria di Careggi, Firenze, Italy

Objective: A case of *Digitalis purpurea* poisoning is reported with the aim to underline the importance of a prompt diagnosis and intervention with the appropriate antidote (digoxin specific Fab fragments). Moreover, the use of Fab fragments in poisoning from natural sources of cardiac glycosides is also established. *Case report:* A 44-year-old male was brought to an emergency department complaining of progressive nausea and vomiting. The patient reported that he was an habitual user of wild vegetables which he ate for supper the day before. The vegetables were picked in the wilderness and reported as borage (*Borago officinalis*, starflower), a frequently eaten wild herb. During the night the patient began to experience nausea and persistent vomiting and for these symptoms he was admitted to the nearest hospital. On arrival at the emergency department, the patient was alert and oriented with a blood pressure of 100/60 mm Hg, pulse 36 bpm, an history of traumatic myocardial infarction. He was taking cardioaspirin 100 mg per day and no other drugs. He denied alcohol and tobacco use and gave no history of diabetes, hypertension, renal disease, stroke, hypercholesterolemia/hyperlipidemia or allergies. Physical examination was significant only for marked bradycardia and irregular rhythm. An ECG showed a sinus bradycardia at a rate of 36 beats/min, with a suspicion of sinus-atrial block and a prolonged PR interval. Laboratory findings were normal on admission. Following poison center consult, with the suspicion of *Digitalis purpurea* intoxication, digoxin plasma concentrations were found to be 2.2 mcg/l (therapeutic range 0.9–2 mcg/l) and the patient was transferred to our Toxicology Unit. Twenty-four hours after *Digitalis purpurea* ingestion, digoxin specific Fab fragments were infused and bradycardia was rapidly resolved. The vegetables eaten were then identified as young plants of *Digitalis purpurea*. On the third day, digoxin plasma concentrations were decreased, the patient had recovered completely and was discharged home. *Conclusion:* We reported a case of acute signs and symptoms of digitalis toxicity from natural sources. Fab fragment therapy was successful and a complete recovery was rapidly achieved.

135. Rosemary or Yew? Unexpected Diagnosis of a Severe *Taxus Baccata* Poisoning Treated with Amiodarone, Intra-Aortic Balloon Pump Counter-Pulsation and Extracorporeal Membrane Oxygenation

Panzeri C,[1] Zavaritt A,[1] Faraoni L,[1] Guidetti V,[1] Ferri F,[2] Rinaldi G,[3] Bacis G.[1]
[1]Bergamo Poison Control Center, Ospedali Riuniti; [2]Cardiac Surgery ICU, Ospedali Riuniti, Bergamo; [3]Botanical Garden 'L. Rota', Bergamo, Italy

Introduction: Yew (*Taxus baccata*) is a conifer known to be toxic since ancient times: Caesar told about Catuvolcus, king of Eburones, who took his own life by ingesting yew leaves.[1] Taxin A and taxin B, the toxic alkaloids of *Taxus baccata*, block the sodium and calcium channels of the cardiac cells. Nausea, vomiting, abdominal pain, cardiac arrhythmias, respiratory distress, coma, seizures and death are the effects of yew poisoning. We describe here the case of a 44-year-old male farmer initially treated for a severe ventricular tachycardia (VT) and hypotension in a suspected myocardial infarction. *Case report:* The patient was admitted to hospital because of vomiting and loss of consciousness. First bradycardia, and then VT were present, and a severe right ventricular dilatation with biventricular dysfunction was observed by transesophageal echocardiogram. The coronarography was normal. He was unsuccessfully cardioverted and treated with amiodarone infusion. A pace-maker was applied and the intra-aortic balloon pump counter-pulsation (IABP) was started due to an intractable severe hypotension. After six hours, and because the therapy had not proved effective, the patient was transferred to our hospital for an extracorporeal membrane oxygenation (ECMO) treatment. In the following hours after ECMO, the cardiovascular symptoms were reduced. After ruling out myocarditis and with a dubious arrhythmogenic right ventricular dysplasia (ARVD), the poison center was consulted for a possible toxic origin of the event. History evaluation for herbal use and laboratory tests for carbon monoxide, drugs of abuse, tricyclic antidepressants, digoxin, antiarrhythmic drugs and pesticides were all negative. In the following days the patient recovered completely and after nine days a huge amount (approximately one hundred) of "rosemary" leaves was observed in his faeces. The hypothesis of *Taxus* was immediately confirmed with a botanical examination. The patient was transferred in good condition to the psychiatric unit 17 days after the yew ingestion. *Conclusions:* In the absence of history about toxic ingestion and of specific laboratory analysis, the intensive treatment of severe cardiovascular symptoms with antiarrhythmic drugs, temporary pacemaker, IABP or ECMO can be life-saving even after a potentially lethal ingestion of Taxus baccata leaves. *References:* 1. Frohne P, Pfander HJ. A Colour Atlas of Poisonous Plants, second edition, Manson Publishing Ltd, London, UK, 2005.

136. Compartment Syndrome after *Bothrops Jararaca* Snakebite: Aspects of Monitoring, Treatment and Outcome

Bucaretchi F,[1] Hyslop S,[1] Fernandes LCR,[1] De Capitani EM,[1] Madureira PR,[1] Vieira RJ,[1] Mello SM,[1] Meirelles GV.[2]
[1]Poison Control Center, University Hospital; [2]Trauma-Surgery Unit, University Hospital, Campinas, Brazil

Objective: To report the outcome of a patient who developed compartment syndrome after *Bothrops* snakebite. *Case report:* A 39 year-old-male was admitted 5h (T5) after being bitten in the upper lateral right leg by *B. jararaca*. Physical examination revealed

two punctures, marked and tense swelling, ecchymosis, paresthesia, intense local pain (degree 8, visual analog pain scale 0–10) that worsened after passive stretching, limited right foot dorsiflexion, and gingival bleeding. The case was classified as moderate/severe and the i.v. infusion of bothropic equine antivenom (8 vials) was initiated. The main laboratory findings on admission included incoagulable blood, a platelet count of 12,000/mm^3, total creatine kinase (CK) serum level of 580 U/L (RV < 170) and a serum venom level of 33.7 ng/ml (ELISA; cut-off, 2.3 ng/ml). High anterior compartment pressure (60 mm Hg, RV < 45) was identified at T8 using a Stryker® device for continuous monitoring. Under right leg postural drainage (30º) we detected progressive lower compartment pressures, and the device was withdrawn at T20 (subfascial pressure = 36 mm Hg). Although the patient showed a slight improvement, moderate pain (receiving tramadol) and limited foot dorsiflexion remained. In addition, progressive CK increase (3,452, T21; 6,729 U/L, T45) and muscular edema plus hemorrhage of the anterior compartment seen at MRI (T48) were also observed. Considering the unsatisfactory evolution, new anterior intracompartmental pressure was obtained at T54 (66 mm Hg), and fasciotomy was then performed at T57. Fasciotomy revealed hemorrhage/necrosis of the medial/distal segments of the anterior tibial muscle, which needed partial resection later. He also developed a local infection, and fibular palsy was then diagnosed. The patient was discharged 30 days after admission, being still under continued physical therapy. *Conclusion:* Since the local effects of *Bothrops spp* venoms may mimic the signs and symptoms of compartment syndrome, the only way to determine whether compartment syndrome has developed is to determine the intracompartmental pressure. Although the patient had shown a transient improvement after non-invasive measures (antivenom, postural drainage), limited motor function remained indicating the fasciotomy. These features heighten the importance of close qualitative (clinical) and quantitative (subfascial pressures) measures in this challenging situation.

137. Plant Poisonings According to the Czech Toxicological Information Centre from 2005 to 2008

Ricarova B,[1] Rakovcova H,[1] Pelclova D,[1] Navratil T.[2]
[1]*Toxicological Information Centre, General University Hospital and 1st Faculty of Medicine, Prague;* [2]*J. Heyrovsky Institute of Physical Chemistry, Prague, Czech Republic*

Objective: To describe the development and course following plant ingestion and the frequency of occurrence. Data based on calls to the Toxicological Information Centre (TIC) with a country wide population of approximately 10 million. *Methods:* Data on plant exposures in the years 2005 to 2008 (to 30.10.2008) taken from the Czech Toxicological Information Centre database. *Results:* Between 2005 and 2008 TIC responded to 4,251 inquiries following plant exposure resulting in 10.8% of total calls to TIC. 98.1% of total calls related to human ingestion (of which 89.2% children, 10.8% adults) and 1.9% related to plant ingestion by animals. TIC answered most calls during summer (45%), 17% during spring, 22% in autumn and 16% in winter. The most frequently ingested plant was *Mahonia aquifolium* (9%), *Taxus baccata* (yew tree) (8%), *Viscum album* (European mistletoe) (4%), *Lonicera xylosteum* (dwarf honeysuckle), *Datura stramonium* and *Diffenbachia seguine* (each 3%). Most cases dealt with oral ingestion (98%), only 2% related to skin exposure (plant dermatitis). The majority of the exposures were accidental (98%), in 1.5% abuse was suspected and in 0.5% a suicidal attempt was registered. In 88.6% of total cases no symptoms were recorded at the time of a call, in 11.2% cases mild symptoms reported (upper dyspeptic syndrome, burning or oedema in oral cavity) and in 0.2% cases severe symptoms were noticed (atropine-like effects, cardiac rhythm alteration etc.). *Conclusion:* Acute plant exposure in this country is primarily accidental and generally carries a good prognosis. This could be a result of 1) informed public who give frequent calls to TIC even in insignificant cases, 2) small amount of plant material ingested in children. Only in plants containing atropine-like alkaloids was systemic toxicity registered. *Acknowledgement:* supported by GA AV CR (project No. IAA400400806).

138. Antivenom Treatment in *Vipera Berus* Bites – Repeated Administration in 66 Cases Treated During the Period 1995 to 2008

Karlson-Stiber C, Salmonson H, Persson H.
Swedish Poisons Information Centre, Stockholm, Sweden

Objective: Specific ovine Fab fragments have since 1995 been used in Sweden in the treatment of significant Vipera berus envenoming. The aim of this study was to evaluate treatment efficacy and identify possible early markers indicating the benefit of a second dose. *Methods:* Consultations to the Swedish Poisons Information Centre concerning patients having received a second antivenom dose 1995 – 2008 were studied. Complementary data were requested from the respective hospitals. *Results:* Antivenom was given to 444 patients - ovine Fab in 415 cases and equine F(ab)2 in 29 patients. A second dose was given to 66 (15%) patients, 65 of whom were treated with Fab. Median time to the first antivenom administration was 3.5 hours (range 1–30 h). The indications were severe systemic poisoning alone (45%) or together with rapidly progressing swelling (42%). A few patients were treated because of progressive swelling only. The second dose was given with a median time of 18.5 hours (range 3–53), most commonly because of recurrent or continuous swelling (77%). A few patients (13) had relapse of systemic symptoms which invariably resolved. The swelling slowed down and in some cases the oedema even started to decrease. In 22 patients the swelling involved parts of the trunk. However, this was already happening in 17 of these patients at the time for the second dose. In a smaller group of patients (11) it was possible to identify the time for the onset of recurrent swelling more precisely and the period 8–12 hours after the first infusion seems to be the most critical. *Conclusion:* The efficacy of antivenom in reversing systemic symptoms is no longer controversial. The remaining issue is the influence on the recurrent local swelling. Obviously the second dose of Fab should be given earlier than was generally done in this material and it may be possible to prevent extensive swelling if antivenom is given within 8–12 hours after the first dose. No early clinical or laboratory parameter indicating the need of a second dose could be identified. Close observation and monitoring of the swelling remain the basis for optimum treatment.

139. A Rare Case of Temporary Coagulopathy Caused by Snake Bite (*Atheris Nitschei*)

Sagoschen I,[1] Sauer O,[1] Jachmann N,[2] Schinzel H,[3] Weilemann LS.[1]
[1]*Poison Control Centre Mainz, Johannes Gutenberg University;* [2]*Department of Laboratory Medicine, Johannes Gutenberg University;* [3]*2nd Medical Department, Johannes Gutenberg University, Mainz, Germany*

Objective: Accidental snake envenomation, a rare event in western Europe, is often caused by domesticated exotic snakes. We here report about an accidental bite of great lakes bush viper (*Atheris nitschei spec*.). In the literature, there is little information about the toxic mechanisms of this snake venom.[1–4] *Case report:* A 27 year old healthy male snake holder was bitten in the glove-covered index finger of his right hand by an *Atheris nitschei*. Since there is no antivenom available for treatment of exposure to *Atheris nitschei*, a clinically guided therapy regimen was advised to the emergency physician including periodic laboratory exams on global coagulation parameters and blood count. Blood examination showed decreased platelet count (90,000/µl), a highly increased partial thromboplastin time (>120 sec) and a lowered prothrombin time (<10%). At the same time, antithrombin (107%) was normal and remained stable (107 → 93%) as well as the initially decreased platelet count (93,000 → 73000 /µl). Due to the fact, that platelet count and antithrombin levels remained stable, an isolated defibrinogenation seemed to be more likely than severe disseminated coagulopathy (DIC) at that time, although ISTH Score for overt DIC showed a result of 6.[5] As a consequence we instigated a therapeutic regimen including the first line substitution of fibrinogen in case of severe bleeding. Within the following days the patient remained stable without major bleeding. Global coagulation parameters remained deranged and seemed to normalize within 6 days of the accident as well as the platelet count. Antithrombin levels remained normal. Subsequent examinations were performed on frozen blood samples including factors II, V, VII, VIII and XIII, vWF:AG, plasminogen and alpha2-antiplasmine. Factor XIII and VIII were decreased, whereas d-dimer and thrombin-antithrombin-complex were highly increased. These results point towards a secondary hyperfibrinolysis. *Conclusions:* Neither initial laboratory nor subsequent analysis could elucidate the underlying pathomechanism. Probably a combined effect of defibrinogenation, anti factor XIII activity (as known from other viper species) and a DIC with secondary hyperfibrinolysis led to results found in the patient. Both should be considered in future treatment recommendations. *References:* 1. Favreau P, Cheneval O, Menin L, et al. The venom of the snake genus Atheris contains a new class of peptides with clusters of histidine and glycine residues. Rapid Commun Mass Spectrom 2007: 21:406–412. 2. Kini RM. Anticoagulant proteins from snake venoms: structure, function and mechanism. Biochem J 2006; 397:377–387. 3. Mebs D, Holada K, Kornalik F, et al. Severe coagulopathy after bite of a green bush viper (atheris squamiger): case report and biochemical analysis of the venom. Toxicon 1998; 36:1343–1340. 4. Pirkle H. Thrombin-like enzymes from snake venoms: an updated inventory. Scientific and Standardization Committee's Registry of Exogenous Hemostatic Factors. Thromb Haemost 1988; 79:675–683. 5. Taylor FB Jr, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001; 86:1327–1330.

140. Monkshood (*Aconitum SP.*): Survival Despite High Blood Levels: Role of Early Treatment and Prolonged Resuscitation

Schenk-Jaeger KM,[1] Kupper J,[1] Freiburghaus D,[2] Kupferschmidt H,[1] Rauber-Lüthy C.[1]
[1]*Swiss Toxicological Information Centre, Zurich;* [2]*Department of Internal Medicine, Hospital Pourtalès, Neuchâtel, Switzerland*

Objective: Garden monkshood is considered one of the most toxic plants in Europe. *Aconitum sp.* contains diterpene (C20) and nor-diterpene (C19) alkaloids, the latter being the most toxic. Death has occurred in patients with blood levels as low as 3.6 ng/ml.[1] Toxicity results from a direct and persistent activation of sodium influx, prolonging depolarization and inducing afterdepolarization with triggered automaticity in cardiomyocytes. Half-life of aconitine has been determined in several cases of poisoning and lies between 3 and 15 hours.[2,3] *Case report:* 47 yo male with no history of severe illness. Ingestion of an unknown amount of *Aconitum sp.* in a suicide attempt. 4 hours after ingestion the patient was found, felt unwell, but was awake. When the ambulance team arrived he rapidly deteriorated with vomiting, hypotension, stupor and various arrhythmias. After intubation he was defibrillated three times for ventricular fibrillation. 4 episodes of ventricular tachycardia were successfully reversed. Upon arrival at the Emergency Department the patient was intubated, sedated and presented fixed mydriasis. Blood pressure was 80/50 mmHg, pulse 136 bpm. Neuroprotective therapeutic hypothermia but no gastrointestinal decontamination was applied. Several episodes of ventricular tachycardia and ventricular fibrillation and various conduction disturbances (bigemini) were observed within the first 6 hours after admission. 12 hours post ingestion the patient returned to normal sinus rhythm at 100 bpm and a mean arterial blood pressure of 80 mmHg. Pneumonia resulting from bronchoaspiration was treated. Uneventful extubation 36 hours after admission. The patient fully recovered within 4 days. Aconitine concentrations:

blood: 50 ng/ml; urine: 917 ng/ml; vomitus: 11920 ng/ml. Urine analysis revealed no other substances (Digoxin was negative) except benzodiazepines and opiates used during resuscitation. Potassium 3.0 mmol/l. Troponin 18 mcg/l and CK elevated due to intensive resuscitation. *Conclusion:* Early treatment and prolonged resuscitation may be crucial for survival in cases of potentially lethal aconitine intoxication because cardiovascular hemodynamic insufficiency is only transient and the half-life of aconitine is short. *References:* 1. Pullela R, Young L, Gallagher B, et al. A Case of Fatal Aconitine Poisoning by Monkshood Ingestion. J Forensic Sci 2008; 53:491–494. 2. Moritz F, Compagnon P, Kaliszczak IG, et al. Severe acute poisoning with homemade Aconitum napellus capsules: toxicokinetic and clinical data. Clin Toxicol 2005; 43:873–876. 3. Fujita Y, Terui K, Fujita M, et al. Five cases of aconite poisoning: toxicokinetics of aconitines. J Anal Toxicol 2007; 31:132–137.

141. Determination of Tryptase Serum Levels in Emergency: A Warning Sign in Insect Bites

Ricci G,[1] Caroselli C,[2] Zannoni M,[1] Codogni R,[2] Pavan M,[2] Rocca G.[2]
[1]*Clinical Toxicology Service, Ospedale Civile Maggiore;* [2]*Emergency Department, Ospedale Civile Maggiore, Verona, Italy*

Objective: To assess the value of the serum dosage of tryptase as a marker for the development of anaphylactic reactions to insect bites. *Methods:* We reviewed the cases of 100 patients admitted to our Emergency Department for insect bite (*Vespa crabro, Polistes gallicus, Apis melifera*). Seventy patients presented with skin rash, urticaria, the other 30 patients presented laringo-tracheal oedema and bronchospasm, leading to the suspicion of anaphylactic reaction. *Results:* The measured levels of tryptase in all the patients with anaphylactic reaction were extremely high compared to normal (N.V. < 11.4 ng/L. average: 28.3 ng/L); we found elevated levels of the enzyme also in 22 of 70 patients with "simple" urticaria, confirming the hypothesis of an allergic reaction and suspecting a sensibilization to a potentially severe allergic reaction that can be triggered from further insect bites. *Conclusion:* In 30 patients with insect bites, the event triggered a potentially lethal allergic reaction. The serum measurement of tryptase should therefore be performed in emergency in order to estimate the potentiality of appearance of anaphylactic shock.

142. Massive Accidental Poisoning with Deadly Nightshade Berries in Adult Patients: Case Reports of the Marseille Poison Centre

Blanc-Brisset I, Hayek-Lanthois M, de Haro L.
Poison Centre, Hôpital Salvator, Marseille, France

Objective: Accidental adult poisoning after ingestion of berries is an uncommon event. Deadly nightshade (*Atropa belladonna*) of the *Solanaceae* plant family contains tropane alkaloids: atropine, hyocyanine and scopolamine in the roots, leaves and fruits. In the literature, poisoning with this species is relatively rare and occurs most often in children. The authors describe case reports concerning adults who ingested deadly nightshade berries after misidentification. *Case report 1:* Two men, 44 and 38 years old, with a previous history of alcoholism, were hunting in the French Alps in September 2004 when they decided to eat wild blueberries (later identified as *Atropa belladonna*). Each of them ate about 50 fruits. Half an hour later, they both suffered visual disturbances and dry tongue and mouth. They arrived at the hospital 4 hours after the ingestion with severe anticholinergic clinical features: tachycardia, mydriasis, hallucinations, warm red skin and peripheral vasodilatation. They were treated with benzodiazepines, which reduced the agitation. Despite this treatment, the younger patient developed delirium 12 hours after ingestion. This complication required levomepromazine and both patient were discharged after 24 hours in the hospital. *Case report 2:* Two ladies, 25 and 31 years old, without previous history, were trekking in the Corsican highlands in September 2008. They ate for lunch wild blueberries (later botanical identification *Atropa belladonna*): about 10 berries for the younger lady and between 20 and 30 berries for the elder. Half an hour later, they both developed visual disturbances, tachycardia and restlessness. At the hospital when they arrived 15 hours later, several symptoms were still present: dry mouth, delirium, asthenia, mydriasis and disorientation. They received benzodiazepines. Urinary retention with a distended bladder was diagnosed in the 31 year old lady: 12 litres of urine were eliminated after urinary catheterization. They were both discharged after a 24 hour stay in the hospital. *Conclusion:* Massive ingestion of deadly nightshade berries may induce severe poisoning even in adult patients. Misidentification as wild blueberries is at the origin of such uncommon intoxications.

143. Death Cap May Thrive in Playgrounds in Urban Areas – A Case Report

Thorsen J,[1] Bang J,[2] Byrsting AM,[3] Hjelt K.[4]
[1]*Department of Clinical Pharmacology, Bispebjerg Hospital;* [2]*The Danish Poison Centre, Bispebjerg Hospital;* [3]*Department of Anaesthesiology and Anaesthesia, Bispebjerg Hospital, Copenhagen;* [4]*Department of Paediatrics, Glostrup Hospital, Copenhagen, Denmark*

Objective: Amanita phalloides, known as the death cap, is a poisonous fungus and when ingested it can have fatal consequences of poisoning. It has high toxic potential, so that even a small intake can cause serious toxicity. Children are considered more sensitive than adults. Besides early gastrointestinal decontamination, there are only a few effective treatment regimens, and a child should therefore always receive treatment if ingestion is suspected.[1] *Case report:* A 14-month old female was found by the staff at a nursery playground with a mushroom in the mouth. The location was suburban and distant from a forest. Albeit the unusual place of growth, the preliminary identification by the poison centre arouse suspicion of an *Amanita phalloides* mushroom. Although there was no observation of the child swallowing the mushroom, which was broken in several pieces, she had been under no observation for minutes and could theoretically have ingested a toxic dose. She was immediately brought to the ER where she was aspirated and treated with activated charcoal. Simultaneously, the mushroom was identified by an expert as *Amanita phalloides*. Treatment with the antidote silibinin was started within 3 hours of ingestion and the child was moved to an intensive care unit for continued treatment. During the following day the child did not show clinical signs of poisoning including gastrointestinal symptoms and the liver parameters remained normal. *Conclusion:* The deadly *Amanita phalloides* may thrive in unexpected surroundings as in the presented case where it grew in the playground in an urban area. It grew together with several similar mushrooms close to a beech hedge. Thus the case represents an unanticipated and in some ways unpreventable risk for serious poisoning in a setting with expected high security standards. The child in our case underwent immediate and relevant treatment in collaboration with the Danish Poison Centre and showed no clinical signs of poisoning or rise in biochemistry. The child was discharged from the hospital on the second day of admission without sequelae. *References:* 1. www.micromedex.dk

144. German Data Exchange Format for Notifications to the Federal Institute for Risk Assessment Pursuant to the Detergents and Cleaning Act

Begemann K, Kolbusa R, Buchert F, Hillebrand J, Hahn A.
National Poison and Product Documentation Centre, Federal Institute for Risk Assessment, Berlin, Germany

Background: The new German Detergent and Cleaning Agent Act came into force on 5 May 2007. Pursuant to the new Act § 10e, the manufacturers of detergents and cleaning agents must submit a data sheet with details of their product ingredients to The Federal Institute for Risk Assessment (BFR) prior to placing their products on the market. BfR passes the electronic information for the purposes of emergency advice to the 9 German poison centres (PC) of the federal states. *Results:* All data notified in accordance with the Detergent and Cleaning Agent Act must be submitted in the Extensible Markup Language (XML) exchange format provided by BfR. The BfR supplies a description of this format "XWRMG" (XWRMG.XSD) as well as an introduction (http://www.bfr.bund.de/cd/10184). Notifiers can extract their data from an existing database and use their own programs to generate a notification file in the XWRMG format. For companies, who are unable to generate an XML file, BfR provides electronic notification assistance in the form of an MS-Excel file (defined columns) with a macro to generate the XML file. This Excel file consists of four sheets: 1) "WRMG notification" This sheet "WRMG notification" is for data input. By clicking on the button "generate WRMG notification" the corresponding XML file is produced. This can be submitted by email, CD/DVD or diskette to BfR. 2) "Instructions", 3) "Example - WRMG notification" and 4) "User categories". *Perspectives:* Currently, the BfR has collected more than 12,000 formulations of detergents using the "XWRMG" format and transferred it electronically via the unique BfR product XML format "XPRODUCT" to the German PCs. There is a very positive feedback from manufacturers and distributors. They like the easy-to-use MS-Excel file with the supplied defined columns and the implemented macro function to generate the XML export. The BfR will extend the electronic principle of the notification of detergents to the other existing notification procedures (dangerous preparations, biocides, voluntary) as soon as possible to support the data transfer to the German PC. The German experience in XML data transfer from industry to PCs could provide groundwork for the future harmonized data exchange proposed in GHS-Direction Art. 45.

145. Differential Effects of Tricyclic Antidepressants in Overdose on the QRS Interval

Galal HKA,[1] Hill S,[2] Gray J,[3] Thomas SHL.[1]
[1]*Wolfson Unit of Clinical Pharmacology, Newcastle University, Newcastle upon Tyne;* [2]*Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne;* [3]*Janine Gray Statistical Consultancy and Training, East Boldon, UK*

Objective: Tricyclic antidepressants (TCAs) are widely prescribed and commonly taken in overdose. Sodium channel blockade caused by these agents results in delayed conduction velocity in His-Purkinje fibres and ventricular myocardium, manifest on the ECG as prolongation of the QRS interval. This, in turn, has been linked with an increased risk of arrhythmia and seizures in some,[1,2] but not all studies.[3] This research was a retrospective cross sectional observational study to compare the effects of individual tricyclic antidepressants on the QRS interval after overdose. *Methods:* Patients were included if they were admitted with a history of TCA overdose between the years 2000 and 2008. Details were recorded from medical notes and 12 lead ECGs coded and analysed blinded to the TCA involved for RR, QRS and QT intervals using a CalComp 9000 digitiser. *Results:* There were 511 first presentations with TCA overdose during the period of study. When available (n = 328), mean (+/– SD) reported doses were higher for lofepramine (1.76 +/– 1.09 g) and dosulepin (1.23 +/– 0.91 g) than amitriptyline (0.72 +/– 0.86 g). QRS intervals, calculated as geometric means due to the skewed nature of the data, were significantly longer for amitriptyline (92.1 ms, n = 268) and dosulepin (92.2 ms, n = 141) than for lofepramine (86.2 ms, n = 75). Multivariate regression demonstrated that QRS duration was positively associated with a past history of cardiac disease ($P = 0.022$) and male sex ($P < 0.001$) but negatively associated with use of lofepramine ($P = 0.011$). No difference between QRS effects were detected comparing amitriptyline and dosulepin. There was a weak relationship between QRS interval and dose ($P = 0.095$) but this analysis was limited by missing data. *Conclusions:* Lofepramine causes significantly less QRS prolongation than either amitriptyline or dosulepin after adjustment for other predictive variables, but there was no difference in effects on QRS interval between amitriptyline and dosulepin. *References:* 1. Boehnert MT, Lovejoy FH Jr. Value of the QRS duration

versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. N Engl J Med 1985; 313:474–479. 2. Shannon MW. Duration of QRS disturbances after severe tricyclic antidepressant intoxication. J Toxicol Clin Toxicol 1992; 30:377–386. 3. Foulke GE, Albertson TE. QRS interval in tricyclic antidepressant overdosage: inaccuracy as a toxicity indicator in emergency settings. Ann Emerg Med 1987; 16:160–163.

146. Poisons Centres Can Provide Substantial Information on Circumstances of Poisonings Needed for Regulatory Risk Assessment - Results From a Prospective Study (DeNaMiC / S 5)

Wagner R,[1] Bauer K,[1] Desel H,[1] Tempowski J,[2] Mathieu-Nolf M,[3] Mrazova K,[4] Pelclova D,[4] McParland M,[5] Edwards N,[5] Heiland A,[6] Lindner O,[6] Heinemeyer G,[6] Wyke S,[7] Duarte-Davidson R.[7]
[1]GIZ-Nord Poisons Centre, University Medical Center Göttingen, Germany; [2]International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland; [3]Centre Antipoison - Toxicovigilance, Lille, France; [4]Toxikologické informacní stredisko, Prague, Czech Republic; [5]Guy's & St Thomas' Poisons Unit, Medical Toxicology Unit, London, UK; [6]Bundesinstitut für Risikobewertung, Berlin, Germany; [7]Health Protection Agency, Chemical Hazards and Poisons Division, Chilton, UK

Objective: The research project 'Description of the Nature of Accidental Misuse of Chemicals and Chemical Products (DeNaMiC)', sponsored by the European Chemical Industry Council (CEFIC), evaluated the use of poisons centres' (PCs) data on chemical exposures for regulatory risk assessment. One subcomponent of DeNaMiC studied the feasibility of collecting additional information supplementing the standard PC case data set to better characterize circumstances of exposure. Furthermore, DeNaMiC evaluated requirements for pooling data from poisons centres to develop recommendations for future data collection. *Methods:* During a six month prospective study four European PCs collected additional data on accidental exposures to selected household products by means of a structured interview conducted within two days after the primary consultation. The interview was based on a 28-point questionnaire and was conducted by trained PC staff. Detailed data were collected on location of the accident, use or storage of the product when the exposure occurred, type of packaging, awareness of risk management measures, evidence that labelling information was understood and the instructions on safe use were followed. To facilitate multicentre data collection a structured multi-language data input tool with automatic translation of pre-defined answer phrases was developed. *Results:* During the study period the PCs received 975 enquiries about the selected products of which 457 (47%) were successfully followed up. Follow-up was more successful when the caller was the person directly concerned with the exposure. Responses to 'neutral' questions, such as location of the exposure, were more consistently obtained than those to questions that could be viewed as more emotionally 'loaded'. Narrative information provided additional details of circumstances. Although this was a feasibility study, it was possible to draw some conclusions from the data e.g. the fact that similar push-pull-closures are used for sports drinks and for dishwashing liquids seems to be responsible for accidents. *Conclusion:* PCs are able to deliver substantial data needed for regulatory risk assessment. Studies on circumstances of exposure may supply detailed data needed to constructively evaluate and improve risk assessment and measures for household chemical consumer products.

147. Mr. Yuk on Youtube

Betz AE,[1] Akhtar J,[2] Krenzelok EP.[2]
[1]University of Pittsburgh Affiliated Residency in Emergency Medicine; [2]Pittsburgh Poison Center, University of Pittsburgh Medical Center Schools of Pharmacy and Medicine, Pittsburgh, US

Objective: YouTube is a popular video-sharing website where users select and view content on a range of topics. Many people use YouTube, for education. We conducted this study to analyze the content on YouTube as it relates to the Mr. Yuk logo or commercial. *Methods:* We conducted a search on YouTube using the keyword "Mr. Yuk". We viewed all clips in their entirety where "Mr. Yuk" referred to the Poison Control Center logo or commercial. The number of times a clip was viewed, total number of comments, and number of times it was listed as a favorite were recorded. We reviewed every comment listed in response to each clip. Each comment was rated as neutral, positive or negative. Neutral was defined as informational or not relevant, positive indicated that the message served its purpose, and negative indicated that the message did not achieve its purpose. *Results:* There were 5 clips where "Mr. Yuk" referred to the Poison Control Center logo or commercial. Clip 1: Added to YouTube 2/20/06. Views as of 10/25/08: 171,138. Total number of comments: 553. Favorited 1721 times. Clip 2: Added to YouTube 8/24/08. Views as of 11/12/08: 721. Total number of comments: 6. Favorited: 2 times. Clip 3: Added to YouTube 8/18/07. Views as of 11/12/08: 2636. Total number of comments: 9. Favorited: 7 times. Clip 4: Added to YouTube 9/20/08. Views as of 11/12/08: 403. Total number of comments: 3. Favorited 2 times. Clip 5: Added to YouTube 10/12/07/ Views: 262. Comments: 0. Favorited: 3 times. When all the comments listed in response to each clip were rated, 230 were neutral, 217 were positive, and 124 were negative. *Conclusion:* Mr. Yuk has great name recognition and should be used by the toxicology community to enhance poison prevention education. It is important that the community tap into You Tube's global reach to be part of mainstream online culture.

148. What Difficulties Does Collective Poisoning Produce in a Paediatric Poison Centre?

Ulmeanu C, Nitescu V, Petran M.
Paediatric Poison Centre, Emergency Clinical Hospital for Children Grigore Alexandrescu, Bucharest, Romania

Objective: To analyze the difficulties faced and the extent of the reaction of a Paediatric Poison Centre to a collective poisoning. *Methods:* We present a collective antifreeze poisoning in children that happened in a school where, due to a technical deficiency, water mixed with antifreeze passed from the heating system into the source of drinking water. Six children presented a few hours later with abdominal pain, vomiting and dizziness. They were sent from the local hospital to the Toxicology Department of the Regional Paediatric Poison Centre. *Results:* At the time of arrival they presented with dizziness, lethargy, abdominal pain, acidosis and oxalate crystals in the urine. They were admitted and treatment with ethanol was started. The following difficulties were noted: insufficient medical staff (only one nurse and one doctor on duty), insufficient ethanol stock in the department, insufficient equipment and staff for haemodialysis if it should be necessary (only two devices),the necessity to announce the event to medical authorities, police and local authorities, the anxiety of the families and the pressure from the media. The actions carried out were the following: two nurses from other departments were temporarily brought and one doctor came from home; triage of the patients was carried out and priorities were established; a pharmacist came from home to prepare the necessary quantity of sterile ethanol; the authorities were informed about the event by phone and by fax; other two children's hospital were contacted to check the possibilities for haemodialysis; information for the parents was arranged; and a press release was organized. *Conclusion:* Even although they are not common situations, collective poisoning can occur in the paediatric population. Consequently, the Paediatric Poison Centres have to prepare special plans for managing these situations. *References:* McKay C. Risk assessment and risk communication. In: Goldfrank LR, Hoffman RS, Howland MS, et al., eds. 8th ed. New York, USA: McGraw-Hill, 2006:1758–63.

149. Is One Notification Procedure for Dangerous Products and Cosmetic Products in the EU Achievable?

De Groot R,[1] Brekelmans PJAM,[1] Meulenbelt J.[1,2,3]
[1]National Poisons Information Centre, National Institute for Public Health and the Environment, Bilthoven; [2]Institute for Risk Assessment Sciences, Utrecht University; [3]Division Intensive Care Centre, University Medical Centre, Utrecht, The Netherlands

Background: Currently, a proposal for a new Cosmetics regulation, which will replace the Cosmetics directive (76/768/EEC) and its amendments, is prepared by the European Council (EC).[1] In this regulation, both the use of frame formulations[2] for the notification of cosmetic products and a new notification procedure become legally implemented. The EC intends to collect electronically (from suppliers) as well as to distribute to governmental authorities (GA) and Poisons Information Centres (PIC) all relevant cosmetic product information. *Discussion:* Besides these proposed changes in the notification of cosmetic product information by the new Cosmetics regulation, notification procedures for dangerous products to GA/PIC will also be changed by the forthcoming EU-GHS legislation. These separate initiatives for cosmetic products and dangerous products will most certainly result in different notification procedures for both product groups to GA/PIC if nothing is done to harmonise these procedures. The consequence will be that GA/PIC need to develop two arrangements for notification of dangerous products and cosmetic products. From a cost/benefit perspective this is undesirable. It has been decided for dangerous products that the EC has three years after EU-GHS becomes effective (planned at the end of 2008) to review the possibility of harmonisation of the notification procedures in EU Member States. In the light of the intended harmonisation of notification of dangerous products, and especially the available time to find ways to realise that, it is now an appropriate moment to also evaluate the notification process of cosmetic products. However, time might be too short to realise such an evaluation and to incorporate the results in the new Cosmetics regulation. Therefore a provision, as was done for dangerous products, needs to be added to the Cosmetics regulation, giving the EC a three year period to evaluate the possibility of a harmonised notification procedure for dangerous products and cosmetic products to GA/PIC in the EU Member States. *Conclusion:* For GA/PIC and industry it will be most cost effective to have only one notification procedure for dangerous products and cosmetic products. *References:* 1. Draft Cosmetics regulation, February 5, 2008 http://ec.europa.eu/enterprise/cosmetics/html/cosm_simpl_dir_en.htm 2. Cosmetic Frame Formulations for EU Poison Centres, EAPCCT/Colipa. http://www.colipa.com/site/index.cfm?SID=15588&OBJ=28453&back=1

150. The Forthcoming EU-GHS Regulation Introduces a New Classification of Substances and Mixtures

De Groot R,[1] Brekelmans PJAM,[1] Meulenbelt J.[1,2,3]
[1]National Poisons Information Centre, National Institute for Public Health and the Environment, Bilthoven; [2]Institute for Risk Assessment Sciences, Utrecht University; [3]Division Intensive Care Centre, University Medical Centre, Utrecht, The Netherlands

Objective: To give an overview of the new health hazard classification of substances and mixtures, as introduced by the EU-GHS legislation. *Background:* The EU-GHS regulation, replacing the Substances Directive (67/548/EC) and Preparations Directive (1999/45/EC), will change the classification and labelling of substances and mixtures (preparations). After entry into force (planned at end of 2008) Poisons Information Centres (PIC) can expect to receive product information with a new classification. Both old and new classifications will exist simultaneously until 2010 for substances and until 2015 for mixtures. *Overview:* Table 1 gives an overview of the changes in health hazard classification. EU-GHS introduces new hazard classes that are subdivided in hazard categories (with new cut-off

Table 1. Health hazard classification of substances and mixtures.[1,2]

Directive 1999/45EC	EU-GHS		
		Categories and signal word	
Classification	**Hazard class**	**Danger**	**Warning**
T^+ R28 / T R25 / Xn R22	Acute toxicity Oral	cat. 1 / 2 / 3	cat. 4
T^+ R27 / T R24 / Xn R21	Acute toxicity Dermal	cat. 1 / 2 / 3	cat. 4
T^+ R26 / T R23 / Xn R20	Acute toxicity Inhalation	cat. 1 / 2 / 3	cat. 4
T^+ R39 / T R39 / Xn R68 / R37 / R67	STOT* - single exposure	cat. 1	cat. 2 / 3
T R48 / Xn R48	STOT* - repeated exposure	cat. 1	cat. 2
Xn R65	Aspiration hazard	cat. 1	
C R35 / C R34 / Xi R38	Skin corrosion/irritation	cat. 1A / 1B / 1C	cat. 2
Xi R41 / Xi R36	Eye damage/irritation	cat. 1	cat. 2
Xn R42	Respiratory sensitisation	cat. 1	
Xi R43	Skin sensitisation		cat. 1
cat.1/2 (T R45/T R49) / cat.3 (Xn R40)	Carcinogenicity	cat. 1A / 1B	cat. 2
cat.1/2 (T R46) / cat.3 (Xn R68)	Germ cell mutagenicity	cat. 1A / 1B	cat. 2
cat.1/2 (T R60/T R61) / cat.3 (Xn R62/63)	Reproductive toxicity	cat. 1A / 1B	cat. 2
R64	Effects on or via lactation		

*Specific Target Organ Toxicity

limits). For the health hazard classes four pictograms are used. The existing 'skull and crossbones' (acute toxicity cat. 1/2/3) and 'corrosion' pictogram (skin corrosion cat. 1A/1B/1C, eye damage cat. 1). New are the 'health hazard' pictogram (STOT cat. 1/2, aspiration hazard, respiratory sensitisation, carcinogenicity, mutagenicity, reproductive toxicity) and 'exclamation mark' (all remaining (lower) categories). The latter replaces the St. Andrews Cross. EU-GHS also introduces signal words: 'danger' for higher categories of hazard classes and 'warning' for lower categories. R(isk)-phrases and S(afety)-phrases will change into respectively H(azard)-statements and P(recautionary)-statements. P310 is interesting: Immediately call a POISON CENTER or doctor/physician. *Conclusion:* PICs should be aware of the new EU-GHS classification concerning hazard communication, which will exist for 7 years simultaneously with the old classification. *References:* 1. GHS legislation: http://ec.europa.eu/enterprise/reach/ghs_legislation_en.htm 2. Comparison between EU and GHS criteria (December, 2007): http://ec.europa.eu/enterprise/reach/docs/ghs/ghs_comparison_classifications_dec07.pdf

151. Implications of the New European Chemicals Regulation (REACH) for Poison Centres

Heinemeyer G,[1] Heiland A,[1] Tempowski J.[2]
[1]Federal Institute for Risk Assessment, Berlin, Germany; [2]World Health Organization, Geneva, Switzerland

Objective: To compare and analyse existing product classifications used by poisons centres and by risk assessors. This study was carried out as part of Subcomponent 3 of the DeNaMiC project. Cooperation between poison centres and the chemical industry is predominantly performed by exchanging information about product composition (manufacturers → PC) and about cases where persons had contacts with chemical products (PC → manufacturers). The new European chemical legislation (REACH) requires industry to take over responsibility for testing and assessing the safety of chemical substances, and the respective chemical products. The question arises whether poison centres can assist manufacturers in fulfilling their obligations under REACH by providing them with information about accidental exposures to their products. Such an exchange of information requires a standardized product classification system that can be used by both poison centres and industry.[1] *Methods:* The classification schemes for chemical products used in the poison centres of London, Lille and Göttingen, the German EVA categories and IPCS-INTOX, were compared with systems used in exposure assessments (e.g. ECETOC TRA, ConsExpo, REACH TGD, EU TGD for existing chemicals, EIS-Chemrisks), and in product registers. *Results:* There was a degree of comparability at the top levels of the product classifications, permitting some merging of data. At the more specific levels, however, there were many differences between PC documentation systems, as well as between PC systems and others. *Conclusion:* Information about chemical products in PCs, regulatory technical guidance documents, and product registers is not harmonised. Although this analysis involved a small number of poisons centres the same is likely to be true across Europe. REACH gives PCs an opportunity to improve cooperation with industry. Such cooperation could be facilitated by the use of a common product classification scheme. Before such a scheme can be developed, however, the aims and needs of both poison centres and regulators / industry need to be clarified. Without harmonisation there will be no functioning system of exchanging data. *References:* 1. Heinemeyer G, Hahn A. Use of product databases for risk assessment purposes. Toxicol Appl Pharmacol 2005; 207:636–644.

152. Regional Poison Center Hourly Call-Taker Staffing and Call Volume

Fernández MC, Cobb DB, Villarreal CL.
Division of Emergency Medicine and the South Texas Poison Center, University of Texas Health Science Center, San Antonio, US

Objective: Methods used to schedule poison center hourly call-taker staff are not well-studied.[1] Although critical to service delivery and cost containment, staffing patterns may not necessarily correspond well with hourly workload.[2,3] We examined the level of correspondence for a regional poison center's staff scheduling and call volume workload within a multi-center poison center network that allows intra-network call diversions for the purpose of minimizing call answering wait times. *Methods:* Average regional poison center inbound call volume was measured over a three-month period. The number of call-taker staff by hour of the day was compared with the average hour-to-hour call volume. *Results:* The center handled an average of 197 calls/day out of an average of 249 calls/day (79%) offered through the network phone system during the three-month period. On average, 23.4% of the total number of calls handled were diverted to our center from other network poison centers, while 22.7% of calls offered to our center were diverted and distributed to other centers. The distribution of call-taker hours generally corresponded well with hours of peak inbound call volume. The volume of call disconnections did not always correspond well with periods having a low ratio of call-takers on duty per hour. *Conclusion:* An evaluation of average hour-by-hour call volume received by a poison center may be useful in helping to determine optimum levels of hour-by-hour call-taker staff scheduling in efforts to improve service delivery and cost containment. A comparison to network-wide call volume and staffing would help to better define optimal poison center staff scheduling requirements. *References:* 1. Alexander JA, Copeland LA, Metzger ME. Explaining differences in operating costs among poison control centers: an exploratory study. Clin Toxicol 2007; 45:440–450. 2. Hauburger NM. Implementation of self-scheduling in the poison center. Vet Hum Toxicol 1997; 39:175–177. 3. Krenzelok EP, Dean BS. Personnel requirements of a poison information center. Am J Hosp Pharm 1987; 44:2084–2086.

153. Do Detergents Cause Corrosive Eye Lesions? A Multinational Analysis of Data from 11 Poisons Centres within the Scope of GHS – Results on Feasibility and Frequency of Exposure

Stürer A,[1] Seidel C,[2] Sauer O,[3] Zilker T,[4] Koch I,[5] Hermanns-Clausen M,[6] Hruby K,[7] Hüller G,[8] Heppner HJ,[9] Tutdibi E,[10] Desel H.[11]
[1]Swiss Toxicological Information Centre, Zurich, Switzerland; [2]Poisons Centre, Childrens University Hospital, Bonn, Germany; [3]Poisons Centre, University Hospital Mainz, Germany; [4]Poisons Centre, University Hospital rechts der Isar, Munich, Germany; [5]Poisons Information Centre, Institute of Toxicology, Berlin, Germany; [6]Poisons Information Centre, Centre for Pediatrics and Adolescent Medicine, Freiburg, Germany; [7]Austrian Poisons Information Centre, Vienna, Austria; [8]Poisons Information Centre, Erfurt, Germany; [9]Poisons Centre, University Hospital, Nuremberg, Germany; [10]Poisons Centre, Department of General Paediatrics and Neonatology, Homburg, Germany; [11]GIZ-Nord Poisons Centre, University Medical Centre, Göttingen, Germany

Objective: Lowering limits together with the "calculation method" owing to "Globally Harmonised System of Classification and Labelling of Chemicals (GHS)" may increase the number of products labelled as corrosive. There is serious concern about inappropriate labelling of domestic cleaning products. An "expert judgement" supported by poisons centres data may help to assign the most appropriate label. There are no data available concerning the frequency of human exposure, particularly eye injuries, caused by cleaning products in Austria, Germany and Switzerland. Few publications provide an overview of eye injuries caused by consumer products in the USA[1] or focus on selected product groups in other countries. Aim of this study - managed by the Society of Clinical Toxicology (Gesellschaft für Klinische Toxikologie, www.klinitox.de, "MAGAM-Study") - was to evaluate the feasibility of case selection with a common categorization system, the collection of data about frequency of cases (part 1) and clinical data (part 2) of eye exposures caused by domestic cleaning products. *Methods:* 9 German PCs and the PCs of Vienna and Zurich retrospectively collected data from 1998 to 2007. Categorization of products was done according to the harmonized TDI categorization system.[2] *Results:* Within 1,841,438 human exposure cases 28,956 (1.6 %) eye exposures were identified. The study focussed on 6 subgroups of household cleaning products (total 110,571 exposures). Most eye exposures within these subgroups were seen with laundry detergents (668) and all purpose cleaners (547). There were fewer exposures to toilet cleaners (400), manual dishwashing products (300), dishwashing tabs and powders (162) and drain cleaners (108). *Conclusion:* The feasibility of case selection with a common categorization system was proved. Frequency of exposure to 6 groups of cleaning products is shown. 2,185 eye exposures will be uploaded in a common database and evaluated in part 2 of the study in spring 2009. *References:* 1. McGwin G Jr, Hall TA, Seale J, et al. Consumer product-related eye injury in the United States, 1998–2002. J Safety Res 2006; 37:501–506. 2. Stürer A, Hüller G, Cordes T et al. TDI-Project: A harmonized category system for products in poisons centres (PC). Clin Toxicol 2003; 41:498.

154. The TDI Categorization System For Agents (Toxicological Documentation and Information Network – Germany): Current Use – Developments – New Version

Stürer A,[1] Begemann K,[2] Binscheck T,[3] Eckart D,[4] Lüde S,[1] Reinecke HJ,[4] Sauer O,[4] Seidel C,[5] Stedtler U,[6] Wagner R,[7] Weilemann I,[4] Zeimentz H,[4] Hüller G.[8]
[1]Swiss Toxicological Information Centre, Zurich, Switzerland; [2]Federal Institute for Risk Assessment (BfR), Berlin, Germany; [3]Poisons Information Centre, Institute of Toxicology, Berlin, Germany; [4]Poisons Centre, University Hospital, Mainz, Germany; [5]Poisons Centre, Children's University Hospital, Bonn, Germany; [6]Poisons Information Centre, Centre for Pediatrics and Adolescent Medicine, Freiburg, Germany; [7]GIZ-Nord Poisons Centre, University Medical Centre, Göttingen, Germany; [8]Poisons Information Centre, Erfurt, Germany

Objective: A categorization system of agents is indispensable for poisons centres (PCs) to work efficiently (e.g. for annual reports). Within the Toxicological Documentation and Information Network (TDI - www.tdi-network.org) a first version of a common categorization system was developed from 1999 until 2006 by German PCs and the German Federal Institute for Risk Assessment.[1] As a final part of this project the categorization system was applied to a collection of 137,689 human exposures of 2005 (7 German PCs).[2] Here we want to report about the current use of the system and the release of the new version. *Methods:* On completion of the TDI project the Society of Clinical Toxicology (Gesellschaft für Klinische Toxikologie - GfKT, www.klinitox.de), respectively the 11 PCs in Austria, Germany and Switzerland, initiated a task-force for the maintenance and further development of this system in 2007. Within 4 meetings until October 2008 the system was revised. *Results:* The new version of the TDI categorization system (2.0, www.klinitox.de/142.0.html) has been available since October 2008 and includes 18,241 hierarchically structured categories (new: 3037 taxonomically categorized mushrooms). The Federal Office of Consumer Protection and Food Safety (BVL) already uses the COLIPA based cosmetic categories for the classification of about 200,000 products prior to the transfer into the PCs. In 2/11 PCs the system is completely integrated into the local database. In 9/11 PCs the TDI classification exists in a parallel manner to the local system and interfaces were established recently. Currently the system is used within a multicentre study for the harmonized selection of domestic cleaning products. *Conclusion:* The usability of the TDI categorization system was proven on various occasions. All GfKT associated PCs are able to use the system, therefore harmonized multicentre data collections are feasible. A task-force for a continuous development of the system is established. Further harmonization with other European PCs is possible and desired. *References:* 1. Stürer A, Hüller G, Cordes T et al. TDI-Project : A harmonized category system for products in poisons centres (PC). J Toxicol Clin Toxicol 2003;41:498. 2. Stürer A, Hüller G, Reinecke HJ, et al. Harmonization of categorization systems for agents: first data from German poisons centres. Clin Toxicol 2007; 45:337.

155. Enquiries to a Poisons Centre from Primary Care Out-of-Hours Services

Casey PB, Tracey JA, Cassidy N.
National Poisons Information Centre, Beaumont Hospital, Dublin, Ireland

Objective: Primary care out-of-hours services (GP co-ops) now account for a significant proportion (19.6%) of enquiries to the National Poisons Information Centre (NPIC). This study was performed to describe enquiries from GP co-ops and to determine how many related to non-toxic exposures. *Methods:* All telephone enquiries to the NPIC from eight GP co-ops about human cases of poisoning between 1 January and 31 December 2007, inclusive, were retrospectively reviewed. Only calls between 8 am and 10 pm were included in this study. Data was collated on patient age, circumstances and location of the poisoning incident, agents, poisoning severity score, and treatment advice. *Results:* GP co-ops made 1641 enquiries about human poisoning during the study period. 1234 (75.2%) patients were children (<14 years), 296 (18.0%) were adolescents or adults and the age of 111 (6.8%) patients was not known. Most exposures (93.2%, n = 1530) were accidental and 96.8% (n = 1590) of all exposures occurred in the home or a domestic environment. Drugs (59.7%) and household products (25.5%) were the most common agents. 1222 (74.3%) patients were asymptomatic at the time of the call, 302 (18.4%) had minor features and 17 (1.0%) had moderate features. Symptoms were not known or were unrelated to poisoning in 99 cases (6.0%). One adult had severe features following intentional overdose and was already en route to hospital at the time of the call. 814 patients (49.6%) required no treatment and a further 339 (20.7%) could be managed at home with advice to seek medical attention if symptoms developed. 289 patients (17.6%) were immediately referred to a hospital emergency department, GP care was recommended for 195 patients (11.9%) and specialist referral was advised for four cases (0.2%). *Conclusions:* The majority of the enquiries from GP co-ops between 8am and 10pm were about accidental, non-toxic exposures in children. Most of these patients required no treatment or could be managed at home. These enquiries represent unnecessary duplication of effort by staff in the GP co-ops and the NPIC. This duplication could be prevented safely, and information provided more efficiently, if members of the public could contact the NPIC directly.

156. Trying to Stay within Our Core Competence – What Happened When the Poison Information Centre Stopped Accepting Calls Concerning Animal Poisoning from the Public

Nyman T, Hoppu K.
Finnish Poison Information Centre, Helsinki University Central Hospital, Helsinki, Finland

Objective: Inquires to our Poison Information Centre (PIC) from the public concerning animal poisonings were increasing rapidly in the first years of the new millennium.[1] The veterinarians seemed to have little interest in attending to poisoning cases, as the PIC took care of them. About 40% of the animal owners first contacting a veterinarian were referred to call to us, without the vet involving her/himself. As our unit has no competence in veterinary medicine and is funded by the human health care providers, interventions were needed. We made the decision to stop answering inquires from the general public concerning animals and referred them to veterinarians starting 1.5.2006. The objective of this study is to look at first results of the intervention. *Methods:* Call statistics 1973–2008, before and after the decision to limit calls, were compared with special focus on the patterns of data after the change. *Results:* 1973, the first year data on animal calls was available from our statistics, 26 (0.8%) of the total of 3170 calls concerned animal poisonings. By 2005 the number had grown to 3343 (8.2%), with 2965 related to suspected or confirmed exposures and 378 being general inquiries. After the change on 1.5.2006 the total number of animal calls has decreased by about 30% to a total of 2066 (5.1% of all calls) in 2007, similar to the number of animal calls received in 2001. Before the change in 2006 roughly 10% of calls came from veterinarians and 90% from the public (2005 346/3343). In 2007 the calls from vets had increased by 73% to 597/2066 or 28%. *Conclusion:* The measures taken to limit calls from the public related to animal poisonings has been only partly successful with a reduction of about 30%. However, at the same time a positive development of more involvement of the veterinarians in the animal poisoning cases seems to be taking place, as the number of calls from veterinarians has increased by 73%. *References:* 1. Nyman T, Hoppu K, Kuisma P. Inquires to the Finnish Poison Information Centre Concerning Acute Poisonings in Animals During 1973–2002 (abstract). J Toxicol Clin Toxicol 2004; 42:533–534.

157. Transfer of Antidotes to Other Hospitals Carried Out by a Regional Antidote Reference Centre: Report of Four Years of Activity

Bianchi S,[1] Zoppellari R,[2] Scanavacca P.[1]
[1]Department of Pharmacy, University Hospital, Ferrara; [2]Department of Anaesthesia and Intensive Care, S. Anna Hospital, Ferrara, Italy

Objective: The Pharmacy Department of the Hospital and University of Ferrara (AOUFE) was chosen as regional reference centre for the supply of some antidotes. This decision comes from the request of the Italian Health Department to select one regional hospital endowed with good antidote stores. *Methods:* This study is the analysis of the antidote transfers carried out by the Pharmacy Department of AOUFE to other hospitals from 1.1.2005 to 15.11.2008. *Results:* The analysis provided 32 cases in which antidotes were supplied to other hospitals in the years 2005 – 2008. The types of transferred antidotes are the following: viper venom antiserum (specific antibodies fab) 12 requests (37.5%), acetylcysteine 4 (12.5%), flumazenil 3 (9.37%), digoxin-specific antibodies (fab)(6.25%), pralidoxime 2 (6.25%), fomepizole 2 (6.25%), methylene blue 1 (3.12%), ethyl alcohol 1 (3.12%), tromethamole 1 (3.12%), penicillamine 1 (3.12%), procainamide 1 (3.12%), nitro prussiate sodium 1 (3.12%), propanol 1 (3.12%). The cost of total treatment was 12,312 Euro. The division in percentage of the geographical areas concerned was 25% to hospitals situated in the province of Ferrara (population 355,809), 62.5% to hospitals of Emilia Romagna (population 4,275,843) and 12.5% to hospitals situated in other regions (population 716,971). Most transfers concerned viper venom antiserum antidote, and this suggests there could be a wider distribution of this medicine, even considering the difficulties in the supply of this antidote due both to the necessity of importing it from other nations and to its low availability. The transfers concerned in decreasing order acetylcysteine and flumazenil, which should always be present in hospitals, so that their request may suggest that the rare use of some antidotes leads to an underestimate of the supplies that make up the essential equipment of every hospital. *Conclusion:* The analysis of the above listed requests points out that sometimes antidote supplies are underestimated, considering the relatively low incidence of intoxications that occur in the different areas of our territory. Finally, the experience of the Pharmacy Department of AOUFE points out that a regional coordination within a national network of antidote availability can enable a quick supply of the antidote requested.

158. Suicide Attempt by Poisoning in Italy: A Preliminary Characterization

Davanzo F,[1] Vignally P,[2,3] Settimi L.[2]
[1]Poison Control Center of Milan, Milano Niguarda Cà Granda General Hospital, Milan, Italy; [2]National Institute of Health, Rome, Italy; [3]Public Health Department, Faculty of Medicine, Marseille, France

Objective: The availability of toxic chemicals and of selected pharmaceuticals tends to facilitate suicide acts by poisoning.[1] Therefore, accurate information about chemicals used and mode of exposure are important in order to devise national strategies and programmes for suicide and suicide attempt prevention. In the present study a preliminary characterization of suicide attempts by poisoning in Italy is provided. *Methods:* The Poison Control Centre of Milan (PCCM) handles about 60% of all cases referred to the PCCs active in Italy. For each patient examined, the PCCM collects the following information: demographic characteristics; exposure characteristics; clinical effects; therapy; outcomes. The PCCM database was searched to identify all cases with intentional exposure due to suicide attempts occurring in Italy in 2005. *Results:* In the period

under study, the PCCM handled 42,483 new cases of human exposure and about 19% of them (n = 6699) were classified as due to suicide attempts. Among these patients there was an over representation of females (70 vs. 30%). The median age was 35 years (range: 8–95). About 83% of cases were exposed to pharmaceuticals, 14% to non pharmaceuticals, and 8% to both pharmaceuticals and non pharmaceuticals in combination. The route of exposure was mainly ingestion (97%), inhalation (1%) and parenteral (1%). The categories of agents most frequently reported were: sedative/hypnotics/antipsychotics (43%), antidepressants (23%), analgesics (13%), anticonvulsants (11%), cardiovascular drugs (7%), and alcohol (7%). The group exposed to agricultural pesticides (1% of cases) was the only one with a higher percentage of men (65 vs. 35%). More than one agent was reported for about 45% of cases. Most of these were exposed to sedative/hypnotics/antipsychotics in combination with other drugs (30%), mainly antidepressants (12%) and anticonvulsants (5%). Combined exposure to drugs and alcohol was reported in 6% of cases. Among these, about half were exposed to sedative/hypnotics/antipsychotics. Poisoning severity was low for 46% of cases, moderate for 48%, elevated for 6%. Death was reported in 5 cases. *Conclusion:* The observations reported here should be considered as a starting point for further analyses focused on specific chemicals and commercial products. *References:* 1. Ajdacic-Gross V, Weiss MG, Ring M, et al. Bull World Health Organ 2006; 86:726–732.

159. Methanol Poisonings in Italy: 2004–2008

Davanzo F,[1] Settimi L,[2] Condò M,[3] Marcello I,[2] Sesana F,[1] Zoppi F,[1] Binetti R.[1]
[1]Poison Control Center of Milan, Niguarda Ca' Granda General Hospital, Milan; [2]National Institute of Health, Rome; [3]Regional Agency for Environment Protection, Palermo, Italy

Objective: To describe methanol poisonings referred to the Poison Control Centre of Milan (PCCM) in 2004–2008 and to characterize lethal exposures due to abuse occurring in Sicily. *Methods:* The PCCM database was searched retrospectively (January 2004–September 2006) and prospectively (October 2006–October 2008) for all cases exposed to methanol. *Results:* In the period considered, the PCCM examined 29 methanol poisonings (none in 2004; 6 in 2005 and 2006, respectively; 15 in 2007 and 2 in 2008). Among them, 17 occurred in Sicily, with a peak of 11 cases in 2007, and 12 in other regions. Sixteen were men and 13 women, with a median age of 49.5 years (range 1–81). Twelve cases were accidental exposures, while 17 cases were intentional exposures (14 due to abuse, 2 to attempted suicide and 1 to misuse). Minor effects were reported in 11 cases, moderate effects in 2 cases; major effects in 5 cases and death in 11 cases. The most frequently reported clinical effects included: coma (14 cases), metabolic acidosis (10 cases), visual loss (3 cases), mydriasis (3 cases), gastric pyrosis (2 cases), constriction of the visual field (2 cases) and vertigo (2 cases). Blood methanol level was reported for 9 cases (<99 mg/dL in 4 cases; 100–499 mg/dL in 4 cases; >500 mg/dL in one case). All cases due to abuse (n. 14) and lethal (n. 11) occurred in Sicily and involved immigrants from East Europe. On the other hand, all methanol poisonings occurring in other Italian regions involved Italian citizens unintentionally exposed and with minor effects, except for one case of attempted suicide with consequent major effects. The investigations performed in Sicily lead to identifying three locally produced and marketed detergents containing more than 70% methanol, improperly labelled and packaged. Furthermore, a detergent for domestic use was identified containing 30% methanol without any labelling information. The observed results were immediately notified to the Italian Ministry of Health and to the local health authorities. Two of the detergents containing more than 70% methanol were withdrawn from the market in November 2007, while the other one, that was identified later, was withdrawn in July 2008.

160. Toxicovigilance Activities: Evaluation of the Contribution of Poison Centres - Results from the DeNaMiC Project

Mathieu-Nolf M,[1] Cezard C,[1] Savitch Y,[1] Heiland A,[2] Wykes S.[3]
[1]Centre Antipoison - Toxicovigilance, Centre Hospitalier Régional Universitaire, Lille, France; [2]Bundesinstitut für Risikobewertung, Berlin, Germany; [3]Health Protection Agency, Chemical Hazards and Poisons Division, Didcot, UK

Objective: Poison centres may be involved in toxicovigilance activities, but the extent of their contribution is not well known at the European level. A study was conducted to quantify and qualify toxicovigilance activities of poisons centres, as a subcomponent of the DeNaMiC project. *Method:* A bibliometric study of published literature for the quantification of scientific activities and a survey by questionnaire for the qualification of toxicovigilance activities within European poisons centres. *Results:* Out of 284 papers found in the literature search 25% concerned toxicovigilance activities for household products and of these poisons centres contributed one third. There were limited data on toxicovigilance in the medical literature. When compared to pharmacovigilance, toxicovigilance represented one fourth of the number of pharmacovigilance publications. There was also limited information on the nature of toxicovigilance activities carried out, however, the number of publications had increased in the last decade. Frequent topics of concern included identifying groups of household products, populations or circumstances at risk, and general statistics on exposures. The questionnaire survey was sent to 89 possible poisons centres in 33 nations. A total of 25 poisons centres from 18 nations replied. From these, 20 (80%) stated they were involved in some form of toxicovigilance activity. In more than half of the centres this was a voluntary rather than officially requested activity. Of the 20 poisons centres, 15 (75%) participated in a toxicovigilance network. The majority of poison centres (23/25) did not receive any specific budget to support toxicovigilance activities. The range of activities described as toxicovigilance was varied. *Conclusions:* There is limited scientific literature on toxicovigilance, however awareness has increased in the last decade and poisons centres are the main contributors. Toxicovigilance activities are not homogenous throughout European poisons centres: there is a variable degree of official recognition and a variable understanding of what constitutes toxicovigilance by the poisons centres themselves. There is limited financial support for toxicovigilance and no specific budget is allocated to this task. European poisons centres should come to a common understanding of what constitutes toxicovigilance in order to put together a persuasive argument for this to be better funded.

161. Product Information and Case Documentation Systems in Poison Centres - Results from a European-Wide Questionnaire Survey (DeNaMiC)

Heiland A,[1] Heinemeyer G,[1] Wyke S,[2] Tempowski J,[3] Desel H,[4] Pelclova D,[5] Mathieu M,[6] Edwards N,[7] Coleman G.[2]
[1]Federal Institute for Risk Assessment, Berlin, Germany; [2]Health Protection Agency, Cardiff, UK; [3]World Health Organization, Geneva, Switzerland; [4]Poison Centre North, Göttingen, Germany; [5]Toxicological Centre, Prague, Czech Republic; [6]Poison Centre, Lille, France; [7]Poison Centre, London, UK

Objective: To compare the tools, terminologies and systems used by poisons centres' (PCs) to record information about exposures to chemical consumer products, to compare the information collected when documenting enquiries, and to assess the extent to which PCs collect information that is useful for industry and risk management. This study was carried out as part of Subcomponent 3 of the research project 'Description of the Nature of Accidental Misuse of Chemicals and Chemical Products (DeNaMiC). *Methods:* A questionnaire was sent to European PCs and other institutions. The questionnaire was structured in six parts: Contact data; General information (tasks, customers and workload in terms of poisons enquiries); Documentation system (Documentation and further processing); Product information (sources, updates, handling); Documented cases (kind of information); Toxicovigilance Activity. *Results:* 26 replies were received from PCs and hospitals that give poisons advice in 19 countries. The product/chemical information system and the case documentation depend on national regulations and number and type of enquiries. Self-created, electronic databases for case records and for product information are common in European PCs even when product databases are provided by a governmental agency. PCs collect the same basic data set about cases (patient data, amount and physical state of chemical, exposure route). The circumstances of poisoning (location, use/storage by the consumer, efficiency of Risk Management Measures (RMMs)) are not documented routinely in all PCs. A number of PCs use the INTOX definition to classify the "circumstances of exposure". *Conclusion:* To gather Europe-wide data about poisonings e.g. for root cause analysis, to check the efficiency of RMMs, PCs need support from industry to maintain their knowledge about products. The classification of products needs improvement and harmonisation. Case documentation would need to be expanded to include some exposure factors, using standardised terminology.

162. Hepatotoxicity Associated with the Use of a Haircare Food Supplement Containing Green Tea Extracts

Segers N,[1] Baert D,[2] Mostin M.[1]
[1]Belgian Poison Centre, Brussels; [2]Department of Internal Medicine, AZ Maria Middelares, Gent, Belgium

Objective: We present a case of hepatotoxicity after daily intake of a food supplement for prevention of hair thinning and hair loss. *Case report:* A 41 year female patient took a dietary supplement during six months on the recommendation of her hair dresser. This product contains 27% green tea extracts *Camellia sinensis*, 11% grape seeds extracts, 11% taurine and zinc gluconate. She presented to the hospital with jaundice, which developed insidiously. Total bilirubin was 13.6 mg/dl, SGOT was 1358 U/l and SGPT 2801 U/l. SGOT decreased to 866 mg/dl after 1 week. Viral hepatitis was excluded. The liver biopsy specimen revealed features of acute drug-induced hepatitis. Hepatotoxicity has been associated with green tea[1,2] and green tea extracts in food supplements.[3,4] The other ingredients are not known to cause liver toxicity. *Conclusion:* Food supplements containing green tea extracts have become popular in preventing and treating an expanding list of health and beauty issues. They found a growing market because they are considered natural. However, there is growing evidence that these extracts are not harmless.[3,4] Our experience adds to previous reports of acute liver toxicity in individuals consuming supplements containing green tea extracts. *References:* 1. Jimenez-Saenz M, Martinez-Sanchez MC. Acute hepatitis associated with the use of green tea infusions. J Hepatol 2006; 44:616–617. 2. Martínez-Sierra C, Rendón Unceta P, Martín Herrera L. Acute hepatitis after green tea ingestion. Med Clin (Barc) 2006; 127:119. 3. Molinari M, Watt KD, Kruszyna T, et al. Acute liver failure induced by green tea extracts: case report and review of the literature. Liver Transpl 2006; 12:1892–1895. 4. Bonkovsky HL. Hepatotoxicity associated with supplements containing Chinese green tea (Camellia sinensis). Ann Intern Med 2006; 144:68–71.

163. Lead Poisoning due to Ayurvedic Remedies

Giampreti A,[1] Lonati D,[1] Vecchio S,[1] Petrolini V,[1] Bigi S,[1] Bonetti C,[2] Locatelli C,[1] Manzo L.[1]
[1]Poison Control Center and National Toxicology Information Centre, IRCCS Maugeri Foundation and University of Pavia, Pavia; [2]Internal Medicine, San Bonifacio Hospital, San Bonifacio, Italy

Objective: Indian remedies in recent years have become common in western countries.[1,2] Apart from being used by 80% of India's population as the traditional system

of healthcare, ayurvedic medicine has gained widespread acceptance in the western world over the last few decades. Several studies from India and other countries showed that ayurvedic preparations can contain toxic concentrations of heavy metals such as lead, mercury, arsenic and cadmium.[3,4] We report a case of lead poisoning in a young man due to chronic consumption of ayurvedic remedies in which an abdominal radiograph showing radiopaque foreign bodies was very useful in providing the diagnosis. *Case report:* A 23 year-old Indian truck driver presented to the emergency department with a six month history of malaise, anorexia and griping abdominal pain for which he was previously treated with appendectomy and then with exploratory laparotomy. On initial examination he appeared clinically anaemic (Hb 10 g/dL); initial investigations presented leukocytosis and moderate increase in transaminases. Abdominal X-ray showed two rounded dense bodies and a further inquiry revealed that for six months he had been taking, as dietary supplements, an ayurvedic preparation purchased in India. Lead poisoning was suspected and further investigations revealed blood lead 56 µg/dl (normal < 30) and red cell zinc protoprphyrin 603 µmol/mol eme (normal 20–85). CaNa2EDTA was administered with a dramatic improvement of his symptoms and haematological and biochemical indices; the examination of blood film revealed basophilic stippling. One year later, the patient was asymptomatic. *Conclusion:* The use of traditional remedies is not usually mentioned by patients, and people presenting to ED should be questioned about their use. Heavy metals, in particular lead poisoning should be suspected and investigated in patients presenting with compatible clinical manifestations and history of use of ayurvedic remedies. *References:* 1. Muzi G, Dell'Omo M, Murgia N, et al. Lead poisoning caused by Indian ethnic remedies in Italy. Med Lav 2005; 96:126–133. 2. Thanacoody HKR. Clinical toxicology of Ayurvedic medicines. Clin Toxicol 2008; 46:381. 3. McElvaine MD, Harder EM, Johnson L, et al. Lead poisoning from the use of Indian folk medicines. JAMA 1991; 264:2212–2213. 4. Saper RB, Phillips RS, Sehgal A, et al. Lead, mercury, and arsenic in US- and Indian-manufactured Ayurvedic medicines sold via the Internet. JAMA 2008; 300:915–923.

164. Recurrent Neutropenia Associated with Monavie® Consumption

Salinger L,[1] Roche KM,[1] Perez A,[2] Ciccone E,[3] Sangalli B,[1] Bayer MA.[1]
[1]Connecticut Poison Control Center, University of Connecticut Health Center, Farmington; [2]Department of Toxicology and Emergency Medicine, Windham Community Memorial Hospital; [3]Department of Infectious Disease, Windham Community Memorial Hospital, Windham, US

Objective: MonaVie® juice blend predominantly contains the açai fruit of the South American palm plant, *Euterpe oleracea Martius*. A recent study suggests antioxidant and anti-inflammatory activity.[1] Despite increased popularity and use of açai and other fruits for their antioxidant properties, no adverse clinical effects have been documented. We describe a patient with leukopenia temporally associated with MonaVie® juice consumption on two separate occasions. *Case report:* A 51 year old male presented with complaints of vomiting, fever, malaise, cough, congestion and loose stools. Past history included chronic alcoholism, Hepatitis C, and IV drug abuse. The patient's exam was unremarkable. Hematology was significant for leukopenia (WBC 0.8, ANC 100). Sepsis, HIV, Lyme disease and rheumatological findings were negative. He received antibiotics for a urinary tract infection and Neupogen® (filgrastim) for leukopenia. On day five post-admission, the patient mentioned ingestion of MonaVie® juice, one ounce twice daily for the past 3 months. A consulting poison center located one reference of açai-induced reduction of HL-60 human leukemia cells *in vitro*.[2] The patient was discharged with instructions to discontinue drinking MonaVie® juice. One month later, he returned with leukopenia (WBC 1.7) and a hand infection. He admitted continued MonaVie® use saying "he never felt as good as when he drank it." Neupogen® (filgrastim) resolved his leukopenia. A subsequent bone marrow biopsy was unremarkable and etiology was not determined. *Conclusion:* We report a case of recurrent neutropenia temporally associated with the ingestion of MonaVie® juice containing açai. There is limited knowledge on potential adverse effects of açai and other fruit phytochemicals. Further studies are needed to determine their impact on human health. *References:* 1. Jensen G, Wu X, Patterson K, et al. *In vitro* and *in vivo* antioxidant and anti-inflammatory capacities of an antioxidant-rich fruit and berry juice blend. Results of a pilot and randomized, double-blinded, placebo-controlled, crossover study. J Agric Food Chem 2008; 56:8326–8333. 2. Del Pozo-Insfran D, Percival S, Talcott S. Açai (Euterpe oleracea Mart.) polyphenolics in their glycoside and aglycone forms induce apoptosis of HL-60 leukemia cells. J Agric Food Chem 2006; 54:1222–1229.

165. Colchicine Poisoning after "Therapeutical" Ingestion of *Colchicum Autumnale* Flowers

Bacis G, Faraoni L, Panzeri C, Zavaritt A, Eleftheriou G.
Bergamo Poison Control Center, Ospedali Riuniti, Bergamo, Italy

Introduction: Diuretic, cathartic and antirheumatic properties of *Colchicum autumnale* has been described and used in the traditional medicine. Colchicine is found in the seeds (0.8%), in the corm (0.6%) and in the flowers (0.1%), and ingestion of as little as 7 mg has resulted in death. Common effects include nausea, vomiting, diarrhea, abdominal pain, tachycardia and chest pain. Hypotension, seizures, bone marrow suppression, coagulopathy and death have been reported less commonly. We present a case-report of colchicine poisoning after "therapeutical" ingestion of *Colchicum autumnale* flowers. *Case report:* A 50-year-old 73-kg woman, for treating her stipsis with a natural remedy, collected and ate approximately 50 grams of flowers of *Colchicum autumnale* (about 0.65 mg/Kg of colchicine). Within one hour she had severe vomiting, abdominal pain and hemorrhagic diarrhoea but she decided to wait and see. Only the day after, the patient was admitted in our hospital with mild abdominal pain, moderate dehydration (Hc 49.3%) and mild compensated metabolic acidosis (pH 7.43, bicarbonates 18.4 mEq/L, BE −5.9 mEq/L). She was treated with normal saline infusion (4 mL/Kg/h) and charcoal administration. Laboratory evaluation showed an increase of transaminases (ALT 438 U/L, AST 678 U/L), bilirubin (3.1 mg/dL), LDH (5810 U/L), CPK (1035 U/L), alcaline phosphatase (446 U/L) and PT INR (1.96). Leucocytosis (22810/mcL) and a moderate PCR increase were also present (6.5 mg/dL). Colchicine blood (8.5 ng/mL) and urine (830 ng/mL) levels were measured and the kinetic of elimination evaluated (half life of 13 hours). Three days after ingestion a platelets count reduction was observed (16000/mcL) with very high level of D-Dimer (>50000 ng/mL) and leukopenia (3690/mcL) so platelet infusion and filgrastim (5 mcg/Kg/day) administration were started. A moderate leukocytosis was observed in the following five days while all the other parameters normalized. The patient was discharged in good condition nine days after *Colchicum autumnale* ingestion. *Conclusion:* The common idea that "natural" therapy with herbs is much better than drugs can expose people to severe poisoning with potential evolution to death: *Colchicum autumnale* ingestion needs rapid and aggressive treatment for saving the life of the poisoned patient.

166. Toad Exposures in Companion Animals

Sturgeon K, Sutton NM.
Veterinary Poisons Information Service (London), Guy's & St Thomas' Poisons Unit, London, UK

Objective: Two species of toad are native to Britain, the common toad (*Bufo bufo*) and the Natterjack Toad (*Bufo calamita*). The common toad is nocturnal and is mostly heard between April and July in the height of the spawning season.[1] This study aims to evaluate the frequency, severity, and timing of reported exposures to the VPIS (Veterinary Poisons Information Service). *Methods:* Essential details from each enquiry are recorded at the time of the call, with a more comprehensive follow-up questionnaire posted subsequently requesting further data on the clinical course and outcome. Case information from 1994 to date for all toad exposures in dogs and cats was extracted from the VPIS database and analysed retrospectively. *Results:* Toad exposures were reported in 181 dogs and 49 cats, with follow-up information available for 62 and 17 cases respectively. Only 3 dogs and 1 cat remained asymptomatic. Gastrointestinal effects were the most common, 40 (68%) dogs and 10 (63%) cats experienced hypersalivation, in 12 (20%) dogs and 4 (25%) cats this led to frothing at the mouth. Vomiting was reported in 13 (22%) dogs and 3 (19%) cats. Shaking was present in 4 dogs, 3 developed twitching, 2 exhibited tremors and 2 showed rigidity. Two cats were ataxic and 1 presented with rigidity. Enquiries most commonly occurred between the hours of ten and eleven in the evening and were notably seasonal, with a higher frequency between June and August. *Conclusion:* This study shows that whilst exposures to toads in companion animals are relatively uncommon, most enquiries occur out of normal veterinary surgery hours when it can be difficult and expensive to seek veterinary advice or treatment. These case data show that although toxic effects are common they are often only mild in severity and therefore could potentially be treated at home. Management can be as simple as home observation and flushing the oral cavity with water. Only animals showing more severe effects should be presented to a veterinary surgeon for appropriate supportive treatment. *References:* 1. Bedford PGC. Toad venom toxicity and its clinical occurrence in small animals in the United Kingdom. Vet Rec 1974; 94:613–614.

167. Incidence of Methaemoglobinaemia in Canine and Feline Paracetamol (Acetaminophen) Poisoning and the Development of Hepatotoxicity

Hawkins LC, Sutton NM.
Veterinary Poisons Information Service (London), Guy's & St Thomas' Poisons Unit, London, UK

Objective: Paracetamol (acetaminophen) poisoning is a common emergency enquiry to the Veterinary Poisons Information Service (VPIS). Methaemoglobinaemia is a recognised complication of paracetamol poisoning in both cats and dogs.[1] This study aims to assess the frequency of methaemoglobinaemia in association with the development of hepatotoxicity in cases of paracetamol poisoning reported to the VPIS (London). *Methods:* Essential details from each telephone enquiry received are recorded at the time of the call, with a more comprehensive postal follow-up questionnaire sent out to request further data on the clinical course and outcome. Case information dating from March 1985 to July 2008 was extracted from the VPIS database. Search criteria included all paracetamol exposures in dogs and cats where methaemoglobinaemia (defined as methaemoglobinaemia and/or cyanosis) and hepatotoxicity (defined as confirmed hepatic damage, hepatic failure, or abnormal elevation of liver enzymes) were reported. *Results:* During the study period 947 (814 canine and 133 feline) cases were available with outcome data. 55 of these animals (13 canine and 42 feline) developed signs of methaemoglobinaemia. Only 7 cases (2 canine and 5 feline) of methaemoglobinaemia were identified with subsequent evidence of hepatotoxicity; conversely 42 cases were identified where there was no indication of methaemoglobinaemia but evidence of hepatotoxicity. *Conclusion:* Although methaemoglobinaemia is a recognised complication of paracetamol poisoning in cats and dogs, the frequency of cases of methaemoglobinaemia reported to the VPIS (London) is relatively uncommon. Methaemoglobinaemia does not appear to be a reliable prognostic indicator for the subsequent onset of hepatotoxicity. *References:* 1. Campbell A. Paracetamol in cats and paracetamol in dogs. In: Campbell A, Chapman M, eds. Handbook of poisoning in dogs and cats. London, England: Blackwell Science, 2000:31–38 and 205–212.

168. Suspected Canine Exposure to Tremorgenic Mycotoxins from Spoilt Foods and Compost

Sutton NM, Campbell A.
Veterinary Poisons Information Service (London), Guy's & St Thomas' Poisons Unit, London, UK

Objective: Tremorgenic mycotoxins are fungal metabolites found in mouldy foods, silage and compost. They can be harmful and severe cases in animals are characterised by tremors, rigidity and convulsions.[1] Although there are a wide variety of tremorgenic mycotoxins a few are of clinical significance, namely Penitrem A and Roquefortine. The mechanisms of action are not completely understood and may vary with the type of mycotoxin.[2] Clinical effects can occur rapidly, with recovery occurring within 96 hours post exposure.[3] This study aims to examine the frequency and clinical course of potential canine exposures reported to the Veterinary Poisons Information Service (VPIS). *Methods:* essential details for each VPIS enquiry are recorded at the time of call, with post-enquiry data being collected via a more comprehensive follow-up postal questionnaire. Case information for all potential tremorgenic mycotoxin exposures in dogs were extracted from the VPIS database and analysed retrospectively for data on clinical effects and outcome. *Results:* Between December 2000 and October 2007, 64 potential cases of canine exposure were reported to the VPIS. Vomiting, tremor, convulsions and ataxia were the most commonly reported clinical effects. The majority of reported exposures regarded ingestion of mouldy or spoilt food (31 cases), while only a few (6 cases) concerned exposure to garden waste. In 20 (31%) cases additional follow up data had been collected by postal questionnaire. In these instances 17 cases exhibited signs of increased muscular activity (convulsions, hyperaesthesia, opisthotonus, restlessness, rigidity, shaking, tremor or twitching). Of the 20 cases with follow-up 2 dogs remained asymptomatic while 18 became unwell but made a full recovery with symptomatic care. *Conclusions:* In the cases reported to the VPIS both case history and the clinical presentation were suggestive of tremorgenic mycotoxin exposure, although treating veterinarians were unable to confirm this with laboratory analysis. Potential cases of exposure to tremogenic mycotoxins are rarely reported to the VPIS, possibly due to a lack of owner and veterinary awareness. Of those that are reported, increased involuntary muscular activity is frequent, although fatalities have not yet been reported to the VPIS. *References:* 1. Arp LH, Richard JL. Intoxication of dogs with the mycotoxin penitrem. J Am Vet Med Assoc 1979; 175:565–566. 2. Schell MM. Tremorgenic mycotoxin intoxication. Vet Med 2000; 95:520–525. 3. Walter SL. Acute penitrem A and roquefortine poisoning in a dog. Can Vet J 2002; 43:372–374.

169. Two Dogs Treated Orally with Imidacloprid and Moxidectin

Lorentzen HR, Seljetun KO, Skjerdal JW.
Norwegian Poisons Information Centre, Directorate of Health, Oslo, Norway

Objective: To describe the reactions in two dogs after oral administration of an insect repellent intended for topical use only. *Case report:* This case report involves two Norwegian elkhounds, which are dogs of medium size (15–20 kg), not known to be ivermectin-sensitive. To prevent parasites, the owner treated them with Advocate®, an antiparasitic spot-on formulation in the evening. By mistake, the solution was given orally instead of topically. Each dog swallowed 2.5 ml, containing the active ingredients imidacloprid (250 mg) and moxidectin (62.5 mg). Imidacloprid is a neonicotinoid insecticide of low toxicity. Moxidectin is a member of the milbemycin class of antimicrobials, related to the avermectins.[1] The following morning one of the dogs was found agitated, drooling, shaking and displaying uncontrolled jerking movements. She was tachycardic and had mydriasis. The dog was taken to the veterinary clinic, treated with acepromazine and fluids and kept under observation all day. In the evening the symptoms were less evident. Examination the following morning revealed mild mydriasis, heart rate in the high normal range, and the dog still showed some agitation. The other dog, which received the same dose orally, showed mild agitation and tremor in the afternoon the day after administration. Both imidacloprid and moxidectin have a wide margin of safety when used topically.[1] Oral exposures to moxidectin in dogs have earlier induced both CNS depression and excitation, in addition to vomiting, salivation and mydriasis. These effects have been seen after repeated dosing or acute intake of unknown amounts.[2] Recommended treatment in moxidectin intoxications consist of supportive care, activated charcoal, and anticonvulsive therapy when needed. Because moxidectin has GABA-enhancing effects, GABA agonists like benzodiazepines or barbiturates should be given with caution.[2] *Conclusion:* Imidacloprid and moxidectin given orally instead of topically to dogs may lead to significant symptoms requiring treatment. Dogs seem to have individual sensitivity, even within the same breed. *References:* 1. The technical manual, Advocate®. Bayer Healthcare, Animal Health, version 3.0-2005. 2. Snowden NJ, Helyar CV, Platt SR, et al. Clinical presentation and management of moxidectin toxicity in two dogs. J Small Animal Practice 2006; 47:620–624.

170. The Ancient Plant *Cycas Revoluta* Caused Disseminated Intravascular Coagulation in a Dog

Holmgren A, Hultén P.
Swedish Poisons Information Centre, Karolinska University Hospital, Stockholm, Sweden

Objective: Cycas species are ancient plants, often mistaken for palms. All parts of the *Cycas species* are toxic and contain three groups of toxic substances.[1,2] These toxins most commonly cause gastrointestinal symptoms, liver damage and occasionally neurological symptoms.[3] In 2008 the Swedish Poisons Information Centre was consulted in three poisonings with *Cycas revoluta* in dogs. Two of these cases displayed typical gastrointestinal symptoms. The third case is presented here. *Case report:* A 9-year-old, 20 kg mixed breed bitch was chewing on roots from *Cycas revoluta*. Within a few hours the dog was vomiting and thereafter developed fatigue and ataxia. At the animal hospital the dog presented with abdominal tenderness, tachycardia, tachypnea and moderate CNS depression. Frequent vomiting and watery diarrhoea during several hours were also noted. Laboratory screening showed that ALT in plasma was slightly elevated. She was treated with fluids intravenously, antacids, antiemetics, anticoagulants and analgesics. The gastrointestinal symptoms ceased approximately 24 hours after ingestion. On day 2, signs of disseminated intravascular coagulation (DIC) were evident including a prolonged APTT (34 sec) and coagulation time (28 sec, ref: <20 sec), decreased antithrombin (72%), and with increased D-dimer (1.8 mg/L). Treatment therefore included repeated blood and plasma transfusions. On day 2 the dog improved shortly but on day 3 the vomiting and diarrhoea returned and a discrete icterus was noted. ALT and bilirubin increased considerably (>10 and >5 times respectively). Blood and plasma transfusions were continued and acetylcysteine was added. On day 5, severe icterus developed. Further laboratory analysis detected severe thrombocytopenia (36×10E9/L), and prolonged APTT (44 sec) and coagulation time (44 sec). These results confirmed a progression of the DIC, which is why the dog was euthanased for ethical reasons. *Conclusion:* This is the first report of *Cycas revoluta*-induced DIC in a dog. *References:* 1. Hooper PT. In: Keeler RT et al, eds. Effects of poisonous plants on livestock. New York, USA: Academic Press Inc., 1978:337–347. 2. Cheeke PR, ed. Natural toxicants in feeds, forages, and poisonous plants. Danville, Illinois, USA: Interstate Publishers, 1998:388–389. 3. Albretsen JC, Khan SA, Richardson JA. Cycad palm toxicosis in dogs: 60 cases (1987–1997). J Am Vet Med Assoc 1998; 213:99–101.

171. ToxAlert: A Collaborative Website for Toxicovigilance Management

Guyodo G,[1] Manel J,[2] Lefevre B,[3] Ccohet A.[4]
[1]Poison Control Center, Paris; [2]Poison Control Center, Nancy; [3]Ministry of Health, Paris; [4]French Institute for Public Health Surveillance (InVS), Saint-Maurice, France

Objective: ToxAlert is a secured website developed by French Poison Control Centers at the request of the French Ministry of Health in order to manage toxic alerts and for toxicovigilance surveys. *Methods:* To achieve these objectives, ToxAlert has two main features: a content management system and an e-form defining and generating system. Each toxic alert or toxicovigilance survey has a dedicated space in the website. User rights are managed for each space: administrator, expert, contributor, reader. The content management system allows users (except for readers) to create or upload files in a space: news, texts, FAQs, pictures, galleries and links. Each file is submitted to referral experts and published only if validated. All appointed users of a space can then access the pool of validated files. ToxAlert also allows e-forms to be defined, generated and published in the website. All completed e-forms are immediately available for authorized users; epidemiologic and statistical analyses can be performed on the data at any time. *Results:* The French toxicovigilance coordination committee uses ToxAlert to share data and files concerning current national toxic alerts and surveys, and to collect data about selected toxic exposures. All committee documents (meeting reports, announcements, e-mails, survey results) are also available on ToxAlert. In the near future, the use of ToxAlert will be extended to regional toxicovigilance networks. Another project would be to connect ToxAlert with the current national PCC database to inform physicians about a related survey as they record a specific case. *Conclusion:* ToxAlert is a useful tool for PCC and French toxicovigilance networks. The European deployment of ToxAlert would allow rapid and homogeneous data collection concerning epidemiological surveys, that are currently not available.

172. Scottish Demand for Poisons Information in the Year 2007/08 – Comparison of Telephone Enquiries and Internet Database Accesses

Jackson G, Adams RD, Laing WJ, Good AM, Bateman DN.
NPIS Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, UK

Objective: To study the pattern of resource use and nature of enquiries by healthcare professionals in Scotland accessing poisons information services 8 years after the UK national launch of TOXBASE on the Internet. *Methods:* In Scotland there are 2 principle sources of poisons information, on-line (TOXBASE) and telephone. Data on numbers of TOXBASE accesses and telephone enquiries were analysed and compared for the year 1 April 2007 to 31 March 2008, with respect to type of enquirer: hospital, NHS 24 (public access health telephone enquiry services), primary care physician (GP); poison; and time of enquiry. *Results:* TOXBASE accesses were 74,754; the main users were hospitals (67.6%) and NHS 24 (29.8%). The telephone service received 2376 enquiries; the main users were GPs (36.8%) and hospitals (35.4%). Hospitals and NHS 24 predominantly used TOXBASE (hospitals: TOXBASE 98.4%; NHS24: TOXBASE 98.1%). In contrast 44.8% of GP contacts were via TOXBASE, and 55.2% by telephone. Paracetamol was the product most commonly accessed via TOXBASE and also the most common telephone enquiry; a further 8 pharmaceuticals were also commonly accessed via TOXBASE and the telephone service: ibuprofen, co-codamol, fluoxetine, diazepam, aspirin, citalopram, tramadol and amitriptyline. The top 10 TOXBASE accesses for hospitals were all pharmaceuticals; for NHS 24 8 pharmaceuticals and 2 household products; for GPs 5 pharmaceuticals, 4 household products and to adder bite. For the top ten telephone enquiries: hospitals 9 pharmaceuticals and 1 chemical (ethylene glycol); NHS 24 8 pharmaceuticals and 2 household products; and GPs 9 pharmaceuticals and 1

household product. The daily pattern of usage via TOXBASE and via the telephone was similar within user groups. Patterns differed between user groups, demand from GPs was highest between 12 and 6pm, NHS 24 peaked at 9pm, and demand from hospitals was high between 9am to 3am. *Conclusion:* Hospitals and NHS 24 predominantly used TOXBASE. GPs accessed TOXBASE almost as frequently as they called. The time profiles of demand for poisons information from TOXBASE and the telephone service varied between user groups, but overall nature of enquiries seems similar. Compared to 2001 TOXBASE use in GPs appears to be increasing (National Poisons Information Service, Annual Report, 2001).

173. The Need for Prevention of Intentional Ingestion of Alcohol Hand Gels in Irish Hospitals

Herbert JX, Cassidy N, Tracey JA.
National Poisons Information Centre, Beaumont Hospital, Dublin, Ireland

Objective: To examine severe toxicity associated with intentional ingestion of AHGs in Irish Hospitals and propose methods to prevent it. *Methods:* For this study we examined all enquiries relating to AHGs received by the National Poisons Information Centre (NPIC) in the years 2006–2007. We also counted the number of hits received on TOXBASE® regarding these products in the same time period. TOXBASE® is the on-line poisons information database of the National Poisons Information Service (NPIS) in the United Kingdom which is used by all Emergency Departments in Ireland. *Results:* In the two years of this study there were eighteen calls to the NPIC regarding toxic exposure to AHGs. Nine calls involved accidental exposure with minimal toxicity and these were excluded from the study. The nine intentional ingestions all involved volumes in excess of 450 mls. In seven of these nine deliberate ingestions there was a history of chronic alcohol abuse noted in the patients chart. All nine patients displayed significant symptoms of intoxication. One patient required intensive care management. There were 14 hits on TOXBASE® for AHG during the study period but no patient data is available. *Conclusion:* AHGs typically contain ethanol and/or isopropanol in a concentration of 60 - 95% (by weight). AHG dispensers are now widespread in all Irish Hospitals. The abuse of AHGs in hospitals is not a new phenomenon and is particularly prevalent in alcoholic patients.[1] The risk: benefit ratio (risk of alcohol toxicity: prevention of infection) is largely in favour of benefit.[2] All healthcare workers need to be informed of the potential of deliberate ingestion occurring, especially in the presence of patients with a history of alcohol abuse. The risk of large deliberate ingestions could be reduced by a simple locking mechanism on dispensers and avoiding the use of large volume containers. *References:* 1. Meyer P, Baudel JL, Maury E, et al. A surprising side effect of hand antisepsis. Intensive Care Med 2005; 31:1600. 2. Tavolacci MP, Merle V, Pitrou I, et al. Alcohol-based hand rub: influence of healthcare workers' knowledge and perception on declared use. J Hosp Infect 2006; 64:149–155.

174. Correlation Between PM10 Inhalation and Respiratory Diseases

Ricci G,[1] Majori S,[3] Zannoni M,[1] Pratticò F,[2] Perfetti P,[2] Rocca G.[2]
[1]*Clinical Toxicology Service, Ospedale Civile Maggiore;* [2]*Emergency Department, Ospedale Civile Maggiore, Verona;* [3]*Department of Medicine and Public Health, Verona University, Verona, Italy*

Objective: To assess if atmospheric pollution can lead to the development or exacerbation of respiratory diseases in the urban population. *Methods:* The relationship between particles with an aerodynamic diameter of less than 10 microns (PM 10) in the atmosphere of Verona and daily counts of emergency hospital admissions for asthma, chronic obstructive pulmonary disease (COPD), and all-respiratory diseases was investigated. Therefore an analysis of all the admissions to our ED for acute respiratory diseases (ARD) from January 1, 2004 to October 31, 2008 was made. *Results:* In that period there were 14,622 ED admissions related to ARD with a daily average of 8.5. During the three days following PM 10 peaks, a significant increase (up to 44%) in mean daily admissions due to ARD was found, thus demonstrating a correlation between respiratory diseases and levels of atmospheric pollution. *Discussion:* The toxicity of PM10 generally arises from any of the following factors. The particles may themselves be toxic (particles containing toxic metals and non metals, such as Pb, Cd, Ni, Hg, As, and radionuclides). Alternatively, the particles may adsorb toxic chemicals, such as carcinogens. Finally, if there are large quantities in the inhaled air, particles may overtax the mucociliary apparatus, thus decreasing the rate of toxic removal from the lungs. In addition, many epidemiological studies have confirmed that total suspended particles (TSP) present in urban areas, are associated with an increased risk of mortality in pneumonia and cardiovascular disease. The risk is particularly elevated in the elderly. In terms of mortality, infants are most susceptible to PM10, particularly when deaths are related to the respiratory system. *Conclusion:* The Authors recommend the adoption of preventative measures in order to limit pollution-linked respiratory diseases in predisposed subjects, through sanitary education and reduction of polluting emissions from cars, industries and domestic heating.

175. 70% Hydrofluoric Acid Cutaneous Decontamination – Comparison of Different Washing Protocols with a New Type of *Ex Vivo* Data

Burgher F,[1] Mathieu L,[1] Fosse C,[1] Lati E,[2] Hall AH,[3] Maibach HI.[4]
[1]*Prevor, Valmondois, France;* [2]*BIO-EC Laboratory, Longjumeau, France;* [3]*School of Public Health, University of Colorado, Denver, US;* [4]*Department of Dermatology, University of California School of Medicine, San Francisco, US*

Objective: To determine the benefit of different rinsing protocols versus no decontamination on an innovative *ex vivo* model. *Methods:* 86 explants human skin in 4 groups, 1 control, 3 exposed to hydrofluoric acid (HF) (20 seconds by topical route from filter paper disks, previously saturated with 30 µl 70% acidic solution). One group without decontamination. One with tap water (15 minutes) plus one topical application of calcium gluconate (CaGlu) 1g/cm^2; one with Hexafluorine® (10 minutes). Histological samples: end of washing, then regularly up to 24 hours. Observation by optical microscopy X40. *Results:* Alterations searched for in *stratum corneum*, basal epidermis, papillary and reticular dermis. Control group: no lesions any layer at anytime. HF-exposed explants without decontamination: severe burns in the 4 layers, from 10 minutes onwards. With tap water plus CaGlu: alterations of the 4 layers after 15 minutes, decreasing after 30 minutes. Resumption of lesions in epidermal cells from the 4th hour onwards and in dermal cells at 24h. Decontamination Hexafluorine®: no epidermal nor dermal cells alteration, even after 24h. These results are in accordance with those obtain on an *ex vivo* model for the eye.[1] The effectiveness of Hexafluorine® decontamination, in this study, can be linked with successful results (without secondary care or systemic effects) obtained on three 70% HF workplace splashes.[2,3] *Conclusion:* This new model helps to compare decontamination methods with 70% HF. Results are closed to those obtained in cases reports. Decontamination with tap water followed by CaGlu validates requirement of several and deeply penetrating applications of CaGlu to improve results. The effectiveness of using Hexafluorine® prior to any other protocol is confirmed. *References:* 1. Spöler F, Frentz M, Först M, et al. Analysis of hydrofluoric acid penetration and decontamination of the eye by means of time resolved optical coherence tomography. Burns 2008; 34:549–555. 2. Soderberg K, Kuusinen P, Mathieu L, et al. An improved method for emergent decontamination of ocular and dermal HF splashes. Vet Hum Toxicol 2004; 46:216–218. 3. Mathieu L et al. Eye and skin hydrofluoric acid splashes: about 32 cases rinsed with Hexafluorine®, poster presented at ISSA congress, Greece, May 2003.

176. Pediatric Suboxone Exposure: How Long is the Initially Symptomatic Child at Risk for Sequellae after Naloxone Reversal? A Case Report and Literature Review

Wiegand TJ,[1] Simone KE.[2]
[1]*Department of Medicine and Emergency Medicine, Maine Medical Center, Portland;* [2]*Northern New England Poison Control, Portland, US*

Objective: Suboxone, a combination product containing buprenorphine and naloxone for sublingual administration, has been approved in the United States for office based opioid maintenance and detoxification treatment by certified, primary care physicians. Literature reports include a significant number of pediatric exposures, some including prolonged or recurrent respiratory depression after Suboxone exposure. Naloxone has been shown to be effective in reversing opioid effects in this population. We present a case in which a child experienced significant toxicity after a single-tablet exposure and discuss appropriate observation and management after use of naloxone to avoid recurrent opioid effect. *Case report:* A 28-month-old, approximately 18 kg boy was found with a single Suboxone tablet (8 mg buprenorphine/2 mg naloxone) in his mouth. The pill, which was moist, however 'intact' was removed and his mouth rinsed out with water. At 1.5 hours post exposure the mother found him lethargic. Paramedics found the child minimally responsive and bradypneic. 0.2 mg of naloxone was given intranasally with improvement in respirations and consciousness. Additional 0.2 mg doses of naloxone were given intramuscular during transport to the ED as, although improved, some symptoms persisted. In the ED, however, the child was appropriately interactive and energetic. He was observed in the Pediatric Intensive Care Unit overnight and remained asymptomatic. *Conclusion:* We present a case in which a child, reportedly, had minimal exposure to a single 8 mg Suboxone tablet yet had significant opioid toxicity. Naloxone reversed the buprenorphine-induced opioid effects in our patient. Although our patient did not demonstrate persistent opioid effects, or have recrudescence of symptoms, literature reports describing significant and persistent opioid effect, necessitating multiple, repeat doses of naloxone or intubation and supportive care, exist.[1] Symptomatic children exposed to Suboxone that have been treated with naloxone, should be monitored overnight to avoid recrudescence of opioid effect as naloxone is eliminated. *References:* 1. Geib, AJ, Babu K, Ewald MB, et al. Adverse effects in children after unintentional buprenorphine exposure. Pediatrics. 2006; 118:1746–1751.

177. Severe Methemoglobinemia: A Case Series

Smith MB, Charlton NP, Thomas JJ, Boyle JS, Holstege CP.
Division of Medical Toxicology, University of Virginia, Charlottesville, US

Objective: Methemoglobinemia can result from exposure to environmental, dietary, and pharmaceutical oxidizing agents. Clinical effects generally correlate with blood levels of methemoglobin, and most published sources, including Goldfrank's Toxicologic Emergencies and Micromedex, state that methemoglobin levels greater than or equal to 70% are lethal. The following cases describe patients presenting with methemoglobin levels greater than or equal to 70% who made a full recovery after an uncomplicated hospital course. *Case series:* Case 1. A 43 year-old female presented with cyanosis, weakness, vomiting, and shortness of breath following procedural administration of topical benzocaine. Initial vital signs: BP 148/76, pulse 106, respirations 22, oxygen saturation 88%; methemoglobin was 71.1%. ECG revealed ST depression in leads V3–V6, I, and AVL. Methylene blue therapy was initiated; within 15 minutes there was appreciable improvement in the patient's symptoms. Repeat ECG showed resolution of ST depressions. Case 2. A 37 year-old male had skin and inhalational exposure to aniline following a workplace accident. Approximately 1.5 hours after exposure the worker experienced lightheadedness, headache, nausea and progressive dyspnea prompting medical evaluation.

Initial vital signs were: BP 138/65, pulse 106, respirations 24, oxygen saturation 74%; methemoglobin was 72%. He received 90 mg of methylene blue after decontamination and symptoms dramatically improved. Case 3. A 41 year-old female presented with cyanosis and dyspnea following procedural administration of topical benzocaine. Initial vital sings: BP 130/48, pulse 115, respirations 24, oxygen saturation 82%; methemoglobin was 70%. Infusion of methylene blue (90mg) was initiated. Within 15 minutes there was appreciable improvement in the patient's symptoms. All patient's were admitted to a monitored floor bed for 23 hours and discharged without sequelae (methemoglobin levels <5%). *Conclusion:* Review of the literature reveals 14 case reports of profound methemoglobinemia (levels greater than or equal to 70%) from which patients fully recovered. Half of those patients required intubation or admission to an intensive care unit, and the majority were noted to have an associated metabolic acidosis or massive hemolysis. The cases reported here are unique in the patient's uncomplicated hospital course and speed of recovery.

178. Alcoholic Ketoacidosis is Under-Recognised among Patients with Increased Anion Gap Metabolic Acidosis

Soghoian S,[1,2] Hoffman RS.[1,2]
[1]*New York City Poison Control Center;* [2]*New York University, New York, US*

Objective: Physicians frequently call the Poison Center (PC) for diagnostic and management assistance when patients present with an increased anion gap metabolic acidosis. We perceived that reporting physicians (RP) are frequently concerned about toxic alcohol poisoning (TAP) and are hesitant to assign the diagnosis of alcoholic ketoacidosis (AKA) in many cases. We hypothesized that toxicologists (TX) would be more likely to assign the diagnosis AKA given the same diagnostic information. *Methods:* We performed a retrospective review of PC human exposure records over 9 years (2000–2008) using the unique AAPCC codes for "acidosis", "increased anion gap", "increased osmolar gap", or "any electrolyte abnormality" when the ingested substance mapped to the generic categories of "alcohols", "automotives", "chemicals", or "cosmetics". Inclusion criteria were a final diagnosis of alcoholic ketoacidosis (AKA), as defined by a history consistent with AKA, an increased anion gap metabolic acidosis, improvement with intravenous fluids and supplemental glucose, documented ketonemia or ketonuria, and the absence of a competing diagnosis. Cases were excluded for miscoding or confirmed non-ingestion. A single investigator recorded the initial diagnostic impression of the RP and TX, and essential diagnostic test results. Tests of frequency were performed. The kappa statistic for inter-rater reliability for the diagnosis of AKA was also calculated. *Results:* Fifty-two cases met inclusion and exclusion criteria. AKA was the initial impression of the TX in 47 (90%) cases, whereas AKA was initially diagnosed by the RP in only 6 (11.5%) cases. The inter-rater reliability for the diagnosis of AKA was low (k = 0.027, SE = 0.016). The initial diagnosis of the RP was TAP in 30 cases (58%), and treatment for TAP was initiated prior to PC contact in 3 cases (hemodialysis, 1; fomepizole, 1; ethanol, 1). In each of these 3 cases the TX initially suspected AKA based on history and initial laboratory tests, and subsequent testing for toxic alcohol concentrations in the blood was negative. *Conclusion:* Alcoholic ketoacidosis is under-recognized by physicians who call the PC about patients with a history of any alcohol exposure and an increased anion gap metabolic acidosis. Failure to recognize AKA can lead to expensive and potentially dangerous therapy.

179. Toxicologists and Reporting Physicians have Divergent Diagnostic Impressions of Patients with Anion Gap Metabolic Acidosis

Soghoian S,[1,2] Hoffman RS.[1,2]
[1]*New York City Poison Control Center;* [2]*New York University, New York, US*

Objective: Physicians frequently call the Poison Center (PC) for diagnostic and management assistance for suspected toxic alcohol poisoning (TAP). We perceived that reporting physicians (RP) based their clinical suspicion for TAP largely on an increased anion or osmolar gap, whereas a broad differential diagnosis for either exists. We hypothesized that toxicologists (TX) would be less likely to suspect TAP when ketoacidosis, lactic acidosis, or ethanol were present, and that RP and TX would have poor agreement in forming diagnostic impressions about the likelihood of TAP. *Methods:* We performed a retrospective review of PC human exposure records over 9 years (2000–2008) using unique AAPCC codes for acidosis, increased anion gap, increased osmolar gap, or any electrolyte abnormality in the presence of alcohols, automotives, chemicals, or cosmetics. Inclusion criteria were any suspicion or diagnosis of toxic alcohol exposure by the RP or TX. Cases were excluded for miscoding or confirmed non-ingestion. A single investigator recorded the initial diagnostic impression of the RP and TX, and essential diagnostic test results. An artificial variable "alternate diagnosis" (ALTDX) defined as the presence of either alcoholic ketoacidosis OR serum lactate >2mmol/L OR serum ethanol > 100 mg/dL (21.7 mmol/L) was created, and the receiver operating characteristic (ROC) of ALTDX for the diagnostic impressions of RF and TX at the time of the first call were calculated. The kappa statistic for inter-rater reliability was also calculated. *Results:* 217 cases met inclusion and exclusion criteria. TAP was the initial diagnostic impression of RP in 179 cases (83%) and of TF in 94 cases (43%). The overall inter-rater reliability score was low (k = 0.008). When the RP and TX did agree, there was usually a clear history of TAP (52/78 cases). The area under the ROC curve of ALTDX for the exclusion of TAP by the RP was 0.577 (SE 0.05) vs 0.729 (SE 0.035) for the TX. *Conclusion:* In the absence of a clear history, toxicologists and reporting physicians have divergent diagnostic impressions about the likelihood of TAP. Attention to ketoacidosis, lactic acidosis or an elevated ethanol concentration may help improved decision making.

180. Phenobarbital Poisoning: The Old Problem Anew - Two Case Reports with Toxicokinetics

Ciszowski K, Szpak D, Wilimowska J, Groszek B.
Department of Clinical Toxicology, Jagiellonian University Medical College, Kraków, Poland

Objective: We present two cases of suicidal phenobarbital poisonings (untreated with phenobarbital previously), to compare the effectiveness of symptomatic and supportive treatment with extracorporeal elimination method. *Case reports:* Case 1. 32-year-old man, physician, was admitted 21 hours after ingestion of 9 grams of phenobarbital. On admission he was in coma (GCS 3), with respiratory failure, haemodynamically stable. Supportive treatment, multiple-dose activated charcoal (MDAC) with cathartics, and alkaline diuresis was instituted. Phenobarbital serum concentration was reduced from 200.0 mg/L on admission to 21.0 mg/L after 87 hours. The consciousness gradually improved, the mechanical ventilation was stopped after 37 hours, and patient was extubated for the next 6 hours. Case 2. 26-year-old woman, veterinarian, ingested 19 grams of phenobarbital 26 hours before admission. She was in coma (GCS 3) with respiratory and circulatory failure. Symptomatic and supportive treatment was started with alkaline diuresis. Bowel sounds were absent, so MDAC was not implemented. Despite supportive and symptomatic therapy phenobarbital concentration raised from 287.0 mg/L on admission to 333.9 mg/L after 30 hours. The patient underwent 8-hour-lasting haemodiafiltration (HDF) procedure, which diminished phenobarbital concentration to 136.9 mg/L. During next 25 hours phenobarbital concentration increased again to 204.1 mg/L. The next 4-hour-long HDF slightly reduced the concentration to 189.2 mg/L, which finally, dropped to 36.8 mg/L after 204 hours of hospitalization. Mechanical ventilation was stopped after 205 hours and over the next 6 hours she was extubated. *Toxicokinetics:* The first case represents two-phase elimination with rapid first phase ($t_{1/2}$ = 16.4 hours) and slow second phase ($t_{1/2}$ = 44.1 hours), replacing one another at the point of 73.1 mg/L (after 49 hours). The elimination in the second case was disturbed by redistribution of phenobarbital from tissues, resulting in two peak concentrations (333.9 and 204.1 mg/L). Probably, the first peak was also connected with delayed absorption of phenobarbital from the gastrointestinal tract. The HDF significantly increased elimination of phenobarbital ($t_{1/2}$ = 3.5 hours) compared to supportive therapy ($t_{1/2}$ = 63.4 hours). *Conclusion:* In severe phenobarbital poisoning the extracorporeal elimination methods are still of great therapeutic value, especially if the clinical status of the poisoned patient does not improve due to symptomatic and supportive treatment and phenobarbital concentration continues to rise.

181. Liver Albumin Dialysis (MARS) in Severe Valproic Acid Poisoning

Hydzik P, Wilimowska J, Groszek B.
Department of Clinical Toxicology, Jagiellonian University Medical College, Kraków, Poland

Objective: Wide therapeutic use of valproic acid (VPA) is responsible for high incidence of acute poisonings. The aim of this report was to evaluate the efficacy of albumin dialysis (MARS) as an extracorporeal enhancement elimination method in VPA overdose, which is known for its high protein binding (90–95%). *Case report:* A 23-year-old female, ingested enteric-coated tablets of VPA in total dose of 65 grams in a suicide attempt. On admission, 2.5 hours post ingestion, she was in verbal contact, with normal vital signs. Gastric lavage was performed and multiple-dose activated charcoal (MDAC) was started. Despite symptomatic and supportive treatment her clinical status deteriorated. At 16.5 hours post-ingestion VPA concentration increased from 284.6 mg/L (on admission) to Cmax =1368.1 mg/L. She was in deep coma (GCS 3) with respiratory and circulatory failure. Albumin dialysis with continuous veno-venous haemodialysis (CVVHD) was started 28 hours post ingestion at VPA serum concentration 1153 mg/L and was finished after 8 hours, when consciousness was completely regained, blood pressure normalized and total VPA concentration decreased to 347.5 mg/L. During MARS treatment blood samples from arterial, vein lines and dialysate were collected every hour, and total and free VPA concentrations were measured. In the course of albumin dialysis VPA concentration differences between venous and arterial line decreased. Albumin dialysis with CVVHD efficiency of VPA elimination was evaluated by calculation of plasma clearance and elimination half-life. The VPA plasma clearance by dialysis was 88.3 ml/min. The calculated half-life of VPA during treatment was about 5-fold shorter than as consequence of only endogenous elimination in overdose (during MARS: $t_{1/2}$ = 4.94 hours, after MARS: $t_{1/2}$ = 26.09 hours). Our study also investigated protein binding dependence on total serum VPA level. Concerning increase total serum VPA level above 300 mg/L percentage of albumin binding VPA was contained in the range from 18.43 to 36.24%. Percentage of protein binding VPA exponential decreased with increase total drug level. The mentioned example showed that VPA protein binding is nonlinear and depends on total VPA level. *Conclusion:* Albumin dialysis removed mainly unbound valproic acid. Decrease of the toxic valproic acid level correlated with clinical improvement in the patient's general state.

182. Naloxone in the Treatment of Non-Fatal Heroin Overdose

Chaparoska D,[1] Pivkova A.[2]
[1]*Toxicology Unit, Medical Faculty;* [2]*Hematology Unit, Medical Faculty, Skopje, FYR of Macedonia*

Objective: To examine the relationship between patient variables and variation in naloxone dose (from standard dose of 2 mg IV) administered in the hospital management of heroin overdose. *Methods:* A retrospective analysis of 185 patients records of non-fatal heroin overdose cases collected in the University Hospital. The main outcome measure was the dose of intravenous naloxone required to increase the level of consciousness and the respiratory rate in patients presenting with suspected heroin overdose. The patient variables influencing the

dose that were recorded included: age, sex, initial patient presentation and reported concurrent alcohol use. *Results:* Patients with higher levels of consciousness and respiratory rates on arrival in the Emergency Department were more likely to receive a less than standard dose of naloxone. Conversely, patients with lower level of consciousness and low respiratory rates received greater than standard doses of naloxone for resuscitation. Patients who received greater than the standard dose of naloxone were 95%CI times more likely to have been under the influence of alcohol when consuming the heroin that resulted in overdose. *Conclusions:* The concurrent use of alcohol with heroin resulted in the use of greater than standard doses of naloxone in resuscitating overdose patients. It is possible that the higer dose of naloxone is required to reverse the combined effects of alcohol and heroin. There was also a link between initial patient presentation and the dose of naloxone required for resuscitation. In light of these findings, it would appear that initial patient presentation and evidence of alcohol use might be useful guides as to providing the most effective dose of naloxone in the Emergency department. *References:* 1. Coffin PO, Tracy M, Bucciarelli A, et al. Identifying injection drug users at risk of non-fatal overdose. Acad Emerg Med 2007; 14:616–623. 2. Yin L, Qin G, Ruan Y, et al. Nonfatal overdose among heroin users in southwestern China. Am J Drug Alcohol Abuse 2007; 33:505–516.

183. Imaging Diagnosis and Classification of Late Complications of Corrosive Ingestion

Antonova D,[1] Galov H,[1] Stankova E,[2] Hubenova A,[2] Brankov O.[3]
[1]*Clinic of Imaging Diagnostics, Emergency Medicine Institute Pirogov;* [2]*Toxicology Clinic, Emergency Medicine Institute Pirogov;* [3]*Children Surgery Clinic, Emergency Medicine Institute Pirogov, Sofia, Bulgaria*

Introduction: Corrosive ingestions are a serious medical problem in Bulgaria, characterized by an ever-increasing incidence rate in all age groups. The severity, dynamics and serious complications define corrosive intoxications as one of the severest forms of acute poisonings in the country. Imaging diagnostic methods contribute to early diagnosing of the extent of the lesion and assessment of therapeutic approach and final outcome of the ingestion. *Objective:* To assess the diagnostic and prognostic value of imaging techniques in acute corrosive ingestions and their complications, as well as the impact on the therapeutic approach and the final outcome. *Methods:* We studied 152 children with acute corrosive ingestion, treated in the Emergency Medicine Institute "Pirogov", Sofia for the period 1992–2007. X-ray examinations were conducted in all children to identify severity of ingestion and to classify type of damage in late corrosive disease. Timing for use of imaging methods and their role in deciding the appropriate therapeutic approach are outlined. *Results:* Various types of localizations, extent and severity of strictures were described. We classified them as: ringlike (25 children, 16.4%), concentrical (17 children, 11.25%), tubular (53 children, 34.9%), multiple (38 children, 25%) and total (19 children, 12.5%). Localized strictures were observed most frequently in the middle third of the esophagus (64 children, 67.3%), then in the upper third of esophagus (24 children, 25.2%), and most rarely in the lower third of esophagus (7 children, 7.4%). Based on these findings ingestions were assessed in regard to prognosis after conservative treatment and dilatation of esophagus. The type of stricture is often related to the outcome of dilatation procedures. Imaging diagnosis has a leading role in establishing the extent of corrosive damage in the upper gastrointestinal tract and the process of choosing the most appropriate treatment technique. *Conclusion:* Although rare, corrosive ingestions have severe pathology that needs timely diagnosis. Establishing the extent of damage is the determinant factor for successful treatment of corrosive poisonings. Severity and complex character of damage necessitates the implementation of active monitoring and good coordination between different specialists (multidisciplinary approach to any patient with corrosive ingestion).

184. Noncardiogenic Pulmonary Edema after Diltiazem Overdose in a Suicidal Attempt

De Capitani EM,[1,3] Lutaif NA,[2] Zeni EM,[1] Ferreira ML,[3] Lorentz GZ,[3] Madureira PR,[1,2] Corso-Pereira M,[3] Bucaretchi F.[1]
[1]*Campinas Poison Control Centre, State University of Campinas;* [2]*Emergency Department/University Hospital, State University of Campinas;* [3]*Division of Pulmonary Medicine, State University of Campinas, Campinas, Brazil*

Objective: To report a case of noncardiogenic pulmonary edema after high dose ingestion of diltiazem. *Case report:* A 18-year-old girl with history of systemic *lupus erythematosus* ingested 1.5 g of diltiazem in a suicidal attempt. She was known to be taking diltiazem due to recurrent episodes of Raynaud's phenomenon. She was brought to the Emergency Department 4h after ingestion (T4). On examination, she was vomiting and hypotensive (90/0 mmHg). Pulse: 70/min. Respiratory rate: 24/min and SpO_2 = 83.7%. The initial chest X-ray showed a normal size heart, and diffuse bilateral heterogeneous confluent gross nodular opacities, suggesting alveolar/interstitial filling. EKG showed a heart rate of 80/min and 2nd degree atrioventricular block. Laboratory findings (T4): pH = 7.42; PaO_2 = 47 mmHg; $PaCO_2$ = 39.6 mmHg; $SatO_2$ = 74%; glucose (serum) = 249 mg/dL. Initial therapy with noradrenaline, dopamine, insulin, and calcium gluconate raised the blood pressure to normal values at T18 and gradually sinus rhythm returned. Echocardiogram done at T24 showed ventricular ejection fraction of 76%, and a computed tomography of the thorax performed at T48 still showed opacities compatible with pulmonary edema. New chest radiograph at T72 showed reversion of the previous alterations. *Conclusion:* Massive ingestions of diltiazem can result in severe sinus bradycardia and heart block. Severe hypotension is common, and in several cases, cyanosis with hypoxemia are seen in the first hours of intoxication. Selective vascular permeability alterations of pulmonary pre-capillary vascular bed have been reported in some cases leading to an increase in transcapillary hydrostatic pressure, increased capillary transudates, and lung interstitial edema.[1,2] As elsewhere reported, calcium infusion, insulin, catecholamine and atropine infusions have been used with success in the management of severe poisonings due to calcium channel blockers. Despite the absence of measurement of pulmonary artery pressure, a normal cardiac index and normal ventricular ejection fraction measured soon after the pulmonary suggest that myocardial depression was not an etiologic factor in this case. *References:* 1. Humbert VH, Munn NJ, Hawkins RF. Noncardiogenic pulmonary edema complicating massive diltiazem overdose. Chest 1991; 99:258–259. 2. De Roos F. Calcium-channel blockers. In: Goldfrank's Toxicologic Emergencies. New York, USA: McGraw-Hill, 2002:762–774.

185. Residues of Pharmaceuticals in Gastric Lavage

Pelclova D,[1] Navratil T.[2]
[1]*Department of Occupational Medicine, Charles University, Prague;* [2]*J. Heyrovsky Institute of Physical Chemistry, Prague, Czech Republic*

Objective: Gastric lavage is considered controversial; however it has frequently been performed already before the enquiry to the Toxicological Information Centre (TIC). The objective was to evaluate the results of gastric lavage in terms of noticeable tablets in gastric lavage and to identify the most frequently found pharmaceuticals. *Methods:* Data about finding of tablet residues after single pharmaceutical overdose were extracted from the documentation of TIC in the years 2005–2008, during gastric lavage at increasing time delay after ingestion. In addition, recommendation of TIC concerning gastric lavage was evaluated if it had not yet been performed. *Results:* A total of 15,872 enquiries involving pharmaceuticals were answered during the years 2005–2008, which represents about 40% of all calls to the TIC. Among the 11,085 drug poisonings with a single pharmaceutical only, gastric lavage had already been started or completed before the phone call in 1,753 cases. Among 1,002 gastric lavage evacuations already finished, identifiable tablets were seen in 32%; among them 66% of residues were found up to 1 hour after ingestion, 26% up to 2 hours, 5% up to 3 hours, and 3% later. The percentage of positive findings for toxic and lethal doses increased with latency time; it was 48%, 60%, 62% and 78% up to 1 hour, 2 hour, 3 hours and later, respectively. The most frequently found drugs in all time intervals (318 cases) were benzodiazepines, neuroleptics, SSRIs and NSA; in the longest delayed time interval (18 cases) also betablockers. TIC recommended gastric lavage in 13% of the calls only, it was contraindicated in 1%, and did not recommend performing it in 86% of the calls. *Conclusion:* Gastric lavage is relatively rarely recommended by the TIC, and the result was optically successful in only 32% of evacuations performed after ingestions of a single pharmaceutical. Toxic and lethal ingestions led more frequently to the positive finding in the longest time interval. Obviously, gastric lavage is futile in many cases of overdose, as the percentage of removed tablets is low; moreover the evidence for efficacy for clinical improvement is currently deficient. *Acknowledgement:* MSM 0021620807.

186. Use of the Intensive Care Unit in Acute Poisonings: A Seven-Year Analysis of 78 Patients

Zoppellari R,[1] Petrini S,[1] Ferri E,[1] Osti D,[1] Vason M,[1] Bianchi S,[2] Brunaldi V,[3] Avato FM,[3] Mantovani G.[1]
[1]*Department of Anaesthesia and Intensive Care, S. Anna Hospital;* [2]*Department of Pharmacy, S. Anna Hospital, Ferrara;* [3]*Institute of Legal Medicine, Ferrara University, Ferrara, Italy*

Objective: The use of the Intensive Care Unit (ICU) in acute poisonings is a challenging medical problem: the poisoned patient may present immediate or delayed severe toxicity. We studied the ICU use in poisoned patients and the related features. *Methods:* Seven year (July 1 2001– June 30 2008) prospective study including all patients admitted to our general ICU with a main diagnosis of acute poisoning. We defined three criteria for ICU admission: the presence of vital function impairment (group 1), the perception that significant organ dysfunction could appear in asymptomatic patients on the basis of toxicokinetics or toxicodynamic (group 2), a clinical judgment for intensive observation in mildly symptomatic patients (group 3). *Results:* Poisoned patients were 78 (2.98% of admitted patients) and 55.1% were caused by miscellaneous agents. All toxic agents were confirmed by toxicological laboratory analysis. The number of patients was 60 for group 1, 8 for group 2 and 10 for the third. The average length of ICU stay (in days) was 3.93, 1.49 ($P < 0.05$ compared to group 1 with Wilcoxon test) and 1.15 ($P < 0.01$ compared to group 1), respectively. Eight patients died: three from paraquat ingestion, four due to a delay between poisoning and resuscitation (two 85-year-old patients from neurodepressant brain injury, one patient from heroin overdose and one from ethylene glycol), one from aspiration pneumonia as a consequence of an organophosphate ingestion. For group 1 the poisons were mainly benzodiazepines (27%), noncyclic antidepressants (15.6%), cyclic antidepressants (11.5%) and antipsychotics (9.8%). The main cause of vital functions impairment was: respiratory failure requiring ventilatory support (78.3%), severe cardiovascular toxicity (6.7%), neurological dysfunction with a Glasgow Coma Score <10 (15%). Group 2 toxins were: acetonitrile (2), digoxin (2), paraquat (2), ethylene glycol and paracetamol; only paraquat caused death. Patients in group 3 did not require ventilatory support and had a good recovery. *Conclusion:* A rational approach to ICU use is described. Many poisonings (76.9%) presented an immediate life-threatening nature, while for patients who were asymptomatic or minimally symptomatic at admission, a short ICU stay was chosen for observation and treatment due the unpredictable clinical course.

187. Hydrofluoric Acid Burns: A New Efficient Model with *Ex Vivo* BIO-EC Human Skin Explants

Burgher F,[1] Mathieu L,[1] Fosse C,[1] Lati E,[2] Hall AH,[3] Maibach HI.[4]
[1]Prevor, Valmondois, France; [2]BIO-EC Laboratory, Longjumeau, France; [3]School of Public Health, University of Colorado, Denver, US; [4]Department of Dermatology, University of California San Francisco School of Medicine, San Francisco, US

Objective: Hydrofluoric acid's (HF) very hazardous properties are due to a double mechanism of action: corrosiveness (H^+), local and systemic toxicity (F^-). A new efficient skin model will allow a better understanding of burn mechanisms and in the future a comparison of first care treatments. *Methods:* 59 human skin explants from abdominoplasty preserved in BIO-ECs Explant Medium at 37° C in a moist atmosphere with 5% CO_2. HF exposure: 20 seconds by topical route from filter paper disks (9 mm diameter) previously saturated with 30 µl of HF 70%. Control group: no exposure. Histological sampling at different times, from 1 minute up to 24 hours. Observation by optical microscopy X40. *Results:* Alterations, during penetration of HF, were searched for in *stratum corneum*, basal epidermis, papillary and reticular dermis. It allows an observation of the progression of the lesions throughout the skin. 1 minute: beginning of penetration in the upper epidermis. 2 minutes: lesions reach epidermis basal layer. 3 minutes: epidermis is totally altered. First lesions in the superficial part of dermis. 4 minutes: clearer alteration of papillary dermis. 5 minutes: alterations reach slightly reticular dermis. Beyond ten minutes, all four layers present significant alterations. These lesions remain stable until the final observation after 24 hours when total epidermal necrosis can be observed. *Conclusion:* Under these operating conditions the kinetics of 70% HF burns can be precisely analyzed. This model completely corresponds to the clinical lesions observed during accidental splashes. The direct effect of the corrosive is extremely rapid and the lesions progress very quickly. This study confirms the need for an urgent and effective decontamination to prevent or minimize the severity of chemical burns due to concentrated hydrofluoric acid.

188. A Case of Accidental Phosgene Poisoning

Giampreti A,[1] Vecchio S,[1] Lonati D,[1] Petrolini V,[1] Bigi S,[1] Agostini M,[2] De Menis E,[2] Locatelli C.[1]
[1]Poison Control Centre and National Toxicology Information Centre, IRCCS Maugeri Foundation and University of Pavia, Pavia; [2]Intensive Care Unit and Internal Medicine, Montebelluna Hospital, Montebelluna, Italy

Objective: Phosgene (P) is a colourless oxidant gas, heavier than air, that can cause life-threatening pulmonary oedema within 24 hours of exposure. P was originally manufactured as an agent for chemical warfare during World War I and it is still widely used in the synthesis of chemicals and plastics. We present one patient who was accidentally exposed to phosgene during an attempt to defuse a World War I bomb. *Case report:* A 33-year-old man was admitted to the emergency department (ED) seven hours after accidental exposure to phosgene in an attempt to defuse a bomb illegally kept in his garage. He immediately manifested lacrimation, shortness of breath and coughing that promptly disappeared with cessation of exposure and reappeared a few hours later. At admission the patient presented acute pulmonary oedema confirmed at chest X-ray and CT-scan. Blood gases showed a progressive decrease in arterial PO_2 (50 mmHg). Pressure support ventilation with positive-end-expiratory pressure was performed and adequate oxygenation was obtained. Symptomatic treatment with aerosolized N-acetylcysteine and beclomethasone was started, combined with intravenous N-acetylcysteine, methylprednisolone and aminophylline. Coughing, dysphonia and ocular irritation continued for 4 days after exposure. A bronchoscopy performed at day 10 showed a diffuse oedema and mild foamy exudates; the broncho-alveolar lavage revealed a decrease of alveolar macrophages and lymphoid cell, and an increase in polymorphonuclear leukocytes count (prevalence of neutrophil granulocytes). Pulmonary function tests performed 13 days after admission revealed bronchostenosis, and beta2-adrenergic agonists were added to therapy. Currently, 19 days after exposure, the patient is still hospitalized, presents episodic dyspnoea, a decrease of arterial PO_2 (68 mmHg) without oxygen administration, and a slight improvement at CT-scan. *Conclusion:* In the modern era phosgene poisoning is uncommon except for accidental exposures. Acute P inhalation may cause immediate irritant effects, and severe pulmonary toxicity may be delayed 24 to 72 hours after exposure. In this accidental case, phosgene was confirmed by fire department environmental analysis. The patient showed a severe clinical course and a pulmonary cytological pattern compatible with the toxic effects of the substance.

189. Multiple Chemical Sensitivity: Clinical Evaluation of 175 Patients

Nogué S,[1] Rovira E,[1] Fernández-Solà J,[2] Fernández-Huerta JM,[2] Amigó M.[1]
[1]Clinical Toxicology Unit, Hospital Clínic; [2]Chronic Fatigue Unit, Hospital Clínic, Barcelona, Spain

Objective: Multiple chemical sensitivity (MCS) is a syndrome characterized by progressive intolerance to multiple environmental chemical agents. The objective of this study was to describe the clinical and epidemiological characteristics of patients with MCS seen in our hospital. *Methods:* Records of patients attending between 2002 and 2007 in the clinical toxicology outpatients clinic were reviewed, selecting those diagnosed with MCS according to the criteria defined by Bartha et al. in 1999.[1] The Quick Environmental Exposure and Sensitivity Inventory questionnaire (QEESI) proposed by Miller et al. in 1999[2] was used to evaluate patients. *Results:* 175 patients were included: mean age 47.4 years (range 27–69 years), 90.9% female. The most-frequent occupations were office workers (28%), nurses (18%) and cleaners (5%). Fifty-three per cent of patients had symptoms of MCS for more than two years. The origin of MCS was occupational exposure to toxic products in 41% of cases, most-frequently pesticides (organophosphates, carbamates and pyrethroids), hydrocarbons (solvents) and irritant gases (glutaraldehyde). In patients with established MCS, the most-frequent agents triggering symptoms were domestic cleaning products, air fresheners, colognes, perfumes, solvents and hydrocarbons. Symptoms included irritation of the ocular, nasal and pharyngeal mucosa, cough, dysphonia, dyspnea, headache, nausea, fatigue and general malaise. Mean QEESI scores were: chemical exposures scale 73 points, other exposures scale 40 points, symptoms scale 69 points, masking index 4 points and impact of sensitivities 56 points. Eighty-one per cent of patients had chronic fatigue syndrome and 62% fibromyalgia. At consultation, 38% of patients were temporarily and 10% permanently work-disabled. *Conclusion:* MCS predominantly affects middle-aged women also diagnosed with chronic fatigue syndrome or fibromyalgia. In 41% of the cases, MCS has an occupational origin due to exposure to pesticides, hydrocarbons or irritant substances. Forty-eight per cent of patients with MCS were work-disabled. *References:* 1. Bartha L, Baumzweiger W, Buscher DS, et al. Multiple chemical sensitivity: a 1999 consensus. Arch Environm Health 1999; 54:147–149. 2. Miller CS, Prihoda TJ. The Environmental Exposure and Sensitivity Inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. Toxicol Ind Health 1999; 15:370–385.

190. First Aid Treatment of Alkali Eye Burns with Phosphate Buffer does not Cause Corneal Calcifications

Damgaard AL,[1] Hovendal MP,[2] Schrøder HD,[3] Saxtorph H,[4] Bollen P.[4]
[1]Plum A/S, Assens; [2]Dept. of Ophthalmology, Odense University Hospital; [3]Dept. of Pathology, Odense University Hospital, Odense; [4]Biomedical Laboratory, University of Southern Denmark, Odense, Denmark

Objective: Phosphate buffered eye wash solutions are commonly used in the first aid treatment of acid/alkali eye burns. It has been reported that long-term use of phosphate buffer may cause corneal calcifications, e.g. after chronic use of phosphate buffered eye drops for contact lenses.[1] A study with experimentally induced alkali eye burns in a rabbit model also showed corneal calcifications. However, the rabbits' eyes were rinsed several times a day with a phosphate buffered solution during 16 days.[2] To our knowledge, no studies have investigated if corneal calcification occurs after initial rinsing with a phosphate buffered eye wash solution, followed by isotonic saline, which is a common first aid procedure. *Methods:* In twenty New Zealand White rabbits, alkali burns were induced in the right eye under general anaesthesia. The right eyes of ten rabbits were immediately rinsed with isotonic saline for 12 minutes. The right eyes of the remaining ten rabbits were immediately rinsed with a phosphate buffered eye wash solution for 2 minutes, followed by rinsing with isotonic saline for 10 minutes. After eight days blinded clinical observations with a slitlamp were made, and, after euthanasia, the corneas were isolated, embedded in paraffin, trimmed and stained with heamatoxylin/eosin and alazerin for pathological examination. The left eyes were used as untreated controls. *Results:* All right eyes showed a varying degree of opacity after the procedure. Clinical observations did not reveal any signs of calcification, and no calcium deposits were observed in the alazerin stained corneas during pathological evaluation. *Conclusion:* First aid treatment of alkali eye burns with phosphate buffer does not cause corneal calcifications. This study was approved by the Danish Animal Experiments Inspectorate. *References:* 1. Reim M, Schrage NF, Becker J. Interaction between ocular surface fluid and cornea related to contact lenses. Eur J Ophthalmol 2001; 11:105–115. 2. Schrage NF, Schlossmacher B, Aschenbernner W, et al. Phosphate in alkali eye burn as an inducer of experimental corneal calcification. Burns 2001; 27:459–464.

191. Does the Toxidrome of Acute Cyanide Poisoning Exist?

Baud FJ, Mégarbane B.
Medical and Toxicological Critical Care Department, Assistance Publique-Hôpitaux de Paris, Paris, France

Objective: Emergency diagnosis of cyanide poisoning is crucial in order to make decisions regarding protection of the rescuers, triage of the victims, and rapid administration of specific antidotes. We attempted to review signs and symptoms reported in acute cyanide poisoning in order to profile the cyanide toxidrome at the time of presentation. *Methods:* Published cases in the English and French medical literature and unpublished cases of cyanide poisonings admitted to our department and for whom advice was required from other departments (excluding exposure from smoke inhalation) were reviewed. Data were collected during the course of the poisoning but before any antidotal treatment. Some parameters were repeatedly checked, to define the cyanide toxidrome, the worst parameters were considered. Quantitative data are presented as medians and 10–90 percentiles. Qualitative data are presented as either a number of reports when the absence of the sign was not reported or percentage when the presence and the absence of the sign were reported. *Results:* One hundred and forty cases of cyanide poisoning were analyzed. Cyanide poisoning resulted from ingestion or inhalation in 90 and16 cases, respectively. A median profile was a 28 year-old (4–55) male (66/34) presenting 30 minutes post-exposure (5–530) with abnormal neurological status (83%) most frequently a coma (70%), abnormal respiratory pattern (95%) and mydriasis (77%). Median heart rate was 96 bpm (0–140), median systolic blood pressure was 77 mmHg (0–140). Median arterial pH was 7.17 (7.01–7.45), median $PaCO_2$ was 25 mmHg (15–44), median blood bicarbonate was 11.7 mmol/l (5.7–21.7) and median plasma lactate was 13.4 mmol/L (4.5–29.5). The mortality rate was 27 percent. *Conclusion:* A toxidrome suggestive of cyanide poisoning does exist using routinely measured clinical and biological parameters. This toxidrome allows presumptive diagnosis of cyanide poisoning at the time of presentation.

192. Methanol Poisoning and Pseudo-Elevation of Serum Creatinine Following Model Car/Aircraft Fuel Ingestion: Was Serum Creatinine a Good Predictor of Severity of Methanol Poisoning?

Wang CH,[1,2] Yang CC,[1,3] Wu ML,[1] Tsai WJ.[1]
[1]*Department of Medicine, Taipei Veterans General Hospital, Taipei;* [2]*Department of Emergency Medicine, Chang Gung Memorial Hospital Linkou Branch, Taoyuan;* [3]*Department of Environmental & Occupational Medicine, National Yang-Ming University, Taipei, Taiwan*

Objective: Ingestion of model car/aircraft fuel that contains nitromethane can result in falsely elevated serum creatinine level using the Jaffé colorimetric method. Ingestion of such fuels may also lead to methanol poisoning because methanol is another major constituent of the fuel. We reported 2 patients with model car/aircraft fuel ingestion and discussed the role of serum creatinine in predicting severity of methanol poisoning. *Case reports:* Case 1 was a 32-year-old alcoholic man who intentionally drank 200 ml of model car fuel. He had 2 prior episodes of model fuel ingestion but the clinical details were unknown. Serum creatinine of 40 mg/dL was noted 4.5 hours post-ingestion and he was referred to our service. Further increase of serum creatinine to 54.5 mg/dL was found 9.5 hours post-ingestion. He remained well until 14 hours later when he manifested dyspnea, agitation, confusion and severe metabolic acidosis. He initially declined hemodialysis and was given oral ethanol therapy for suspected methanol poisoning. Serum methanol level returned as 115.8 mg/dL on the next day. Because of persistent dsypnea, fomepizole therapy was commenced 36 hours post-ingestion, followed by hemodialysis. His condition markedly improved thereafter and he was discharged on day 5 with slightly elevated creatinine (1.6 mg/dL). Case 2 was a 30-year-old male who attempted suicide by drinking 300 ml of model aircraft fuel. Serum creatinine of 6.7 mg/dL was noted on arrival and ethanol was given orally as a prophylactic measure for methanol poisoning. Peak serum creatinine (9.2 mg/dL) was noted 5 hours post-ingestion; laboratory data were also remarkable for serum ethanol 221 mg/dL, creatine kinase 621 U/L, alanine transaminase 114 U/L and aspartate transaminase 285 U/L. Serum methanol level was returned as 18 mg/dL on day 2. With supportive therapy, serum creatinine dropped to 1.7 mg/dL and he was discharged on day 4. *Conclusion:* Ingestion of model car/aircraft fuel can occasionally result in severe methanol poisoning. Findings from our patients and previously reported cases suggest that falsely elevated serum creatinine levels in such patients may not be a good predictor of the severity of methanol poisoning because the concentrations of nitromethane/methanol probably vary between different products.

193. Case Report: An Accidental Exposure to the Chlorine Gas in Swimming Pool of a Spa Hotel in Tallinn

Põld K, Oder M.
Estonian Poison Information Centre, Chemicals Notification Center, Tallinn, Estonia

Objective: To describe an accidental exposure to chlorine gas in a spa. *Case report:* On the 1st of July, 2008 a chemical leak in the basement of a Spa Hotel in Tallinn caused marked air pollution in the area. Following a spill of approximately 1 litre of 40% sulphuric acid and 15 litres of 12% sodium hypochlorite, chlorine gas was formed. The emergency service received a call concerning the accident at 18:05. At 18:20 the cause of the accident was identified and all the guests were evacuated. At 18:46 a chemical pollution rescue group covered the spill with adsorbent. At 19:04 the ventilation system was turned off. The chlorine concentration in the air was measured several times: at 20:30 30 cm above the covered spill area - 2–3 ppm; at 24:00 10 cm above the cleaned pollution area - 2 ppm, and 1 metre above the spill area after the pollution was cleaned - 0.5 ppm. By 00:30 the whole hotel area had been inspected and the visitors were allowed to return to their facilities. The swimming pool area remained closed until the next day. Altogether 39 persons required medical attention. Three of the patients were not transported to the hospital - 2 refused hospitalization and one 7 month old baby had no symptoms. 28 patients were transported to hospitals by ambulance, 8 presented to the emergency departments using their own transportation. Median age was 20 years (7 month - 59 years); male 13, women 26. Symptoms: cough in 21 (53.8%), nausea and vomiting 5 (12.8%), dyspnoea 11 (28.2%), auscultatory crepitations 6 (15.4%), irritation of mucosal membranes 17 (43.6), irritation of eyes 5 (12.8%), fatigue and vertigo 1 (2.6%), leucotcytosis 2 (5.1%) and no symptoms in 5 (12.8%) cases. Nine patients were hospitalized, 7 of them until the next day and 2 patients (co-morbidity of asthma and aortic valve stenosis) until 3rd of July. *Conclusion:* The exact concentration at the time of the accident remains unknown because the first measurement was done after the spill was covered with adsorbent. On the basis of symptoms the concentration of chlorine at the time of the accident was probably higher than the measured maximum concentration.

194. Accidental Ingestion of Chemicals in the Swedish Elderly Population

Hägerkvist R, Palmborg M, Walter J, Persson H.
Swedish Poisons Information Centre, Stockholm, Sweden

Objective: Ingestion of chemical products for household use is a persistent problem among elderly suffering from dementia and may cause severe symptoms, even fatalities.[1,2] The aim of this study was to investigate circumstances of the accident, age and gender of patients, product types, severity of symptoms and compliance to advice from the Swedish Poisons Information Centre (SPIC). *Methods:* All inquiries to the SPIC concerning ingestion of chemicals among elderly people (>70 years) were registered during eight months, February 1 until September 30, 2008. Follow up interviews were performed and hospital case records were collected. Severity of symptoms was graded according to the Poisoning Severity Score (PSS). *Results:* The number of inquiries was 309, related to 248 cases. The majority of inquiries (56%) came from staff at geriatric institutions, followed by home settings (20%), hospitals (17%) and ambulance service (6%). In total 95 cases (57 women and 38 men) were studied in detail (mean age 84 years). Follow up interviews were performed in 75 cases and hospital records were received concerning 20 patients. Cleaning products containing surfactants were involved in half of the cases followed by alcohol containing disinfectants, soap, dishwashing agents, kerosene and all purpose cleaners. In most of cases there were no (PSS 0) or mild symptoms (PSS 1). In three cases symptoms were graded as moderate (PSS 2) and two patients developed aspiration pneumonia with complications (PSS 3) after ingestion of products containing surfactants and kerosene respectively. The advice given by the SPIC was followed in 82% of the cases. *Conclusion:* Although most patients showed no or mild symptoms, surfactant containing products still remain a risk for this elderly vulnerable population. As the outcome of these accidents is difficult to assess, a certain overtreatment is probably difficult to avoid. We therefore propose that more effort should be put into limiting the access to such products in the geriatric institutions. *References:* 1. Axelsson L, Söderström L, Torell E, et al. Fatalities among elderly people due to accidental ingestion of household detergents. A prospective study of cases reported to the Swedish Poison Information Centre. Bull Soc Sci Med 1990; 127:301–305. 2. Hahn A, Begemann K, Michalak H, et al. Death after ingestion of surfactants: a particular risk for patients suffering from dementia (abstract). Clin Toxicol 2007; 45:384–385.

195. Advanced Methods in Pharmacovigilance and Toxicosurveillance

Edwards RI.
The Uppsala Monitoring Centre, Uppsala, Sweden

Objective: To demonstrate how useful knowledge can be extracted from collected individual case report data, and from longitudinal health care records. *Methods:* Data mining approaches using a Bayesian methodology[1] within an artificial intelligence network have been applied to the WHO international database of over 4 million adverse drug reaction reports from 90 countries.[2] The data mining process uses Bayesian logic both in the sense that, as new information is gathered into the database, the probability that any drug/chemical and any clinical event reported with it will stand out from the background with demonstrably increased probability and confidence. Bayesian statistics are also applied within the data mining algorithm which has a conservative prior assumption of no relationship between the drug/chemical and the clinical event, and includes a damping factor so that limited, novel information does not cause too early a disproportionality signal.[3] The general aim of the mining process is to highlight associations which are quantitatively worth further attention through a clinical triage algorithm, which considers qualitative aspects of the signal through clinical review.[4] Broadly, for example in the WHO global adverse reactions database, increasing disproportionality of observed to expected drug/adverse reaction pairs, and diverse country of origin of reports determine which drug/ADR paired association has further clinical review for factors such as seriousness, plausible time relationships and dose response. Data mining in longitudinal patient records[5] allows one to look for drug event pairs that occur disproportionally to an unselected control background, as well as being able to conduct a case-cohort using the patient's record before the relevant intervention as a control for what happens after. *Results:* The following new ADR signals were first found from longitudinal health care records: 1. Calcipotriol and tooth supporting tissue problems 2. Paroxetine and dyspareunia 3. Atenolol and palmar fascial fibrosis 4. Malathion and motion sickness 5. Trimethoprim and motion sickness 6. Doxazosin and phlebitis/thrombophlebitis 7. Xylometazoline and anxiety. In addition it was possible to explore the past medical histories of patients who had suicidal ideation after the use of SSRI drugs, as well as to examine their effectiveness for different indications. This showed that patients with suicidal ideation tended to have a long preceding history with little change after SSRI treatment, apart from a short term improvement. In individual case report data, it was sometimes possible to identify new drug adverse reaction signals year before regulatory action was taken, e.g. topiramate and glaucoma, three years before. The ability to find signals depends on the quality and frequency of reporting, and other database characteristics. *Conclusion:* Data mining is a proven method for developing useful hypotheses from large amounts of data which should then be evaluated further by other methods.[6] *References:* 1. Bate A. Bayesian confidence propagation neural network. Drug Saf 2007; 30:623–625. 2. Edwards IR, Lindquist M, Bate A, et al. Data Mining. In: Mann RD, Andrews EB, eds. Pharmacovigilance. Chichester, England: John Wiley & Sons Ltd, 2002:291–300. 3. Bate A, Orre R, Lindquist M, et al. Explanation of data mining methods. BMJ 2001; 322:1207–1209. 4. Lindquist M. Use of triage strategies in the WHO signal-detection process. Drug Saf 2007; 30:635–637. 5. Norén GN, Bate A, Hopstadius J, et al. Temporal pattern discovery for trends and transient effects: its application to patient records. In: International Conference on Knowledge Discovery and Data Mining. Proceeding of the 14th ACM SIGKDD International Conference. Las Vegas Nevada, USA, 2008:963–71. 6. Norén GN, Bate A, Orre R, et al. Extending the methods used to screen the WHO drug safety database towards analysis of complex associations and improved accuracy for rare events. Stat Med 2006; 25:3740–3757.

196. Clinical and Experimental Evidence of Italian Viper Venom Neurotoxicity

Lonati D,[1] Rossetto O,[2] Cintra-Francischinelli M,[2] Locatelli C,[1] Giampreti A,[1] Vecchio S,[1] Bigi S,[1] Petrolini V,[1] Sacchi R,[3] Bernini F,[3] Gentilli A,[3] Manzo L,[1] Montecucco C.[2]
[1]*Poison Control Centre and National Toxicology Information Centre, IRCCS Maugeri Foundation and University of Pavia, Pavia;* [2]*Department of Biomedical Sciences, University of Padova, Padova;* [3]*Department of Animal Biology, University of Pavia, Pavia, Italy*

Objective: Peripheral neurotoxic effects (PNE) after European viper envenomation have been reported both in Italy and South-Eastern France. PNE involve mostly

cranial nerves and can be related to the presynaptic toxicity of phospholipases-A2 (PLA2) that causes neuromuscular paralysis. Currently PLA2 in Italian viper has never been demonstrated. The aims of this study are to identify PNE observed in patients referred to Pavia Poison Centre after viper bites, and describe the presence and activity of PLA2 in the Italian viper venom. *Methods:* Clinical data: Patients with PNE after viper bite observed between 2001–2008 were reviewed and valuated for local, neurological and non-neurological manifestations. Experimental data: Venom milked from 3 adults of the Italian Vipera aspis was analyzed through polyacrylamide gel electrophoresis. Venom activity was tested with mouse phrenic nerve-hemidiaphragm and stimulated by supramaximal stimuli of 3–6 V amplitude and 0.1 millisecond pulse with a frequency of 0.1Hz; isometric muscle contraction was monitored and a curve of paralysis was registered. Immortalized motor neuron cell line was incubated with venom. *Results:* Clinical data: Eighteen patients were observed (3–75 years). PNE included bilateral ptosis (16/18 patients), diplopia (6/18), dysphagia (3/18). Patients showed mild (6/18), moderate (10/18) or massive limb oedema (2/18). Systemic non-neurotoxic effects were vomiting (12/18), abdominal pain (6/18) and diarrhoea (5/18). Five patients showed PNE as unique systemic manifestation. PNE were observed 3–30 hours after the bite; systemic non-neurotoxic effects occurred earlier. Experimental data: SDS-gel electrophoresis of venom showed proteins with molecular mass resembling PLA2. Venom added to mouse hemidiaphragm caused a biphasic curve of paralysis without impairment of muscle contraction. Incubation of neuronal cells with venom induced a defined swelling of synaptic sites with formation of bulges similar to other snake neurotoxins with PLA2 activity. *Discussion:* The PNE observed seems potentially connected with the action of PLA2. PNE can occur with delayed onset, even in patients presenting with only local effects. PLA2 was detected in all venom samples analyzed. Nevertheless patients without signs of neurotoxicity are reported, and this could be related to the amount of venom injected, the concentration of PLA2 and a possible individual susceptibility.

197. Can a Local Poison Centre Shorten the Length of Hospital Stay of Poisoned Patients? Results of a Retrospective Cohort in One Emergency Department of Manaus, Amazonas, Brazil

Galvão TF,[1] Silva MT,[2] Silva CD,[1] Barotto AM,[3] Gavioli IL,[4] Bucaretchi F,[5] Atallah AN.[6]
[1]Amazonas Poison Centre, Getúlio Vargas University Hospital, Manaus; [2]Department of Science and Technology, Ministry of Health, Brasília; [3]Santa Catarina Poison Centre, University Hospital, Florianópolis; [4]Rio Grande do Sul Poison Centre, State Foundation of Production and Research, Porto Alegre; [5]Campinas Poison Control Center, University Hospital, Campinas; [6]Medicine Department, Federal University of São Paulo, São Paulo, Brazil

Objective: To observe the difference in the length of stay (LOS) in poisoned patients with (case) and without (control) Poison Centre (PC) assistance. *Methods:* Using data from "Hospital e Pronto Socorro 28 de Agosto" - an emergency department (ED) of Manaus, Amazonas - we performed a retrospective cohort study of all patients with poisoning diagnosis admitted to the ED from 2005 to 2007. Study variables were: year of admission, sex, age, admission date, discharge date, LOS and group (case or control). LOS was calculated using admission and discharge date. The group classification was obtained, independently, through name of the patient and admission date search in the Amazonas Poison Centre (PC) database. Data was tabulated and then analysed with Epidat 3.1 to obtain descriptive statistics and weight mean difference. *Results:* 198 patients were identified with hospitalization for poisoning in the period, of those, 36 were case and 162 control. Mean age (±SD) was 37.5 (±11.6), 69.7% patients were men. Records showed a total of 1,568 days of hospitalization due to those poisonings (mean = 7.92±11.65). Mean LOS of the case group was 5.50 ± 6.20 days, and for control patients, 8.46 ± 12.50. PC reduced, on average, LOS by 3.43 days (0.77–6.10; CI 95%) for hospitalized poisoned patients in the ED of study, in comparison to no assistance. *Conclusion:* The reduction in LOS due PC in the ED of study was statistically significant, and represents a very important way to contain costs in tertiary health care, which are constantly growing. Similar reduction was found in another study.[1] In this report, only 18.2% of poisoned patients hospitalized in the ED in the period of study had PC remote assistance, clearly evidencing the need for promotion of this kind of service in local EDs. *References:* 1. Vassilev ZP, Marcus SM. The impact of a poison control center on the length of hospital stay for patients with poisoning. J Toxicol Environ Health A 2007; 70:107–110. *Financial Aid:* Galvão TF has financial support of FAPEAM RH-POSGRAD Program.

198. Electrophysiological Correlates of Respiratory Failure in Organophosphate Poisoning, Evidence for Differential Roles of Muscarinic and Nicotinic Stimulation

Jayawardane P,[1,2] Senanayake N,[2] Eyer P,[2] Buckley N,[2] Dawson A.[2]
[1]Department of Pharmacology, University of Sri Jayewardenepura, Nugegoda; [2]South Asian Clinical Toxicology Research Collaboration, University of Peradeniya, Peradeniya, Sri Lanka

Objective: Respiratory failure in acute organophosphate (OP) poisoning can occur early and relatively late in the clinical course. This study aims to investigate the pathophysiology of both syndromes. *Methods:* Consenting symptomatic patients with acute OP poisoning were assessed prospectively with daily physical examinations and repetitive nerve stimulation (RNS) studies. RNS was done on right and left median and ulnar nerves at 1, 3, 10, 15, 20 and 30Hz. Serial blood was collected in a subset to assess red blood cell acetylcholinesterase (RBC-AChE) and serum OP level. Outcomes such as need for ventilation and development of intermediate syndrome (IMS) were noted. Early respiratory failure was defined as occurring within 24 hours of ingestion *Results:* 78 patients were recruited for the clinical and electrophysiological study and 59 patients ingesting chlorpyrifos were recruited for the biochemical study. 7 developed respiratory failure within 24 hours of ingestion with overt muscarinic signs and no electrophysiological abnormalities on intubation. 3/7 later developed *forme fruste* IMS. 40 patients developed RNS changes and clinical signs consistent with IMS spectrum disorder. In most cases these were detectable within 24 hours and then got progressively worse. 10 patients developed severe IMS (<3/5 weakness) and 5 developed late respiratory failure. All 10 patients showed progressive RNS changes correlating with the severity of IMS. The 48 hour AUC of RBC-AChE inhibition and chlorpyrifos was significantly associated with the development of IMS spectrum disorder (Mann Whitney U test p values - 0.0005 and 0.0027 respectively). *Conclusion:* The presence of normal RNS in many patients developing early respiratory failure suggests that this may be predominately a muscarinic syndrome. This supports the need for early rapid atropinisation to be the initial priority, whereas treatments to combat nicotinic effects are less urgent. Late respiratory failure is associated with prolonged RBC-AChE inhibition, higher pesticide levels and nicotinic neuromuscular failure. Continued stimulation of postsynaptic nicotinic receptors or direct effects of OP may explain the pathogenesis of IMS and late respiratory failure. Further studies with antidotes that increase elimination of OP or block nicotinic receptors are needed.

199. The Usefulness of 99mTc-HMPAO-SPECT Brain Imaging and Neuropsychological Examination in Assessment of Carbon Monoxide Neurotoxicity

Pach D,[2] Hubalewska-Dydejczyk A,[2] Groszek B,[1] Pach J,[1] Szczepanska L.[1]
[1]Department of Clinical Toxicology, Jagiellonian University Medical College; [2]Nuclear Medicine Unit Chair of Endocrinology, Jagiellonian University Medical College, Kraków, Poland

Objective: The aim of the study was to evaluate functional status of the central nervous system (CSN) after acute carbon monoxide (CO) poisoning, using 99mTc-HMPAO brain SPECT imaging and neuropsychological examination. An attempt to establish the relationship between CO poisoning severity and incidence of late neurological sequelae was also undertaken. *Methods:* The study included 80 patients (mean age 29 ± 11 years) treated because of accidental acute CO poisoning. The CO poisoning severity was estimated on admission, considering age, duration of exposure, COHb, lactate concentration and neurological state. All 80 patients were evaluated in the acute phase of CO poisoning and 38 of them 6 months post exposure by using 99mTc-HMPAO brain SPECT imaging. Neuropsychological tests were also performed to diagnose a cognitive dysfunction. The control group for establishing normal values of 99mTc-HMPAO brain SPECT consisted of 31 healthy individuals aged 33.32±10.99 years. *Results:* A statistically significant decrease in regional cerebral blood flow (rCBF) in frontal, temporal and occipital lobes after CO poisoning was found, both in the initial and the control SPECT study ($p=0.006$). The results of neuropsychological examination were indicative of frontal and temporal lobes cognitive dysfunctions; the incidence and intensity of which depended on duration of CO exposure (OR = 1.01; $p=0.037$) and poisoning severity ($p=0.014$). The relationship between the results of initial and control neuropsychological examinations was statistically significant ($p<0.001$). In the acute phase of CO poisoning ($p=0.034$) as well as in the control survey ($p<0.001$) statistically significant relationship between the abnormal results of neuropsychological examinations and rCBF abnormalities in the brain lobes, but not in the basal ganglia, was noted. *Conclusion:* An examination of regional cerebral blood flow using 99mTc HMPAO SPECT and synchronous neuropsychological testing enables an assessment of metabolic and functional state of CNS in the acute insult of CO poisoning, and allows the prognosis and monitoring of late neurological sequelae.

200. Severe Toxicity Associated with MDMA ('ECSTASY') Presentation to the Emergency Department Appears to be more Common in those with Lone MDMA Ingestions

Dargan PI,[1] Bishop CR,[1] Greene SL,[1] Garnham F,[2] Wood DM.[1]
[1]Guy's and St Thomas' Poisons Unit, Guy's and St Thomas' NHS Foundation Trust; [2]Emergency Department, Guy's and St Thomas' NHS Foundation Trust, London, UK

Objective: MDMA use is common in the UK, with 1.8% of those aged 16–59 having used it in the last year.[1] MDMA toxicity is a common reason for presentation to the Emergency Department. There are numerous reports of significant toxicity however there is limited data on the frequency of severe harm associated with MDMA. *Methods:* Routine exposure, clinical and outcome data is collected on a purpose-designed database on all poisoned patients presenting to our Emergency Department (ED). This database was interrogated retrospectively, for the period 1st May 2005–30th June 2008 to identify all recreational drug presentations. More detailed data was collected on presentations related to self-reported MDMA ingestion: co-ingestants and clinically significant harm (arrhythmias, hyperthermia, seizures, death). *Results:* During the study period there were 1612 recreational drug presentations, 382 (23.7%) of these involved self-reported MDMA ingestion. 58 (15.2%) of these related to lone MDMA ingestion, the remainder were 'mixed MDMA' ingestions with other recreational drugs and/or ethanol. Of the 324 mixed ingestions, 49.6% had ingested 1 other agent, 33% had ingested 2 and 17.4% had ingested 3 or more. The commonest co-ingested drug was ethanol (79.8%); others included cocaine (24.1%), GHB/GBL 22.5% and ketamine (20.6%). Arrhythmias, seizures, hyperthermia and/or death were significantly more common in the lone MDMA presentations compared to the mixed MDMA presentations (27.6% -vs- 7.4%, $p<0.0001$). Lone MDMA presentations were more likely to have arrhythmias (6.9% -vs- 1.2%, $p=0.02$), seizures (15.5% -vs- 4%, $p = 0.002$) and hyperthermia (10.3% -vs- 2.8%, $p = 0.02$). Of particular note, severe hyperthermia (>40°C) only occurred in lone MDMA ingestions (n=4). There was one death in the

lone MDMA and the mixed MDMA presentations, although both resulted from out-of-hospital cardiorespiratory arrests. *Conclusion:* MDMA is a common reason for presentation to the Emergency Department, but the majority of individuals have taken one or more other recreational drug(s) in addition to the MDMA. A significant minority develop severe clinical features (seizures, hyperthermia, arrhythmias or death), and it appears that these are more common with lone MDMA ingestions. *References:* 1. United Nations office on drugs and crime. World Drug Report 2008. http://www.unodc.org/documents/wdr/WDR_2008/WDR_2008_eng_web.pdf (last accessed 19 Nov 2008)

201. Mechanisms and Treatments of Cardiovascular Failure in Severe Suicidal Beta-Blocker Poisonings

Mégarbane B, Ouardani R, Deye N, Baud FJ.
Réanimation Médicale et Toxicologique, Hôpital Lariboisière, Paris, France

Beta-blockers (BB) represent the most frequent cardiotoxicant poisonings. Mild intoxications result in bradycardia and hypotension; however, cardiovascular failure is possible. Our objective was to characterize BB poisoning-related cardiac effects. *Methods:* Retrospective review of BB-poisoned patients admitted during 2001–2008 in our ICU with hypotension requiring catecholamines; measurement of blood flow and BB concentrations using HPLC (Remedi®); description (median [25–75%-percentiles]; comparisons using Mann-Whithney and Chi-2 tests. *Results:* Fifty-three patients (39F/14M; 44 years [36–53]; underlying cardiac diseases (36%); SAPSII score: 52 [26–66]) were included. The most frequent BB (doses; concentrations) were propranolol (N=20; 2.0 g [1.0–4.0]; 5.9 µmol/l [1.9–29.2]), acebutolol (N=11; 6.0 g [3.8–11.0]; 24.1 µmol/l [20.8–41.3]), atenolol (N=8; 2.4 g [0.7–2.8]; 33.0 µmol/l [24.2–64.6]), and sotalol (N=5; 2.4 g [2.2–4.2]; 44.4 µmol/l [11.6–92.4]). Multidrug ingestion included psychotropic (60%) and cardiotropic drugs (40%). Patients presented with systolic pressure of 77 mmHg [60–85], diastolic pressure of 40 mmHg [32–49], and heart rate of 50 /min [41–60]. Median plasma lactate was 2.7 mmol/l [1.8–5.1], serum creatinine 87 µmol/l [68–123], aspartate aminotransferase (AST) 40 IU/l [22–86], and prothrombin ratio 60% [34–73]. Electrocardiograms showed atrioventricular blocks (34%) and QRS enlargement (0.10 s [0.08–0.12]). Four patients presented with cardiac arrest on admission. Cardiovascular monitoring was based on echocardiography (32/53), right-heart catheterism (13/53), and PICCO® (8/53). Shock was cardiogenic (57%, blood flow: 2.8 l/min [1.3–3.1]), vasoplegic (9%) or mixed (25%). Patients received charcoal (21%), mechanical ventilation (66%), sodium bicarbonate (25%), dobutamine (74%, 12.5 µg/kg/min [10.0–8.8]), isoprenaline (30%), epinephrine (59%, 4 mg/h [1.4–7.0]), norepinephrine (40%, 3.8 mg/h [2.0–4.4]), dopamine (17%), and glucagon (72%). Eight patients required extracorporeal life support (ECLS) allowing favourable outcome in 5/8 cases. Regarding outcome (death rate: 13%), blood pressure ($p = 0.0001$), QRS length ($p = 0.01$), lactate concentration ($p = 0.004$), creatinine concentration ($p = 0.01$), AST concentration ($p = 0.01$), epinephrine infusion rate ($p = 0.02$), and SAPSII score ($p = 0.004$) were significantly different between survivors and non-survivors. *Conclusions:* Severe BB intoxications are most frequently responsible of cardiac failure characterised by a mild elevation in lactate concentrations. Early identification of prognostic factors may help identifying patients with refractory cardiogenic shock who should benefit from ECLS.

202. Inaccuracy of Electrocardiogram Interpretations Reported to the Poison Center

Prosser JM,[1,2] Smith SW,[1,2] Olsen D,[3] Nelson LS,[1,2] Hoffman RS.[1,2]
[1]*New York City Poison Center;* [2]*New York University School of Medicine, New York;* [3]*St. Barnabas Hospital, Bronx, US*

Objective: The ECG is an important diagnostic tool in the management of poisoned patients. Poisons Center (PC) consultants often make critical management recommendations based on the caller's interpretation of the ECG. The objective of this study is to determine the accuracy of ECG interpretations reported to the PC. *Methods:* All hospital callers to the PC were prospectively asked to fax the initial ECG obtained for each patient. The inclusion criteria were that both an ECG was faxed and the caller's interpretation was reported. Exclusion criteria were illegible faxes, ECGs that could not be matched with cases in the PC database and ECGs without a recorded interpretation by the caller. Data were collected over a three month period. A blinded cardiologist interpreted the ECGs. Cases with a difference in interpretation between the caller and the cardiologist were submitted to three experienced medical toxicologists for review. The toxicologists were asked to determine if there was a clinically significant difference between the callers' and cardiologist's interpretations, and if that difference would have changed management recommendations given during the initial call. *Results:* 200 hundred ECGs met the inclusion criteria. There was complete agreement in interpretation between the cardiologist and the PC caller in 75. In another 24 cases, the difference only related to nonspecific ST changes which were, by design felt to be clinically insignificant. The remaining 101 ECGs were reviewed by the three medical toxicologists. In 27/101 at least 2 toxicologists agreed that there was a clinically significant difference in the interpretations and in 23/101 cases agreement the difference that would have prompted a change in management recommendations. Examples of significant caller misinterpretation included: a case of sodium channel blockade assessed as ventricular tachycardia resulting in an attempt at cardioversion, failure to recognize significant QTc prolongation >600 ms and failure to recognize junctional rhythms. *Conclusion:* The initial interpretation of the ECG reported to the PC is frequently inaccurate. In approximately 10% of cases this error effects management recommendations. Poison centers and their consultants should attempt to review all ECGs to improve the quality of clinical recommendations.

203. Correlation Between the Neuromuscular Transmission Failure and the Acetylcholine Esterase in Acute Organophosphate Poisoning

Jayawardane P,[1,2] Senanayake N,[2] Eyer P,[2] Buckley N,[2] Dawson A.[2]
[1]*Department of Pharmacology, University of Sri Jayewardenepura, Nugegoda;* [2]*South Asian Clinical Toxicology Research Collaboration, University of Peradeniya, Peradeniya, Sri Lanka*

Objective: Progressive neuromuscular transmission failure (NTF) leads to intermediate syndrome (IMS) following acute organophosphate (OP) poisoning. The objective was to assess a correlation between the NTF and the Red blood cell acetylcholinesterase (RBC-AChE) in acute OP poisoning. *Methods:* A prospective case series of 78 consenting symptomatic patients with acute OP poisoning were assessed with Repetitive Nerve Stimulation (RNS) studies on R/ L Median and Ulnar nerves at 1, 3, 10, 15, 20 & 30 Hz. The ratio between the amplitude of the 2nd compound muscle action potential (CMAP) and 1st CMAP was calculated at 24 hours and 48 hours following admission as a surrogate measure of the severity of NTF. RBC-AChE level was assessed on admission 1, 4, 12, 24 hours after admission and daily thereafter in a sub-set of patients using modified Elman technique. Area under the curve (AUC) for serial RBC-AChE levels up to 24 and 48 hours were calculated as a summary measure of RBC-AChE inhibition at 24 and 48 hours. AUC RBC-AChE at 24 and 48 hours were correlated using Spearman's coefficient correlation with respective C2:C1 ratios at all frequencies. *Results:* The C2:C1 ratio is significantly correlated to the RBC-AChE inhibition. *Conclusion:* Thus AChE inhibition is associated with the development of NTF. However the contribution of other factors merits further investigation.

Table. The correlation between 24 and 48 hour C2:C1 ratio at 1, 3, 10 15, 20 and 30 Hz and the 24 & 48 hours AUC of RBC-AChE level

Parameter	1Hz		3Hz		10Hz		15Hz		20Hz		30Hz	
Time	24h	48h	24h	48h	24h	48h	24h	48h	24h	48h	24h	48h
XY pairs	46	42	46	42	46	43	45	39	43	41	43	39
Spearman's r	.196	.378	.254	.419	.266	.345	.353	.441	.369	.521	.369	.520
P value	.191	.014	.088	.006	.074	.023	.017	.005	.015	.000	.015	.001

204. Comparison of Poisoning Severity Grades Allocated by Enquirers and Poisons Information Staff in Pesticide Exposures

Adams RD, Lupton D, Good AM, Bateman DN.
NPIS Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, UK

Objective: To examine poisoning severity gradings allocated in pesticide exposure cases by enquirers and poisons information staff in adults and children. *Methods:* The National Poisons Information Service Edinburgh Unit (NPISE) monitors pesticide exposures following internet (TOXBASE) or telephone enquiries. Exposures are followed up by questionnaire. Enquirers are requested to grade exposure severity at admission/presentation as:- "Not at all serious", "Minor", "Moderate", "Major", "Uncertain". Cases are also graded by NPISE using the PSS[1] based on the symptoms reported (None 0, Minor 1, Moderate 2, Severe 3, Uncertain). Questionnaires were grouped by pesticide type or ingredient (e.g. ant killers, rodenticides, glyphosate, paraquat) and divided into adult (>12y) and childhood (12 y and less) exposures. Cases graded "uncertain" were excluded. Severity gradings of 0–3 were allocated to compare with PSS. Means were calculated for NPISE and enquirer gradings in adults and children for each pesticide. Wilcoxon, Mann-Whitney and Spearmans rank tests were used to compare severity assessments and correlate scores between grader types. *Results:* See table. *Conclusion:* Overall enquirer severity grading correlated with NPISE PSS ($p<0.001$) Enquirers graded toxicity higher than did PSS; differences were greater in children than adults. Findings in individual pesticides were less consistent. Although there are few exposures of higher severity these findings suggest inherent differences in enquirer perception of pesticide toxicity. *References:* 1. Persson HE, Sjoberg GK, Haines JA, et al. Poisoning Severity Score. Grading of acute poisoning. J Toxicol Clin Toxicol 1998; 36:205–213.

Table. Mean NPISE and enquirer severity grades for different pesticide groups

Category	Enquirer Mean	NPISE PSS Mean	Difference in means	Paired Wilcoxon test Z and 2 tail P value	Spearman rank correlation coefficient
All products Children (685)	0.58	0.16	0.42	Z = 12.34 P <0.001	R_s = 0.13 P <0.001
All products Adults (495)	**0.89**	**0.74**	**0.15**	Z = 4.04 P <0.001	R_s = 0.34 P <0.001
Mann-Whitney Value (P2)	Z = –6.92 P = <0.001	Z = –15.36 P = <0.001			
Rodenticide Children (272)	**0.57**	**0.06**	**0.51**	Z = 8.85 P <0.001	R_s = 0.03 P = 0.59
Rodenticide Adults (34)	**0.59**	**0.32**	**0.27**	Z = 1.9 P = 0.06	R_s = 0.25 P = 0.15
Mann-Whitney Value (P2)	Z = 0.08 P = 0.94	Z = –2.02 P = 0.04			
Ant Killer Children (104)	**0.56**	**0.16**	**0.40**	Z = 4.94 P <0.001	R_s = 0.19 P = 0.06
Ant Killer Adults (45)	**0.64**	**0.76**	**–0.12**	Z = –1.12 P = 0.26	R_s = 0.45 P < 0.01
Mann-Whitney Value (P2)	Z = –0.65 P = 0.52	Z = –5.73 P = <0.001			
Glyphosate Children (26)	**0.58**	**0.31**	**0.27**	Z = 1.35 P = 0.18	R_s = –0.03 P = 0.91
Glyphosate Adults (55)	**1.02**	**0.69**	**0.33**	Z = 2.62 P <0.01	R_s = 0.3 P = 0.02
Mann-Whitney Value (P2)	Z = –2.44 P < 0.02	Z = –2.49 P < 0.02			

205. Peripheral Burning Pain Predicts Higher Plasma Paraquat Levels and Mortality in Paraquat Poisoning

Gawarammana IB,[1] Dawson AH.[2]
[1]Department of Clinical Medicine and South Asian Clinical Toxicology Research Collaboration, University of Peradeniya, Peradeniya, Sri Lanka; [2]Asian Clinical Toxicology Research Collaboration, University of Peradeniya, Sri Lanka and School of Population Health, University of Newcastle, Australia

Objective: Self poisoning with paraquat has a case fatality ratio (CFR) over 65% in Sri Lanka. To date, the best prognostic tool is the plasma paraquat[1,2] concentration which is not routinely available in most clinical settings. Surrogate clinical markers of plasma paraquat concentration will help predict outcome in order to educate patients and relatives as early as possible. Anecdotal reports by staff suggested that patients who complained of burning sensation (BS) (described as if their skin is on fire) of the body had a poor prognosis and a prospective study was initiated. *Methods:* This was a prospective observational study in 3 hospitals in Sri Lanka. We collected demographic data, presence or absence of burning sensation and major outcome and estimated plasma paraquat concentration within 24 hours post ingestion. *Results:* There were 142 patients (95 males) with a median age of 27 years (IQR 21–38). Outcome was recorded in 122 patients with 67 deaths. Others were lost to follow up after discharge. Median time to develop BS was 1 day (IQR1-1). BS was associated with a significantly higher plasma paraquat level (2.67 µg/mL (95% CI 0.84–14.2) vs 0.022 µg/mL (95% CI 0.005–0.78); ($p<0.05$)) and a higher risk of death (84.4% (95% CI 72–91) vs 28% (95% CI 18–40); ($p<0.001$) (risk ratio: 3(95% CI 2–4.5). BS has specificity of 83.6% (95%CI 731–91), a sensitivity of 73% (95%CI 61–82) and a positive predictive value of 84.4(73–91) in predicting death. *Discussion:* It is possible that this sign may help discriminate between patients who have no chance of survival and those who may potentially benefit from interventions. The mechanism is not clear but could include either a direct concentration related effect or be a marker of oxidative stress. *Conclusion:* Presence of burning sensation is associated with high plasma paraquat levels and is strongly predictive of death. *References:* 1. Hart TB, Nevitt A, Whitehead A. A new statistical approach to the prognostic significance of plasma paraquat concentrations. Lancet 1984; 2:1222–1223. 2. Jones AL, Elton R, Flanagan R. Multiple logistic regression analysis of plasma paraquat concentrations as a predictor of outcome in 375 cases of paraquat poisoning. QJM 1999; 92:573–578.

206. Adverse Drug Reactions and their Relevance to Poison Centers

Thomas SHL.
Wolfson Unit of Clinical Pharmacology, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom

Introduction: An adverse drug reaction (ADR) is any undesirable effect of a drug beyond its anticipated therapeutic effects that occurs during normal clinical use.[1] ADRs are of substantial public health importance: a meta-analysis has concluded that ADRs caused 1.5M admissions per year and more than 100,000 deaths in the United States.[2] In the United Kingdom, 6.5% of 18,820 hospital admissions involved an ADR and in 80% of these the ADR was responsible for the admission; 9% were definitely and 63% possibly avoidable and 17% were related to drug interactions. The overall case fatality was 2.3%.[3] In a German study, 6.4% of ITU admissions were due to an adverse drug reaction.[4] *Classification:* ADRs are classified using the Rawlins-Thompson method into types A and B. Type A ('augmented') ADRs are dose-related and predictable from the primary pharmacological actions of the drug. They occur in any individual given enough, although individual susceptibility varies. Similar effects occur following drug overdose. Although many type A reactions are not severe, life-threatening effects can occur; many of the severe ADRs that provoke regulatory action are Type A. Type B ('Bizarre') ADRs are unpredictable, not directly dose-related (although risks of some may be increased with higher doses) and sometimes severe or fatal. They may occur due to immune mechanisms and/or unpredictable individual susceptibility. Further sub-classification has been proposed, e.g. Type C ('chronic treatment effects') Type D ('delayed effects'), Type E ('end of treatment effect's) and Type F ('failure of therapy'). However, some overlap exists between these various groups. A three dimensional approach to classifying adverse drug reactions has also been suggested, based on dose, time, and individual susceptibility (the 'DoTS' classification) (5). *Diagnosis:* Factors important for diagnosis include the timing of the reaction in relation to institution of therapy, dose changes, drug discontinuation and/or rechallenge (when appropriate), as well as exclusion of other causes. Diagnosis is easier if the suspect drug is known to cause the ADR. Some clinical syndromes are often due to an adverse drug reaction, e.g. confusion, gastrointestinal bleeding, or (less commonly) torsade de pointes. *Individual susceptibility:* Risk of ADRs is increased in children, the elderly, women, those with co-morbidity (including renal or hepatic dysfunction), those receiving polypharmacy and can be increased pharmacogenetic factors, e.g. cytochrome p450 polymorphisms, G6PD deficiency, malignant hyperthermia, etc. *Relevance to poisons centers (PCs):* Many PCs provide advice about suspected adverse reactions and their management and staff need to be appropriately trained. For example, of 2.4 million human exposure enquiries handled by US PCs in 2006, 60,524 (2.5%) were logged as adverse reactions.[6] Furthermore, the patterns of dose-related adverse drug reactions observed during drug development are of interest to poisons centers because they provide preliminary information on features expected following overdose. Data collected by PCs are also of potential value for pharmacovigilance, the process by which drug safety is monitored over the life span of the product. The addition of data collected by PCs to pharmacovigilance datasets (e.g. Medwatch data in the US) would increase the information available; there is some evidence that ADR data from PCs involves a different pattern of drug types than conventional spontaneous ADR reports.[7] However, reporting of ADRs by PCs has previously been incomplete.[8] PC data are of potential value in studying patterns of adverse drug reactions. Analysis of Toxic Exposure Surveillance System (TESS) cases identified groups of drugs more commonly associated with ADR enquiries in older adults.[9] PC data has also been used to demonstrate previously undocumented adverse reactions, e.g. those associated with dietary supplements.[10] Searching poisons center data for adverse drug reaction data relating to specific drugs can provide additional information on patterns and risk factors for ADRs to specific drugs, e.g. atomoxetine.[11] ADRs also occur with treatments recommended by PCs, e.g. antidotes, and it is important to have mechanisms for monitoring the safety of these. *Conclusion:* ADRs are commonly encountered by poisons centers; the data that they collect is of potential value for pharmacovigilance, while ADR data collected during drug development is also useful for predicting toxic effects of new drugs. Poisons centers and regulatory agencies would benefit from improved data sharing and communication. *References:* 1. Pirmohamed M, Breckenridge AM, Kitteringham NR, et al. Adverse drug reactions. BMJ 1998; 316:1295–1298. 2. Lazarou J,

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207. Studying Drug Safety in the Real World

Juurlink D.
Sunnybrook and Women's College, University of Toronto, Toronto, Canada

Randomized controlled trials are widely regarded as the best means to characterize a drug's efficacy - that is, whether a drug can improve clinical outcomes under optimal circumstances. However, the clinical trial setting is different in many ways from real world clinical practice, in which patients are typically sicker, less carefully selected, and less closely monitored. As a result, information about the benefits and harms of drug treatment obtained from a clinical trial may not reflect the situation in practice. Drug-related harms that are infrequent or, conversely, very common and therefore expected in the population of interest are often not appreciated in premarket studies. Consequently, the introduction of a new drug or drug class amounts to a mass experiment upon a population. Characterizing the harms and benefits of drug therapy in real-world practice is the primary goal of pharmacoepidemiology. Nonrandomized study designs, so-called because the intervention is not under the control of the investigator, are the primary means of exploring drug safety. Most often, these take the form of retrospective cohort or case-control studies, although self-matched designs such as case-crossover and case time-control studies are increasingly common and hold special appeal because they minimize confounding by implicitly controlling for fixed patient characteristics. Less commonly, the unit of analysis is an aggregate of patients rather than individual patients themselves; such studies are termed ecological analyses. The impetus for an observational study of drug safety often comes from a 'signal' - for example, one or more reports of a putative adverse event published in the medical literature, reported to a federal monitoring program, or encountered during one's own clinical practice. Alternately, simple awareness of a drug's pharmacologic properties can itself generate testable hypotheses, even in the absence of such reports. By virtue of their sample size, observational studies typically afford far greater power to characterize drug safety than corresponding clinical trials. All observational studies require, at a minimum, data on drug exposure and outcomes that can be linked at the level of individual patients. In many jurisdictions, prescription claims databases and hospital records, coroner's data, physician visits, and laboratory data serve this purpose, and allow for rapid, relatively inexpensive, and exceptionally powerful assessment of drug-related harms. However, such databases often suffer from a lack of important clinical detail, such as non-prescription drug use, disease severity, socioeconomic factors and smoking status, for example. These problems can be minimized by the use of registries, which provide extremely detailed patient information, but these can be expensive and may be underpowered to study certain aspects of drug safety. Regardless of the datasets used, several important considerations are essential when undertaking or critically evaluating an observational study of drug safety. These include the thoughtful identification of the outcome(s) of interest and selection of the optimal study design, because several options are typically available for each, and for any given analytical approach there are countless considerations, many of which are subtle yet important. The goal of these steps is to maximize the signal-to-noise ratio, because even the largest datasets can fail to identify important associations if appropriate respect is not afforded to this fundamental construct. Finally, it is important to be mindful about the limitations of the data at hand, because drug-disease associations uncovered by observational studies are just that: associations. In truth, they may reflect bias or cofounding rather than actual cause-and effect, and advancing the argument for causality is a major challenge in drug safety research.

208. Regulatory Impact of Toxicity of Medicines in Overdose

Hoppu K.
Poison Information Centre, Helsinki University Central Hospital, Helsinki, Finland

Objective: To review the regulatory impact of toxicity of medicines in overdose. *Results:* The aim of regulatory control of medicinal products is to promote the health and safety of the citizens. Regulatory authorities assess quality, safety and efficacy of a medicinal product before it receives a marketing authorisation (MA), and follow its quality and safety after the product is on the market.[1,2] In the marketing authorisation application (MAA) of a new medicinal product data on use in humans is limited and on poisonings usually non-existent. The MAA has to include a critical analysis of safety taking in consideration all data available, including any on reactions due to overdose, the potential for dependence and abuse, or the lack of data on these issues. Any important risks indentified in the MAA assessment, including important potential risks, are considered and may lead to requirement for risk minimisation. In the assessment of potential for overdose special attention is given to medicinal products with a narrow therapeutic margin, significant toxicity, and/or increased risk of overdose in the target population. Risk minimisation methods may include control of prescription size or validity, and/or a small pack size.[3] Overdose risks are also important in deciding, whether a medicinal product will be licensed as subject to a medical prescription or for OTC-sales.[4] Available relevant information, also in regard to overdose, has to be included in the Summary of Product Characteristics (SPC) and the package leaflet.[5] Special mentioning is recommended for those medicinal products, which can cause a fatal poisoning in the special risk group of young children if just a single tablet is ingested. Relevant information on overdose is generally accumulated through pharmacovigilance/toxicosurveillance after a medicinal product is placed on the market. In the postmarketing phase, MA holders are required to collect safety information related to their products, including any available on overdose, abuse and misuse.[2] Reports of these should be routinely followed up to ensure that information is as complete as possible with regard to early symptoms, treatment and outcome. The MA holder should report cases of overdose, abuse and misuse that lead to serious adverse reactions on an expedited basis. This includes cases of intended suicide. The MA holder should also continuously monitor and evaluate the potential impact of overdose, abuse and misuse on the overall risk-benefit balance of the medicinal product, and address potential for overdose, abuse and misuse and the associated risks in the Periodic Safety Update Reports (PSUR) and the Risk Management Plan.[2] The regulatory impact of the toxicity of a medicine in overdose is dependent on the overall risk-benefit balance, and also on the incidence of poisonings relative to the extent of use in the population. When toxicity in overdose is considered a problem, the regulatory authorities have several possible interventions available, primarily aimed to improve or restrict use. These include issuing safety warnings, use of educational interventions, restricting prescription status and/or package size, and even complete withdrawal from the market.[2] Medicinal products for which toxicity in overdose has lead to interventions by the regulatory authorities include astemizole, barbiturates, chloroquine, dextropropoxyphene, paracetamol, and promazine. Such medicinal products were typically associated with high overdose morbidity and/or mortality in relation to the extent of use. Many were abused or used for abusers of other substances (barbiturates, dextropropoxyphene and promazine). Typically symptoms of overdose developed rapidly or insidiously and were life-threatening, like respiratory depression (barbiturates, dextropropoxyphene), or cardiac arrhythmias (astemizole, chloroquine, dextropropoxyphene). When medicinal products disappeared from the market because of toxicity in overdose, it was often after long use when they were already more or less outdated (barbiturates, dextropropoxyphene) making the overall risk-benefit balance negative. In most cases increased awareness by prescribers of the toxicity in overdose and questionable risk-benefit balance lead to loss of sales and removal of the product from the market by the MA holder. Withdrawal of a medicinal product from the market by regulatory authorities due to toxicity in overdose has remained rare, and usually a terminal measure. The competent regulatory authorities have for various reasons tended to react slowly in response to accumulating evidence of toxicity in overdose. In a few cases response to detected safety signals has been more rapid and interventions like reduction of availability (limiting OTC package size of paracetamol, or prescription status of chloroquine) has allowed the product to remain on the market. *Conclusions:* Regulatory impact of toxicity of medicines in overdose is linked to overall risk-benefit balance, and incidence of poisonings relative to the extent of use in the population. Withdrawal of a medicinal product from the market by a regulatory authority due to toxicity of a medicine in overdose has been rare. More commonly information, education and/or reduction of availability of a product have lead to loss of sales and removal from the market by the MA holder. In some cases reducing the availability of a medicinal product in response to overdose safety signals has been considered adequate and the product has remained in the market. *References:* 1. 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209. Medication Errors: The Perspective of a National Poison Center

Lavon O, Ben-Zeev A, Bentur Y.
Israel Poison Information Center, Rambam Health Care Campus, Haifa, Israel

Objective: Medication errors (ME) are a major concern to health systems. While most studies deal with ME in health-care frameworks, only a small number focus on

ME reported directly by the public. National poison center (NPC) data-bases are a valuable tool for evaluating ME as they contain calls from both public and health-care facilities. The objective of this study is to evaluate ME from the perspective of a NPC. *Methods:* This is an on-going prospective cohort study of all ME calls to a NPC. In each ME case, a detailed questionnaire is filled and a follow-up call is performed. The Data collected include demographic details, circumstances and type of error, and outcome. *Results:* During August-September 2008, 511 consecutive ME cases were reported to the NPC; 275 (53.8%) patients were female. The prominent age groups were children younger than 6 (295, 57.7%) and adults (144, 28.1%). Most cases were reported by the public (472, 92.4%). The main culprit was the parent (298, 58.3%) and in about 1/3 of cases the patient himself (156, 30.5%). The main types of ME were a wrong medication (159, 31.1%), a wrong dose (158, 30.9%), or an extra superfluous dose (116, 22.7%). The common groups of pharmaceuticals involved were analgesics (151, 29.5%), antimicrobials (66, 12.9%), and ear/eye/nose/throat preparations (36, 7%). The most frequent type of preparation involved was liquid intended for oral use (233, 45.6%). The main causes for the ME were look-alike packaging (159, 31.1%), misunderstanding instructions (119, 23.3%), and additional intake due to forgetfulness (101, 19.8%). Most ME were single isolated cases (457, 89.4%). Follow-up was possible in 347 (68%) cases; 331 (95.4%) of these were asymptomatic or mildly affected. 71 (20.5%) cases were evaluated in a medical facility. *Conclusion:* Most calls to the NPC due to ME are made by the public and are not errors of health-care providers. Although most patients suffered no significant sequela, the high referral rate may pose marked burden on the health-care system. Proper labeling and meticulous patient instruction by health-care providers on the appropriate usage of medications are imperative to reduce the magnitude of ME.

210. Cutaneous and Systemic Nickel Toxicity: Can it be Prevented and Managed Effectively?

White IR.
St. John's Institute of Dermatology, St. Thomas' Hospital, London, UK

Introduction: The first patent on nickel plating was granted in 1880 and six years later occupational dermatitis from nickel was noted. In the next 50 years nickel dermatitis remained an occupational problem in the nickel-plating industry. Imports of nickel into Europe decreased during the Second World War and the incidence of nickel dermatitis declined. From the end of the War, there was a steady increase in nickel dermatitis among consumers as occupational cases decreased as occupational hygiene improved. *Nickel allergy:* Nickel remains the most common contact allergen in the EU (and elsewhere). The incidence of nickel allergy in women is 10% in the general population and up to 30% of those with dermatitis (> 3–10 greater than in men). The most common cause of sensitization is ear piercing. The primary sites of dermatitis develop as a result of direct skin contact with nickel-releasing metal. *Mechanisms of toxicity:* Only the free nickel ion acts as a hapten. The most important factor for the induction and elicitation of nickel contact allergy is the dose of nickel per unit area of skin ($\mu g/cm^2$). The nickel ion may be either present in the occupational environment or be leached from nickel-plated surfaces or nickel alloys easily corroded by the influence of human sweat. The primary risk factor for nickel contact allergy is the amount of nickel released from the metal not the total concentration of nickel in it. Based on elicitation studies, a limit of exposure of 0.5 $\mu g/cm^2$ per week of nickel release has been suggested. Alloys releasing less than this amount (stainless steel or white gold), will rarely elicit a reaction in nickel-allergic individuals; alloys releasing >0.5 $\mu g/cm^2$ per week (nickel-plated items) provoke allergic reactions in previously sensitized individuals. *Systemic allergic dermatitis:* Many patients with severe suspender dermatitis in the 1950s had widespread dermatitis similar to that seen in systemic allergic dermatitis and thought to be caused by systemic exposure from the absorption of nickel in the area of the dermatitis. Systemic allergic dermatitis is symmetrical and may include the neck and face, elbow flexures and forearms, hands, inner thighs, anogenital region but may be generalized. In a double-blind study,[1] 12 nickel-allergic individuals were given an oral dose of 5.6 mg nickel. Of the 12 patients, nine developed systemic allergic dermatitis, in particular vesicular hand eczema, after an average of 8 h. Such observations have been confirmed by others with evidence for immunological specificity including flare-up reactions at previous nickel contact sites. Few patients react to <0.5 mg nickel as a single oral dose with most requiring >5 mg, though no clear dose–response relationship has been found. Systemic nickel dermatitis has been reported following intravenous administration of nickel.[2] *Role of dietary nickel:* The induction of systemic nickel dermatitis from daily dietary nickel intake remains controversial. The normal dietary nickel intake is 150 - 500 µg daily. Foods with high nickel content include whole-grain flour, oats, soybeans, legumes, shellfish, nuts, liquorice, and chocolate. Nickel toxicokinetics are the same in nickel-allergic women and age-matched controls. Chelating medicaments (e.g. disulfiram) can interfere with nickel absorption and metabolism and in that way provoke systemic allergic dermatitis. Dietary intervention has been advocated for nickel-sensitive patients with vesicular hand eczema or more widespread systemic allergic dermatitis, if elimination of cutaneous exposure does not settle the dermatitis. *Prostheses:* Nickel released from dental braces and from older types of orthopaedic prostheses has caused systemic nickel dermatitis and/or loosening of the prostheses. Metal plates on bones can initiate a dermatitis, which occurs particularly over the areas of the plate. It is now accepted that nickel allergy is not a contraindication to a modern metal hip of stainless steel or vitallium types; there is no convincing evidence that these are able to sensitize or exacerbate a pre-existing dermatitis, or lead to rejection of the hip. Despite this, it is common practice to recommend titanium when nickel contact allergy has been raised as an issue. *Desensitization:* Although desensitization is not possible, immune tolerance to nickel can be produced in animals fed nickel prior to attempted experimental sensitization. The development of tolerance has been confirmed in adolescents who have dental braces (causing ingestion of nickel) prior to ear piercing; they develop less nickel contact allergy. Oral administration of nickel sulphate 5.0 mg weekly for six weeks in nickel-allergic individuals lowered their degree of contact allergy as measured by the patch test reactions. Legislation: The EU Nickel Directive (Council Directive 94/27/EC, OJ No. L 188 of 22.7.94) is directed at the prevention of nickel allergy and covers metal items in direct contact with skin, piercing materials, and has requirements on resistance to wear. The nickel release threshold is 0.5 $\mu g/cm^2$ per week; the impact of this limit has already paid dividends in Denmark, where a sharp reduction in nickel allergy is now evident. It seems that the same is now happening elsewhere in Europe.[3–5] *Conclusions:* Although nickel remains an important contact allergen with clinical implications of concern, the relevance of allergy is decreasing as a result of elicitation-based European legislation to limit consumer exposure. In the next generations of European citizens, nickel contact allergy will be uncommon. Other regions should follow the European model. *References:* 1. Christensen OB, Möller H. External and internal exposure to the antigen in the hand eczema of nickel allergy. Contact Dermatitis 1975; 1:136–141. 2. Olerud JE, Lee MY, Ulvelli DA, et al. Presumptive nickel dermatitis from haemodialysis. Arch Dermatol 1984; 120:1066–1068. 3. Basketter DA, Angelini G, Ingber A, et al. 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211. Cadmium-Induced Nephrotoxicity: A Biochemical or Clinical Disease

Vale JA.[1,2]
[1]*National Poisons Information Service (Birmingham Unit) and West Midlands Poisons Unit, City Hospital, Birmingham;* [2]*School of Biosciences and College of Medical and Dental Sciences, University of Birmingham, UK*

Introduction: Low concentrations of cadmium occur naturally in the environment. Non-occupational human exposure occurs mainly from ingested foods (particularly shellfish and kidneys) and smoking, though high oral intakes may also occur in areas contaminated by emissions from cadmium-related industries. Substantial exposure is most likely to occur from the inhalation occupationally of cadmium-containing dust and fumes produced in the manufacture of nickel-cadmium batteries, smelting operations involving copper/zinc-cadmium ores and alloys, soldering with silver-cadmium containing solder and welding with cadmium containing materials. *Nephrotoxicity:* Substantial exposure to cadmium causes renal damage, which was first identified in the late 1940s in Sweden. Tubular proteinuria is the first feature, usually detected as an increased urine excretion of low molecular weight proteins, such as β2 microglobulin, retinol binding protein, α1-microglobulin, or enzymes such as N-acetyl-β-glucosaminidase. The risk of developing tubular proteinuria is well established at a urine cadmium concentration exceeding 10 µg/g creatinine. This risk increases almost linearly with the urine cadmium concentration from an expected prevalence of tubular proteinuria around 10% for urine cadmium concentrations slightly above 10 µg/g creatinine to more than 20% when urine cadmium concentrations exceed 20 µg/g creatinine.[1] If exposure continues, tubular dysfunction progresses and glomerular damage with a decrease in the GFR will ensue. While these changes have been demonstrated repeatedly[2–5] in those exposed occupationally, the clinical relevance and the course of tubular proteinuria in those only exposed environmentally remains uncertain and raises the rhetorical question posed in the title. *Predictive significance of tubular proteinuria in workers:* In a series of studies, Roels et al.[2–5] examined the course and predictive significance of tubular proteinuria in workers. In a retrospective study of 19 workers exposed for 16–42 years, renal markers were measured on average 1.2 years before and 4.2 years after removal from exposure.[2] Although renal dysfunction was unlikely to progress after cessation of exposure, cadmium-induced nephropathy was not reversible. Twenty-three workers removed from exposure (25 years on average) because of the discovery of microproteinuria,[3] were assessed six years later. It was found that cadmium-induced microproteinuria was not only irreversible, but also that serum creatinine and ß2-microglobulin concentrations had increased significantly with time. The estimated GFR had decreased five times more rapidly than could be expected due to aging alone. Roels et al.[4] also investigated whether a body burden of cadmium not yet sufficient to induce microproteinuria could affect the filtration reserve capacity of the kidney. When elevated microproteinuria was present (n=12), the filtration reserve capacity of the kidneys was lost, but there was no functional impairment at a renal cadmium burden (n=31) not yet causing microproteinuria. In 32 workers the evolution of cadmium-induced microproteinuria was found to depend on the extent of the body burden of cadmium and the severity of the initial microproteinuria at the time high exposure was reduced or ceased.[5] When reduction of cadmium exposure took place at the time ß2-microglobulinuria did not exceed 0.3 mg/g creatinine, the risk of developing tubular dysfunction at a later stage was low, even in cases with historical urine cadmium concentrations occasionally >10 but always <20 µg/g creatinine. If the urine cadmium concentration never exceeded 20 µg/g creatinine and the ß2-microglobulinuria was mild (<1.5 mg/g creatinine) at the time exposure was reduced, there was some evidence that the tubulotoxic effects were reversible. When ß2-microglobulinuria >1.5 mg/g creatinine was found in combination with historical urine cadmium concentrations >20 µg/g

creatinine, cadmium-induced tubular dysfunction was progressive in spite of reduction or cessation of cdmium exposure. *Predictive significance of tubular effects in those environmentally exposed:* Some studies have reported that cadmium-induced renal effects are not only irreversible[6] but also progressive[7] even after cessation of exposure, whereas other studies have suggested that the proteinuria reported in those with environmental cadmium exposure is not associated with progressive renal dysfunction and most likely represents a non-adverse effect[8] *Conclusions:* There is overwhelming evidence that occupational cadmium exposure can lead not only to tubular proteinuria but also to glomerular damage. Environmental exposure to cadmium may lead either to a biochemical abnormality (proteinuria) or to a progressive clinical disease, depending on the degree of exposure. Even if the biochemical abnormality is benign, it is an indicator of a renal effect that eventually may lead to serious health consequences. Measures should therefore be taken to reduce exposure to cadmium in the general population to ≤30 µg day[9] A urine cadmium concentration ≤1.0 µg/g creatinine should prevent the onset of tubular and glomerular disease.[10] *References:* 1. Bernard A. Renal dysfunction induced by cadmium: biomarkers of critical effects. Biometals 2004; 17:519–523. 2. Roels H, Djubgang J, Buchet J-P, et al. Evolution of cadmium-induced renal dysfunction in workers removed from exposure. Scand J Work Environ Health 1982; 8:191–200. 3. Roels HA, Lauwerys RR, Buchet JP, et al. Health significance of cadmium induced renal dysfunction: a five year follow up. Br J Ind Med 1989; 46:755–764. 4. Roels HA, Lauwerys RR, Bernard AM, et al. Assessment of the filtration reserve capacity of the kidney in workers exposed to cadmium. Br J Ind Med 1991; 48:365–374. 5. Roels HA, Van Assche FJ, Oversteyns M, et al. Reversibility of microproteinuria in cadmium workers with incipient tubular dysfunction after reduction of exposure. Am J Ind Med 1997; 31:645–652. 6. Kido T, Honda R, Tsuritani I, et al. Progress of renal dysfunction in inhabitants environmentally exposed to cadmium. Arch Environ Health 1988; 43:213–217. 7. Kido T, Nogawa K, Ishizaki M, et al. Long-term observation of serum creatinine and arterial blood pH in persons with cadmium-induced renal dysfunction. Arch Environ Health 1990; 45:35–41. 8. Hotz P, Buchet JP, Bernard A, et al. Renal effects of low-level environmental cadmium exposure: 5-year follow-up of a subcohort from the Cadmibel study. Lancet 1999; 354:1508–1513. 9. Satarug S, Haswell-Elkins MR, Moore MR. Safe levels of cadmium intake to prevent renal toxicity in human subjects. Br J Nutr 2000; 84:791–802. 10. Suwazono Y, Sand S, Vahter M, et al. Benchmark dose for cadmium-induced renal effects in humans. Environ Health Perspect 2006; 114:1072–1076.

212. High Rate of Adverse Effects in Patients Treated with DMPS for Acute Arsenic Poisoning

Lefebvre L,[1] Nantel AJ.[2]
[1]Centre de toxicologie, Institut national de Santé publique du Québec, Québec; [2]Direction des risques biologiques, occupationnels et environnementaux, Institut national de Santé publique du Québec, Montréal, Canada

Objective: To report a series of adverse effects in patients treated with sodium 2,3-dimercapto-1-propanesulfonate (DMPS) following acute arsenic poisoning. *Case series:* In May 2000, several individuals from the same university department complained of nausea, vomiting, abdominal pain, dizziness, blurred vision and fatigue. An employee noticed the relation between drinking coffee from the vending machine located in the department and the individuals showing the symptoms. Analysis of the coffee from the machine revealed high concentrations of arsenic. Analysis of urine samples from 49 individuals who had ingested the tainted coffee revealed levels of non-alimentary arsenic ranging from less than 0.10 to 15.0 micromol/L (<7.5 to 1124 micrograms/L). In order to prevent the long term health effects of arsenic poisoning, it was decided to administer DMPS chelation therapy to all individuals showing urinary arsenic levels above 0.7 micromol/L (50 micrograms/L). Thirty-three patients underwent a medical examination at the Department of Family Medicine (DFM) at Laval University Medical Centre and subsequently received DMPS at a dose of 100 mg orally, three times a day for one week, followed by a 24-hour urine collection for arsenic quantification. After a week of treatment, all patients showed a significant decrease in urinary arsenic levels and were supplied with another week of DMPS. One week later, some patients noticed the appearance of a sun sensitive skin rash and were told to consult at the DFM. DMPS therapy was stopped and antihistamines were prescribed. Another patient was admitted at the hospital with generalised erythematous skin rash, oedema, fever, fatigue; mouth, vaginal and anal ulcerations. Stevens-Johnson syndrome (SJS) was diagnosed and it was decided to stop DMPS therapy for all patients. Over the following 2 weeks, we observed 8 cases of erythema multiform. A total of four patients required hospitalisation; two were released within 5 days of treatment with intravenous corticosteroids and two who were diagnosed with SJS were released after 8 days and could resume professional activities after a month. *Conclusion:* This case series suggest a high rate of adverse effects during DMPS therapy including SJS, and this should be considered in the risk-benefit analysis of chelation.

213. Case of Mass Thallium Poisoning in a Factory

Ostapenko YN,[1] Luzhnikov EA,[2] Goldfarb YS,[2] Badalyan AV,[2] Luzanova IS.[3]
[1]Research and Applied Toxicology Centre, Federal Agency on Public Health and Social Development, Moscow; [2]Moscow City Poisonings Treatment Centre, N.V. Sklifosovsky Research Institute for Emergency Medicine, Moscow; [3]Moscow City Forensic Medicine Bureau, Moscow, Russian Federation

Objective: Description of a case of mass thallium poisoning in a factory. *Case series:* Analysis of case reports of 8 patients aged between 19 to 66 years with inhalation and skin contact with an unknown powdery material during their workday in a factory. None employed personal protective measures. On one day 6 persons experienced abdominal pain and weakness, 2 had similar complaints on subsequent days. Thereinafter 7 patients developed pains and numbness in their lower limbs, 5 pains in knee and ankle joints, 2 thoracic muscle pains, 3 loss of appetite, 5 alopecia, and 3 encephalopathy. All patients were hospitalized in the Moscow Poisonings Treatment Centre from 18–42 days following exposure. Thallium was discovered in the urine of 7 patients by atomic-absorption spectrophotometry. On the basis of clinical presentation 2 patients were considered critically ill with thallium concentrations of 892 and 2440 microgram/litre. Moderate severity of poisoning was found in 3 patients with thallium levels of 324, 528 and 1690 microgram/litre, 3 demonstrated mild poisoning with thallium concentrations from 0 to 46 microgram/litre (the safe thallium level in urine =1,7 microgram/litre). The treatment included use of sodium dimercaptopropansulfonate, potassium iodide, enterosorption with activated charcoal, gut lavage, vitamin therapy, and symptomatic therapy. Two patients with severe poisoning were sent for 2 haemodialysis sessions with a subjective improvement of their general state. Repeated urinalysis showed 8.6–89.6% (51.5 ± 12.9%) decrease of thallium level after 18–21 days of treatment including 2 patients after haemodialysis showing an 89.6% and 53.4% decrease in their thallium levels. Duration of hospital stay was 14–41 days; all patients being discharged with full clinical recovery. *Conclusion:* Skin and inhalation thallium exposures caused the typical clinical picture of thallium poisoning. Abdominal pain and weakness, pains in lower limbs, arthralgia, polyneuropathy and alopecia were significant diagnostic symptoms. The level of urine thallium concentration correlated well with the severity of clinical picture, but treatment with use of antidotes, activated charcoal and gut lavage promoted its reduction. Haemodialysis promoted the improvement of patient condition and could be recommended in the most severe poisoning cases.

214. Should Chelation Therapy ever be Considered for the Treatment of Manganese Exposure?

Brent J.
Toxicology Associates, University of Colorado Health Sciences Center, Aurora, US

Manganese is an essential element necessary for a variety of enzymatic and other physiological functions. Excessive body burdens of this element, however, can cause neurotoxicity. Manganese toxicity most often occurs as a result of occupational exposures or as a consequence of other pathological processes. Occupational manganism is best described in very heavily exposed miners and smelter workers. Affected workers tend to have blood manganese concentrations of several hundred ug/liter[1] (normal 4–14). Potential non-occupational sources of excessive doses of manganese are total parenteral nutrition solutions and the injection of permanganate-contaminated metcathinone (ephedrone). In the latter instance potassium permanganate is utilized as an oxidizing agent in the conversion of ephedrine or pseudoephedrine to metcathinone.[2] Manganese is almost exclusively excreted through the biliary system. Patients with severe chronic hepatic or biliary disease may not be able to excrete manganese normally and may thus develop manganism. Advanced chronic liver disease is associated with loss of integrity of the blood brain barrier, further predisposing to manganese accumulation in the central nervous system. Manganism is primarily characterized by a parkinsonian syndrome consequential to the deposition of this element in the *globus pallidi*. This condition is both phenotypically and pathophysiologically distinct from Parkinson's disease. The latter is due to destruction of neurons in the *substantia nigra pars compacta*, a structure unaffected by in manganism.[3] There are many features that distinguish Parkinson's disease and manganism. For example, the former is characterized by an asymmetrical rest tremor and responsiveness to levodopa therapy, while the latter more often involves dystonia, muscle rigidity, and toe-walking. If evaluated during, or within 6–12 months, of manganese exposure, patients with manganism will have an increased T1 relaxation time of their *globus pallidi* on magnetic resonance scans. Manganese accumulation in the brain is reversible with reported half-lives varying from than 2 months to over 200 days.[4] The hepatobiliary system very efficiently clears excess circulating manganese, which is excreted bound to a low molecular weight molecule. Toxicokinetically, manganese distribution and clearance best fits a 3 component model. Following intravenous administration there is an ultrafast phase during which 75% is cleared from the circulation[5] within 3 hours. This is followed by a fast phase and finally a slower process with half-lives of 4 days and 39 days, respectively.[6,7] The clearance of manganese, therefore, is much faster than that of other common metals. The excretion of manganese is non-saturable under the experimental conditions in which it has been studied.[6–9] To the contrary, the half-life of manganese excretion decreases, and the percentage excreted increases, as the dose is raised, both in rats[9] and human volunteers and exposed miners.[7] The administration of calcium edetate enhances urinary manganese excretion.[10] There have been no clinical trials assessing the efficacy of chelation in manganism. In a case report in which the authors suggested that chelation was temporally associated with clinical improvement there was no effect on blood manganese concentrations.[10] A number of case series, however, have concluded that chelation did not affect the clinical course in manganism.[2,8] The apparent lack of beneficial effect of chelation is consistent with the pharmaco- and toxicokinetics of manganese. Calcium edetate does not cross the blood brain barrier and thus could affect central nervous system manganese levels only indirectly by increasing the concentration gradient between the blood and the brain. Because of the rapid clearance of manganese, and the lack of documented effects of chelation on blood concentrations, this mechanism is unlikely to occur. Given the lack of apparent clinical efficacy of chelation therapy based on both patient experience and theoretical considerations, its routine use in manganism should not be considered standard

therapy. There are a number of unanswered questions concerning chelation therapy of manganese intoxication. A well-designed controlled clinical trial would best answer the question of the benefit, if any, of chelation. The data reviewed above does not address any possible prophylactic benefit of chelation if given shortly after an acute very large dose of manganese. The excretion of manganese in patients with severe hepatobiliary disease has not been well characterized. Because these patients are both at risk for developing manganism and may have decreased manganese excretion it is possible that enhancing urinary clearance with calcium edetate would be beneficial. *References:* 1. Rodier J. Manganese Poisoning in Moroccan Miners. Br J Ind Med 1955; 1:21–35. 2. Stepens AR, Inara L, Viesturs I, et al. Parkinsonian Syndrome in Methcathinone Users and the Role of Manganese. N Engl J Med 2008; 358:1009–1017. 3. Perl DP, Olanow CW. Neuropathology of Manganese-Induced Parkinsonism. J Neuropathol Exp Neurol 2007; 66:2007. 4. Kim Y. High signal intensities on T1-weighted MTI as a biomarker of exposure to manganese. Ind Health 2004; 42:111–115. 5. Klaassen CD. Biliary excretion of manganese in rats, rabbits and dogs. Toxicol Appl Pharmacol 1974; 29:458–468. 6. Mahoney JP, Small WJ. Studies on Manganese III. The biological half-life of radiomanganese in man and factors which affect this half-life. J Clin Invest 1968; 47:643–53. 7. Mena I, Marin O, Fuenzalida S, et al. Chronic manganese poisoning. Clinical picture and manganese turnover. Neurol 1967; 17:128–136. 8. Keen CL. Manganese. In: Freiden E (ed). Biochemistry of the Essential Ultratrace Elements. New York, USA. Plenum Press, 1984:80–132. 9. Schuehammer AM, Cherian MG. The distribution and excretion of manganese: The effects of manganese dose, L-DOPA, and Pretreatment with Zinc. Toxicol and Appl Pharmacol 1982; 65:203–213. 10. Discalzi G, Pira E, Hernandez EH, et al. Occupational Mn Parkinsonism: Magnetic Resonance Imaging and Clinical Patterns Following CaNa2-EDTA Chelation. Neurotoxicology 2000; 21:863–866.

215. Accidental Iatrogenic Intoxication by Manganese Sulphate

Munné P,[1] Torra M,[2] Juan N,[3] Germán A,[4] López R,[4] Nogué S.[1]
[1]Toxicology Unit, Hospital Clínic, Barcelona; [2]CDB Toxicology Laboratory, Hospital Clínic, Barcelona; [3]Medical Department, Clínica Teknon, Barcelona; [4]Emergency Department, Hospital Mutua Terrassa, Barcelona, Spain

Objective: To describe an accidental episode of acute intoxication due to ingestion of manganese sulphate. *Case series:* In April 2008, 25 people began a seven-day course of liver detoxification. On the last day, they were instructed to take 4 spoonfuls of Epsom salts separated in 4 doses (in total, 60–80 grams). Due to a labelling error, the bottle of Epsom salts contained manganese sulphate instead of magnesium. Seven people did not seek medical care for an episode of self-limiting gastroenterocolitis. Of the remaining 18 people, four were hospitalized and 14 remained under observation in the emergency department for between 24 and 48h with a favourable outcome. The initial symptoms in the cases were repeated vomiting and abundant diarrhoea. A 50-year-old man was admitted to the ICU with dehydration and severe hypotension (70/35), which evolved to refractory shock with severe liver dysfunction, renal and respiratory failure and biochemical pancreatitis. Sepsis, intestinal ischemia or perforation and necrohaemorrhagic pancreatitis were ruled out. Symptomatic treatment included hydroelectrolytics, vasoactive drugs, blood products, empirical antibiotics and corticosteroids. EDTACaNa2 was not administered as the correct diagnosis was not initially made, as this was the first case. The correct diagnosis was made when new cases appeared and confirmed by determination of serum manganese (1980 micrograms/L, normal reference values from 0.3 to 2.5 micrograms/L). The patient died from multiorgan failure three days after admission. The three remaining hospitalized patients evolved favourably with various degrees of hepatic cytolysis (peak levels 754 UI of AST) and slightly elevated pancreatic enzymes (peak levels of 152 U/L, reference values 20–104). Manganese levels were 47, 45 and 14 microgram/L in serum and 110, 27 and 5 micrograms/L in urine, respectively. EDTA CaNa2 increased urinary manganese excretion (peak of 6142 micrograms / 24h). *Conclusion:* 1. Ingestion of a large amount of an inorganic manganese salt is highly toxic even though it is not easily absorbed. 2. Ingestion of about 60 grams of manganese sulphate is potentially fatal. 3. EDTA CaNa2 effectively increases urinary excretion of manganese.[1] *References:* 1. Barceloux DG. Manganese. J Toxicol Clin Toxicol 1999; 37:293–307.

216. Lead Poisoning in Pregnancy: Prevention and Treatment

Bacis G.
Bergamo Poison Control Center, Ospedali Riuniti, Bergamo, Italy

Introduction: Lead poisoning is a serious health problem and the exposure may occur from diverse sources: food, beverages, drinking water, contaminated soil, lead pipes, lead solder, storage batteries, lead-based paints (banned since 1977), dyes, pottery glazes, intentional pica, wood preservatives, retained bullets and some traditional medications.[1] The total lead intake by ingestion and inhalation is in general about 100–200 mcg/day.[2] In mothers with blood lead levels (BLL) that exceed 10 mcg/dL there is a link to spontaneous abortion, impaired fetal growth, prematurity, low birth weight and reduced neurobehavioral development.[3] Lead is freely transferred across the placenta as early as the 12th to 14th week of gestation by both passive diffusion and active transport. Blood lead levels in the fetus are comparable to those in the mother. Fetal bone and liver may have higher lead concentration levels than maternal tissues.[4]. *Results:* TERATOGENIC EFFECTS: Only minor congenital anomalies were associated with higher blood cord lead levels. In a recent study, of the live born infants exposed to lead during pregnancy, only 3 of 65 (4.6%, 95% CI 1.2–13.7) had malformations.[5] Also paternal exposure was responsible for an increased risk of cleft palate.[6] ABORTION: Low-to-moderate lead exposures may increase the risk for spontaneous abortion. Lead oxide has been used as an abortifacient. PREMATURITY / LOW BIRTHWEIGHT: Lead poisoning during pregnancy and also paternal exposure has been associated with impaired fetal growth, prematurity and low birth weight. COGNITIVE DELAY: An increased prevalence of mental retardation in populations with high lead levels in water was reported. The evaluation of performance on mental tests in children was inversely correlated with lead levels at birth, suggesting that prenatal lead exposure may affect postnatal mental development.[3] These effects were dose-related in the high exposure group (BLL > 10 mcg/dL). Poorer performance on tests of motor coordination was also seen in children with higher neonatal BLL. Impaired mental development is also probably attributable to mobilization of maternal bone lead stores.[7] A recent study[8] also found that lead exposure in pregnancy and childhood disrupts brain development. LEAD MOBILIZATION: Pregnancy may increase the mobilization of lead from the maternal skeleton and increase lead gut absorption. As the bone calcium is needed during pregnancy, stored lead will become solubilized[9] and this has also been studied with K-X-ray fluorescence[8] Maternal alcohol abuse or other stressors (i.e. maternal blood hypertension) might cause lead mobilization and fetal accumulation. PREVENTION AND TREATMENT: Simple preventative measures like avoiding dust containing lead and maintaining good personal hygiene (hand washing) can minimize lead exposure. It is appropriate to monitor blood lead levels during pregnancy in chronically exposed women and women with a history of lead intoxication. If BLL is >10 mcg/dL they should receive risk reduction counselling based on the risk assessment for reducing and eliminating the exposure. Also regular meals and a diet rich in iron and calcium (1200 mg/day) reduces the absorption of lead. If BLL is >30 mcg/dL or the patient has symptoms of lead poisoning, chelation treatment should be started. Disodium calcium edetate, the usual chelating agent used to treat lead toxicity, although it increases the incidence of congenital anomalies in experimental animals, is unlikely to pass the placenta barrier.[10,11] But the risk of enhancing oral lead absorption, lead redistribution from bone to soft tissue (maternal and fetal liver and brain) and excretion of essential trace metals, makes this chelator a second choice. Because dimercaprol is rarely used for lead poisoning and the necessity for intramuscular administration with the risk of several adverse effects, it is a poor candidate for maternal administration for fetal benefit. Succimer (DMSA) seems to be the best chelating agents for lead poisoning in pregnancy.[10] although it was ineffective in reducing maternal and fetal blood lead levels in one case-report.[12] Succimer fetotoxicity and teratogenicity were observed in mice and rats but at doses > 10 times human therapeutic dose.[13] The precaution is to avoid the period of organogenesis and to evaluate maternal zinc levels. After delivery, blood lead levels must be evaluated in the baby and if greater than 30 mg/dL chelation therapy must be started. *Conclusion:* The high risks of lead poisoning, especially in pregnancy, need all the efforts for minimizing the paternal, maternal, fetal and childhood exposure, in particular in reducing environmental contamination. *References:* 1. Bentur Y, Koren G. The common occupational exposures encountered by pregnant women. In: Koren G, ed. Maternal-fetal Toxicology. A clinician's guide. 3rd ed. New York, USA: Marcel Dekker Inc, 2001:536–40. 2. 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217. Epidemic of Lead Poisoning Caused by Adulterated Marijuana

Bergmann I,[1] Busse F,[2] Stumvoll M,[2] Hentschel H.[1]
[1]Poisons Information Centre, c/o HELIOS Klinikum GmbH, Erfurt; [2]Department of Internal Medicine, University Hospital Leipzig, Leipzig, Germany

Objective: Unexpectedly, many young people fell ill with occasionally severe symptoms of lead poisoning in the area around the city of Leipzig (Saxony, Germany) in summer and autumn 2007. None of these persons was occupationally exposed to lead. The source of lead uptake had to be elucidated. Decisions for further diagnostic and therapeutic measures were to be decided. *Case series:* Marijuana adulterated with metallic lead was ascertained as the causative factor for this poisoning series.[1] Firstly, the public were informed through a press conference about health hazards, if such marijuana should be smoked continuously.

PIC published complementary information for patients on its website. Secondly, the local health authority arranged a regular service for anonymous blood collection and measurement of blood lead level (BLL) for marijuana consumers. Finally, a therapeutic guideline for this special situation was established. From October 2007 to June 2008, the BLL was measured in 599 persons, of whom 235 had BLL above the German human biomonitoring value (HBM I 100µg/L), a further 163 had BLL above HBM II (150µg/L for adolescents and women in child-bearing age; 250µg/L for others). The highest BLL measured was 4570µg/L. Due to the uncertainty of the consumers' histories it was impossible to establish a correlation between the BLL, the frequency of consumption and the severity of symptoms. All persons with BLL above HBM II were treated for at least four weeks with succimer. The majority of patients suffered recurrent intestinal cramps. By mistake exploratory laparotomy was carried out in one patient. *Conclusion:* Drug abuse should be considered in otherwise unexplained poisoning symptoms. Adulteration of illegal drugs may cause unexpected mass poisoning. The cooperation of treating physicians, hospitals, PIC, and local health authorities is absolutely necessary in such a situation. *References:* 1. Busse F, Omidi L, Timper K et al. Lead poisoning due to adulterated marijuana. N Engl J Med 2008; 358:1641–1642.

218. A Study to Assess the Use of Pre-Hospital Charcoal in South East England

Dines AM,[1] Butler C,[2] Taylor I,[2] Ovaska H,[1] Rowland A,[2] Wood D M,[1] Dargan P I.[1]
[1]Guy's & St Thomas' Poisons Unit, Guy's & St Thomas' NHS Foundation Trust, London; [2]South East Coast Ambulance Service, Banstead, UK

Objective: The use of activated charcoal (AC) in the pre-hospital management of poisoned patients is recommended by the UK National Institute for Health and Clinical Excellence,[1] but there is little evidence to support this and no studies have assessed the feasibility of pre-hospital administration in the UK. Therefore a study was undertaken to determine the feasibility of pre-hospital administration of AC by ambulance personnel. *Methods:* Clinical toxicologists and specialists in poisons information (SPIs) trained ambulance personnel from six ambulance stations on AC administration. Those trained were asked to contact the poisons centre when attending an acutely poisoned patient to determine whether administration of AC was indicated. The poisons centre used specified criteria (amount ingested, time since ingestion, toxic dose of substance(s) ingested) to determine if AC administration was appropriate. Exclusion criteria were: age <16 years; inability to consent; Glasgow Coma Scale <14/15. *Results:* During the three month study 296 ambulances were dispatched for poisoning / overdose cases. The poisons centre received 32 (10.8%) enquiries about the potential administration of AC by ambulance personnel. In 10 (31.3%) of these enquiries AC was indicated and it was administered in 5 (50%) of these cases (15.6% of all calls about potential AC use). The most common reasons that AC was not indicated were: >1 hour post-ingestion (13, 59.1%); non-toxic ingestion (6, 27.3%). *Conclusion:* The main problem which limited patient recruitment to this study was that ambulance personnel did not contact the poisons centre to discuss inclusion of patients into the study. Possible reasons for this may be that a case was considered non-toxic, involved excess alcohol only or a reluctance of staff to contact the poisons centre and/or administer AC. However, when the poisons centre was contacted, AC was indicated and administered in a significant proportion of cases. Further studies are required to determine whether ambulance personnel can administer pre-hospital AC without the support or advice of a poisons centre. *References:* 1. National Institute for Clinical Excellence (NICE). Self harm. The short-term physical and psychological management and secondary prevention of self-harm in primary and secondary care, Clinical Guideline 16, 2004. www.nice.org.uk/CG016NICEguideline.

219. Current Methods in Toxicovigilance and their Limitations

Buckley NA.
Prince of Wales Hospital Clinical School, University of NSW, Sydney, Australia

There have been a range of methods used to provide human data on the toxicity of pharmaceuticals and agrochemicals. Simple clinical and post-mortem case reports and series provide evidence of the spectrum of clinical effects and the minimum lethal blood concentration or reported ingested dose or maximum survived dose or concentration. Coronial databases and hospital coding can provide an indication of the burden of disease, the extent of morbidity and mortality attributed to different agents. However, a considered regulatory response requires measures of the toxicity of the agent compared to other substances that might be used for the same purpose. This concept of relative toxicity has been applied to pharmaceuticals (e.g. which are the least toxic anti-depressant drugs), agrochemicals (e.g. which are the least toxic non-selective herbicides) but is relevant and could be applied to any area of toxicology including even drugs of abuse and occupational hazards. The first attempts to compare the relative toxicity were very simple adjusted death rates and relied on extreme differences in toxicity to persuade people to overlook the lack of sophistication in the methodology. So King and Moffat contrasted the 10 to 100 fold greater number of poisoning deaths per prescription with barbiturates compared to benzodiazepines and also first coined the term 'fatal toxicity index' (FTI).[1] Calculations of FTI were in the next 20 years enthusiastically applied to other drugs, antidepressants in particular. There were some improvements in the statistical methodology over the years, which mostly allowed more provision for numerous potential sources of uncertainty, but the broad concept remained the same. Using the FTI as a measure of lethality in overdose makes a number of assumptions including that data on the 'cause of death' are not biased by previous literature, that drugs are taken in overdose with similar frequency and in similar amounts. The perceived risk of overdose has the potential to confound by altering a number of variables. For example, "less toxic" drugs may be preferentially prescribed to patients at higher risk of poisoning and suicide, but perhaps also less likely to be listed as the sole cause of death from overdose. This is most likely to affect comparisons between older "toxic" and newer "safe" drugs. Thus similar FTIs calculated for venlafaxine and clomipramine may not actually indicate equivalent toxicity.[2] Lacking in these crude indices was any indication of the mechanism for the increased numbers of deaths with certain agents. This would provide the necessary causal mechanism that would be needed to justify a conclusion that the difference in a fatal toxicity index was not simply confounded (for example by a factor that altered the frequency with which it was taken in overdose). This lead to a second type of relative toxicity study comparing the severity and frequency of clinical manifestations of toxicity. Perhaps the first example of this was a report based on poison center calls about tricyclic antidepressant overdoses which showed desipramine had a very much higher rate of seizures.[3] Again, many further studies were done which improved on the methodology, largely by attempting to reduce the possibility of referral and reporting bias, but the broad concept remained the same. Attempts to correlate fatal toxicity with pharmacological or chemical properties did not demonstrate any properties more useful than the animal LD50 in predicting FTI.[4] This is not surprising as both FTI and relative toxicity studies repeatedly show that pharmacological classes cannot be regarded uncritically as *de facto* toxicological classes. An ideal relative toxicity study would be able to measure both case-fatality and clinical symptomatology. However, the case-fatality for most substances is too low and thus data from much larger populations are required. The one exception to date has been pesticides, where the very high case-fatality allows both fatal toxicity to be compared and the mechanism behind differences to be explored in the same cohort.[5] Future applications of toxico-surveillance need to be able to be used prospectively rather than simply report on previous disasters. For example, where there is a range of agents with low toxicity and a new agent enters the market, we need to consider how best to detect those with disproportionate toxicity in a timely fashion. It is clear that death data accumulate and are reported too slowly to provide a clear signal that might avert unnecessary deaths. Prospective clinical and forensic data collection with regular oversight might provide a solution, but there is little coordination of different efforts and it is unlikely that more single centers in isolation doing prospective collection will increase the timeliness of toxico-surveillance signals. The solution to detecting less extreme differences may lie in using a Bayesian framework to provide greater reassurance about the relative safety of specific agents. For example, if we have data on a variable number of non-lethal exposures to a number of different agents, we should still be able to infer that there will be less lethal toxicity for the agents which caused less potentially life-threatening complications, and incorporate estimates from previous studies in animals. Without such a framework, a simple FTI approach simply assumes the agent with the most exposures without lethality has demonstrated the greatest safety in overdose (as it has the narrowest confidence interval around zero). This sort of modeling is commonly implicitly relied on in regulatory toxicology decisions about chronic and acceptable exposures. However, the methodology of doing this in relation to making judgments about the potential risk of a fatal outcome with acute poisoning needs further development. In particular the most useful clinical and laboratory biomarkers predictive of fatal toxicity with different types of agents need to be better defined. *References:* 1. King LA, Moffat AC. Hypnotics and sedatives: an index of fatal toxicity. Lancet 1981; 1:387–388. 2. Buckley NA, McManus PR. Fatal toxicity of serotoninergic and other antidepressant drugs: analysis of United Kingdom mortality data. Br Med J 2002; 325:1332–1333. 3. Wedin GP, Oderda GM, Klein-Schwartz W, et al. 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220. The Value of Toxicity Information Collected by Poisons Centres for Patient Safety

Benkirane R, Rhalem N, Abouali F, Soulaymani R.
Moroccan Poison Control Centre and Pharmacovigilance Centre, Rabat, Morocco

The National Patient Safety Agency has described patient safety as the process by which an organization makes patient care safer. This should involve: risk assessment, the identification and management of patient related risk, the reporting and analysis of incidents, and the capacity to learn from and follow up incidents and implement solutions to minimize the risk of them recurring.[1] Poison Control Centres are systematically concerned with problems of adverse drug events, and may be contacted by physicians and the public for advice on both drug overdoses and medication errors.[2,3] The experience gained in the poison control centres is an important source of human toxicological data. Some success stories emphasize the importance of Poison Control Centers as a valuable source of information on patient safety and also as a model for public health surveillance. Drawing on its observations and experience, a poison control centre can contribute to the prevention of poisoning by encouraging manufacturers to employ less toxic formulations, pack-size restrictions (e.g. paracetamol),[4] to improve the packaging and labelling of their products (e.g. look alike or sound alike drug names)[5] and to lead to drug withdrawals in some cases (e.g. association of paracetamol and dextropropoxyphene in UK).[6] Poison control centres have also educational responsibilities that extend to the training of medical practitioners and other health care professionals likely to encounter medication errors, and to the communication with the population to become more active in their

own care.[7] Further more, a close collaboration between the Pharmacovigilance Centre and Poison Control Centre allow greater input and harmonization of the adverse drug events data collection in order to ascertain those related to medication errors to develop prevention strategies. Thus, Poison control centres have the responsibility of contributing to patient safety in collaboration with Pharmacovigilance centres and other institutions established for that purpose. *References:* 1. http://www.clinicalgovernance.scot.nhs.uk/section5/definition.asp 2. Volans GN, Karalliedde L, Wiseman HM. Poisons Centres and the reporting of adverse drug events: The case for further development. Drug Saf 2007; 30:191–194. 3. Ballesteros S, Ramón F, Martínez-Arrieta R, et al. Ten years of iatrogenic intoxications from the Spanish poison control center. Vet Hum Toxicol 2003; 45:93–94. 4. Morgan O, Griffiths C, Majeed A. Impact of paracetamol pack size restrictions on poisoning from paracetamol in England and Wales: an observational study. J Public Health 2005; 27:19–24. 5. http://www.jointcommission.org/NR/rdonlyres/C92AAB3F-A9BD-431C-8628-11DD2D1D53CC/0/lasa.pdf 6. Hawton K, Simkin S, Deeks J. Coproxamol and suicide: a study of national mortality statistics and local nonfatal self-poisoning. BMJ 2003; 326:1006–1008. 7. McGoodwin L. Self-reported therapeutic errors to a poison control center. J Okla State Med Assoc 2003; 96:522–525. 8. Safety monitoring of medicinal products. Guidelines for setting up and running a Pharmacovigilance Centre. WHO. The Uppsala Monitoring Centre for International Drug Monitoring, Uppsala, Sweden. http://www.who-umc.org/graphics/4807.pdf

221. Delivery of Aggregate Poison Data Using a Web Service to Facilitate Building Federated Surveillance Systems

Bronstein AC,[1] Wruk KM,[1] Espino JU.[2]
[1]*Rocky Mountain Poison Center, Denver Health, Denver;* [2]*RODS Laboratory, Center of Biomedical Informatics, University of Pittsburgh, Pittsburgh, US*

Objective: The National Poison Data System (NPDS) aggregates information in near real-time from 61 US poison centers. Modern public health surveillance systems advocate a federated approach when integrating existing data sources. We sought to create a reusable, standard service for external systems to obtain, combine, analyze and visualize poison center (PC) data in ways not currently available with existing NPDS tools using a web service (WS) to support the construction of federated public health surveillance systems. *Methods:* We used standard technology (Simple Object Access Protocol or SOAP) to design and build the WS in 8 weeks. The initial WS allows authorized users to request (call) NPDS data. WS users may request aggregate case counts by 1) total case volume, 2) human exposure volume or 3) clinical effect counts by ZIP code and arbitrary time periods from the year 2000 forward. NPDS data can then be dynamically combined, visualized and/or analyzed within the external surveillance system. External systems can display PC data in their existing user interfaces and analyze the information using local outbreak detection algorithms. *Results:* Two different computer data systems have developed information visualization approaches for NPDS data including interactive maps by state and county with time series drill down. Both systems utilize an open source client and Application Programming Interface (API) collaboratively developed by the authors. More than 17711 WS calls have been executed for custom maps and time series. *Conclusion:* The WS approach to sharing NPDS information offers a more robust and cost effective approach than older methods that built individual data feeds between systems and created redundant copies of existing information. A major advantage is that NPDS data is always current and available in real-time to other surveillance systems. Another advantage is reuse; the same PC database can be used by multiple external surveillance systems. Finally, the distribution of an open source client to access the NPDS WS encourages the development of novel PC data applications. The WS allows NPDS to operate as part of a potential worldwide federated surveillance system, permitting real-time signal integration and opened the door to many new uses of PC data.

222. Ant-Killer Exposures and Poisoning

Good AM, Lupton D, Adams RD, Bateman DN.
NPIS Edinburgh, Royal Infirmary of Edinburgh, Edinburgh, UK

Objective: To describe exposures to ant killer products reported to a poisons service pesticide surveillance project. *Methods:* All patient related accesses to pesticides of interest on TOXBASE (UK internet poisons database) between 1 April 2004 and 30 September 2008 were automatically notified electronically to NPIS Edinburgh. Enquirers were asked to complete an online questionnaire or paper questionnaire printed at the time or sent subsequently. All pesticide related telephone enquiries to NPIS Edinburgh were also followed up. Enquiries from outside the UK, and those involving animals are excluded. Ant killer exposures were analysed for age, gender, agents, circumstances and symptoms. *Results:* Data on 498 cases of exposure were captured. The age range was <1 - 91 years (mean 13.9 years, median 2 years, 129 aged <2 years). The male:female ratio was 0.95:1. Twenty-seven exposures involved deliberate self-harm and the remainder were accidental. The majority (99.2%) were acute exposures. The products involved contained pyrethroids (257), borax (125), carbamates (53), organophosphates (25) and fipronil (9). 55.8% of exposures involved ingestion, 8.8% inhalation, 7.6% skin contact, 3.8% eye contact, 22.1% multiple routes and the remaining 9 "other" or not known. Symptoms occurred in 25% of cases (126). Gastrointestinal features were most common. Features at the time of the enquiry were categorised using the Poisoning Severity Score[1] as PSS 0 (372); PSS1 (120); PSS2 (6); PSS3 (0). No deaths or serious poisonings were recorded. Exposure, where known, occurred predominantly after the bait had been put down (58.1%). In 20% it was due to unsatisfactory storage, in 17% the patient was using the product, and only 5% while someone else was using the product. *Conclusion:* Most exposures to ant killer products occurred in children under the age of 5 years and were not serious. Care in storing the products and in placing the products for use would help to reduce these exposures. *References:* 1. Persson HE, Sjöberg GK, Haines JA, et al. Poisoning severity score. Grading of acute poisoning. Clin Toxicol 1998; 36:205–213.

223. Consequences of 40 Years' Dioxin Intoxication

Pelclova D,[1] Fenclova Z,[1] Dubska Z,[2] Malik J,[3] Navratil T.[4]
[1]*Department of Occupational Medicine, Charles University;* [2]*Department of Ophthalmology, Charles University;* [3]*3rd Medical Department, Charles University, Prague;* [4]*J. Heyrovsky Institute of Physical Chemistry, Prague, Czech Republic*

Objective: To evaluate the consequences of severe intoxication with 2,3,7,8-tetrachloro-dibenzo-p-dioxin (dioxin) in herbicide production (trichlorophenoxyacetic acid) during the years 1965–1968 and to compare recent findings with previous examination in 2003. Dioxin is a chemical with about an 8 year plasma half-life, chronically affecting especially the cardiovascular system and the CNS. *Methods:* In 11 men (out of about 80 in 1965), mean age 64 years, examination in 2008 included: blood lipids, atherogenic index in plasma defined as log (TG/HDL-cholesterol), ultrasonography of the carotid artery (intima-media thickness), eye fundus and internal examination. Dioxin level was measured by HRGC/HRMS. Two-sample t-test (paired) was used for statistical evaluation. *Results:* Mean dioxin level in 2008 was 270±130 pg/g blood lipids (reference level is 2–3 pg/g), mean cholesterol 4.27±0.75 mmol/l (7 patients treated with statins), triacylglyceroles (TG) 2.00±0.74 mmol/l (4 patients treated with fibrates). It was found that body mass index had not changed substantially in 2008 compared with 2003 in the investigated group (28.9 ± 3.7 and 28.7 ± 3.2 kg.m-2, respectively, $p=0.760$). Both mean cholesterol and TG in plasma lowered due to the hypolipidemic treatment, however atherogenic index in plasma did not decrease (3.22±0.57 and 3.27±0.50, $p<0.01$) and mean intima-media thickness increased from 0.84 ± 0.11 mm in 2003 to 1.06±0.11 mm in 2008 ($p=0.05$). All the patients had atherosclerotic changes on the eye fundus, 9 (82%) patients were treated for hyperlipidemia, 8 (73%) for hypertension, 6 (55%) for diabetes, 5 (45%) for ischaemic hearth disease, 4 (36%) for psychic disorders and 3 (27%) had lipomas. *Conclusion:* 40 years after intoxication, blood level of this carcinogen is still 100 fold higher than in the general population. Progression of intima-media thickness may be caused both by direct toxic effect of dioxin (1,2) and chronic hyperlipidemia. Subjects need continuous intense hypolipidemic and neuropsychological treatment. *References:* 1. Dalton TP, Kerzee JK, Wang B, et al. Dioxin exposure is an environmental risk factor for ischemic hearth disease. Cardiovasc Toxicol 2001; 1:285–298. 2. Vogel CFA, Sciullo E, Matsumura F. Activation of inflammatory mediators and potential role of ah-receptor ligands in foam cell formation. Cardiovasc Toxicol 2004; 4:363–373. *Acknowledgement:* MSM 0021620807.

224. International Transport of Fumigated Containers, a Risk for Dock Workers

Scholtens EJ,[1] de Vries I,[1,2] Meulenbelt J.[1,2,3]
[1]*National Poisons Information Centre, National Institute for Public Health and the Environment, Bilthoven;* [2]*Intensive Care Centre, University Medical Centre, Utrecht;* [3]*Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands*

Introduction: In the Netherlands considerable attention is paid to incidents with fumigated import containers. Recently the import from China has increased tremendously: in 2007 ten million containers originating from Asia (45%), Europe (37%) and the Americas (16%), were transferred in the Dutch container ports. To prevent global distribution of pests and diseases, specific cargo and packaging timber are fumigated. An overview of fumigants used in import containers and the exposure and risks arising from these containers is presented. *Methods:* Air sampling of containers was done by the Dutch Ministry of Housing, Spatial Planning and the Environment, and the National Institute for Public Health and the Environment (RIVM). In addition, from April 2005 - November 2008 consecutive cases of container incidents were evaluated by the poisons information centre with regard to number of exposed persons, involved chemicals and clinical symptoms. *Results:* About 20% of the import containers still contain (sometimes high) concentrations of hazardous gaseous compounds such as methyl bromide, phosphine, formaldehyde, sulfuryl fluoride, ammoniac gas, chloropicrin and organic solvents. Most containers did not have the obligatory warning sign identifying the type and amount of the fumigant. Random sampling showed that 80% of the fumigated containers had been treated unnecessarily. The poisons centre recorded 20 container incidents, in which 40 dock workers developed health effects such as nausea, vomiting, headache, dizziness, and lung injury. Two men were exposed to high concentrations of methyl bromide and developed severe toxicity with long lasting neurological symptoms. *Conclusion:* Although the number of incidents is small considering the millions of import containers being transferred, very severe poisonings occur. Considering the cargo, it seems that much more attention should be paid to whether fumigation is really mandatory. If fumigated, containers should be labelled accordingly. Regulations in the Netherlands require that when fumigating containers is mandatory for export, these containers need to be degassed in the Netherlands as well before being transported. On an international level this practice should be strongly propagated, thus diminishing the risk for those unloading the containers. *References:* Schols E. Human and environmental risks of containers containing dangerous volatile substances. RIVM Report 609021054 (2007).

225. Code Black: A Structured Approach to the Agitated Patient in the Emergency Department

Downes MA,[1,2] Healy P,[1] Page CB,[1] Bryant JL,[3] Isbister GK.[2]
[1]*Department of Clinical Toxicology and Pharmacology, Calvary Mater Hospital;* [2]*Department of Emergency Medicine, Calvary Mater Hospital;* [3]*Department of Liaison Psychiatry, Calvary Mater Hospital, Newcastle, Australia*

Objective: Behavioural disturbance and aggression in the ED is an increasing problem. This study describes the characteristics of patients with acute behavioural disturbance and their emergent treatment in an ED with a structured team approach to the agitated patient. *Methods:* This was a retrospective review of acute behavioural emergencies that required response from the Code Black (CB) Team (duress response team) in the ED during 2006. The hospital security log and hospital incident reporting system identified all documented CB and the patients' medical records were reviewed. Information extracted included patient demographics and presenting complaint, details of the CB, the use of pharmacological sedation, physical restraint, patient disposition and injuries to hospital staff. *Results:* There were 122 patients, median age 32yrs (interquartile range [IQR]:24–43yrs, range: 14–81yr) with 71 males (58%) who accounted for 143 CB activations. The primary problems were deliberate self-poisoning or self-harm (38%), alcohol and illicit drug intoxication (33%) and psychiatric, organic illness and drug withdrawal (29%). One hundred and eight (89%) patients had a past history of alcohol/illicit drug abuse or psychiatric illness. Indications for CB activation were threatening harm to others or behaving violently in 67% of cases. Combined pharmacological sedation and physical restraint were required on 66 (46%) occasions, pharmacological sedation alone on 20 (14%), physical restraint alone on 14 (10%), and neither on 43 (30%) occasions. Benzodiazepines were most commonly used for initial sedation, including midazolam (49%) by the intramuscular route in two thirds, diazepam (42%) and antipsychotics (9%), most commonly droperidol. More diazepam and droperidol were used for repeat pharmacological sedation. A staff member was injured on only one occasion (0.7%). *Conclusion:* In this study, acute behavioural disturbance in the ED was mainly in patients with self-harm and drug/alcohol issues. Minimal staff injuries occurred if a structured team approach is used. Parenteral benzodiazepines were commonly used for sedation.

226. Poisoning-Related Mesenteric Ischemia: Characteristics and Outcome

Nault JC,[1] Mégarbane B,[1] Théodore J,[1] Deye N,[1] Nemeth J,[2] Valleur P,[3] Baud FJ.[1]
[1]*Réanimation Médicale et Toxicologique, Hôpital Lariboisière;* [2]*Service d'Anatomie et Cytologie Pathologiques, Hôpital Lariboisière;* [3]*Service de Chirurgie Générale et Viscérale, Hôpital Lariboisière, Paris, France*

Objective: Mesenteric ischemia (MI) is a rare complication of poisoning. Its incidence and risk factors are unknown. Our objective was to describe the characteristics of poisoning-related MI in comparison to the usual MI. *Methods:* Retrospective review of clinical data of patients hospitalized in our intensive care unit in 2001–2008 with MI diagnosis; description (median, [25–75%-percentiles]; comparison between poisoned and non-poisoned patients using Mann-Whitney and Chi-2 tests. *Results:* Seventeen patients (11F/6M, 66 years [55–72], SAPSII: 60 [48–66]) including 5 poisoned patients (main ingested toxicants: amlodipine, nicardipine, propranolol, dextropropoxyphene, and turpentine). Clinical presentation and severity were comparable between both groups. However, poisoned patients were significantly younger ($p = 0.03$) with less past cardiovascular diseases ($p = 0.04$) or risk factors ($p = 0.008$) (Table). Typical injury following acute poisoning was a short jejunal ischemia without ileal spreading. MI occurred with a delay after the use of elevated doses of vasopressors for shock (maximal infusion rates: 15.5 mg/h [4.5–30.0] norepinephrine and 6.0 mg/h [4.9–6.3] epinephrine, supporting the hypothesis of an iatrogenic etiology.

Table. Age, risk factors, cardiovascular disease and patients and controls.

	Poisoning (N=5)	Non-poisoning (N=12)	p
Age (years)	50 [32–60]	68 [58–81]	0.03
SAPS II score	54 [48–62]	61 [46–67]	0.7
Risk factor (N)	0 [0–1]	3 [2–5]	0.008
Past cardiovascular diseases (%)	0	58	0.04
Delay between maximal catecholamine infusion rate (h)	48 [36–60]	0 [0–24]	0.06
Ischemic bowel (cm)	90 [28–135]	375 [170–500]	0.008
Ileal ischemia (%)	20	100	0.002
Mortality (%)	20	92	0.009

Mortality was significantly lower in poisoned patients ($p = 0.008$). *Conclusions:* MI may complicate the use of huge doses of vasopressors after severe acute poisoning, despite the lack of cardiovascular risk factors. It occurs typically 48 hours after catecholamine infusion. Any gastrointestinal symptom in this situation should be suspected to be a MI.

227. Amisulpride Overdose Causes QT Prolongation and Torsade de Pointes – A National Study

Isbister GK,[1,2,3] Balit CR,[3] Macleod D,[4] Joy JP,[5] Duffull SB.[5]
[1]*Department of Clinical Toxicology, Calvary Mater Newcastle Hospital, Newcastle, Australia;* [2]*Tropical Toxinology Unit, Menzies School of Health Research, Darwin, Australia;* [3]*NSW Poison Information Centre, The Childrens Hospital at Westmead, Sydney, Australia;* [4]*Victorian Poison Information Centre, The Austin Repatriation Hospital, Melbourne, Australia;* [5]*School of Pharmacy, University of Otago, Dunedin, New Zealand*

Objective: Amisulpride is an atypical antipsychotic that is relatively free from side effects and was not reported to cause cardiotoxicity in clinical trials. Following cases of Torsade de Pointes (TdP) being reported following amisulpride overdose we undertook a prospective study to examine the clinical and electrocardiographic (ECG) features of amisulpride overdose. *Methods:* Cases of amisulpride overdose were identified by specialist poison information staff at two State poison information centres. A one-page datasheet was faxed to the treating hospital with a request for clinical information and a copy of all ECGs to be faxed back. In all patients ingesting >4 g it was recommended that they be observed for a minimum of 16 hours with regular ECGs. Medical records were contacted if clinical information and ECGs were not faxed back, to obtain clinical information and ECGs. Data collected included patient demographics, details of ingestion, Glasgow coma score (GCS), complications (hypotension [sysBP<90 mmHg], arrhythmias, dystonias and seizures), and treatment (intubation and ventilation, treatment of arrhythmias). ECG parameters (HR, QRS and QT intervals) were manually measured on all ECGs as previously described, and plots of QT-HR pairs were compared to the QT nomogram. *Results:* The study included 51 amisulpride overdoses over a 4 year period. The patient median age was 26 years (interquartile range [IQR]: 22 – 39 yr) and 26 were female (51%). The median dose ingested was 9.1 g (IQR: 4 – 14.1g, range: 0.6 – 32g). Central nervous system depression was uncommon with a median GCS of 14 and only five patients having a GCS<9 who required intubation. There were no seizures and three patients had dystonic reactions. Bradycardia occurred in 12 cases (24%) and hypotension occurred in 11 patients (22%). One patient died following TdP and cardiac arrest in a small peripheral hospital. There were 254 ECGs available showing a time dependent increase and then resolution of QT prolongation. An abnormal QT-HR pair consistent with a prolonged QT occurred in 34 of the 51 overdoses (67%) and TdP occurred in 4 overdoses (8%) with doses 4.2 g, 20 g, 32 g and 32 g; all were treated with DC shocks. Widening of the QRS complex did not occur in any case except transient rate-dependent bundle branch block in one case. *Conclusion:* Amisulpride is an uncommon overdose that causes profound QT prolongation, hypotension and bradycardia. TDP occurred in a significant proportion of cases, mainly with massive ingestions. Other effects were uncommon, but included central nervous system depression and dystonias.

228. Homicidal Poisoning Deaths in the United States 1999–2005

Shepherd G,[1,2] Ferslew BC.[1]
[1]*College of Pharmacy, University of Georgia, Augusta;* [2]*Department of Emergency Medicine, Medical College of Georgia, Augusta, US*

Objective: Describing the victims of homicidal poisoning death in the United States during 1999–2005. *Methods:* National Mortality Statistics were queried using "homicide" as injury intent, and "poisoning" as injury mechanism for the years 1999–2005. Counts and rates were obtained for sub-grouping by using specific ICD-10 codes, geographic data, age, race, and gender. *Results:* A total of 523 cases of homicidal poisoning were identified. The overall rate for homicidal poisoning for the period was 0.26 per million per year. The rate of homicidal poisoning was greater among males (0.30 per million) than females (0.22 per million). Homicidal poisoning deaths occurred most frequently at extremes of age. In children less than 1 year old the rate was 2.05 per million and at ages greater than 85 years the rate was 0.56 per million. Homicidal poisoning rates also varied by race and was more common among African Americans (0.43 per million). ICD 10 codes indicated that code X85, Assault by drugs, medicaments and biological substances (65%, n = 333) was the most common method of poisoning. Based on geographic distribution, rates were slightly higher in the West and Midwest than in the South and Northeast. *Conclusion:* In the United States, the overall homicidal poisoning death rate was relatively low between 1999 and 2005. Medications are the most commonly used substances in homicidal poisonings. Substantially higher rates were observed in vulnerable populations at extremes of age, particularly infants, and among African Americans. This challenges common notions of who victims of homicidal poisoning are and the underlying motivations of their poisoners.

229. Differential Clinical Toxicity of Tricyclic Antidepressants in Overdose Following Acute Hospital Admission

Galal HKA,[1] Hill S,[2] Hodson K,[2] Gray J,[3] Thomas SHL.[1,2]
[1]*Wolfson Unit of Clinical Pharmacology, Newcastle University, Newcastle upon Tyne;* [2]*Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne;* [3]*Janine Gray Statistical Consultancy and Training, East Bolden, UK*

Objective: Tricyclic antidepressants (TCAs) continue to be widely used for the treatment of depression and chronic pain and are often encountered in overdose. Epidemiological evidence suggests that more overdose deaths occur per million prescriptions for dosulepin (dothiepin) than for other TCAs, although there are potential confounding factors that are not taken into account, including doses prescribed and indication for therapy. One hospital based study has reported a higher risk of fits and arrhythmias with dosulepin compared with other TCAs. This study was therefore performed to investigate the comparative toxicity of TCAs in a cohort of patients presenting to hospital. *Methods:* Patients were included if they were admitted with a history of TCA overdose between the years 2000 and 2008. Details were recorded from medical notes and 12 lead ECGs coded and analysed blinded to the TCA involved for RR, QRS and QT intervals using a CalComp 9000 digitiser. *Results:* There were 511 first presentations with TCA overdose during the period of study. No deaths occurred. When available, mean (+/- SD) reported doses were higher for lofepramine (1.76 +/- 1.09 g) and dosulepin

(1.23 +/– 0.91 g) than amitriptyline (0.72 +/– 0.86 g). Using amitriptyline as a reference, odds ratios [95% CI] for specific adverse outcomes, calculated by logistic regression and adjusted for potential confounders, were not significantly different from 1.0 for dosulepin but were significantly reduced for lofepramine. These adverse outcomes included Glasgow Coma Scale of < 9 (dosulepin 0.92 [0.65, 1.61], lofepramine 0.37 [0.03, 0.33]), acidosis (dosulepin 1.23 [0.61, 2.49]; lofepramine dropped due to no cases) and length of stay > 2 days (dosulepin 0.82 [0.50, 1.34]; lofepramine 0.10; [0.06, 0.51]). *Conclusion:* Lofepramine is significantly less toxic than either amitriptyline or dosulepin using these outcome measures. However, this large series provides no evidence for a difference in rates of these adverse outcomes between dosulepin and amitriptyline, even though reported doses of dosulepin, when available, were significantly larger than those of amitriptyline. *References:* 1. Henry JA, Alexander CA, Sener EK. Relative mortality from overdose of antidepressants. Brit Med J 1995; 310:221–224. 2. Buckley NA, McManus PR. Fatal toxicity of serotoninergic and other antidepressant drugs: analysis of United Kingdom mortality data. Brit Med J 2002; 325:1332–1333. 3. Morgan OWC, Griffiths C, Baker A, et al. Fatal toxicity of antidepressants in England and Wales, 1993–2002. Health Stat Q 2004; 23:1–7. 4. Cheeta S, Schifano F, Oyefeso A, et al. Antidepressant-related deaths and antidepressant prescriptions in England and Wales, 1998–2000. Br J Psychiatr 2004; 184:41–47. 5. Buckley NA, Dawson AH, Whyte IM, et al. Greater toxicity in overdose of dothiepin than of other triyclic antidepressants. Lancet 1994; 343:159–162.

230. Sodium Chloride and Glutamate Poisoning after Stock Cubes Ingestion

Faraoni L,[1] Eleftheriou G,[1] Butera R,[1,2] Zavaritt A,[1] Panzeri C,[1] Manzo L,[2] Codeluppi V,[3] Zardin M.[3]
[1]*Bergamo Poison Control Center, Ospedali Riuniti, Bergamo;* [2]*Poison Control Center, IRCCS Maugeri Foundation and University of Pavia, Pavia;* [3]*Intensive Care Unit, Presidio Ospedale Destra Secchia, Pieve di Coriano, Italy*

Objective: Stock cubes contain sodium chloride 50%, sodium glutamate 17%, and vegetable and animal extracts 33%. We describe an unusual case of stock cube ingestion, with subsequent severe poisoning. *Case report:* A 73-year-old female patient, with initial dementia, was brought to the Emergency Department because of recurrent seizures and hyperthermia (T 40°C). Routine blood chemistry showed severe hypernatremia (Na 188 mEq/L) and mild hypokalemia (K 2.5 mEq/L). History revealed that the patient had ingested during the night 26 stock cubes (NaCl 130 g, sodium glutamate 44.2 g). The patient was sedated, intubated and admitted to Intensive Care Unit (ICU), where hypernatremia correction was started at the rate of 0.5 mEq/L/h: sodium levels decreased to 172, 159, 147 and 141 mEq/L at 24, 48, 72 and 76 hours after hospital admission. Treatment included supportive measures and i.v. vitamin B6. The main clinical features in the first 24 hours were hyperthermia and myoclonus unresponsive to midazolam administration. From the nasogastric tube a broth-like material was still present at 36 hours after admission: gastric lavage and administration of water were continued. On day 2, cerebral CT scan displayed multiple hypodense areas (previous lesions already known). On day 3, the patient was afebrile; myoclonus was still present. On day 4 she deteriorated, with coma, myoclonus, and rigidity with extensor hypertonus at the 4 limbs; a new CT scan showed diffuse cerebral edema with sulcal effacement and ventricular asymmetry. The patient was discharged from ICU one month later, with severe neurological damage. *Conclusion:* In the patient described, the acute nature of hypernatremia and the gradual correction suggest that other mechanisms could have had a causal/concausal role, in addition to the well known complications of hypernatremia.[1] Glutamate is both an excitatory neurotransmitter and an organic osmolyte (OO) involved in the regulation of cellular volume in cases of hypernatremia: experimental data suggest that within 48 hours of hypernatremic cellular dehydration the amount of OO is significantly increased in cerebral cells.[2] The availability of exogenous glutamate may have altered physiological regulation of this compensatory mechanism, with an overload of intracellular OO that can explain the delayed cerebral edema. *References:* 1. Adrogué HJ, Madias N. Hypernatriemia. N Engl J Med 2000; 342:1493–1499. 2. De Petris L, Lucchetti A, Emma F. Cell volume regulation and transport mechanisms across the blood-brain barrier: implications for the management of hypernatraemic states. Eur J Pediatric 2001; 160:71–77.

231. Premedication for Coronary Computed Tomographic Angiography Produces Symptomatic Atrio-Ventricular Dissociation

Morrissey RP,[1,2] Howland MA,[1,2,3] Hoffman RS,[1,2] Nelson LS.[1,2]
[1]*New York City Poison Control Center;* [2]*Department of Emergency Medicine, New York University Medical Center, New York;* [3]*College of Pharmacy, St John's University, New York, US*

Objective: Coronary computed tomographic angiography (CCTA) is a new minimally-invasive modality used to risk-stratify patients with coronary artery disease. Optimum visualization of coronary arteries and minimizing radiation exposure necessitates a slow and regular heart rate, which is often facilitated pharmacologically.[1–5] We describe a complication of the requisite CCTA premedication. *Case report:* A previously-well 74 year-old woman developed dyspnea, dizziness, and palpitations shortly after undergoing CCTA at an outpatient imaging center. In preparation for CCTA she was instructed to double her morning dose of 240 mg verapamil ER, and was given 50 mg metoprolol PO and 2.5 mg isosorbide dinitrate SL one hour prior to angiography. Atropine and fluid bolus en route provided no symptomatic relief. Vital signs in the ED were: BP 85/58 mmHg; pulse 56/min; respirations 24/min; SpO_2 99% on nonrebreather mask; afebrile. She denied LOC, chest pain, nausea/vomiting, orthopnea, or change in exercise tolerance. Physical examination was normal. ECG showed 3º AV block with a junctional escape rhythm and lateral T-wave inversions, and chest radiograph revealed mild congestion. Symptoms promptly resolved after 2 mg glucagon IV and 1 gram CaCl IV, and her vital signs normalized. A repeat ECG revealed sinus rhythm with normal T-waves. Laboratory studies (including TSH and serial troponins) were normal. Echocardiogram was normal. She had no dysrhythmic events while admitted on telemetry service, and was discharged the following day. *Conclusion:* Premedication for CCTA carries the potential for cardiovascular complications; given its expanding utilization, systematic investigation is warranted. *References:* 1. Pannu HK, Alvarez W Jr, Fishman EK. Beta-Blockers for Cardiac CT: A Primer for the Radiologist. Am J Radiology 2006; 186:S341–S345. 2. Schoepf UJ, Zwerner PL, Savino G, et al. Coronary CT Angiography. Radiology 2007; 244:48–63. 3. Decramer I, Vanhoenacker PK, Sarno G, et al. Effects of Sublingual Nitroglycerin on Coronary Lumen Diameter and Number of Visualized Septal Branches on 64-MDCT Angiography. Am J Roentgenol 2008; 190:219–225. 4. Giesler T, Baum U, Ropers D, et al. Noninvasive visualization of coronary arteries using contrast-enhanced multidetector CT: Influence of heart rate on image quality and stenosis detection. Am J Roentgenol 2002; 179:911–916. 5. Paul JF, Abada HT. Strategies for Reduction of Radiation Dose in Cardiac Multislice CT. Eur Radiol 2007; 17:2028–2037.

232. Metformin-Associated Lactic Acidosis (MALTA) in the Intensive Care Unit: Outcome and Toxicokinetic Analysis

Mégarbane B,[1] Adjibade AN,[1] Touizer E,[2] Bardin C,[3] Méas T,[2] Deye N,[1] Baud FJ.[1]
[1]*Réanimation Médicale et Toxicologique, Hôpital Lariboisière;* [2]*Service de Médecine Interne B, Hôpital Lariboisière, Paris;* [3]*Pharmacie, Hôpital Hôtel Dieu, Paris, France*

Objective: Metformin-associated lactic acidosis (MALTA) is a rare but severe complication (0.08/1,000 patients/year) of metformin treatment in type-II diabetes. Metformin impairs neoglucogenesis and liver lactate clearance in the presence of a disease that enhances its production. Although frequently used, there are no recommendations regarding hemodialysis in this poisoning. *Methods:* Retrospective analysis of MALTA (lactic acidosis >5 mmol/l + metformin concentrations >4 µmol/l using HPLC-UV detection) admitted to our ICU in 2003–2008; description (median [25–75% percentiles]; comparisons using Mann-Whithney and Chi-2 tests. *Results:* Sixteen patients (12F/4M; 57 years [47–63]; Body mass index: 28 kg/m^2 [21–32]; creatinine clearance: 75 ml/min [57–91]) were included. Poisoning was related to accidental (N = 8; documented aetiologies: infection (N = 4), radiology opacification (N=2), dehydration (N=2)) or suicidal overdoses (N=8; ingested doses: 9.7 g [4.5–22.5]). On admission, patients presented profound lactic acidosis with arterial pH 7.19 [6.84–7.31], serum bicarbonate 11.0 mmol/l [6.8–15.6] and plasma lactate 17.2 mmol/l [9.8–19.7]. Early symptoms associated coma (50%), asthenia (47%), vomiting (27%), abdominal pain (27%), and diarrhoea (20%). Renal function was significantly altered (creatinine clearance: 37 ml/min [14–54]; $p<0.001$). All patients received massive alkalinization, 12/16 (75%) were hemodialyzed while 10/16 (63%) were mechanically ventilated and received catecholamines. Six patients (38%) died in the ICU. Duration of ICU stay was 3 days [3–10]. There were no significant differences regarding MALTA severity and treatments between suicidal and accidental poisonings. Neither lactic acidosis severity nor acute renal failure was predictive of death. There was no correlation between prognosis and the time-course of plasma metformin concentrations, with or without dialysis. Toxicokinetics showed significant tissue distribution when the patient was admitted early or plateaued concentrations if he was admitted later and survived, even though his situation improved and his lactates decreased. Metformin dialysance suggested an interest for extra-renal elimination enhancement although its impact on survival could not be analysed based on this limited study. *Conclusions:* Our study showed that MALTA is severe with elevated mortality in ICU whether the poisoning is accidental or intentional. Metformin toxicokinetics are useful case by case to better understand the patient's outcome.

233. Potential Drug-Drug Interactions and Admissions Due to Drug-Drug Interactions in Patients Treated in Medical Departments

Fokter N,[1] Mozina M,[2] Bunc M,[1,3] Brvar M.[1]
[1]*School of Medicine, University of Ljubljana, Ljubljana;* [2]*Poison Control Centre, University Medical Centre;* [3]*Department for Cardiology, University Medical Centre, Ljubljana, Slovenia*

Objective: Due to increasing life expectancy patients regularly take a growing number of drugs, which augments the possibility of drug-drug interactions that can lead to adverse drug reactions and admissions. In order to check drug-drug interactions and take appropriate preventive measures, we need to know exactly which drugs patients are taking. The aim of this study was to assess the quality of hospital documentation regarding patient medication, check the potential drug-drug interactions at hospital admission and discharge, and to evaluate admissions due to drug-drug interactions. *Methods:* We reviewed 3% of randomly selected medical records of patients treated in the medical departments of University Clinical Centre Ljubljana in 2006. We then checked whether all information on patient medication was documented on hospital admission and discharge. Potential drug-drug interactions on hospital admission and discharge were checked using the Drug-Reax interaction-screening program. The proportion of patients who were admitted due to drug-drug interactions was estimated. *Results:* 520 patients were included in the study. 216 patients (41.5%) had incomplete information on drug names and doses in their medical documentation on admission and 121 (23.3%) had incomplete medication information in their discharge letter. 323 patients with complete information on drug names were included in the analysis of potential drug-drug interactions. 166 patients (51.4%) had at least one potential drug-drug interaction present on hospital admission,

and 204 (63.2%) had at least one potential drug-drug interaction present on discharge (p = 0.001). 41 patients (12.7%) had at least one major potential drug-drug interaction present on hospital admission, and 59 (18.3%) had at least one major potential drug-drug interaction present on discharge (p = 0.001). ACE inhibitor and spironolactone was the most common major potential drug-drug interaction and represented 20.0% of all drug-drug interactions on admission and 25.6% on discharge. 4 patients (1.2%) were admitted due to drug-drug interactions. *Conclusion:* The information on patient medication on hospital admission and discharge is incomplete. Half of the patients on admission and two thirds of the patients on discharge took drugs with possible drug-drug interactions. Adverse drug reactions due to drug-drug interactions were the cause of 1.2% of admissions to medical departments.

234. The Frequency of Adverse Drug Reaction Related Admissions According to Detecting Method, Admission Urgency and Medical Department Specialty

Brvar M,[1,2] Fokter N,[2] Bunc M,[2,3] Mozina M.[1]
[1]Poison Control Centre, University Medical Centre, Ljubljana; [2]School of Medicine, University of Ljubljana; [3]Department for Cardiology, University Medical Centre, Ljubljana, Slovenia

Objective: Adverse drug reactions (ADRs) have been regarded as a major public health problem. Unfortunately, there is a wide variation of ADR related admissions among different studies. The aim of this study was to evaluate the frequency of ADR related admissions depending on reporting and detecting methods, urgency of admissions and included medical departments reflecting department/hospital type within one study. *Methods:* The specially trained specialists retrospectively reviewed 520 randomly selected medical records (3%) of patients treated in the medical departments of the primary city and tertiary referral hospital for ADRs causing admissions that were recognised and documented by the treating physicians. The hospital information system was checked for whether ADR related diagnoses were properly coded and the database of a national spontaneous reporting system was searched for patients with ADRs included in this study. *Results:* The established frequency of admissions due to ADRs recognised and documented in medical records by the treating physicians was 5.8%, detected by employing a computer-assisted approach using an ICD-10 coding system 0.2%, and no patient admitted due to ADRs was reported to the national reporting system. The recognized frequency of ADR related admissions also depends on the department's specialty (p = 0.001) and acceptance of urgently admitted patients (p = 0.001). Gastrointestinal bleeding due to NSAID, acetylsalicylic acid and warfarin was the most common ADR that resulted in admission and represented 40% of all ADRs. *Conclusion:* The established frequency of ADR related admissions depends on the detection method, department specialty and proportion of urgently admitted patients reflecting hospital type. The treating physicians recognise ADR related admissions and note them in medical records, but coding and reporting to the authorities by physicians who are not specially trained and stimulated are not useful methods for the estimation of ADR related admissions.

235. Evaluation of Poisoning by Chemical Agents in Spain. Comparison of Two Sources of Data for Toxicosurveillance

Ferrer-Dufol A,[1] Nogue Xarau S,[2] Menao Guillen S,[1] Ramos M,[1] Royo R,[1] Civeira Murillo E,[1] Martinez Arrieta R,[3] Ballesteros S,[3] Ramon F.[3]
[1]Toxicology Unit, Clinical University Hospital, Zaragoza; [2]Toxicology Unit, Clinical Hospital, Barcelona; [3]Toxicology Information Center, National Institute of Toxicology, Madrid, Spain

Objective: Acute poisonings in Spain have shown a consistent pattern in recent decades characterized by a majority of overdoses coming from drug abuse, followed by suicide attempts with medication. The exposures to other chemical agents (i.e. toxic gases, solvents, caustics, cleaning agents) account for 15% of the total cases. Interest in surveying these chemical poisonings led to the development of a Toxicosurveillance Program (TSP) by means of a collaboration between the Spanish Health Ministry and AETOX's section of clinical toxicology, running from 1999 up to now. Another source of data about these chemical incidents is the Toxicology Information Service (SIT) of the Spanish Institute of Toxicology (INT), the Spanish PCC. We are comparing the epidemiological profiles of poisoning by chemical agents in Spain from these two sources to show the similarities and differences related to these two different points of observation. *Method:* To compare the age, sex, type of poisoning and chemical agent involved in the TSP cases and the SIT cases in 2007. *Results:* TSP has accumulated 5259 chemical cases between 1999 and 2007. SIT cases by chemical agents in 2007 were 33502. Their profiles are shown in table 1. They can be explained by the bias produced by the origin of the SIT cases (64% from the general public). *Conclusion:* Different sources of data produce different results for evaluating chemical poisonings. Data from the PCCs are broader but present some bias and should be complemented by cases coming from the EDs, which are more representatives of real poisonings.

Table 1. Profiles of chemical cases

		SIT N=33502	TSP N=5259
Age	< 15 years	49%	13%
Sex	Men	48.90%	50%
	Women	41.90%	50%
Type of poisoning	Domestic accident	56%	67%
	Occupational	5.50%	17%
	Suicides	2.20%	12%
Type of chemical	Caustics	8.30%	28.10%
	Pesticides	10.31%	9.20%
	Solvents	2.80%	9.70%
	Irritant Gases	1.90%	12.90%
	Toxic gases	0.40%	26.10%

236. How Complete is Patient Inclusion in Emergency Department Studies for Driving Under the Influence?

De Paepe P,[1,2] Lemoyne S,[1] Vankeirsbilck C,[1] Buylaert W,[1] Verstraete A.[3]
[1]Department of Emergency Medicine, Ghent University Hospital, Ghent; [2]Heymans Institute of Pharmacology, Ghent University; [3]Department of Clinical Chemistry, Microbiology and Immunology, Ghent University, Ghent, Belgium

Objective: Emergency physicians have a duty to provide useful data on driving under influence (DUI) for policy makers. However, figures may be invalidated due to limitations like incompleteness of inclusion and need for informed consent (IC). Our literature review revealed very few studies reporting on these limitations. We therefore analyzed patients in our emergency department (ED) who participated in a large European survey on DUI. *Methods:* Inclusion criteria were: driver of a motor vehicle or bicycle, age ≥18 years, primary admission, trauma with maximum abbreviated injury scale (MAIS) ≥2, blood sample separate from routine within three hours after the accident and IC. Ethanol, commonly used psychotropic and illegal drugs were analysed and a questionnaire was completed. Anonymity was guaranteed and the protocol was approved by the ethics committee. All ED personnel were informed on modalities of intake. A research assistant checked the completeness of data and during working hours supervised the inclusions. *Results:* Between January 21 2008 and July 8 2008, 448 patients were screened for inclusion. 311 were excluded because MAIS <2, leaving 137 patients. Of these 36 were not included. Refusal of IC because of fear of a puncture or unwillingness to give a blood sample, lack of trust in the anonymity and an unknown reason accounted for 4, 4 and 1 patients respectively. 27 patients could not be enrolled because the blood sample was missing for the following reasons: inclusion was not considered (n=15), error in assessment of inclusion criteria (n = 5), sample not taken due to circumstances or lost (n = 4) and unknown reasons (n = 3). *Conclusion:* Despite training of personnel and supervision by a research assistant, our survey on DUI misses 19.7% of the patients. The need for giving IC to some extent contributes to the drop out (6.6%) and may induce either under- or overestimation of the percentage of patients DUI. Furthermore, setting the trauma severity level at MAIS ≥2 resulted in a drop out of 69.4% of the screened drivers. When providing data on the number of patients admitted after trauma when DUI, one should report on completeness of enrolment, which is rarely done.

237. Electrocardiographic Ischemic Changes in a Patient with Lithium Toxicity

George M,[1] Burns M.[2]
[1]Crystalrun Healthcare, Middletown; [2]Harvard Medical Toxicology Fellowship, Children's Hospital Boston, Boston, US

Objective: Electrocardiographic evidence of ischemia has rarely been reported with lithium toxicity. We present a case of significant ST elevations in a patient with a toxic lithium level. *Case report:* A 58-year-old female who was on chronic lithium therapy, presented to a local emergency department (ED) complaining of a one month history of slurred speech, nausea, and vomiting which significantly worsened over the past week. Except for slight tremor, no hyperreflexia or ocular clonus were noted. The lithium level was 2.4 mmol/L and her creatinine concentration was 1.5 mg/dL. The ECG showed new 1–1.5 mm ST segment elevations in the precordial and inferior limb leads compared to a prior tracing. The ECG intervals were normal. The creatinine kinase level was 50 U/L and troponin I was 0.01 µg/L. An echocardiogram showed no segmental or global dyskinesis. The patient was managed conservatively without dialysis. On day three, the lithium level improved to 0.8 mmol/L and the ST segment elevations had resolved. *Conclusion:* The most commonly reported ECG abnormalities in lithium toxicity are T-wave changes and atrioventricular conduction delays. Few case reports have described this unusual ECG presentation. Myocardial ischemia[1] and the unmasking of a Brugada pattern have been described.[2] In an animal model, the activation of K-ATP channels by lithium has also been proposed.[3] Lithium, the drug of choice for bipolar disorder, appears to cause atypical electrocardiographic changes. Our present case supports this hypothesis. Further studies are needed to investigate the causes and risk factors of these events. *References:* 1. Perrier A, Martin PY, Favre H, et al. Very severe self-poisoning lithium carbonate intoxication causing a myocardial infarction. Chest 1991; 100:863–865. 2. Darbar B, Yang T, Churchwell K, et al. Unmasking of Brugada syndrome by lithium. Circulation 2005; 112:1527–1531. 3. Abdel-Zaher AO, Abdel-Rahman MM. Lithium chloride-induced cardiovascular changes in rabbits are mediated by adenosine triphosphate-sensitive potassium channels. Pharmacol Res 1999; 39:275–282.

238. Life-Threatening Lactic Acidosis in a Patient Using Therapeutic Doses of Metformin and Ace-Inhibitor

Hagset IB,[1] Krogh AV,[1] Froyshov S.[1,2]
[1]Norwegian Poisons Information Centre, Oslo; [2]Department of Acute Medicine, Ullevaal University Hospital, Oslo, Norway

Objective: We present a case of life-threatening lactic acidosis in a patient using an ACE-inhibitor and metformin therapeutically. *Case report:* A 58-year-old man on ACE-inhibitor and metformin, with non-insulin dependent diabetes mellitus and coronary artery disease,

was admitted to hospital after some days with thirst and trouble regulating his blood sugar. On admission at the local hospital he had severe acute renal failure and metabolic acidosis resistant to treatment. Laboratory values: pH 6.82 (7.35–7.45), base excess −31 mmol/l (−3 to 3 mmol/l), lactate >20 mmol/l (0.3–1.5 mmol/l), anion gap 42 mmol/l (6–20 mmol/l), S-creatinine 1060 micromol/l (70–125 micromol/l), S-potassium 8.6 mmol/l (3.5–5.0 mmol/l), S-glucose 21 mmol/l (3.0–5.5 mmol/l), no ketonuria. The hyperkalemia was assumed to be secondary to the renal failure and acidosis. Metformin-induced lactic acidosis was suspected. The patient had cardiac arrest before transferral to another hospital for hemodialysis, and once again during preparation for this procedure. Continuous veno-venous hemodialysis (CVVHD) was started during resuscitation. After return of spontaneous circulation, one hour of conventional hemodialysis was performed as well. Therapeutic hypothermia was applied for 24 hours. The patient gradually improved, and over the next days his renal function returned to normal; CVVHD was stopped after 6 days. He was discharged to his home without permanent sequelae. His plasma concentration of metformin on admission to hospital was 412 micromol/l (therapeutic: 0.1–1 micrograms/ml[1] = 0.6–6 micromol/l). His acute renal failure was believed to be secondary to dehydration due to hyperglycemia, and ACE-inhibitor medication. *Conclusion:* Severe lactic acidosis during treatment with metformin needs rapid recognition and treatment with hemodialysis. Patients should be made aware of the possibility of lactic acidosis, and be encouraged to stop taking metformin in case of acute illness with dehydration, especially when concomitantly using ACE-inhibitor medication. *References:* 1. Metformin monograph in: Klasco RK (Ed): DRUGDEX® System. Thomson Healthcare, Greenwood Village, Colorado (Edition expires 12/2008).

239. Renal Failure after Dipyrone Overdose

Abu-kishk I,[1,2] Goldman M,[1,2] Mordish Y,[1,2] Berkovitch M,[1,2] Kozer E.[1,2]
[1]Paediatric Emergency Unit, Assaf–Harofeh Medical Center, Zerifin; [2]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Objective: Dipyrone is a non steroidal anti-inflammatory agent, exhibiting analgesic, antipyretic and mild anti-inflammatory activity. In a large series of 243 patients with dipyrone overdose only mild symptoms were reported. None of the patients developed serious toxic effects. During the last few years, we identified several cases of acute renal failure following dipyrone overdose. The objective of the current study was to describe the incidence of acute renal failure after dipyrone overdose in children. *Methods:* We retrospectively reviewed the medical records of all patients up to 18 years of age presenting to the pediatric emergency department at Assaf Harofe Medical Center due to medication overdose between January 1st 2005 and December 31st 2007. Patients were identified using the hospital computerized data base and toxicology consult charts of the toxicology unit. The incidence of acute renal failure in patients with dipyrone overdose and all other patients was compared. *Results:* Four hundred twenty nine patients were included. Mean age was 8.85+6.65 years. Dipyrone ingestion was reported in 23 (5.3%) cases. The median age of patients with dipyrone ingestion was 15.5 years compared with 6.5 years in all other patients ($p<0.001$). Most patients with dipyrone overdose suffered from minor gastrointestinal symptoms. Within a week following ingestion three patients (13%) with dipyrone overdose suffered from acute renal failure. Only one patient with renal failure was found among 403 patients with other ingestions ($p<0.001$). The renal failure resolved spontaneously in all patients. *Conclusion:* Dipyrone overdose may cause acute renal failure. Renal functions should be monitored in such patients.

240. A Case of Refractory Hypoglycaemia after Consumption of Erectile Dysfunction Drug Adulterated with Glibenclamide

Chan CK, Tse ML.
Hong Kong Poison Information Centre, United Christian Hospital, Hong Kong, China

Objective: We report the clinical course of a patient who presented with refractory hypoglycaemia after consumption of erectile dysfunction drug adulterated with glibenclamide. *Case report:* Since January 2008, there is an epidemic in Hong Kong with patients presenting with refractory hypoglycaemia after using erectile dysfunction drug. The drugs are typically bought over-the-counter (OTC) in Hong Kong or China. Urine analysis detected sildenafil and glibenclamide in all cases. Our patient is a 69 year old gentleman who has no previous history of diabetes mellitus or oral hypoglycaemic agents use. He presented with persistent dizziness and subsequent loss of consciousness at 30 hours after taking a capsule of erectile dysfunction drug bought in China. The blood glucose was 1.4 mmol/L on presentation. Although the ingredients of the drug was unknown, glibenclamide adulterated erectile dysfunction drug induced hypoglycaemia was suspected. The patient regained full consciousness after receiving 40 ml 50% dextrose injection. However the patient developed refractory symptomatic hypoglycaemia despite of repeated boluses and continuous dextrose infusion. Octreotide 50 microgram subcutaneous injection was given every 6 hourly for 36 hours. During octreotide treatment, the dextrose requirement and the frequency of symptomatic hypoglycaemia were reduced. Intravenous dextrose supplement can be stopped after using octreotide for 24 hours. After stopping octreotide, the patient was further observed for 48 hours and remained asymptomatic and euglycaemic. The patient was discharged after 4 days of hospitalization. Laboratory analysis of the remaining drug and patient's urine revealed the present of sildenafil and glibenclamide. *Conclusion:* There are reports of OTC erectile dysfunction drug adulterated by glibenclamide. In patient presented with unexplained hypoglycaemia, it is essential to ask for the use of erectile dysfunction drug in the drug history enquiry.

241. Uvular Angioedema in a Non-Paracetamol Poisoned Patient Treated with N-Acetylcysteine and Physostigmine

Hernandez SH,[1,2] Nelson LS,[1,2] Borke JA,[3] Kim J,[3] Rao R.[1,3]
[1]New York City Poison Control Center; [2]New York University Medical Center; [3]New York-Presbyterian/Weill Cornell Medical Center, New York, US

Objective: Inability to obtain a paracetamol concentration within 8 hours of ingestion is an accepted indication for initiation of therapy prior to confirmatory laboratory values. However, data suggests that low paracetamol concentrations and late presentation increase the risk for anaphylactoid reactions to N-acetylcysteine (NAC).[1,2] We present a case of angioedema following NAC and physostigmine in a patient with a negative paracetamol concentration. *Case report:* A 36-year-old woman was brought to the ED agitated and incoherent. She was found with a bottle of paracetamol with diphenhydramine, an empty bottle of vodka, and a suicide note. Only 18 tablets of 100 remained in the bottle. Vital signs were: BP 187/103 mmHg; pulse 177/min (sinus tachycardia on ECG); respirations 27/min; temperature 37.6C. Physical examination was remarkable for 4 mm reactive pupils, dry mucus membranes, hypoactive bowel sounds, flushed warm skin, and dry axillae. The 21-hour regimen of intravenous NAC was empirically started. She also received 1 mg physostigmine intravenously, which lowered her BP and pulse (160 mmHg systolic and 140 bpm). Her mental status normalized. Approximately 48 minutes after the physostigmine and 70 minutes into her NAC infusion, she complained of throat swelling and had significant uvular edema and hoarseness. She received intravenous methylprednisolone and famotidine, and nebulized racemic epinephrine. Fiberoptic examination noted mild edema of aryepiglottic folds and intubation was performed for airway protection. Laboratory values were significant for a paracetamol concentration <10 umol/L (drawn 16.5 hours after patient's reported time of ingestion), a blood ethanol level of 47 mmol/L and a diphenhydramine positive blood toxicology screen. She was admitted to the MICU for supportive care and extubated the following morning without incident. *Conclusion:* An anaphylactoid reaction developed in association with administration of NAC in the presence of two risk factors: low serum paracetamol concentration and late presentation. The contribution of physostigmine to anaphylactoid reaction in this case is uncertain. 1. Waring WS et al. Lower incidence of anaphylactoid reactions to N-acetylcysteine in patients with high acetaminophen concentrations after overdose. Clin Toxicol 2008;46:496–500. 2. Lynch RM, Robertson R. Anaphylactoid reactions to intravenous N-acetylcysteine: a prospective case controlled study. Accid Emerg Nurs 2004;12:10–15.

242. Lactic Acidosis Associated with Metformin Treatment: A Risk Still Underestimated

Vecchio S,[1] Bigi S,[1] Petrolini V,[1] Lonati D,[1] Giampreti A,[1] Valli A,[2] Rocchi L,[2] Papa P,[2] Locatelli C,[1] Manzo L.[1]
[1]Poison Control Centre and National Toxicology Information Centre, IRCCS Maugeri Foundation and University of Pavia, Pavia; [2]Laboratory of Analytical Toxicology, Clinical Chemistry Service, IRCCS Policlinico San Matteo Foundation, Pavia, Italy

Objective: Metformin is widely used in diabetes mellitus type II. Its plasma increase may cause severe lactic acidosis. The risk is relevant in patients with dehydration, renal failure, severe cardiac or hepatic disease, septicaemia, ingestion of cationic drugs, conditions that themselves can induce the development of lactic acidosis and/or metformin accumulation. To evaluate frequency, characteristics and risk factors in all cases of acute metformin poisoning due to accumulation referred to Pavia Poison Centre (PPC). *Methods:* Cases of acute metformin intoxication referred to PPC between 01/2007-11/2008 were retrospectively analyzed for personal data, co-morbidity and treatments, symptoms preceding admission, metformin plasma levels and blood-gas analysis at admission and during hospitalization, clinical course, treatment and outcome. *Results:* Of 24 patients (8 males, 16 females; mean age 62 ± 12.6), 11 had suffered on previous days from gastroenteric symptoms and general malaise, 5 complained of drowsiness and nausea, 2 had a cerebrovascular accident, one had already been hospitalized for pulmonary oedema and renal failure. All patients displayed severe lactic acidosis and renal failure at admission. Coma or drowsiness was present in 11 patients, hypoglycemia in 4, hypotension, brady-, tachyarrhythmias and shock in 6, and cardiac arrest in 3 cases. Twenty-one patients underwent dialysis or continuous-haemofiltration that successfully reduced metformin levels. Twelve patients needed respiratory support and 4 had cardiac complications during hospitalization. Fourteen had favourable outcome, 7 died (33%), 2 were lost at follow-up. Mean dosage of metformin ranged between 4.6–100 mcg/ml (average 59.6 mcg/ml±32.3 DS; therapeutic levels 0.18–1 mcg/ml). In 2 cases plasma metformin was not determined, while 3 revealed concomitant accumulation of atenolol, digoxin, acenocoumarol. Eight patients had at least one contraindication to metformin prescription (heart, hepatic, renal disease, chronic alcoholism, age over 80, digoxin therapy). *Conclusion:* Metformin poisoning from accumulation is a severe and often lethal complication that must be suspected in diabetic patients with lactic acidosis, renal failure, gastrointestinal symptoms, hypotension, drowsiness. According to the literature, there is no correlation between metformin levels and the severity of lactic acidosis and intoxication. Risks of toxicity from metformin could be reduced by respecting contraindications to its prescription.

243. Tramadol Dispensing Erogator and Poisoning Due to Erroneous Administration

Vecchio S, Petrolini V, Bigi S, Lonati D, Giampreti A, Locatelli C, Manzo L.
Poison Control Centre and National Toxicology Information Centre, IRCCS Maugeri Foundation and University of Pavia, Pavia, Italy

Objective: Tramadol is a centrally-acting opioid analgesic. The most common adverse effects are asthenia, nausea, vomiting, vertigo, constipation, headache and somnolence. Oral solution of Contramal® (tramadol hydrochloride) is marketed in Italy in two different 10% formulations: 10 ml with dropper and, since 01/2002, 30 ml with dispensing erogator (one erogation corresponds to 5 drops). The aim of this study is to evaluate all cases referred to Pavia Poison Centre in order to identify frequency and clinical manifestations of tramadol overdose due to erroneous use of dispensing erogator as if it was a dropper. *Methods:* All cases involving patients erroneously poisoned with tramadol from 01/2002 to 10/2008 were included. Patients were evaluated for history, single or repeated ingested dose, clinical evaluation at ED-admission, time from ingestion, overall management and antidotal therapy. *Results:* 106 cases (61±18 years) were enrolled, representing 26% of all patients with tramadol poisoning. The average number of drops ingested was 99 ± 43 (corresponding to an average of 20 erogations); in 20/106 cases a repeated dose was ingested. Clinical signs and symptoms registered were nausea/vomiting (41/106; 38%), sedation (31/106; 29.5%), asthenia and vertigo (19/106; 18%) and miosis (1/106; 1%). At first evaluation 32/106 (30.5%) were asymptomatic whereas 22/106 (21%) had more than one symptom. The average time between ingestion and first call ranged from 10 minutes to 24 hours. The antidote (naloxone) was administered in 25/106 cases (24%); the outcome was positive for all patients. *Conclusion:* The contemporary presence on the market of the Contramal® new dispensing erogator and the pre-existing drops formulation resulted in many cases of accidental poisoning, especially in older patients. The hypothesized causes of erroneous use could be the lack of medical/pharmacist instruction to the patient concerning proper drug administration, and the similarity of packages and leaflets of both formulations. All cases observed required an ED evaluation. Adverse drug reaction cards have been sent for pharmacovigilance: subsequently, the producer agreed to partially modify the Contramal® leaflet. Poison Control Centres can play a key role in toxicovigilance and in detection of newly emerging poisonings.

244. Anaphylaxis to Ovine Fab-Fragments in a Child Envenomed by European Viper

Petrolini V,[1] Bellini A,[2] Arrica M,[2] Bigi S,[1] Giampreti A,[1] Vecchio S,[1] Lonati D,[1] Locatelli C.[1]
[1]Poison Control Centre and National Toxicology Information Centre, IRCCS Maugeri Foundation and University of Pavia, Pavia; [2]1st Department of Anesthesia and Intensive Care, University Hospital of Parma, Parma, Italy

Objective: Specific Fab-fragments should be used as an antidote in severe European Viper envenomations. Two kind of Fab-fragments (horse- or sheep-derived) are available in Europe. We describe a case of anaphylaxis to ovine Fab-fragments. *Case report:* A thirty-two month-old child was bitten by a viper on his right foot: two typical fang-marks were present, and severe local effects developed in 4–6 hours. Initially, the bitten foot was tender, red and swollen: within 30 hours, the local lesion progressively involved the leg that became swollen and ecchymotic up to the groin. Leukocytosis (16,950/mm^3), neutrophilia (77%) and elevated D-dimer (1,395 ng/ml) were present. An infusion of ViperaTab® (200 mg in 30 minutes) was started. Within ten minutes the child rapidly became diffusely erythematous and started coughing; respiratory stridor, facial angioedema, hypotension and tachycardia appeared, with sudden restlessness and progressive reduction of peripheral oxygen saturation (90%). Fab-fragment infusion was immediately interrupted, and oxygen, intravenous chlorphenamine, hydrocortisone and epinephrine (5 mcg) were administered. Mild anaemia (Hb 10.2 g/dl) and elevated plasma tryptase concentration (58.6 mcg/l) were detected. Intravenous fluid infusion and midazolam were administered, and low-molecular-weight heparin prophylaxis was started. A repeated Doppler-ultrasound study showed no alterations of arterial blood flow. The extension of oedema, swelling and ecchymosis gradually reduced, haemodynamic status improved, plasma D-dimer decreased (588 ng/ml), and hemoglobin concentration began to rise on the fourth day from admission. Five days after the snakebite, the child was discharged home. *Discussion:* The incidence and the severity of adverse reactions to Fab-fragment administration against European vipers are still unknown, even if it is generally believed to be extremely rare. Only a few minor adverse reactions have been reported to equine fragments, whereas no adverse reactions have ever been reported to ovine viper Fab-fragments. This is the first time that an anaphylactic reaction following administration of ovine Fab-fragments (ViperaTab®) is described. Nevertheless, the patient recovered completely. The possibility of anaphylactic reactions, although infrequent, should be considered when evaluating the balance between possible risks and benefits.

245. Multi-System Pharmacosurveillance of Pediatric Nonprescription Cough and Cold Medications: The Role of the National Poison Data System

Green JL, Bronstein AC, Dart RC.
Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, Denver, US

Objective: Pharmacosurveillance of nonprescription drugs is difficult due to the unsupervised use of these products and reliance on spontaneous reporting systems. Multiple data sources are essential to provide independent views of the issue. We used the National Poison Data System (NPDS) as one data source to assess the incidence and root causes of adverse events associated with nonprescription cough and cold medications. *Methods:* A surveillance definition with automated alert capability was established in NPDS to identify each case that fulfilled 3 criteria: 1) age <12 years, 2) medical outcome of moderate effect, major effect, death or death indirect, and 3) exposure to at least one product of interest (brompheniramine, chlorpheniramine, dextromethorphan, diphenhydramine, doxylamine, guaifenesin, phenylephrine, pseudoephedrine). Any product with at least one of the active ingredients of interest as listed in the Micromedex (Thomson Reuters) products database was included. Generic codes were not used due to the limitations with mapping of products to generic codes. An email is generated for each case meeting these criteria and sent to AAPCC. The case record including notes for that case is requested from the poison center (PC) involved. These records are then evaluated by an independent expert panel to evaluate causal relationship to the exposure and root cause analysis. Quarterly results of this program are submitted to the US Food and Drug Administration (FDA). *Results:* 212 cases were detected from 31 July through 31 October 2008 from 54 US PCs. Eight cases were excluded after updates to the case changed eligibility; 3 were downgraded to minor effect, 2 initially reported incorrect age, 1 was deleted, 1 was a confirmed nonexposure and 1 involved *in utero* exposure. The current PC participation rate (74%) is expected to increase as pending institutional review board applications are approved. Overall, records for 71% of detected cases have been submitted by PCs with an average turnaround time of 9 days from identification by NPDS to receipt of the case. *Conclusion:* NPDS is a valuable real-time system used to detect cough/cold medication exposures in children. There are many potential applications for this surveillance methodology using NPDS.

246. A Case of Compartment Syndrome Associated with Massive Ingestion of Diphenhydramine

Vearrier DJ, Curtis JA.
Department of Emergency Medicine, Drexel University College of Medicine, Philadelphia, US

Objective: Antihistamines are often implicated in both intentional and unintentional exposures. Rhabdomyolysis is a rare effect of antihistamine overdose, but has been reported several times in the medical literature. To our knowledge compartment syndrome has never been reported following antihistamine ingestion. *Case report:* We report the case of a 28 year-old female who presented complaining of bilateral leg swelling, skin mottling, and pain nine hours after ingesting 1.45 grams of diphenhydramine a in a suicide attempt. Initial laboratory studies were notable for phosphorus of 7.2 mg/dL, an ethanol level of 42.4 mg/dL, and a creatine kinase of 106,050 U/L. Urinalysis was significant for 4 + blood, and 5–10 red cells/hpf. Urine drug screening was negative and coagulation studies, salicylate level, and acetaminophen level were all within normal limits. Treatment was initiated with isotonic fluid. Seven hours after arrival the creatine kinase level had increased to 200,197 U/L. Fifteen hours after arrival, the patient developed bilateral lower extremity compartment syndromes that required a left thigh fasciotomy and bilateral leg fasciotomies. The creatine kinase level peaked at 233,900 U/L 21 hours after the patient's arrival. Serial serum urea and creatinine remained at baseline values. *Conclusion:* The mechanism of antihistamine induced rhabdomyolysis is unclear, but may be related to a direct toxic effect on skeletal muscle. In this case, there was no history of injury, hyperthermia, seizures or prolonged immobility that would explain the elevation of serum creatine kinase. In this case, muscle damage was severe enough to require fasciotomies for elevated compartment pressures. Clinicians should be aware of the risk of rhabdomyolysis and compartment syndrome in massive diphenhydramine overdose. *References:* 1. Frankel D, Dolgin J, Murray BM. Non-traumatic rhabdomyolysis complicating antihistamine overdose. J Toxicol Clin Toxicol 1993; 31:493–496. 2. Emadian SM, Caravati EM, Herr RD. Rhabdomyolysis: A rare adverse effect of diphenhydramine overdose. Am J Emerg Med 1996; 14:574–576. 3. Stucka KR, Mycyk MB, Leikin JB, et al. Rhabdomyolysis associated with unintentional antihistamine overdose in a child. Pediatr Emerg Care 2003; 19:25–26.

247. Low Dose Phenazopyridine-Induced Acute Renal Failure

Young AC,[1] Kleinschmidt KC,[1] Wax PM,[1] Goto CG.[2]
[1]Department of Emergency Medicine, University of Texas Southwestern Medical Centre; [2]Department of Pediatrics, University of Texas Southwestern Medical Centre, Dallas, US

Objective: Phenazopyridine-induced acute renal failure (ARF) has been rarely reported in the absence of methemoglobinemia. We report a case of phenazopyridine-induced ARF without methemoglobinemia. In addition, this case reflects the lowest dose of phenazopyridine associated with ARF. *Case report:* A 16-year-old male developed ARF two days after ingesting 6 tablets (570 mg) of Azo-Standard 95 mg. He presented with vomiting, abdominal pain, body aches, and anuria. The phenazopyridine was taken to interfere with urine drug testing for ecstasy used 5 days previously. He had a history of depression treated with escitalopram and risperidone. Initial vital signs: BP 140/91 mmHg; RR 18/min; HR 63/min, T 36.6°C, weight 59 kg. Physical findings were unremarkable. BUN was 36 mg/dL and creatinine 8.3 mg/dL. CBC, electrolytes, and liver function tests were normal. Methemoglobin was 0.9%. CK peaked at 406 U/L. FeNa was greater than 8.5%.

A standard urine drug screen (UDS) was negative while a comprehensive UDS was positive for nicotine, citalopram, lidocaine, acetaminophen, and bupivicaine. The serum phenazopyridine level was undetectable 3 days after ingestion. A renal sonogram showed normal size kidneys with echogenic parenchyma. Renal biopsy revealed acute tubular necrosis. On hospital day 2, he was started on a nicardipine infusion for worsening hypertension. On hospital day 3, the first of 3 rounds of hemodialysis was initiated for worsening renal function (creatinine 10.7 mg/dL). Over the next 8 days, the creatinine decreased to 1.4 mg/dL. Two weeks later, the patient had normal renal function but persistent hypertension responsive to amlodipine. *Conclusion:* We report the lowest dose of phenazopyridine associated with ARF. The absence of methemoglobinemia suggests that phenazopyridine-induced ARF is caused by direct tubular toxicity. The undetectable serum phenazopyridine level, due to rapid metabolism, is consistent with prior studies. Acetaminophen, a metabolite, was detected in his comprehensive urine drug screen. The patient reported no prior use of acetaminophen. This case suggests phenazopyridine and its metabolites caused ARF.

248. Toxicity Profile of Varenicline: A 15-Month Study from the French Poison and Toxicovigilance Centres

Saviuc P,[1] Garnier R,[2] Aymard I,[3] Castot A,[4] National Coordination Committee for Toxicovigilance.[5]
[1]Toxicovigilance Centre, University Hospitals, Grenoble; [2]Poison and Toxicovigilance Centre, University Hospitals, Paris; [3]Poison and Toxicovigilance Centre, University Hospitals, Marseille; [4]French Health Products Safety (AFSSAPS), Saint Denis; [5]French Institute for Public Health Surveillance (InVS), Saint Maurice, France

Varenicline is a new molecule used in smoking cessation. It is suspected that it increases depressed mood risk and suicidal thoughts. The French health products safety agency (AFSSAPS) asked the French committee of toxicovigilance to assess its toxicity profile. *Objective:* To collect varenicline poisonings from the French poison and toxicovigilance centres (CAPTV) database. *Methods:* From February 1st, 2007 (date of marketing in France) to April 15th, 2008, cases involving varenicline were collected. Co-ingested drugs, circumstances of exposure, age, estimated ingested dose (EID) and symptoms were recorded. *Results:* 97 files were collected; 83 cases were related to an exposure of which 47 were symptomatic. The patients were classified into the following exposure circumstances: i) 32 accidental exposures, 20 were asymptomatic (17 children; EID 0.25–3 mg). 12 cases were symptomatic: 10 children (1.5–7 years) presented with pallor, nausea, vomiting, drowsiness, clouded mental state, nightmares or excitation (EID 0.5–3 mg); 2 adults (40 and 44 years) felt faint and presented with tremor (EID 1 mg); ii) 9 suicide attempts: 3 patients were asymptomatic (EID 15–20 tablets of 0.5 or 1 mg); 3 ingested only varenicline and presented with low blood pressure, fear/anxiety, nausea or vomiting (EID 6–40 mg); in the other cases, co-ingested drugs could explain all the symptoms; iii) 18 treatment errors: 12 were asymptomatic (maximal EID 3 mg); 4 adults presented with nausea, headache, dizziness, sleep disorders and palpitations (EID 1 mg); 1 patient (37 years) had precordial pain (unknown EID); in the last case, associated drugs could explain the symptoms; iv) 24 adverse effects with therapeutic dose: most of the signs were well-known side effects. Four subjects reported suicidal thoughts or attempted suicide; 3 other patients presented signs following cessation of varenicline use: in 2 cases, a withdrawal syndrome was suspected (nausea, vomiting, abdominal pain or dizziness). *Conclusion:* Although our series is small, with few overdoses, suicide attempts of patients treated with varenicline and possible cases of withdrawal syndrome were shown. The acute toxicity of varenicline remains to be extensively studied. Thus, the surveillance of varenicline poisonings must and will be maintained.

249. Acute Toxicity of Schedule II Analgesics: Is Propoxyphene a Drug with an Unfavourable Risk-Benefit Profile?

Saviuc P,[1] Garnier R,[2] Manel J,[3] Harry P,[4] Boutron C-M.[5]
[1]Centre de Toxicovigilance, CHU, Grenoble; [2]Centre Antipoison et de Toxicovigilance, Hôpital Fernand Widal, Paris; [3]Centre Antipoison et de Toxicovigilance, CHU, Nancy; [4]Centre Antipoison et de Toxicovigilance, CHU, Angers; [5]Agence Française de Sécurité Sanitaire des Produits de Santé, Saint Denis, France

Objective: The safety profile of d-propoxyphene (DPP) has been questioned in the United Kingdom (UK) and Sweden. The French Health Products Safety Agency (AFSSAPS) requested the French committee of toxicovigilance to assess DPP safety profile in poisoning conditions. To compare the risks of poisonings with DPP, tramadol (TRA) and codeine (COD), data collected between 2000 and 2005 in the French PCC information system were analysed. *Methods:* Case definition was a poisoning in which DXP, TRA or COD was involved. Fatal and serious (seizures or severe respiratory or cardiovascular complication) cases were collected. Results were adjusted on sales data. As acetaminophen was present in some drugs (limited to 8 grams per package in France), the number of treatments per month and not the numbers of distributed packages was considered. *Results:* Among 1,098,755 poisonings, 16,217 cases involved DPP, TRA or COD (respectively 9,768, 2,854 and 3,595): 58 had a fatal outcome (35, 13 and 10), 92 described seizures (26, 62 and 4), 169 respiratory (77, 63 and 29) or 342 cardiovascular complications (180, 90 and 72). Results adjusted on sales data are summarized in table I. *Conclusion:* The higher risk of death reported with DPP in Sweden and UK was not confirmed in these French series. Lower accessibility to DPP and its association with acetaminophen (limiting the amount of DPP per box in France) are possible explanations. In spite of some methodological limitations, this study showed that, compared to other available step II analgesics, DPP was associated neither with more poisonings nor more severe poisoning.

250. Toxicity Profile of Rimonabant: A 12-Month Study from the French Poison and Toxicovigilance Centres

Saviuc P,[1] Garnier R,[2] Lagarce L,[3] Pulce C,[4] Castot A,[5] National Coordination Committee for Toxicovigilance.[6]
[1]Toxicovigilance Centre, University Hospitals, Grenoble; [2]Poison and Toxicovigilance Centre, University Hospitals, Paris; [3]Poison and Toxicovigilance Centre, University Hospitals, Angers; [4]Poison and Toxicovigilance Centre, University Hospitals, Lyon; [5]French Health Products Safety (AFSSAPS), Saint Denis; [6]French Institute for Public Health Surveillance (InVS), Saint Maurice, France

Objective: Rimonabant, a selective inhibitor of the cannabinoid receptors, has been marketed in France since March 29th, 2007 for obesity treatment. Most side effects are neuropsychic disorders (depression, suicide attempt). The French health products safety agency asked the French Committee of Toxicovigilance to assess its toxicity profile. *Methods:* All poisoning cases involving rimonabant reported to the French poison and toxicovigilance centres from April 1st, 2007 to April 15th, 2008 were analyzed. Associations with other drugs, circumstances of exposure, age, estimated ingested dose (EID) and symptoms were recorded. *Results:* 36 files were collected; 29 were related to an exposure, among which 20 were symptomatic: i) the only suicide attempt with rimonabant alone was asymptomatic; ii) 4 accidental exposures involved children: in one case, co-ingested drugs could explain all the symptoms; one presented with vomiting (EID 10 mg) and another one with drowsiness and clouded mental state (EID 80 mg); a 10-month-old boy had several brief episodes of pallor, tremor of the lips and clonic contractions of the chin between the 4th and the 7th hour after ingestion (EID 10 mg); iii) 3 treatment errors involved 50–70 year-old patients who presented with nausea, headache, dizziness, loss of memory, tremors, tinnitus, confusion or asthenia (EID 40–60 mg); iv) 8 cases had adverse effects at a therapeutic dose (20 mg); they were 30–69 year-old patients with vomiting, abdominal pain, fainting, dizziness, headache, fear, tremors, sleep disorders, loss of consciousness or myalgia. *Conclusion:* Only a small series of cases was reported and this study does not produce any new information on rimonabant toxicity. The only noticeable case involved a 10-month-old boy who presented with seizures following rimonabant ingestion. During the same period, no suicide attempt was reported in the Periodic Safety Update Reports (June, 2006 - December, 2007); in these documents, only 15 cases of poisoning were recorded; seizures were also observed in one of them, concerning a 23-month-old epileptic who presented with seizure and coma (EID 160 mg). Seizures were also observed during clinical trials and experimental studies. In the end, rimonabant has been banned in European countries since October 23rd, 2008 because of a proven suicidal risk.

Table I. Numbers of poisoning cases, deadly cases, cases with seizures, respiratory or cardiovascular complications per 1,000,000 treatment months

	Poisoning	Death	Seizures	Respiratory complications	Cardiovascular complications
COD	328.3	0.91	0.37	2.65	6.58
DPP	162.7	0.58	0.43	1.28	3.00
TRA	167.8	0.76	3.64	3.70	5.29

251. Aminophylline for Adenosine-Induced Asystole: A New Use for an Obsolete Drug

Kirrane BM,[1] Hoffman RS.[2]
[1]Department of Surgery, Yale University School of Medicine, New Haven; [2]Division of Medical Toxicology, NYU School of Medicine, New York, US

Objective: Adenosine is a naturally occurring nucleoside which causes receptor mediated effects, such as enhanced outward K^+ flux, shortened atrial refractory times, and shorter action potentials. Adenosine stress tests are often used as an alternative to exercise stress tests in sedentary patients, due to adenosine's vasodilatory properties on coronary arteries.[1]. Adenosine is metabolized through adenosine deaminase, which is inhibited by carbamazepine and dipyridamole. Methyxanthanines, (caffeine, theophylline) are similar in structure to adenosine, and consequently block its receptor. Aminophylline attenuates coronary hemodynamic effects when given to patients undergoing adenosine stress test.[2] However, its effectiveness in treating adenosine toxicity is unknown. We present a case of severe bradycardia and hypotension that occurred during an adenosine stress test in a patient taking dipyramidole which was successfully treated with atropine and aminophylline. *Case report:* A 71 year old man with a history of cardiac transplant (1996), CVA, and hypertension presented for an adenosine stress test. Medications included diltiazem, mycophenolate mofetil, cyclosporine, simvastatin and Aggrenox (aspirin/extended release dipyramidole). Vitals signs on presentation were: BP, 110/80 mmHg; pulse, 90/min; respirations, 16/min; temperature, 37C. Shortly following administration of the adenosine infusion (10 mg/min) the patient became altered, hypotensive (60/40 mm Hg) and bradycardic (30/min), with both a second and third degree heart block noted, followed by 5–6 seconds of asystole. He was treated with oxygen, IV fluids, atropine (1mg) x 2 doses, and IV aminophylline 50 mg. His vital signs returned to normal, and he was transferred to

the ER with no further return of symptoms. He was monitored for 24 hours, and discharged with no further incident. *Conclusion:* Medication reconciliation failed to identify a potential dipyramidole-adenosine interaction because a trade-name of a combination drug was used. This is the first known reported case of aminophylline, an adenosine receptor antagonist, being used for prolonged adenosine toxicity. Further prospective study is needed to confirm its utility. *References:* 1. Wilson R, Wyche K, Christensen BV, et al. Effects of adenosine on human coronary arterial circulation. Circulation 1990; 82:1595–1606. 2. Nahser PJ, Brown RE, Oskarsson H, et al. The effect of aminophylline on pharmacological stress with intravenous adenosine. Am J Cad Imaging 1996; 10:149–153.

252. Dystonia and Myocardial Infarction Secondary to Sertaline Use

Eleftheriou G,[1] Butera R,[1,2] Faraoni L,[1] Lorenzi F,[1] Carrara M,[1] Bacis G,[1] Manzo L.[2]
[1]Bergamo Poison Control Center, Ospedali Riuniti, Bergamo; [2]Poison Control Center, IRCCS Maugeri Foundation and University of Pavia, Pavia, Italy

Objective: Sertraline is one of the most common antidepressants and it is generally well tolerated. Dystonia can occur during selective serotonin reuptake inhibitor treatment; coronary spasm has been described once.[1] We report a case of acute dystonia induced by sertraline, complicated by myocardial infarction. *Case report:* An 83-year-old woman developed acute mandibular dystonia after taking the third dose of sertraline, 25 mg. Other medication included lorazepam 2.5 mg, oxazepam 30 mg and triazolam 0.125 mg daily. Dystonia worsened over the subsequent nine days. The psychiatrist, in spite of the clinical picture, increased the dose to 50 mg. On the 12th day after the first sertraline administration, oculogyric crisis, oromandibular dystonia, limb dystonia and drowsiness ensued. On the 13th day the patient was admitted in our hospital, unable to follow simple commands. Cerebral CT scan was negative for intracranial hemorrhage or ischemia, EEG normal for the patient's age. EKG revealed ST elevation into inferior-lateral heart wall, with increased troponin levels (9.27 ng/ml, normal values up to 0.07 ng/ml). A transthoracic echocardiogram revealed a reduction of the ejection fraction to 40%. The initial hypothesis of serotonin syndrome was excluded by normal CK levels and the absence of fever. Thrombolytic treatment begun soon after the admission; diazepam 10 mg infusion did not relieve the dystonic reaction, which resolved spontaneously 2 days after admission. Sertraline levels were 50 ng/ml (normal range 50–200 ng/ml) 48 hours after the last administration. The patient died 8 days later in septic shock. *Conclusion:* SSRIs are the drugs of choice in the management of depression after myocardial infarction (MI), since they reduce platelet activation via platelet serotonin depletion;[2] moreover, MI is not described during sertraline therapy. However, it has been postulated that in patients with atherosclerotic coronary arteries sertraline can induce vasoconstriction due to endothelial dysfunction.[1] In the case reported here, prolonged sertraline-induced vasoconstriction may have resulted in the observed myocardial infarction. *References:* 1. Sunderji R, Press N, Amin H, Gin K. Unstable angina associated with sertraline. Can J Cardiol 1997; 13:849–851. 2. Schlienger RG, Meier CR. Effect of selective serotonin reuptake inhibitors on platelet activation: can they prevent acute myocardial infarction? Am J Cardiovasc Drugs 2003; 3:149–162.

253. Torsade de Pointes Presenting as New-Onset Seizure in a Methadone Maintenance Patient

Lugassy DM,[1,2] Nelson LS,[1,2] Hoffman RS,[1,2] Howland MA.[1,2,3]
[1]New York City Poison Control Center; [2]New York University Medical School; [3]St. John's University College of Pharmacy and Allied Health Professions, New York, US

Objective: Methadone prolongs the QTc, which can lead to life-threatening torsade de pointes (TdP). We present a patient on daily methadone who developed TdP which was misinterpreted as a new-onset seizure. *Case report:* A 40 year-old man presented to the ER complaining of palpitations, dizziness, and two "seizures." He had a history of hepatitis C and cirrhosis and was taking furosemide 40 mg daily. He was also on methadone 90 mg/day for opioid addiction, which was increased from 80 mg/day one month prior. The cardiac monitor demonstrated multiple episodes of non-sustained ventricular tachycardia (VT) and TdP. A 12-lead ECG showed a prolonged QTc of 700 ms. An ECG done on admission for cirrhosis 2 months earlier showed a QTc of 521 ms. IV magnesium terminated the TdP, but short runs of non-sustained VT persisted. Pertinent initial laboratory findings: potassium 2.9 mmol/L, total calcium 1.85 mmol/L, magnesium 0.8 mmol/L, creatinine 0.071 mmol/L, AST 37 IU/L; ALT 152 IU/L, albumin 15 g/L. Potassium was supplemented in the ER, and he was admitted to the CCU. Methadone was discontinued on this admission and after normalization of all electrolytes his dysrhythmias abated, but his QTc remained abnormal until hospital day seven. Interestingly, he was seen in the same ED one week earlier with two "witnessed seizures" and was diagnosed with new-onset seizure disorder and discharged on levetiracetam. An ECG was not performed at that time. Methadone's dose-dependent prolongation of QTc can be exacerbated by hypokalemia, and increased serum concentrations can result from hepatic dysfunction.[1] *Conclusion:* Cardiovascular causes of syncope can mimic seizures. TdP likely resulted from an increase in methadone dose, impaired methadone metabolism, and concomitant electrolyte abnormalities. This patient had several well recognized risk factors of methadone associated TdP, but failure to appreciate their significance lead to this adverse drug event. *References:* 1. Justo D, Gal-Oz A, Paran Y, et al. Methadone-associated Torsades de Pointes (polymorphic ventricular tachycardia) in opioid-dependent patients. Addiction 2006; 101:1333–1338.

254. Lidocaine Toxicity in a 48 Year-Old Female Undergoing Outpatient Liposuction

Haggerty DA, Bailey H, Greenberg MI.
Department of Emergency Medicine, Drexel University College of Medicine, Philadelphia, US

Objective: Lidocaine is an amide-containing local anesthetic used extensively throughout clinical medical practice, both as an anesthetic and anti-arrhythmic. While traditional guidelines have stated that toxicity of lidocaine with epinephrine occurs at levels of 7 mg/kg, newer tumescent solutions used commonly in outpatient liposuction procedures employ much higher dosages of low concentration (<0.5%) lidocaine. Such high dose solutions are generally accepted as safe within the plastic surgical community, even though lidocaine dosing often varies between 35–90 mg/kg. *Case report:* We present a case of a 48 year-old female who underwent outpatient liposuction with such a tumescent solution and subsequently developed status epilepticus, respiratory collapse, and cardiac arrest. Testing of serum lidocaine levels revealed a concentration of 14.7 mcg/ml, well beyond established therapeutic ranges. *Conclusion:* This case illustrates the dangers associated with high-dose tumescent lidocaine solutions. *References:* 1. Klein JA. Anesthesia for liposuction in dermatologic surgery. J Dermatol Surg Oncol 1988; 14:1124–1132. 2. Brown DL, Skiendzielewski JJ. Lidocaine toxicity. Ann Emerg Med 1980; 9:627–629.

255. Nitrofurantoin Induced Hepatitis and N-Acetylcysteine Therapy

Murphy CM,[1] Murphy GS,[1] Whitlow KS.[2]
[1]Department of Emergency Medicine, Virginia Commonwealth University School of Medicine; [2]Virginia Poison Center/Department of Emergency Medicine, Virginia Commonwealth University School of Medicine, Richmond, US

Objective: Propose N-acetylcysteine (NAC) therapy, steroids and drug cessation to return to normal liver function in healthy patients with uncommon nitrofurantoin induced liver injury. *Case report:* A 38 y/o pharmacist presented with five days of gastrointestinal upset. The patient's only medication was nitrofurantoin three times weekly for urinary tract infection prophylaxis. This was discontinued at onset of symptoms. No other history was reported. During initial evaluation, liver enzymes were AST of 1507/ALT of 1638. A CT scan demonstrated dilated intrahepatic ducts and splenomegaly. Three days later scleral icterus and jaundice developed. A referral to a private hepatologist occurred and a transjugular hepatic biopsy demonstrated submassive hepatic necrosis involving 80% of sample. Additional testing was negative. The patient's AST/ALT continued to rise, peaking at 2325/2053. Another referral to a hepatology clinic at an academic medical center followed. Upon presentation, the patient was admitted for inpatient care. On admission, the patient was icteric, jaundiced, awake, alert and oriented. No asterixis was noted and AST/ALT were 1423/1700. The INR was 2.4 and ammonia was 47. A toxicology consult was obtained. A detailed exposure history was negative except for chronic nitrofurantoin ingestion. Toxicology recommended intravenous NAC and steroids. The AST/ALT rapidly improved after institution of NAC and steroids. On hospital day six, the patient became disoriented with an ammonia level of 160. Rifaxamin therapy was initiated and the patient was placed in the intensive care unit. An ultrasound found marked liver heterogenicity, dilatation of main portal vein with appropriate flow, and no focal lesions. An MRI demonstrated cirrhosis with portal hypertension and altered enhancement. Twenty-four hours later, the symptoms resolved and the patient was transferred to the floor within 48 hours. The INR and AST/ALT improved during hospital course. Discharge occurred on hospital day 13. During the six months following discharge, the patient's liver enzymes have continued to trend downward. *Conclusion:* Nitrofurantoin is an uncommon cause of hepatic injury. Chronic use in healthy patients may be a factor in eliciting such injury. Early initiation of NAC, steroids, exposure cessation and symptomatic/supportive care may improve liver injury therefore decreasing morbidity, and associated health care costs.

256. Childhood Lead Poisoning Screening in the Paris Area: 1992–2006

Nikolova N,[1] Villa A,[1] Guyodo G,[1] Carre N,[2] Garnier R.[1]
[1]Poison Center, Fernand Widal Hospital, Paris; [2]Paris area interregional epidemiological cell, Paris, France

Introduction: Childhood lead poisoning was rediscovered in France in the 1980s with the diagnosis of several cases of severe lead poisoning due to ingestion of lead-based paint from old buildings. Lead poisoning screening was organized progressively and the Regional Childhood Lead Poisoning Surveillance System for the Paris Area (SSSIILF) was created in 1992 in order to record and describe screened children, and assess blood lead screening and lead poisoning management strategies. The National Childhood Lead Poisoning Surveillance System (SNSPE), based on the regional system in the Paris area, was created in 1995. The purpose of this study is to describe blood lead screening in children in the Paris area since 1992. *Methods:* Data from the Regional Childhood Lead Poisoning Surveillance System for the Paris Area were used. In France, clinicians prescribing a blood lead test for a person younger than 18 must fill out a standardized questionnaire. The data collected concerns the child, the blood lead level and the risk factors for lead exposure. *Results and discussion:* Blood lead screening in children in the Paris area (about 60% of the blood lead screening activity in France) remained relatively stable between 1992 and 2001 (an average of 2,421 children per year), but clearly increased during 2002–2004 (6,820 children in 2004) and then decreased (4,748 children in 2006). The geographic distribution in the area was very heterogeneous. Clinicians most commonly prescribing blood lead testing were physicians from Mother and Child Welfare and hospital physicians, with a greater proportion of general practitioners over recent years. Most children were younger than 6 (mainly between 1 and 3

years old). The presence of lead-based paint in buildings built before 1949 was the main reason for screening. The incidence of lead poisoning (blood lead level ≥ 100 micrograms/l) decreased considerably between 1992 (1,131 children) and 2006 (247 children).

257. Metals Urinary Excretion Following Acute Liver Failure

Hantson P,[1] Haufroid V,[2] Hoet P.[2]
[1]Department of Intensive Care, Cliniques St-Luc, Brussels; [2]Laboratory of Industrial Toxicology, Université catholique de Louvain, Brussels, Belgium

Objective: To investigate the urinary excretion of some metals in non professionally exposed patients presenting acute liver failure (ALF) from toxic and non toxic origin. *Methods:* Inclusion criteria were: age greater than 18-yr, acute liver failure defined as a rapid elevation of ASAT and ALAT, with a peak value higher than 1000 IU/l within less than 48 hours after disease onset and a rise in prothrombin time (INR > 2). All etiologies for ALF were considered. Acute renal failure (ARF) was defined according to the RIFLE criteria. Thirty-three consecutive ICU patients (pts) were enrolled. The most common cause of ALF was ischemia/hypoxia (n = 21) due to either septic shock (8), hemorrhagic shock (6), cardiogenic shock (1), eclampsia (1), ischemia-reperfusion syndrome after liver transplantation (4). Among the toxic causes (n=12), suicidal paracetamol ingestion was noted in 2 cases, unintentional overdose or adverse reactions to therapeutic doses of paracetamol in 9 cases, and amanita poisoning in one case. Urine was collected over the first 24 hr following admission for the determination of Al, Sb, Pb, Cu, Zn, Cd, Ba, Mn. The variables analysed were: age, pre-existing liver disease, smoking habits, etiology of ALF, presence of ARF, encephalopathy and outcome. Statistical analysis was performed using the Kruskall Wallis test. *Results:* In comparison with reference values for a non professionally exposed population, Al excretion was increased in 27 pts (50-fold in 3 patients, 10-fold in 8 patients). Zn and Cu excretion increased in the majority of patients (with a 100-fold ratio for Cu in 3 patients). No significant change was observed for Pb, but was for Ba and Sb in some individuals. Cd excretion was high in all except 2 patients. No correlation was found between the type and amount of metals excreted and the different variables. *Conclusion:* Some individuals are presenting significant metals urinary excretion following ALF. However, in case of associated multiple organ failure, other organs are probably also responsible for metals release. The influence of metals release on clinical outcome is unknown as the prognosis is mainly related to the severity of ALF.

258. Subcutaneous Injection of Elemental Mercury: A Case Report with Blood and Urine Levels During Therapy

Seidel C.
PCC Bonn, Children's University Hospital, Bonn, Germany

Objective: It is well known that intravenous, subcutaneous or intramuscular injection of mercury may result in granuloma formation which need surgical removal. The need for chelation in an asymptomatic patient is debated, chelation is recommended in symptomatic patients. *Case report:* A healthy young woman injected elemental mercury in the soft tissue of her cleavage in order to escape from a forced marriage. She presented herself three months later with considerable granulomas in her cleavage. First x-ray showed multiple radio dense punctate lesions. The lateral x-ray two weeks after the surgical excision revealed just a few mercury globules left. Urine levels were 219 µg/l (n: 50 µg/l, BAT: 200 µg/l) before the excision and rose to 558 µg/l afterwards. She started to complain about headache and concentration difficulties. For that reason she was started on chelation therapy with DMPS which she was taking irregularly because of gastrointestinal disturbances. Urine levels continued to be elevated (250–280 µg/l) over the next 9 months. When urine level fell to 160 µg/l and blood level fell to a normal value (11.5 n: 5–20 µg/l) DMPS was stopped. Next control 4 weeks later showed elevated level (urine 308 µg/l, blood 109 µg/l) again. A second surgical excision was done. Afterwards no radiodense elements were seen on the x-ray. Urine-levels rose from 308 to 390, but blood levels fell continuously down to normal values. The patient was lost to follow up three months later. She had announced the intention to flee. *Conclusion:* In case of a subcutaneous injection of elemental mercury complete and extensive surgical removal is essential even in a cosmetically difficult area such as the décolleté. Rising urine levels and falling blood levels are the signs of complete removal. We assume that she fled because she did not have any more health problems.

259. Interest of Late and Prolonged Treatment by Prussian Blue in Acute Thallium Poisoning

Villa AF,[1] Poupon J,[2] Catanese V,[3] El Balkhi S,[2] Nikolova N,[1] Dupont A,[3] Garnier R.[1]
[1]Poison Center, Fernand Widal Hospital; [2]Toxicological Laboratory, Fernand Widal Hospital, Paris; [3]Critical Care Unit, Fontainebleau Hospital, Fontainebleau, France

Case report: A 45-year-old man with no medical history was hospitalized on 2/22/2008 with peripheral neuropathy and paresthesia of the extremities of all 4 limbs for 2 days. Clinical examination revealed an erythematous papular rash on the face and folliculitis on the lower limbs associated with hyperesthesia of the feet and hands. Electromyogram showed severe polyneuropathy. The patient had a cardiac arrest on 3/2/2008 followed by post-anoxic coma. This patient worked in a technical crystals factory and handled thallium, bromide, cesium, and iodide. On 22 March, urinary thallium concentration determined by Electrothermal Atomic Absorption Spectrometry (ETAAS) was very high: 5118 micrograms/g of creatinine. After calling the poison center, despite the late diagnosis, treatment with Prussian blue (Radiogardase®) was initiated on 4 April 2008 until 28 April 2008 at a dosage of 6 g three times daily. Urinary thallium concentrations decreased from 1333 micrograms/g of creatinine to 166 micrograms/g of creatinine. After evaluation of the efficacy of treatment, another course was administered from 20 June 2008 to 20 July 2008, when the patient died. Urinary thallium concentrations decreased from 86 micrograms/g of creatinine to 3 micrograms/g of creatinine. The slopes of urinary thallium excretion curves (log-transformed data) during the 3 phases (1st course, discontinuation of treatment, second course) were - 0.0640, - 0.0063 and –0.0470, respectively, indicating a marked reduction of urinary thallium excretion with Prussian blue. *Conclusion:* We report a case of acute thallium poisoning with late diagnosis and treatment (more than one month after the poisoning). Urinary thallium excretion was decreased tenfold and sevenfold during the 2 courses of treatment. This finding is concordant with the case reported by Kamerbeek et al.,[1] in which a sevenfold increase of fecal thallium excretion was observed. *References:* 1. Kamerbeek HH, Rauws AG, ten Ham M, et al. Prussian blue in therapy of thallotoxicosis. An experimental and clinical investigation. Acta Med Scand 1971; 189:321–324.

260. Analysis of Calls Concerning Mercury-Containing Measuring Devices to UK National Poisons Information Service

Dyke N, Cooper GA, Thompson JP.
National Poisons Information Service (Cardiff), University Hospital Llandough, Cardiff, UK

Objective: The European commission has proposed a directive amendment to restrict the sales of mercury in all clinical thermometers and in other, new, measuring devices to the general public. This is anticipated to reduce the impact on the environment and therefore reduce toxicity to humans and wildlife both acutely and in the long-term. In the UK this will come into effect on 3rd April 2009 as an amendment to the Controls on Dangerous Substances and Preparations Regulations. In light of this, a retrospective study to determine the percentage of mercury related calls due to these measuring devices was undertaken. *Methods:* Calls to the National Poisons Information Service (NPIS) from 1 January 2007 to 31st December 2007 concerning mercury were examined and the percentage of calls relating to thermometer, sphygmomanometer and barometer analysed as well as other calls concerning mercury. The calls were also assessed to determine 1) how many of these calls needed advice on disposal indicating that a spill had occurred or 2) how many needed referral to hospital. *Results:* There were 132 calls involving mercury; the majority of calls were regarding thermometers, 87 (67%). Barometers accounted for 6 (5%) and sphygmomanometers 4 (3%) of calls, therefore calls concerning all mercury-containing measuring devices implicated in the directive change accounted for 97 (75%) mercury calls. 48 (50%) of calls regarding measuring devices required advice on clean-up due to spillage. Only one call regarding a thermometer resulted in advice to attend A&E because of respiratory symptoms after inhalation. *Conclusion:* Calls regarding measuring devices containing mercury accounted for the vast majority of all mercury calls with clinical thermometers being the principal enquiry. Half of these calls needed advice on clean-up of a spillage, indicating potential loss of mercury into the environment. The proposed directive may decrease public exposure from elemental mercury, decrease public exposure and environmental impact and decrease enquiries to the NPIS. *References:* Directive 2007/51/EEC of the European parliament, 2007. Controls on Dangerous Substances and Preparations Regulations (S.I.2006 No. 3311) Schedule I, 2006.

261. Acute Poisonings in Geriatric Patients in Bulgaria

Stankova E,[1] Hubenova A,[1] Mechkarska B.[2]
[1]Toxicology Clinic, Emergency Medicine Hospital Pirogov, Sofia, Bulgaria; [2]Sector for toxico-chemical analysis and control, Emergency Medicine Institute Pirogov, Sofia, Bulgaria

Introduction: Aging is becoming an important feature of modern society worldwide. Bulgaria is among the countries with the most rapidly aging population. Elderly patients (people over 60 years of age) represent a distinctive group of toxicological patients that needs separate attention. *Objective:* To study the clinico-epidemiological characteristic of acute poisonings in patients over 60 years of age based on the data of Toxicology Clinic, Sofia for the period 1992–2003. *Methods:* Retrospective and prospective studies were done. Research focused on particularities of acute intoxication in these patients according to age and sex distribution, types of poison, causes for and severity of poisonings, clinical course, outcome and complications, concomitant disease. The collected data were analyzed using statistical programs for data processing. *Results:* 1551 patients were studied: 691 men (45%) and 860 women (55%). A control group of 478 patients (18 – 60 years) was used. We define five age-subgroups: I – 60–64 years; II – 65–69 years; III – 70–74 years; IV – 75–79 years and V – over 80 years. Frequency of acute poisonings over 60 is low - 7.7%, but has an increasing trend throughout the years, both in absolute and relative number of poisonings. We observed prevalence of poisonings amongst females; suicidal poisonings (54%); upward tendency of accidental poisonings (especially in the group above 80); poisonings with medicines; high incidence of cardiovascular diseases as concomitant diseases; higher level of depression amongst elderly. Severity of poisoning, complications and outcome shows statistically significant correlations. Clinical symptoms have specificity: protracted course with prolonged hospital stay, fluctuating character of symptoms, higher percentage of complications (53.4%), aggravation of existing diseases and high lethality (16%). A difference in motivation of suicidal attempts and in clinical course of acute poisoning among the young and elderly individuals was detected. *Conclusion:* A substantial database was collected, using methods of contemporary epidemiology for non-infectious diseases. Based on clinico-epidemiological analysis, we define age

above 60 years as a risk for toxicological pathology. The study has medical and social importance, which necessitates the joint targeted actions of various specialists. We propose a diagnostic and therapeutic model for treatment of patients over 60 with poisonings and trends for prophylaxis.

262. Disk Battery Ingestion by Children

Sofidiotou V, Fountas K, Tsamadou A, Touloupaki V, Kalostou A, Papathanassiou V, Neou P.
Poison Information Centre, Children's Hospital P&A Kyriakou, Athens, Greece

Objective: To estimate the risk of disk battery ingestion, in correlation with clinical manifestations. To clarify treatment procedures, as there are different views. *Patients:* 31 cases (17 boys and 14 girls, from 10 months to 10 years old, 52% of whom were less than 4 years of age) were reported to our department during a four-month period. 23% of them came from the area of the capital and 77% from the rest of the country. 28 children ingested one disk battery each, whereas 3 children ingested 2 batteries each. *Results:* The time elapsed from ingestion to the pursuit of medical advice ranged from 5 minutes to 10 days. No oesophageal impaction or choking was observed. Our recommendation was for an x-ray to exclude the localization in the respiratory tract, which should be repeated on the 6th day after ingestion, if the battery was not found in the stools. In 25 cases the first X-ray was carried out during the first 48 hours and in one case on the 10th day. In 5 cases no X-ray was done, either because they did not follow our advice or the battery was expelled during the first 48 hours. All children remained at home, with the exception of one child, who was subjected to endoscopic removal of the battery, which was still in the stomach, on the 10th day post-ingestion. Dark stools were reported in 3 cases and diarrhoea in one. In 27 children the battery was excreted in the stools between the 1st and the 6th day post-ingestion (most often on the 3rd day). *Conclusion:* Disk battery ingestion by children is frequent. Prevention by the family, X-ray during the first 24 hours and emergency endoscopic removal in case of oesophageal impaction are needed. Children without symptoms can stay at home. They can have an additional X-ray and re-evaluation after the 6th day. Only if there are clinical symptoms, should endoscopic removal be carried out.

263. Morbidity and Mortality Due to Acute Chemical Poisonings in Russia

Ostapenko YN, Litvinov NN, Rozhkov PG, Pugachiov AN, Loginova EV.
Toxicology Center of Federal Agency on Public Health and Social Development, Moscow, Russian Federation

Objective: Presentation of new data characterizing the problem of acute chemical poisonings in Russia. *Methods:* Analysis of the data from Board of Forensic Medical Expertise, reports of the Russian Federation Ministry of Health and Social Development and our own data on morbidity and mortality due to acute chemical poisonings and their etiological factors for 2005–2007. *Results:* Each year in Russia there were 500–600 thousand cases of acute chemical poisonings, 98% of which occurred in the domestic setting. According to Board of Forensic Medicine data annual incidence over the last 6 years was stable at about 90,000 cases, with 71037 fatal outcomes in 2007. In 2005–2007 the principal causes of mortality for acute poisonings were alcohol and also methanol, ethylene glycol and different organic solvents which caused 58.1 to 52.6% of the fatalities. Other causative agents included carbon monoxide (24.1–22.6%), narcotics (6.7–11.5%), corrosive toxicants such as acetic acid (up to 5%), and medicines (2–5%). In 87.3% death occurred at the location of exposure. According to data of poisonings monitoring in Moscow 55.1% of deaths due to alcohol occurred at home and 33.8% on the street or in public places; corresponding values for narcotics were 78.9% and 15.7%. For carbon monoxide 98% of fatalities occurred at the site of exposure. Severe clinical courses and a high lethality of 11.7–14.6% following hospital admission were characteristic for the, usually suicidal, poisonings involving acids or alkalis, with poisonings by alcohol surrogates (methanol, ethylene glycol) reaching 11.3–10.2% in some cases. The most susceptible contingent was able-bodied fertile people. Our data reveal that in different regions of the country the number of people aged 15–60 dying from acute poisoning in 2005–2007 was between 57.7 to 68.1%, the majority being between the ages of 30–50. *Conclusion:* The principal causes of acute poisonings in Russia were alcohol, medicines, narcotics and corrosives, which caused about 80% of total mortality due to acute chemical pathology. These data prompted recommendations and measures to decrease this value by official governmental controls on availability of potentially dangerous toxicants within the home.

264. Analysis of Suicidal Poisonings in Children and Adolescents According to the Data of Moscow Pediatric Toxicology Center

Sukhodolova GN,[1] Ostapenko YN,[1] Usacheva EM.[2]
[1]*Research and Applied Toxicology Center, Moscow;* [2]*Pediatric Toxicology Center, NF Filatov Pediatric Hospital No. 13, Moscow, Russian Federation*

Objective: Revealing social-psychological aspects of suicidal behaviour in children with the view of optimization of psycho-correctional effects for prevention of the repeated suicidal attempts. *Methods:* Analysis of the results of examination in 234 in-patients at the Pediatric Toxicological Center of Moscow aged from 8 to 14 years with acute suicidal poisonings by medical agents from 2002 to 2004. In all cases the fact of poisoning was supported by chemical-toxicological investigation. *Results:* 197 cases (84%) were female and 37 (16%) male. In the above 12 year age group the female/male ratio was almost 6. In 98.3% medications and in two cases (0.8%) corrosive fluids were used for self poisoning. In 30% of cases the poisonings were accompanied by self-harm incisions from sharp instruments, predominantly on the forearm in adolescents, without risk to life. In 9% of poisoning cases occurred under influence of alcohol. Among medical agents used for poisoning, psychotropic agents prevailed (51.3%), mainly tranquilizers and neuroleptics, and 41.7% from other pharmacologic groups. Drugs selected were connected with ease of availability owing to use by parents and other relatives, and the selection of drug was deliberate. If the agents used were mixed, their selection was generally random. The causes for suicidal poisonings were conflicts within the family (50%), with leaders in the given age group (6%), with teachers at schools or sport clubs (4%), with boyfriend/girlfriend (20%), and also expulsion from school (8%), fear of impending important exams (12%). Examination of 48 (20.5%) patients by psychiatrists elicited diagnoses of depression or depressive episodes in 20, psychopathy in 6 patients, and schizophrenia was suspected in 2 children. 31 patients were transferred to the Childrens Psychiatric hospital. All children had consultations with a medical psychologist. *Conclusion:* With a view to preventing suicidal activity it is necessary to develop programs for diagnosis of suicidal inclination and rehabilitation for such children, including individual and group sessions applying cognitive-behavioural techniques and other directions in psychotherapy, as well as psychiatric consultations for patients to determine the need for special treatment.

265. Poisoning Deaths in Children and Adolescents Younger than 16 yrs of Age in Finland 1969–2003

Kivistö JE,[1] Hoppu K.[2]
[1]*Paediatric Research Centre, University of Tampere, Tampere;* [2]*Poison Information Centre, Helsinki University Central Hospital, Helsinki, Finland*

Objective: To investigate the cause and secular trend of poisoning deaths among Finnish children and adolescents. *Methods:* Copies of all death certificates of all Finnish children aged 0–15 years who died due to poisoning between 1969–2003 were obtained from the Statistics of Finland. The Finnish Official Cause-of-Death Statistics are in practice 100% complete. The accuracy of the death certificates and their cause-of-death codes are verified by medico-legal autopsies performed in all cases suspected to be due to poisoning. *Results:* During the study period 121 children aged 0–15 years died of poisoning in Finland. Among children below 5 years of age with a total of 35 deaths, the number and incidence of poisoning deaths declined to practically zero by the beginning of 1980s. One child below 5 years of age died of unintentional ingestion 1982–2003, while 2 died in collateral suicides. Half of the 10 deaths by carbon monoxide in this age group were collateral suicides. Pharmaceuticals caused 14 (40.0%), and non-pharmaceuticals including carbon monoxide 18 (51.4%) of poisoning deaths in this age group. Five to 15-year-olds accounted for 86 (71%) of all fatal poisonings, and the number and incidence of poisoning deaths varied during the study period. Pharmaceuticals caused 33 (37.2%), carbon monoxide 18 (20.9%) and other non-pharmaceuticals 23 (26.7%) of poisoning deaths in this age group. 57 deaths (66.3%) were classified as intentional by self and 26 (30.2%) as related to substance abuse. Among 5-15-year-old girls, up to 53% of the deaths were classified as suicides, 20% among boys ($p = 0.017$). Substance abuse was involved in 54% of the fatal poisonings among boys and in 9% among girls in this age group ($p < 0.001$). Six of the poisoning deaths (7%) were intentional by another person, all were collateral suicides caused by carbon monoxide. *Conclusion:* Accidental poisoning deaths in children below 5 yrs cannot be markedly reduced in Finland, but poisoning prevention efforts should be continued to avoid pediatric poisonings and to prevent unnecessary deaths due to intoxications. In older children the poisoning deaths are almost all suicides or related to abuse, requiring a different focus of prevention.

266. Silica Gel: A Non-Toxic Ingestion with Prominent Epidemiologic Significance

Lavon O, Bentur Y.
Israel Poison Information Center, Rambam Health Care Campus, Haifa, Israel

Objective: Silica gel (SG) is a common desiccant, often found as granules or powder wrapped in plastic bags within product packaging. It is recognized as a non-toxic substance, which its ingestion is largely discounted. Nevertheless, it is an allegedly very frequent exposure that should be examined for its epidemiologic significance. We evaluated the extent and characteristics of silica gel ingestion and the direct cost and burden for health services. *Methods:* Prospective-historic poison center chart review from November 2007 to October 2008. *Results:* During the study period, 546 cases of SG ingestions were recorded. This constitutes 2.1% of all the calls to the poison center. Most of the ingestions were in young children; 356 (65.2%) were younger than 2 years and 143 (26.2%) were between the ages 2 to 6. The main source of silica gel ingested was shoe boxes. We identified seasonal variation in SG ingestions with peaks during weather transitions, holidays and prior to the new school year, all related to shoe shopping trends ($p < 0.00001$). Symptoms were reported in only 15 (2.7%) cases, mostly mouth and throat discomfort. All of these were mild, self-limited, and did not require any referral. Sixty (10.1%) calls were from clinics and emergency departments (43 and 17, respectively); to where concerned parents brought their children after SG ingestion without consulting the poison center. The minimal annual direct cost of these unnecessary visits was 15360 NIS (approximately 4200 US$). *Conclusion:* SG is one of the most frequent ingested substances reported to our poison center, especially in young children. Contrary to its clear non-toxic nature, its ingestion is still a major concern in the public and it poses a relatively significant burden and cost for health services. Improved awareness to poison center availability and contribution, spreading specific public information about SG low risk, and proper labeling of SG packaging can reduce unnecessary burden

and save cost. Routine meticulous evaluation of poison center calls including non-toxic exposures and their relative implications for health services is advised for further intervention and improvement.

267. Suicide by Poisoning in Danish Adolescents, Time Trends for the Years 1970–2006

Kryger A,[1] Juel K,[2] Jacobsen P.[1]
[1]*Clinic of Occupational and Environmental Medicine and the Danish Poison Centre, Copenhagen University Hospital Bispebjerg, Copenhagen;* [2]*National Institute of Public Health, Copenhagen, Denmark*

Background: Attempted suicide and other suicidal behaviour have been reported to be an increasing problem among adolescents and children in western countries, including Denmark.[1,2] For completed suicide the trends has been more equivocal.[3,4] *Objective:* To assess long-term and recent trends in poisoning suicides in Denmark in age groups younger than 20 years. *Methods:* Identification of poisoning suicides through the Danish Death Registry for the years 1970–2006. Calculation of age and period specific mortality for suicides stratified on type of poisoning. *Results:* 174 poisoning suicides were recorded for the study period - 56% of these were males and 97% aged 15–19 years. Pharmaceuticals were used in 60% of all and in 85% of suicides committed by females. In contrast 60% of suicides by males were by carbon monoxide. Suicide rates declined significantly from approximately 20/106 person years (p.y.) in the eighties to less than 5/106 p.y. for the period 2000–06. No single substance showed increasing trend during the most recent periods. *Conclusion:* Increasing suicidal behaviour in adolescence contrasts to generally declining rates of completed suicide for Danish adolescents. 1. Larkin Gl, Smith RP, Beautrais AL. Trends in US emergency department visits for suicide attempts. Crisis 2008; 29:73–80. 2. Jensen BF, Christiansen E. Selvmordsforsøg I Fyns Amt I perioden 1990–2003 ("attempted suicide in Funen County in the periode 1990–2003). Nyt fra Center for Selvmordsforskning 2005; 2 no. 4. In Danish. 3. Bridge JA, Greenhouse JB, Weldon AH, Campo JV, Kelleher KJ. Suicide trends among youths aged 10 to 19 years in the United States, 1996–2005. JAMA 2008; 300:1025–26. 4. McClure GMG. Suicide in children and adolescents in England and Wales 1970–98. Br J Psychiatr 2001; 178:469–74.

268. Epidemiology of Antipsychotic Drug Poisonings in Slovakia – A Ten Year Review

Caganova B, Plackova S, Kresanek J, Ficekova Z.
National Toxicological Information Centre, University Hospital, Bratislava, Slovakia

Objective: To document the current pattern of poisonings by antipsychotics in Slovakia (5.4 million inhabitants) and to compare with the situation ten years earlier. *Methods:* Poisonings were analysed on the basis of data gathered from telephone consultations and medical reports forwarded to the National Toxicological Information Centre (NTIC) in Bratislava from the whole of Slovakia during the three-year-period 2005–2007. The epidemiological data were documented and the cases were graded according to the Poisoning Severity Score (PSS). The results were compared with those of a corresponding study from 1996–1998. *Results:* A total number of 3585 drug intoxications were reported to the Slovak NTIC during the study period of which 380 (10.6%) involved antipsychotic drugs. Suicidal poisonings (82.4%) were more prevalent than accidental poisonings (16.6%). The majority of cases were adults (70.8%), the most frequently involved age group were those aged 19–30 years. Atypical antipsychotics had been taken in 65.78% of the cases. The majority of patients who overdosed with antipsychotics were asymptomatic (11.6%) or developed only mild toxicity (68.2%). Moderate or severe symptoms occurred in 18.68%. Severe symptoms were caused more frequently by older types of medication. In the observed period 2005–2007 the NTIC did not register any antipsychotic poisoning resulting in fatal outcome. A comparison with corresponding data from 10 years earlier showed that since 1996 the number of antipsychotic poisonings has grown by 112%. Annually there has been an increase in the number of intoxications by atypical antipsychotics together with their rising prescriptions. Atypical antipsychotics, with lower acute toxicity, have to some extent replaced traditional antipsychotics. Although the total number of antipsychotic poisonings has increased there has been a decline in the severity of poisoning. *Conclusion:* Poisonings involving both traditional and atypical antipsychotics are among the more common inquiries to the Slovak NTIC. In intoxications with antipsychotics clinical symptoms occur early and are usually of mild to moderate severity. Even in the cases where there are no clinical symptoms developed the patients are often hospitalized for observation. Among the problems of acute poisonings we cannot disregard the economic viewpoint. Acute intoxications with antipsychotics present a relevant medical problem, especially in small children, where ingestion of a single tablet may cause poisoning with prolonged symptoms.

269. Attempted Homicide/Homicide-Related Children Poisoning in Taiwan Between 1986 and 2007 – A Poison Center-Based Study

Yang CC,[1,2] Deng JF.[2]
[1]*Department of Environmental & Occupational Medicine, National Yang-Ming University, Taipei;* [2]*Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*

Objective: In Taiwan, attempted homicide/homicide-related children poisoning is not infrequently reported in the media because some suicide-committing parents may attempt to kill their children simultaneously in a belief that the children would suffer a great deal in the absence of their care. Epidemiologic data on such poisonings however are scarce. *Methods:* We conducted a retrospective analysis of all poisoning inquiries regarding children aged less than 12 years reported to the PCC-Taiwan from 1986 through 2007. We compared the baseline characteristics of children with and children without attempted homicide/homicide-related poisoning by employing chi-squared test and logistic regression analysis. We further analyzed the data of all children with attempted homicide/homicide-related poisoning. *Results:* A total of 16,766 children poisonings, including 120 (0.7%) attempted homicide/homicide-related poisonings, were eligible for final analysis. As compared to children without attempted homicide/homicide-related poisoning, children with such poisoning were more frequently inquired by physicians/nurses, had less acute and oral exposure, were more likely to be exposed to agrochemicals or drugs, manifested more severe effects, and tended to be aged between 6 and 12 years. Among the 120 children with attempted homicide/homicide-related poisoning, benzodiazepines (n = 32) were the leading cause of poisoning, followed by heroin (n = 18), paraquat (n = 12), amphetamine and related agents (n = 8), organophosphate insecticides (n = 6), and zolpidem (n = 4). Children aged less than 1 year (n = 29) were usually poisoned because their mother abused illicit substances, while the other children were mainly poisoned by their parents. Seven children (6%), including 3 paraquat exposures, 2 insecticide exposures, 1 benzodiazepine poisoning with suspected concomitant strangulation, and 1 amphetamine exposure, died following poisoning. *Conclusion:* Attempted homicide/homicide-related poisonings accounted for only a minor proportion of children poisoning in Taiwan. However, children with such poisoning, especially those with agrochemical exposures, usually manifest more severe effects and/or even death, which may result in an underestimate of the true incidence of such poisonings in this PCC-based study. Prevention of substance abuse among pregnant women, limiting the parents' accessibility to hazardous agrochemicals, and increasing family and social support to parents at risk of suicide attempt should help in future control of such poisonings.

270. Registry of Severe and Fatal Poisonings at Grenoble University Hospital: Results of the First Year of the Study

Fouilhé Sam-Laï N,[1] Saviuc P,[1] Castillo C,[1] Moisan A,[1] Buclez A,[1] Danel V.[2]
[1]*Toxicovigilance Centre, University Hospital;* [2]*Mobile Emergency Care Services, University Hospital, Grenoble, France*

Objective: Little information is available on the incidence of severe and fatal poisonings at a local, regional or national level. To assess the situation at the Grenoble University Hospital, a prospective system of registration was set up in 2007. *Methods:* Severe poisoning was defined as a pathology related to a toxic cause and requiring a treatment in an intensive care unit. The cases were notified to the Grenoble Toxicovigilance Centre by Intensive Care Units. Ten hospital units agreed to take part (intensive care units, emergency departments, mobile emergency units). Medical files of each case were studied. The following were collected: age, sex, poisoning circumstances, ingested substances, clinical status and biologic and toxicologic analysis. *Results:* Over the year 2007, 154 cases were registered. Each case was notified by 1 to 4 units. There were 7 toxic deaths and 147 severe poisonings. Toxic deaths involved 6 women and 1 man and 6 were self-poisoning. Paracetamol was involved in 3 deaths. The most common other substances were: diazepam, loxapine, olanzapine, chloroquine, digoxin. The 147 severe poisonings involved 82 women and 65 men, aged 2 to 88 years, and 144 (98%) severe poisonings were self-poisonings. Clinically, 86 patients were comatose (GCS ≤ 7), 27 had circulatory collapse (blood pressure ≤ 80 mmHg) and 83 were intubated. From the case history, one to 8 substances were involved. The most frequently encountered substances were: ethanol (n = 60), paracetamol (n = 28), cyamemazine (n = 26), bromazepam (n = 24), meprobamate+acepromazine (n=21), alprazolam (n = 18). *Conclusion:* This study made it possible to raise 3 points: 1) the most frequent substances involved were ethanol, paracetamol, neuroleptics, hypnotics and anxiolytics; these substances are not necessarily responsible for the severe and fatal poisonings, 2) one must be careful with paracetamol poisonings whenever hospital admission is delayed and with cyamemazine, the second most frequent drug, because of its powerful sedative effect, 3) The death rate of these severe poisonings was 4.5% (7/154).

271. Deaths by Self-Poisoning in Oslo and the Surrounding Area During One Year

Bjornaas MA,[1,2] Teige B,[3,4] Hovda KE,[1] Heyerdahl F,[1] Ekeberg O,[1,2] Jacobsen D.[1]
[1]*Department of Acute Medicine, Ullevaal University Hospital, Oslo;* [2]*Department of Behavioural Sciences in Medicine, University of Oslo;* [3]*Institute of Forensic Medicine, University of Oslo;* [4]*Division of Forensic Toxicology and Drug Abuse, Norwegian Institute of Public Health, Oslo, Norway*

Objective: To study deaths by self-poisoning both in- and outside hospitals in Oslo and the surrounding area during one year. Toxicological and psychosocial factors were evaluated, as well as the intention behind the self-poisoning. *Methods:* Fatal self-poisonings in Oslo and the surrounding area (Asker and Baerum counties) were consecutively included in a cross sectional multicentre study from April 1st 2003 – March 31st 2004. The material consisted of medico-legally examined cases as well as fatal poisoning in adult patients (≥16 years) in contact with health care services during the period studied. The catchment area had a total population of 682 952, of which 552 857≥16 years. *Results:* A total of 119 persons died of self-poisoning during one year; annual mortality rate 22 per 100 000. Thirteen died in hospital, 106 were declared dead at the scene. Sixty-nine percent were males; median age was 42 years (range 19 - 86). Of those who died in hospital, a medico-legal autopsy was performed in three out of 13 cases. The main toxic agents were opiates/opioids in 76 (64%) of the cases, ethanol in seven (6%), tricyclic anti-depressants in six (5%) and neuroleptics in

six (5%). Serotonin reuptake inhibitors were the main agents in one of the cases and additional agents in 17 (14%) of the cases. Heroin/morphine was found in 62 (52%) of the cases, methadone in seven (6%), codeine in five (4%), whereas the specific opiate/opioid compound were unknown in two cases. Seventy-eight deaths (66%) were evaluated as accidental deaths, 38 (32%) as suicides (definite or possible). In two cases the intention was thought to be an act of appeal, and one case was not evaluated. Depression or other psychiatric symptoms were known in 14% of the cases; in 41% of those evaluated as possible suicides. According to the ICD-10 criteria, 52% were classified as opiates/opioid dependent, 14% were classified as alcohol dependent and 5% as dependent on prescription drugs. *Conclusion:* Ninety percent of deaths by self-poisonings occurred outside hospital and opiates/opioids were the main toxic agent. Half of the cases were classified as opiate/opioid addicts. One third of the cases were considered suicides.

272. Suicidal Self-Poisoning – One Year Epidemiological Study

Radenkova-Saeva JV, Vanev PI.
Toxicology Clinic, Emergency Hospital N.I. Pirogov, Sofia, Bulgaria

Objective: To investigate the epidemiological characteristics of suicidal poisoning in Toxicology Clinic, Emergency Hospital "Pirogov" Sofia in relevance to age, gender and socioeconomic factors. *Methods:* This was a retrospective review of all patients with attempted suicide, admitted for treatment of acute self-poisoning from January 1st, to December 31st, 2007 in the Clinic. The indicators investigated were of demographic, socio-economic and of substance relevance. *Results:* A total of 360 patients with attempted suicide were included in the study, over a period of 12 months. The oldest patient presented was 89 years old and the youngest was 12 years old. The age group of the majority of the patients was 26–35 years. 20.6% were males and 79.4% were females. Suicide attempt intoxications were more common in unmarried persons (150 cases - 41.8%) and in patients with a regular job (147 cases - 40.8%). Medicines were the leading cause of self-poisoning. 350 patients (97.2%) had taken various medicines. In 10 other patients we documented different domestic products, pesticides etc. On a monthly basis, admissions during January, March, and June were most common (37, 34 and 33 patients, respectively). The most frequent cause for committing suicidal attempts by self poisoning found in both genders was: depression as separate disease; various social and economic reasons, isolation from social or family life. 5.28% (19 cases) had at least one previous suicidal attempt. There were 5 (1.39%) deaths reported among the cases. *Conclusion:* Suicidal behaviors are common in our society. Age group between 26 to 35 years in both genders proved to be associated with suicidal attempts. Female prevailed over the male, but males tend to make more severe attempts with the intention of completing it. Though depression was a major culprit, social or family problems were found to be the most frequent cause of suicide attempts.

273. Acute Methanol Poisoning – Epidemiological Study in a Period of 6 Years

Radenkova-Saeva JV,[1] Atanassova RB.[2]
[1]*Toxicology Clinic, Emergency Hospital N.I. Pirogov;* [2]*Sector for Toxicological Analysis and Control, Emergency Hospital N.I. Pirogov, Sofia, Bulgaria*

Methanol poisoning is an extremely hazardous form of intoxication. The mechanism of methanol toxicity is due to direct toxic effect of formic acid which is generated from methanol as well as injury secondary to anoxia and acidosis. Methanol intoxication produces a well recognized clinical picture characterized by gastrointestinal, ocular and nervous system symptoms. *Objective:* To examine methanol poisoning cases, to define the demographic features and determine mortality rates of the patients. *Methods:* The records of the Toxicology Clinic, Emergency Hospital "N. I. Pirogov" were reviewed retrospectively for all methanol poisonings during the period from January 1, 2001 to December 31, 2006. The patient's age, gender, methanol blood levels and outcome of intoxication were recorded. *Results:* The number of patients, hospitalized in our Clinic due to methanol poisoning, was 30 during that period of time. There were 22 men (73.3%) and 8 women (26.7%), median age 57 (range 29–76) and 39 (range 28–57) years, respectively. The largest age group was 41 –50 years old (40%). The methyl alcohol blood concentrations ranged widely from 0.12 to 5.1%. The reason for ingestion was accidental in 22 cases (18 man and 4 women), suicide attempt in 8 cases (4 men and 4 women). The number of deaths due to the methanol poisoning was 19 (63.3%) during that period of time. *Conclusion:* Methanol poisoning is a rare but extremely hazardous form of intoxication, generally occurring after suicidal or accidental events. In order to decrease the mortality due to methanol intoxication, some precautions should be developed that could prevent the production and consumption of alcoholic beverages illegally produced.

274. Mushroom Inquiries and Mycological Analysis Provided by the Slovak Toxicological Information Centre

Plackova S, Caganova B, Kresanek J, Ficekova Z.
National Toxicological Information Centre, University Hospital, Bratislava, Slovakia

Objective: Every year the National Toxicological Information Centre (NTIC) in Bratislava responds to about 3,000 inquiries from all over Slovakia. Mushroom poisoning represents 4.7% of all cases collected by NTIC. Inquiries concerning mushrooms are among the most severe. To obtain more information we performed a retrospective review of all telephone calls and mycological analysis provided by our centre. *Methods:* All the calls and mycological analysis provided between 2003–2007 by NTIC were reviewed to identify the cases concerning exposure to mushrooms. *Results:* Among 12,678 calls reported to the NTIC between 2003–2007, 585 were related to mushrooms, 6 of them were fatal (4 adults, 2 children). The deaths were caused by *Amanita phalloides*. In 296 cases, spores in biological material (vomit, gastric lavage, remainder of food, mushroom-fresh, dried, frozen) were analysed in our centre. On the basis of the microscopic analysis the gastrointestinal syndrome was noted in 216 patients out of 296 intoxicated patients, which formed 72.97% of the total number, among which there were 81.94% adults (average age 41 years) and 18% children (average age 13 years). Clinical symptoms started at 3–10 hrs post ingestion. By microscopic analysis mostly spores of *Boletaceae* 24.26 % and *Agaricaceae* 18.66% were identified. The second most frequently occurring syndrome was a cyclopeptide syndrome identified in 25 patients, 8.45% of the total number, of these poisoning was severe or even fatal in 6 cases. Adults corresponded to 92% (average age 44 years) and children to 8% (average age 7 years). The clinical symptoms of ingestion such as nausea, vomiting and abdominal pain appeared at 6–13 hrs post ingestion. Clinical symptoms of the muscarinic syndrome represented 7.77% of cases, pantherine syndrome 6.76%, psilocybe 3.04% and orellanine syndrome 1.01%. *Conclusion:* Slovakia, like many other European countries, is rich in wild poisonous mushrooms that can be easily mistaken for edible ones. *Amanita* poisoning was mostly confused with *Macrolepiota* (44%), *Russula* 36% and *Agaricus* (20%) species. This retrospective analysis showed the severity of mushroom poisoning. It also demonstrated the issue that people tend to underestimate the problem of mushroom ingestion because of the latent period before the onset of gastrointestinal effects. This resulted in late presentation to hospital and late treatment.

275. Epidemiology of Acute Chemical Poisonings in Azerbaijan

Afandiyev IN.
Republican Toxicology Center MoH, Baku, Azerbaijan

Objective: Epidemiologic data on acute chemical poisonings in Azerbaijan Republic is very limited.[1]. The purpose of this pilot study was to evaluate and analyze the rate and characteristics of acute chemical poisoning cases in Azerbaijan. *Methods:* This investigation was performed on the data of poisoned patients admitted to the Republican Toxicology Center of the Ministry of Health of Azerbaijan in Baku city from 1st January to 31st December, 2007. *Results:* There were 1182 hospitalizations in the Republican Toxicology Center's (RTC) intensive care unit. 65.3% of patients were admitted to RTC within 2 hours of exposure. The mean length of hospitalization was 3.2 days. The youngest patient was ten days old and the oldest 82 years old. Acute intoxications were more frequent among males (51.4 %) and in 20–40 age group. The majority of patients (84.4%) were urban inhabitants. Pharmaceuticals were the most common cause of poisonings (31.9%). Among the pharmaceutical drug poisonings psychotropic medicines (45.6%) were the most frequent. The other cases of poisonings were inhalation of gases (14.6%); corrosives (14.9%); pesticides (3.3%); hydrocarbons (1.5%); alcohol (4.2%); opiates (4.2%); snake and spider bites (5.7%); mushrooms (0.4%) and others (19.3%). The most frequent cause was accidental poisoning (56.9%), followed by intentional and occupational poisonings. The mortality rate was 3.1%. Corrosive liquid (especially - concentrated acetic acid) poisonings were the most frequent cause of fatalities (40.5% of total mortality). *Conclusion:* These data provide preliminary epidemiological information about acute chemical poisoning cases in the Azerbaijan Republic. Further research is required. *References:* Afandiyev IN. Description of acute chemical poisoning cases in the first half of 2007. Azerbaijan Med J 2007; 4:53–56.

276. Slimming Tablet Enquiries Recorded by National Poisons Information Service (Cardiff)

Davies MD, Thompson JP, Cooper GA.
National Poisons Information Service (Cardiff), University Hospital Llandough, Penarth, UK

Objective: To analyse the incidence of slimming tablet enquiries between 2004 and 2008 reported to National Poisons Information Service (Cardiff). To examine the variety of the slimming preparations recorded and to discuss the potential toxicity of their ingredients. *Methods:* NPIS (Cardiff) electronic call records were reviewed and analysed. Details of enquiries involving slimming tablets were collated (based on their main active ingredient) into the following groups: orlistat, rimonabant, herbal preparations (containing fucus, boldo & dandelion (F,B and D)), appetite suppressants, bulking agents, sympathomimetics, levocartinine, dinitrophenol, liothyronine and slimming tablets not known (nk). *Results:* There were a total of 240 enquiries received by NPIS (Cardiff) regarding slimming tablets during the 4 year period; 70 enquiries involved prescribed medications and 170 involved non-prescribed preparations. Tablets containing a sympathomimetic agent received the highest number of enquiries. The ingredients contained within the different slimming tablets recorded varied greatly and many tablets contained more than one active ingredient. *Conclusion:* The

Table. Number of slimming tablet enquiries

Agent	Orlistat	Rimonabant	F, B & D	Appetite sup.	Bulking Agent
Total Enquiries	65	5	50	10	3
Agent	Sympatho.	Levocartinine	Dinitrophenol	Liothyronine	Slimming Nk
Total Enquiries	66	3	2	3	33

majority of the enquiries involved non-prescribed slimming tablets and the most common active ingredient was a sympathomimetic agent. Slimming tablets containing dinitrophenol, liothyronine or a sympathomimetic agent were identified as having the greatest potential to cause toxicity in overdose. This study highlights the considerable variation in the potential toxicity of different slimming preparations and emphasizes the need for greater awareness and control of non-prescribed slimming tablets.

277. Acute Poisonings in Poland – 30 Years of Experiences

Kotwica M, Czerczak S.
National Poison Information Centre, Nofer Institute of Occupational Medicine, Lodz, Poland

Objective: The aim of the present paper was to trace the trends and characteristics of acute poisonings in Poland, including the rate, type, and causal agents, over a long period of time (since 1970) to define the dynamics of changes and major causes of poisoning-related mortality. *Methods:* The analysis was based on data from the patients' records submitted by all poison centers in Poland. *Results:* Drugs were the most frequent group of chemical substances, responsible for more than 50% of all admissions for acute poisonings.[1,2,3,4] Since 1980 (3,4) the rate of drug poisonings has slightly decreased (from 56.4% to 49.2%). Ranked second with respect to the prevalence rate were alcohol poisonings. A clear upward tendency was noted in this category; from the level of 8.0% to as much as 30.3%.[1,2,4] Poisonings with carbon monoxide became less frequent, from 15.3% to 5.1%. The percentages of poisonings by pesticides, corrosives and metal compounds have been reduced in recent years.[1,2] The greatest number of lethal outcomes was also due to poisonings by alcohols and drugs.[3,4] The highest mortality ratio was recorded for ethylene glycol, methanol and *Amanita phalloides* poisonings.[3,4] *Conclusion:* The still increasing number of cases of acute poisonings in Poland makes it necessary for all medical and other professionals handling them (clinical toxicologists, diagnostic laboratory staff, and poison information specialists) to increase and coordinate their efforts. *References:* 1. Bogdanik T, Jaraczewska W, Szymanska S. An analysis of the causes and course of acute poisonings in toxicological centers. Stud Mat Monogr 1980; 1:14–34. 2. Czerczak S, Jaraczewska W. Acute Poisonings in Poland, J Toxicol Clin Toxicol 1995; 33:669–675. 3. Jaraczewska W, Czerczak S. The pattern of acute poisonings In Poland. Vet Hum Toxicol 1994; 36:228–233. 4. Kotwica M, Rogaczewska A. Acute poisonings in Poland during the period 1997–1999. An analysis of files from the National Poison Information Centre. Przegl Lek 2002; 59:318–324.

278. Antidepressant Prescribing to Deliberate Self-Poisoning Patients the Last Year Prior to the Deliberate Self-Poisoning Episode

Heyerdahl F,[1] Gjelsvik B.[2]
[1]*Department of Anaesthesiology, Ullevaal University Hospital, Oslo;* [2]*Department of Psychology, University of Oslo, Oslo, Norway*

Objectives: The aim was to investigate the amount of antidepressants prescribed to deliberate self-poisoning (DSP) patients the year prior to the index DSP episode. More antidepressants dispensed to this group compared with the general population would be expected,[1] but so far this has not been assessed reliably by means of registry data. The Norwegian Prescription Database (NorPD) provides reliable information on an individual level of all prescription drugs dispensed in Norway. *Methods:* The study employs a longitudinal design including registration of medication dispensed the year prior to the index DSP episode. Consecutive inclusion of 84 patients, 18 years or older, admitted to Ullevaal University Hospital because of DSP between January 2006 and March 2007 (29.2% males (n=25), 70.2% female (n = 59), response rate 71.8%. Registry data on antidepressant prescriptions dispensed to these patients were retrieved from the NorPD. Antidepressants were identified at 3rd ATC-level, i.e. N06A, as well as 4th level to allow for identification of antidepressant subgroups. Defined daily dosage (DDD) refers to the assumed average maintenance dose per day for a drug used for its main indication in adults.[2] Regular users were defined as patients collecting > 365 DDD of antidepressants in the last year or > 2 prescriptions indicating daily use minimum the last 3 months prior to the DSP episode. *Results:* In the year prior to the DSP episode, 54.8% of the sample (n = 46), of which 32.6% male (n = 15), 67.4% female (n = 31)) collected a total of 278 prescriptions of antidepressants [of which SSRIs (ATC N06AB) accounted for 41.1%, others (ATC N06AX) 47.5% and TCA (ATC N06AA) 11.1%]. The mean total DDD was 301.6 DDD (Sd 481.93); 15.1 times higher than the general population in the catchment county Oslo. 38.1% (n = 32) were meeting criteria for regular user. *Conclusions:* Antidepressant medication load is huge, indicating both widespread depressive symptoms and easy access. One third of patients collecting antidepressants did not get enough for regular use, potentially indicating compliance problems or side effects. *References:* 1. Haw C, Hawton K, Houston K, et al. Psychiatric and personality disorders in deliberate self-harm patients. Br J Psychiatr 2001; 178:48–54. 2. http://www.whocc.no/atcddd/

279. Serial Repetitive Nerve Stimulation in Organophosphorus Poisoning Provides Clear Evidence of Two Distinct Pathophysiological Processes in Patients with Intermediate Syndrome

Buckley NA,[1,2] Dawson AH,[2] Jayawardane P.[2,3]
[1]*University of New South Wales, Sydney, Australia;* [2]*South Asian Clinical Toxicology Research Collaboration, University of Peradeniya, Peradeniya, Sri Lanka;* [3]*University of Sri Jayawardenepura, Nugegoda, Sri Lanka*

Objective: To explore the pathophysiology of the intermediate syndrome (IMS) by re-analysis of repetitive nerve stimuli (RNS) and nerve conduction studies in organophosphorus pesticide (OP) poisoning. *Methods:* We more closely examined the nerve conduction studies performed on ten patients with IMS and 30 patients with '*forme fruste* IMS' following OP poisoning.[1] These patients had sequential daily RNS over the first few days of their poisoning. *Results:* RNS at 3 to 30 Hz in these patients revealed a decrement-increment response, which was always more noticeable at high frequencies (as has been reported previously). By overlaying the frequencies, we demonstrated that in some cases this was due to a consistent refractory period after the first supramaximal impulse that was not rate dependent (the amplitude of the CMAP at 0.3 seconds after the initial impulse was similar no matter how many intervening stimuli there had been). In other cases, in particular in the most severe cases who were developing respiratory failure, a severe rate-dependent effect was observed. When severe, this rate dependent effect was obvious as a progressive decrement at high frequencies. However, overlay of the RNS at a range of frequencies demonstrated that this rate-dependent block may be present in RNS that superficially appear the same as those with just a refractory block. We suggest the two blocks can be quantified by three parameters – the ratio of the second to the first block (C2/C1), the duration of refractory block (AUC of the loss of CMAP amplitude of the C2 at 3 to 30 Hz), and the extent of rate dependent exacerbation of block (ratio of C2@3Hz to C10@30Hz). *Conclusion:* There appear to be (at least) two distinct pathophysiological abnormalities detectable on RNS in OP poisoning. The rate-dependent loss of CMAP amplitude is associated with more severe weakness and a high risk of respiratory failure. *References:* 1. Jayawardane P, Dawson AH, Weerasinghe V, et al. The spectrum of intermediate syndrome following acute organophosphate poisoning: A prospective cohort study from Sri Lanka. PLoS Med 2008; 5:e147.

280. Severe Dyspnoea after Spraying a Pesticide Containing Glyphosate – Lung Damage Histologically Confirmed

Burger R, Begemann K, Meyer H, Hahn A.
National Poison and Product Documentation Centre, Federal Institute for Risk Assessment, Berlin, Germany

Introduction: Glyphosate is a non-selective foliar herbicide used to control monocotyledonous and dicotyledonous weeds in arable farming, viniculture and pomiculture, in the cultivation of ornamental plants, on meadows and grazing land, on lawns and in forests. The substance inhibits the enzyme, 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), whose presence is required for the synthesis of aromatic amino acids such as phenylalanine, tryptophan and tyrosin. The case presented is characterized by extreme respiratory manifestations and histologically confirmed toxic inflammatory reaction of the lungs. *Case report:* A 59-year-old farmer had applied 600 mL of a pesticide containing glyphosate in a wooded area over a period of about three hours and under very warm weather conditions. The herbicide had been diluted at the prescribed ratio and applied by means of a knapsack sprayer. Respiratory protection equipment had not been used. First symptoms developed about seven hours after the pesticide had been sprayed. Initially, the patient complained of aching muscles in his chest, then he developed rapidly increasing shortness of breath, initially only under conditions of exercise, later also while at rest, in the absence of expectoration and cough. Simultaneously, his body temperature rose to ca. 38°C. He was admitted to a hospital. After X-ray examination had resulted in pathological findings, bronchoscopy together with lung biopsy was performed. The expert opinion based on histological findings emphasized that the histomorphological picture was compatible with lung damage induced by an irritant gas and was unlike that shown in the case of a conventional bacterial infection. *Conclusion:* The main component of the pesticide used is a glyphosate salt in aqueous solution, the wetting agent contained is tallow amine. Since, according to contemporary knowledge, the active substance, glyphosate, has only a low toxicity, it has been assumed that the complete formulation, i.e. in particular the combination of the surface-active wetting agent, tallow amine (surfactant) with the active substance, glyphosate, was the cause of the toxic effect observed. For reasons of preventive health care, the BfR therefore deems it necessary to have all pesticides containing glyphosate and tallow amines labelled, in addition to appropriate safety warnings, with possible health risks which may affect the respiratory system.

281. Acute Carbamate Poisoning Treated in the National Poison Control Centre During the Ten Years Period

Vucinic S,[1] Jovanovic D,[1] Antonijevic B,[2] Vucinic Z,[1] Djordjevic D,[1] Potrebic O,[1] Rezic T.[1]
[1]*National Poison Control Centre, Belgrade;* [2]*Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia*

Carbamate pesticide poisonings due to reversible inhibition of cholinesterase tend to be less severe and shorter than organophosphate poisonings, although the diagnosis may not always be straightforward especially in mild cases. A controversy exists over the use of oximes which do not appear to provide benefit compared to the atropine alone in carbaryl poisoning, but some authors suggest that oximes should be used in potentially fatal poisonings with unknown cholinesterase inhibitors. *Objective:* To assess the pattern and the severity of carbamate poisoning and the efficacy of the applied therapy. *Methods:* Retrospective study of 535 patients with pesticide poisoning, treated from 1998 - 2007. *Results:* Carbamate poisoning was registered in 21 (3.92%) patients: 16 (76.2%) had carbofuran, 2 (9.5%) carbosulfan, and 1 (4.8%) patient respectively propoxur, methiocarb and unknown methylcarbamate poisoning. Seventeen patients had ingested carbamates for suicidal purposes and 4 poisonings were inhalational. The majority (76.2%) of patients had mild and moderate poisoning, 9.5% had severe poisoning, and 3 (14.2%) patients died. The lowest rate of AChE inhibition

(<12%) was registered in 3 patients and carbofuran concentrations in blood were 0.02 mg/L to 5.95 mg/L. Atropine doses were 2 mg - 250 mg. In the patient who presented as unknown poisoning, pralidoxime methylsulphate was applied for one day, but with no significant improvement of clinical condition or reactivation of AChE. In the patients who died, besides severe cholinergic crisis, ARDS and pulmonary thromboembolism were registered. Risk factors for fatal outcome were high ingested doses (>200 ml) of carbamates, patient's age (>65 years), late admission to hospital (>4 hours) and complications of poisoning. *Conclusion:* Carbamate poisoning is not so frequent in Serbia but it can be severe, depending on the compound, dose and duration of exposure. In severe cases with unknown cholinesterase inhibitor poisoning, beside atropine, oxime therapy should be taken into consideration. *References:* Gupta RC. Carbofuran toxicity. J Toxicol Environ Health 1994; 43:383–418.

282. Two Cases of Acute Human Flufenoxuron Insecticide Poisoning

Suh JH,[1] Oh BJ,[2] Roh HK.[1]
[1]*Department of Internal Medincine/Clinical Pharmacology, Gachon Medical Center Gil Hospital, Incheon;* [2]*Department of Emergency Medicine, Asan Medical Center, Seoul, South Korea*

Objectives: The insecticide acylurea (flufenoxuron) restricts growth by inhibiting chitin synthesis (1). Human toxicity has been presumed to be minimal. We describe the first reported acute human acylurea insecticide poisonings. *Case series:* A 23-year-old male presented with refractory vomiting 2 h after ingestion of 250 mL of 5% flufenoxuron. He was alert on admission but his mental status was altered and he was hypotensive 30 min later. His arterial blood gas analysis was in the normal range at admission but his HCO_3- was 15 mEq 6 h later. His mental status improved 8 h following admission. On the fifth day of hospitalization, the patient did not complain of any symptoms and his physical status was good. We referred him to a psychiatrist for further management. The second case is a 59 year-old female who was brought to the emergency department after ingesting 150 mL of 5% flufenoxuron and 3 tablets of doxylamine (hypnotic) approximately 4 h earlier. The patient presented in a coma and in profound shock (i.e. hypotension, anuria, severe metabolic acidosis). Her respiratory function improved 23 h later and her mental status was improved by 2 days later. Significant laboratory findings for the patient were serum amylase 1992 U/L, creatine phosphokinase 5294 U/L, blood gas pH 7.05, and blood gas HCO_3- 6.9mEq. She was discharged 10 days after admission without any abnormal symptoms or laboratory findings. *Conclusion:* Acute poisoning by flufenoxuron ingestion may cause severe metabolic acidosis and mental alteration. Further studies are needed to explain the mechanisms of flufenoxuron toxicity in humans.

283. Pesticide Exposure Inquiries to the New Zealand Centre: A 6 Year Survey

Mason RW.
Poisons Information Centre, Dunedin School of Medicine, Dunedin, New Zealand

Objective: To describe the epidemiological characteristics of human pesticide exposures referred to the New Zealand Poisons Information Centre. *Methods:* A 6 year retrospective survey of telephone inquiries involving human pesticide exposures was conducted covering the period July 2002 to June 2008. Patient demographics, product names, active ingredients and pesticide classifications, exposure characteristics and treatment advice were collated. *Results:* 180,656 inquiries were received of which 7,091 or 3.9% (yearly range 3.7 to 4.3%) related to human pesticide exposures (3,975 males, 2,953 females, 163 unknown). The principal agents were pyrethroids (18.6%), glyphosate (12.8%), coumarins (11.7%), boric acid (11.5%), organophosphates (6.6%), metaldehyde (4.3%) and chlorophenoxy acids (3.7%). Eighty three percent of reported exposures (97.5% acute) occurred at home, 51% in children and 48% in adults, and 11.6% (86% acute) in the workplace (76.3% males, 21.0% females, 2.7% unknown). Home exposures involved ingestion (57.7%), skin (17.6%), inhalation (16.8%) and eye contact (6.5%); most were child exploratory (47.9%) or adult unintentional (46.9%). Medical referral was recommended in 38.7% of all exposures and for more than 50% of herbicide and fungicide exposures. Medical referral was most frequent with pyrethroids (533), glyphosate (454) and organophosphates (303). Inquiries from medical facilities where referral was not required was notable with products containing boric acid (97% of medical centre inquiries, 71% of hospital inquiries), coumarins (89% of medical centre inquiries, 58% of hospital inquiries) and metaldehyde (74% of medical centre inquiries). Intentional exposures accounted for 4% (287) of all human pesticide exposures (149 males, 138 females), most commonly glyphosate (68 cases, 63 medical referrals), coumarins (49 cases, 44 referrals), pyrethroids (31 cases, 22 referrals), paraquat (23 cases, all referred) and organophosphates (21 cases, all referred). *Conclusion:* Human pesticide exposures account for approximately 4% of all inquiries and require medical referral in approximately 40% of cases. Most exposures occur in the home, in males and females equally. Occupational exposures are much less commonly reported and occur mainly in males. Intentional exposures are comparatively uncommon. The majority of inquiries from medical facilities relating to exposure to products containing boric acid, coumarins or metaldehyde can usually be managed in the home.

284. Poisoning by Methyl Bromide. Description of 2 Cases

Climent B,[1] Panos R,[2] Botella J,[2] Jannone R,[2] Bonastre J,[2] Garrido-Lestache E.[3]
[1]*Clinical Toxicology Unit, Hospital General, Valencia;* [2]*Intensive Care Department, Hospital La Fe, Valencia;* [3]*Legal Medicine Institute, Valencia, Spain*

Objective: Methyl bromide is a colorless gas. It is the most toxic of those used in industry. It is absorbed by ingestion, dermally and by inhalation and is especially toxic to the central nervous system (CNS). 2 cases of accidental poisoning by inhalation of methyl bromide are reported. *Case report:* The patients were 2 brothers, 27 (1st case) and 26 (2nd case) years, with no personal medical history, admitted to the intensive care unit (ICU) with seizures. In the first case, symptoms began with headache, difficulty in swallowing and then vomiting and seizures. Upon his arrival at the hospital he was intubated and mechanically ventilated because of *status epilepticus* with no response to conventional treatment. A CT-scan was performed with no pathological images. Several electroencephalograms (EEG) were performed which showed persistent though minor, discharge activity. Since the patient had started with refractory hypoxemia ($pO2/FiO_2$: 101), it was attributed to infection with a radiological image compatible with pneumonia. The patient stayed in a state of shock and respiratory distress that led to death on the 6th day of admission. The 2nd brother was admitted 4 days later with myoclonus jerks without deterioration in the level of consciousness. Neither the CT-scan or ECG showed pathological findings. The lumbar puncture performed was normal. *Anamnesis:* exposure to a "Substance" used for the fumigation of a closet that had termites in the room next to the sleeping room (conducted 24 hours before the onset of symptoms). According to the company spraying, the substance used was primarily permethrin to 23.5% ("Ecorex Action"). However, the cupboard was covered by some awnings that had been used to fumigate with methyl bromide. Given the high suspicion of bromide toxicity hemodialysis was started. The urine samples sent to the National Center for Toxicology confirmed the presence of the product. The subsequent evolution of the patient was satisfactory. *Conclusion:* The high toxicity of methyl bromide is its potential to penetrate by inhalation without being noticed. The effect on the central nervous system can be confused with functional or psychogenic effects. A high index of suspicion by the clinic is crucial for diagnosis.

285. The Pattern of Acute Pesticide Poisoning Admitted in ICU II Toxicology – Emergency Clinical Hospital Bucharest Between 1997–2007

Macovei R,[1,2] Danescu I,[1] Ionica M,[2] Caragea G.[2]
[1]*ICU II Toxicology, Emergency Clinical Hospital, Bucharest;* [2]*Army Center of Medical Research, Bucharest, Romania*

Objective: Acute pesticide poisoning, a medical emergency requiring prompt treatment, is a common problem in our country due to widespread use of these compounds. We present an epidemiological profile of acute pesticide poisoning admitted in our department between 1997–2007. *Methods:* The medical records of the cases were reviewed retrospectively. *Results:* During 11 years, 922 cases of acute pesticide poisoning were recorded. The frequency in total poisoning was: 1997 – 3.13% (106 cases), 1998 – 4.05% (126), 1999 – 3.31% (89), 2000 – 4.80% (118), 2001 – 5.03% (107), 2002 – 3.98% (84), 2003 – 4.93% (74), 2004 – 4.38% (58), 2005 – 4.98% (56), 2006 – 4.45% (53), 2007 – 3.89% (51). The most common occupations were associated with agriculture. The seasonal distribution peaked in spring and autumn months. In most cases oral ingestions was reported. The majority (86%) were suicide attempts and the remainder (14%) was accidental exposures. The most frequently implicated was the 21–30 year group for both males and females. Of the patients studied, 49.27% was females and 50.73% males. The products involved were: organophosphates 42%, carbamates 30%, other insecticides and herbicides 18%, rodenticides 8%. In 76% of admitted patients there were severe symptoms (coma 46%, respiratory failure 42%, cardiac troubles 18%). In 46% of the patients mechanical ventilation was initiated. Specific therapeutic strategy: 62% received atropine, 14% received cholinesterase reactivators. Blood pseudocholinesterase measurements were regularly performed. The mortality was 4% in the total mortality from poisonings, through cardiac arrhythmias and respiratory disturbances, higher in the males group and in the patients with associate morbidities. All patients with suicide attempts were referred to a psychiatry specialist. *Conclusion:* Acute pesticide poisoning counts for 4.15% of the total number of poisonings admitted in our department. The number of patients decreased in the last years because of legal measures limiting availability of these products and the use of more non-toxic substances. Most of the cases admitted were suicidal with oral route of exposure and in severe condition. Organophosphates show a higher proportion of severe and fatal cases. To decrease the morbidity and mortality through pesticide poisoning, it a more severe control of the sale and use of these products is needed.

286. Amitraz Poisoning in South Africa: An Analysis of Cases Over the Past 5 Years

Veale DJH, Müller GJ, Wium CA.
Tygerberg Poison Information Centre, University of Stellenbosch, Cape Town, South Africa

Objective: The aim of this study was to report on the incidence of amitraz poisoning in South Africa. Amitraz is a novel pesticide widely used as an ectoparasiticide in veterinary medicine and as an insecticide in agriculture. Its main toxic effects in humans relate to stimulation of alpha 2-adrenoceptors. *Methods:* The incidence of amitraz poisoning consultations at the Tygerberg Poison Information Centre over the past 5 years was evaluated. Data relating to telephonic consultations were extracted from standard consultation forms and analyzed for the incidence of amitraz poisoning in pesticide poisoning consultations; prevalence of poisoning in adults compared to children; whether the poisoning was accidental or intentional; characteristic signs and symptoms; type of exposure; and clinical details in cases of significant toxicity where the clinical progress of the patient was followed for 3 days. *Results:* During the 5 year

period reviewed, 2.5% of the pesticide poisoning consultations (2346 of a total of 13749 consultations) were amitraz-related and this comprised 0.5% of all poisoning consultations. Ectoparasiticide formulations were responsible for at least 77% of amitraz exposures. Poisoning in children was reported in 30% of cases and in adults in 70% of cases. Poisoning was intentional in 58% of cases as opposed to 42% cases of accidental exposure. This differs from international demographics where poisoning was most often reported in children and was predominantly due to accidental exposure. Intentional poisoning in adults was 83% in this study compared to 64% reported in existing international literature. Ingestion of amitraz accounted for 88% of cases and poisoning by dermal exposure represented 12% of cases. Symptoms and signs of clinical toxicity were recorded in 40% of consultations. The most frequent clinical findings reported were central nervous system depression, miosis, bradycardia and hypotension. *Conclusion:* This is the first report of the incidence of amitraz poisoning in South Africa and it highlights a different demographic pattern compared to the existing literature. It reflects the highest recorded incidence of adult poisoning and the highest recorded incidence of intentional ingestion in a country. Clinical findings were similar to those reported in the literature.

287. Intentional Ingestion of Diquat: A Case Report with Fatal Outcome

Tsamadou A, Fountas K, Sofidiotou V, Kalostou A, Papathanassiou V, Zoniou S, Neou P.
Poison Information Centre, Children's Hospital P&A Kyriakou, Athens, Greece

Objective: Diquat is a pesticide chemically related to paraquat but with differentiated clinical picture. When ingested, the main difference between them is that diquat does not accumulate in the lung and does not cause pulmonary fibrosis. It is a strong poison. In human diquat poisonings, approximately 50% of patients have neurologic effects. The cause of these effects is not known. Some cases have involved progressive development of neurological effects within 72 to 96 hours. Hemorrhagic cerebral and brainstem infarctions may occur. Unlike the more frequent paraquat poisonings, diquat poisonings are rare. Below we describe the first case of intentional diquat ingestion which has been referred to our poison information centre for at least 5 years. *Case report:* A 30 year old man with a medical history of depression proceeded to the hospital after intentional ingestion 50 ml diquat. He was admitted to the Intensive Care Unit. Gastric decontamination was immediately performed and activated charcoal was administered in repeated doses. Hemofiltration was started within 4 hours post ingestion. The patient developed acute renal failure and hemodialysis continued after the first 24 hours. He showed moderate hepatic impairment (enzyme levels about 250–300, INR 1.4, bilirubin around 2). 72 hours post ingestion he developed neurological findings, GCS 3 and absence of brainstem reflexes. CT showed exaggerated cerebral swelling without response to aggressive therapy. The patient was intubated (he could not maintain his own breathing) with no evidence of pulmonary damage. MRI was not performed, therefore we do not know if there were brainstem infarctions. There was no improvement for the next 18 days and the patient died with evidence of multiple organ failure.

288. Potassium Homeostasis in Patients with Acute Organophosphorus Poisoning

Gawarammana IB,[1] Kularathna KS,[2] Dawson AH.[3]
[1]Department of Clinical Medicine and South Asian Clinical Toxicology Research Collaboration, University of Peradeniya, Peradeniya, Sri Lanka; [2]Toxicology Unit, Teaching Hospital, Peradeniya, Sri Lanka; [3]South Asian Clinical Toxicology Research Collaboration, University of Peradeniya, Sri Lanka and School of Population Health, University of Newcastle, Australia

Objective: Although only 2% of total body potassium (70–100meq) remains in the extracellular compartment, it plays a critical role in maintaining cell membrane resting potential (RMP). Relatively small changes in extracellular potassium concentration can significantly alter RMP and functional activity of electrically excitable cells. Hypokalaemia was noted on admission in 5/60 patients with organophosphate poisoning.[1] This phenomenon may compound the weakness due to inhibition of acetylcholine esterase by organophosphorus compounds (OP). K is tightly balanced in that urinary K excretion (1 - 1.5 mmol/Kg/day) is directly proportional to the total body potassium and is a good marker of total body K. *Methods:* We prospectively measured serum K and urinary potassium excretion on day 1 to 3 in consenting patients following ingestion of OP. *Results:* There were 35 patients (median age 45 years - IQR 24–45, 18 males) in acute cholinergic phase. 41% ingested chlorpyrifos. Median serum K remained in the lower range of normal. Median K excretion was 0.08 mmol/Kg (IQR 0.3–1) which is lower than the average 1–1.5 mmol/Kg/day. There was a significant reduction in median K excretion on day 2 (0.2 mmol/Kg/day; IQR0.1–0.6) ($p = 0.004$) which did not differ between OP type and gender. *Conclusion:* Potassium homeostasis appears to be altered in acute organophosphate poisoning with evidence suggesting renal conservation of potassium. Potential causes include intracellular shift, poor intake, gastrointestinal loss and changes in aldosterone and cortisol levels. It is possible that alterations in K may alter neuromuscular junction function in OP poisoned patients or alter cardiac conduction and contribute to the overall mortality and morbidity. *Conclusion:* Patients with OP poisoning seem to conserve excretion of K to maintain normal serum K even on day 1 which reached a maximum on day 2. Further studies should be done to investigate the causes of this phenomenon and the effect of routine K replacement to K excretion and RMP. *References:* 1. Balali-Mood M, Afshari R, Kahrom M, et al. Use of high doses of sodium bicarbonate in acute organophosphorous pesticide poisoning is advancing. Clin Toxicol 2007; 45:92–93.

289. Triphasic Waves Encephalopathy and Delayed Guillain Barré Syndrome in a Chlorophenoxy Herbicide Poisoned Patient

Schoonjans A,[1] Van Pesch V,[2] Van Snick S,[2] Van den Bergh P,[2] Mostin M,[3] Hantson P.[1]
[1]Department of Intensive Care, Cliniques St-Luc; [2]Department of Neurology, Cliniques St-Luc, Brussels; [3]Poison Control Center, Brussels, Belgium

Objective: Chlorophenoxy herbicide poisoning is relatively uncommon but may be complicated by serious neurological events. The possibility of delayed peripheral neuropathy has been discussed in rare observations. *Case report:* A 46-year-old man ingested 200 ml of a chlorophenoxy herbicide (containing 70 g/l 4-chloro-2-methylphenoxyacetic acid (MCPA), 70 g/l 2,4-dichlorophenoxyacetic acid (2,4-D), 42 g/l 4-chloro-2-methylphenoxypropionic acid (MCPP) and 20 g/l 3,6-dichloro-2-methoxybenzoic acid (dicamba)). The patient was drowsy, disorientated and restless. No verbal response was obtained and the initial GCS was 8/15 (E2, V1, M5). Neurological examination otherwise revealed normal muscle tone and deep tendon reflexes; no fasciculation was observed, but well myotonia in the upper limbs. Miosis and nystagmus were also present. The only significant biological sign was an increase in serum creatinine concentration (1.6 mg/dl) in the absence of rhabdomyolysis, with a mild increase in arterial lactate level (2.8 mmol/l). The electroencephalogram (EEG) disclosed triphasic waves encephalopathy. Encephalopathy with agitation persisted for 40 hours. Then, the patient awakened relatively abruptly with a complete amnesia of the in-hospital period. Urine alkalinisation was proposed to promote herbicide elimination. The patient was readmitted 8 weeks later. He was unable to walk and the diagnosis of Guillain Barré syndrome (GBS) was made according to the clinical and electrophysiological findings combined with a high protein concentration in the cerebrospinal fluid. No usual precipitating factor for GBS (infection, vaccine) was found. He received a 5 days course of intravenous immunoglobulins and recovered muscle strength after a few weeks. *Conclusion:* Chlorophenoxy herbicide poisoning is relatively uncommon, but may result in serious and sometimes fatal sequelae according to the amount ingested. Encephalopathy with triphasic waves mimicking non convulsive *status epilepticus* is possible following chlorophenoxy poisoning. Delayed peripheral neuropathy is a rare complication and in the present case, the relationship between GBS and herbicide exposure remains speculative.[1] The treatment of chlorophenoxy poisoning is supportive. There is no evidence that urine alkalinization is helpful. *References:* 1. O'Reilly JF. Prolonged coma and delayed peripheral neuropathy after ingestion of phenoxyacetic acid weedkillers. Postgrad Med J 1984; 60:76–77.

290. Evaluation of Therapeutic Error-Related Fatalities in Older Adults Using National Poison Center Data

Hayes BD, Klein-Schwartz W.
Maryland Poison Center, University of Maryland School of Pharmacy, Baltimore, US

Objective: Therapeutic errors in older adults are a significant cause of morbidity and mortality.[1,2] The objectives of this study of national poison center data were to identify the scenarios (reasons) and medications involved in therapeutic errors that resulted in death and to evaluate the accuracy of coded poison center data compared to written fatality abstracts for each case. *Methods:* A retrospective analysis of fatalities due to unintentional therapeutic errors reported to the American Association of Poison Control Centers' National Poison Data System from January 1, 2002 to December 31, 2006 for adults ≥ 65 years old was performed. Data were analyzed for age, chronicity, substances, and case scenario details. Written fatality abstracts for these cases were also examined. *Results:* There were 143,901 older adults with reported therapeutic errors of which 110 died. The medications most frequently involved in the fatalities were digoxin, acetaminophen, theophylline, and colchicine. The most common case scenario details were other/unknown therapeutic error, other incorrect dose, health professional/iatrogenic error, and patient confused or mentally incompetent. In 21 of the 110 cases (19.1%), additional or alternative case scenario detail reasons were found by evaluating the written abstracts. *Conclusion:* These data help elucidate the medications and causes of therapeutic error-related deaths in older adults. Coded poison center data may under-represent the number and type of reasons associated with unintentional therapeutic error cases. *References:* 1. Budnitz DS, Pollock DA, Weidenbach KN et al. National surveillance of emergency department visits for outpatient adverse drug events. JAMA 2006; 296:1858–1866. 2. Gurwitz JH, Field TS, Harrold LR et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA 2003; 289:1107–1116.

291. A Scopolamine Overdose as a Consequence of Different Prescription Policies in Different Countries

Leenders MEC,[1,2] van Velzen AG,[1] de Vries I,[1] Meulenbelt J.[1,3,4]
[1]National Poisons Information Centre, National Institute for Public Health and the Environment, Bilthoven; [2]Perioperative and Emergency Care, University Medical Center; [3]Intensive Care Center, University Medical Center, Utrecht; [4]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands

Objective: To draw attention to medication errors due to differences in dose notation with prescriptions sent from one country to another, illustrated by a case of scopolamine intoxication. *Case report:* The number of email prescriptions using the world wide web is booming. Differences in dose notation may lead to medication errors with very unpleasant consequences as described here in a case of three men with scopolamine intoxication. For a Dutch television program three healthy young men wanted to make a Zero G flight to experience a condition of zero-gravity. As this has a

high incidence of motion sickness they were advised to take a preparation with scopolamine one hour in advance of the flight. A prescription was provided by Kennedy Space Center in the USA and was prepared in the Netherlands. The prescription included scopolamine .4 mg, chlorpheniramine 8 mg and caffeine 200 mg.[1] The pharmacist who prepared the medication did not recognize the .4 mg without a leading zero (in the Netherlands this would be written as 0,4 mg) and delivered 4 mg, a 10 times higher dose. Soon after taking the medication the men experienced the classical symptoms of scopolamine intoxication like dizziness, sedation, a flushed face, a dry mouth and blurred vision. For three days they experienced lively hallucinations and tachycardia. Two of the men complained of fatigue, anxiety and difficulty in concentration until three weeks after the flight. Complaints lasting much longer than five times the biological half-life of scopolamine are also described by Van Sassenbroeck et al.[2,3] *Conclusion:* A USA prescription with a decimal without a leading zero was wrongly interpreted by a Dutch pharmacist leading to an overdose of scopolamine with very unpleasant consequences. *References:* 1. ACOG Committee Opinion No. 331. Safe use of medication. Obstet Gynecol 2006; 107:969–972. 2. Renner UD, Oertel R, Kirch W. Pharmacokinetics and pharmacodynamics in clinical use of scopolamine. Ther Drug Monit 2005; 27:655–665. 3. Van Sassenbroeck DK, Hemelsoet DMR, Vanwalleghem P, et al. Three cases of substitution errors leading to hyoscine hydrobromide overdose. Clin Toxicol 2005; 43:861–865.

292. A Dose as Low as 100 mg of Clozapine can Lead to Severe Toxicity in Clozapine-Naive Individuals

Havnen GC, Beck LIF, Lindqvist R.
National Poisons Information Centre, Directorate for Health, Oslo, Norway

Objective: An inquiry to our Poisons Information Centre (PIC) drew our attention to the issue of toxicity caused by administration errors with clozapine. An elderly man received another patient's dose of clozapine (325 mg), became comatose and showed signs of pulmonary hypersecretions. Our objective was to investigate whether 1) this was an isolated case, and 2) if similar cases are described in the standard toxicity literature. The SPCs of clozapine describe life-threatening comatose conditions in a few adults, with doses as low as 400 mg, affecting primarily those not previously exposed to clozapine. The manufacturers advise a maximum daily dose of 900 mg. *Method:* The PIC uses an internal database to record all inquiries. In our study we collected data concerning administration errors of doses less than 400 mg of clozapine in clozapine-naive adult patients (study period February 2004 - October 2008). The included patients had developed symptoms at the time of the inquiry. Secondly, the standard toxicity literature (Goldfrank's ed. 2006, Dart ed. 2004, Haddad ed. 2007 and Poisindex vol. 138) was reviewed. *Results:* We collected 19 cases of maladministration of clozapine in the dose range 100 - 350 mg. Of these cases, 18 were deemed to show signs of moderate to severe toxicity. The dominating symptoms were CNS-depression varying from somnolence to coma (n = 16) and hypotension/tachycardia (n = 5). Two patients showed signs of pulmonary hypersecretion. In our material ten patients (53 %) were ≥70 years, and six of these patients (60 %) became comatose after receiving clozapine doses ranging from 100–325 mg. Two of these patients received doses as low as 100 mg. The review of the literature did not support our findings. *Conclusions:* Our PIC has received several inquiries of drug administration errors concerning clozapine in clozapine-naive patients. Our data stand in contrast to the documentation in the literature and clearly indicated that administration of doses lower than 400 mg can cause severe toxicity in adults. Elderly patients seem to be most vulnerable. In this patient group a single dose of no more than 100 mg of clozapine can cause severe poisoning.

293. Medication Error Resulting in Intravenous 1% Alum Administration

Farmer BM,[1,2] Mehta RR,[3] Nelson LS,[1,2] Howland MA,[1,4] Hoffman RS,[1,2] Rao RB.[1,3]
[1]New York City Poison Control Center; [2]Dept. of Emergency Medicine, New York University School of Medicine; [3]New York Presbyterian Hospital, Weill-Cornell Medical Center; [4]St John's University College of Pharmacy and Allied Health Professions, New York, US

Objective: Intravesicular administration of 1% alum is often used for chronic hemorrhagic cystitis. We report a medication error that resulted in the first case of intravenous alum administration. *Case report:* A 69 y/o man with lymphomatous invasion of his bladder underwent 2 days of continuous bladder irrigation with 1% alum for hemorrhagic cystitis. His symptoms improved and bladder irrigation was discontinued. The night before discharge the patient developed pain and swelling at the IV site where a normal saline infusion had been initiated. The infusion was moved to the other arm, but similar symptoms developed. After 3 hours of infusion, the nurse realized that the patient was receiving IV alum (1%) instead of normal saline. The infusion was stopped and serum laboratories are obtained. Creatinine was 2.1 mg/dL (185.6 micromol/L). The PCC was called and deferoxamine (DFO) 15 mg/kg/day followed by daily hemodialysis was recommended due to concern of developing acute aluminum toxicity in setting of renal insufficiency. An ultrasound of the upper extremities revealed bilateral thrombophlebitis at the sites of the IVs. After 3 days of therapy DFO and HD were discontinued due to the patient's continued normal neurologic examination. The kinetics of aluminum during the procedure are pending. *Conclusion:* Acute aluminum toxicity resulted in local thrombophlebitis. This error resulted in prolonged hospitalization, chelation therapy (DFO), and exposure to an invasive procedure (HD) due to the risk of severe toxicity from acute aluminum poisoning. It may have been prevented if the connections between a 3 way bladder irrigation foley and peripheral IV were not compatible.

294. Inadvertent Intravenous Infusion of Polyethylene Glycol and Electrolyte Solution in a 3 Year-Old Girl

Hernandez SH,[1,2] Hoffman RS,[1,2] Howland MA,[1,3] Nelson LS,[1,2] Bouchard NC.[1,4]
[1]New York City Poison Control Center; [2]New York University Medical Center; [3]St John's University College of Pharmacy and Allied Health Professions, New York; [4]Columbia University Medical Center, New York, US

Objective: Polyethylene glycol and electrolyte solution (PEG/ELS) is an enteral isosmotic solution used for bowel cleansing. It has a good safety profile when used appropriately. Rare reports of inadvertent intravenous infusion suggest minimal toxicity.[1,2] The theoretical risks of intravenous infusion include fluid and electrolyte disturbances, toxic metabolites of polyethylene glycol, and infection from the nonsterile solution. We report a case of inadvertent intravenous infusion of PEG/ELS with no adverse effects. *Case report:* A 3 year-old girl (15 kg) with no significant past medical history presented to the pediatric ED with abdominal pain and hard stools. Her initial vital signs were within normal limits for her age. The physical examination was unremarkable and an abdominal x-ray demonstrated fecal impaction. A packet of 227.1 g PEG/ELS was reconstituted in a 1 gallon container of sterile water and transferred into an enteral feeding bag. The PEG/ELS was to be administered via nasogastric tube using an infusion pump. Approximately 75 mL was inadvertently infused through a peripheral intravenous catheter over 90 minutes. The patient had no complaints and developed no change in clinical status. Within 30 minutes after the infusion was discontinued, serum analysis demonstrated electrolytes that were within normal limits, with an anion gap of 12 mmol/L and osmolal gap of 2 mOsm/L. The patient was admitted to the pediatric ICU for observation. For the first 24 hours the patient received prophylactic intravenous pipericillin-tazobactam and azithromycin. Repeated electrolytes, CBC, ECGs, and monitoring of clinical status remained normal. *Conclusion:* We report a case of inadvertent intravenous infusion PEG/ELS with no apparent toxicity. This case suggests when PEG/ELS appropriately reconstituted with sterile water to produce an isosmotic solution and a small amount is inadvertently infused, the risk of fluid and electrolyte disturbance and toxicity from the metabolism of polyethylene glycol remain low. A systems based approach must be undertaken to prevent future errors of this kind. *References:* 1. River W, Velez LI, Guzman DD, et al. Unintentional intravenous infusion of golytely in a 4-year-old girl. Ann Pharmacother 2004; 38:1183–1185. 2. Tucker V, Cramm K, Martinez J, et al. Accidental large intravenous infusion of golytely (abstract). J Toxicol Clin Toxicol 2002; 20:87.

295. Hypoglycemia Induced by Insulin Glargine Overdose

Hernandez SH,[1,2] Hoffman RS,[1,2] Howland MA,[1,3] Nelson LS.[1,2]
[1]New York City Poison Control Center; [2]New York University Medical Center; [3]Saint John's University College of Pharmacy and Allied Health Professions, New York, US

Objective: Insulin glargine is a long-acting recombinant human insulin analog relatively new to the market with little clinical experience in overdose. Because it mimics normal basal insulin secretion without pronounced peaks it is not expected to induce hypoglycemia. However, pharmacokinetics may be unpredictable in overdose. We report a case of insulin glargine overdose causing recurrent symptomatic hypoglycemia. *Case report:* An 81 year-old type 2 diabetic woman was brought into the ED because she was diaphoretic and minimally responsive. Upon arrival the physical exam was unremarkable and no focal neurologic deficit was observed. All vitals were reported to be within normal limits. Her capillary blood glucose was 1.7 mM/L (30 mg/dL). The patient became alert, following commands and answering questions after 50 grams of intravenous dextrose. History revealed that her new home health aid had administered 80 units of insulin glargine (Lantus) three times a day rather than once daily for a total of 240 units within 18 hours at different sites. A total of three episodes of symptomatic hypoglycemia occurred within 6 hours from the last dose. The patient received 50 grams of dextrose after each event, a 10% dextrose solution infusion, liberal oral food intake, and 50 micrograms of subcutaneous octreotide (discontinued after absence of oral hypoglycemic agents was confirmed). In the ICU the patient was monitored for hypoglycemia with hourly capillary blood glucose for the first 12 hours and clinically thereafter. Potassium was replaced after repeat chemistry demonstrated a drop in serum potassium from 4.2 to 2.8 mM/L. After 24 hours of admission with increasing glucose levels, treatment for hypoglycemia was discontinued and insulin glargine was restarted at the correct dose. *Conclusion:* Hypoglycemia can occur with insulin glargine overdose and medical management can be difficult due to prolonged hypoglycemia. Repeated dosing of D50 may induce hypokalemia and in a patient with the capacity for endogenous insulin release, potentiate that insulin release and hypoglycemia. Further study is warranted to develop recommendations for management in insulin glargine overdose.

296. A Review of Calls Received by the UK National Poisons Information Service Involving Medical Errors in Hospitals, Care Homes and GP Surgeries from April 2007 to March 2008

Cooper GA, Spears RA, Thompson JP.
National Poisons Information Service (Cardiff), University Hospital Llandough, Cardiff, UK

Objective: To investigate medical errors occurring in hospitals, GP surgeries and care homes over a twelve month period using call data from the National Poisons Information Service (NPIS). *Methods:* Records of all telephone enquiries received by the NPIS between 1 April 2007 and 31 March 2008 were reviewed. Enquiries involving

medical errors in a hospital, GP surgery or care home were examined and details of the nature of error noted. *Results:* The NPIS received a total of 52,386 calls, of these 6946 (13.3%) related to medical errors. The majority of these (89%) occurred in the home, mainly patients taking extra doses of medication or confusing their medication with that of another's. A significant number of calls related to cases of medication error occurring in hospitals (301), GP surgeries (77) and care homes (263), where medicines are typically administered by a carer or healthcare professional. In hospitals, 203 cases (67.4%) involved an excess of medication. Of these 17.2% were due to the shifting of a decimal point, leading to a ten-fold increase in medication; 15.7% the doubling of prescribed dose; 6.9% weekly or monthly medication given daily; and 5.9% an increased infusion rate of intravenous medication. The incorrect medication accounted for 35 cases (11.6%) of hospital errors, while medication being administered via the incorrect route 34 cases (11.3%). In GP surgeries, 58 cases (75.3%) related to errors in administration of vaccinations. Of these 43 calls (74.1%) concerned an excessive dose or extra dose and 14 (24.1%) the incorrect vaccine. Of calls about medical errors in nursing or care homes, most were regarding either the administration of an excess of medication (39.2%) or a patient being given someone else's medication (39.5%). *Conclusion:* Medical errors account for a small but significant number of enquiries to NPIS. The most common error was that of excess dosing, either due to miscalculating or misreading the prescribed dose. Less common was the administration of incorrect medication, usually another patient's. Errors should be avoided by improving documentation of patient notes, more thorough systems for checking medication, and writing prescriptions more clearly.

297. Medication Errors: The Experience of the National Poisons Information Centre of Ireland

Cassidy N, Tracey JA.
National Poisons Information Centre, Beaumont Hospital, Dublin, Ireland

Objective: To characterise the incidence, epidemiology, and type of medication errors reported to the National Poisons Information Centre (NPIC). *Methods:* A 1-year prospective observational study of telephone enquiries to the NPIC was conducted from 1st January 2007 to 31st December 2007, inclusive. Telephone enquiries between 8am to 10pm, were prospectively reviewed by a single investigator to identify incidents involving medication errors. Information on patient demographics, enquiry source, location, pharmaceutical agent(s), type of medication error, and treatment processes was collated. Medication errors were classified as (i) Dosing error (involving an extra dose or the wrong dose) (ii) Administration error (involving the wrong medication, administration via the wrong route, or at the wrong time, (iii) Dispensing error (pharmacy error), (iv) Prescribing error (physician error). *Results:* During the study period, the NPIC received a total of 8,552 enquiries between 8am–10pm. Therapeutic medication errors relating to 724 patients (388 females, 319 males, 17 unknown gender) were reported. 390 children under 18 years of age and 334 adults experienced a medication error. Enquiries originated from General Practitioners (n = 114, 15.75%), GP-out-of-hours cooperatives (n = 252, 34.82%), hospitals (n = 85, 11.74%), pharmacists (n = 64, 8.84%), nursing homes (n = 21, 2.9%), and members of the public (n = 188, 25.96%). Most medication errors occurred in a domestic setting (n = 655) but a small number of incidents occurred in healthcare facilities: nursing homes (n=36), hospitals (n=18), and GP surgeries (n=13). Two incidents occurred in an occupational setting. In children, medication errors with non-prescription pharmaceuticals predominated but in adults, the majority of medication errors involved prescription pharmaceuticals. 402 patients (55.52%) did not require medical treatment, 66 (9.12%) were referred to a hospital emergency department, 64 (8.84%) were referred to a GP, 103 (14.23%) were advised to seek medical advice if symptomatic. Symptomatic and supportive care was recommended for 89 patients (12.29%) already undergoing medical assessment in healthcare facilities. 66.4% of medication errors involved a dosing error (n = 481), 30.7% (n = 222) were administration errors, and dispensing and prescribing errors accounted for 2.1% (n = 15) and 0.8% (n = 6) of errors respectively. *Conclusion:* Medication errors represented a significant proportion of NPIC enquiries and dosing errors were prevalent.

298. Methadone-Related Ventilatory Patterns in Various Experimental Conditions of Administration in Rats

Chevillard L,[1] Mégarbane B,[1,2] Risède P,[1] Baud FJ.[1,2]
[1]*INSERM U705, University Paris-Diderot, Paris;* [2]*Réanimation Médicale et Toxicologique, Hôpital Lariboisière, Paris, France*

Objective: Methadone is responsible for respiratory depression causing severe or fatal intoxications. Circumstances of poisoning in drug addicts are various, including overdoses, psychotropic drug co-ingestions (benzodiazepines), and drug-drug interactions. Interindividual variations in cytochrome P450 (CYP)3A4 or 2D6 expression, both enzymes that play a key-role in methadone biotransformation, may also account for the variability of methadone respiratory effects. We studied methadone-related ventilatory patterns in rats in three different conditions of administration. *Methods:* We performed an experimental study in Sprague-Dawley rats using arterial blood gases and plethysmography (N = 8 rats/group). Body temperatures were measured using telemetry devices, intraperitoneallly (IP) implanted 72h before experimentation. Three conditions of methadone administration were tested, including 1)- methadone dose incrementation (1.5, 5, and 15 mg/kg, IP); 2)- diazepam (20 mg/kg subcutaneous) and methadone (5 mg/kg; IP) co-administration; 3)- dexamethasone pretreatment (100 mg/kg during 3 days; IP; shown to induce CYP3A). We calculated the area under the curve from T0 to measurement completion for each animal and each parameter. Plasma methadone concentrations were measured using high-performance liquid chromatographic-mass spectrometric assay. Comparisons were performed using ANOVA for repeated measurements followed by Bonferroni post-tests. *Results:* Methadone administration resulted in a dose-dependent significant increase in inspiratory (TI, $p<0.01$) and for 15 mg/kg in expiratory time, resulting in a significant decrease in respiratory rate and total volume ($p<0.01$). Diazepam pre-treatment (20 mg/kg) significantly increase methadone- related effects on TI ($p<0.01$). Dexamethasone pre-treatment significantly reduced methadone-related effects on $PaCO_2$ and TI ($p<0.01$). PK/PD relationships supported a pharmacodynamic mechanism for the alteration of methadone-related respiratory effects in both cases. *Conclusions:* In rats, methadone is responsible of dose-dependent respiratory effects characterized by an increase in TI. BZD co-administration and dexamethasone pretreatment alters response to methadone with a predominantly pharmacodynamic mechanism.

299. Involvement of the Different Opioid Receptors in Respiratory Depression in Rats

Chevillard L,[1] Mégarbane B,[1,2] Risède P,[1] Baud FJ.[1,2]
[1]*INSERM U705, University Paris-Diderot, Paris;* [2]*Réanimation Médicale et Toxicologique, Hôpital Lariboisière, Paris, France*

Objective: Opioid analgesics (morphine and fentanyl) and maintenance treatments (methadone and buprenorphine) are known to induce respiratory depression characterized by an increase in inspiratory time (TI) and a decrease in respiratory rate. However, their role on expiratory time (TE) is unknown. We aimed to characterize the respective role of the different opioid receptors in the control of ventilation in order to identify opioid-specific respiratory patterns. *Methods:* The respiratory effects of 4 opioids were studied in Sprague-Dawley rats using arterial gases and plethysmography (N = 8 rats/group). Body temperatures were measured using telemetry devices intraperitoneallly (IP) implanted 72h before experimentation. Drugs were IP administered at equivalent doses to 80% of the lethal dose-50% (80 mg/kg-morphine, 1.7 mg/kg-fentanyl; 15 mg/kg-methadone, and 160 mg/kg-buprenorphine). Opioid-receptor (OR) antagonists, including intravenous 10mg/kg-naloxonazine at 5 min [mu-OR antagonist], subcutaneous 30mg/kg-naloxonazine at 24h [mu1-OR antagonist], subcutaneous 3 mg/kg-naltrindole at 45min [delta-OR antagonist], and subcutaneous 5 mg/kg-Nor-binaltorphimine at 6h [kappa-OR antagonist] were pre-administered to test the role of each receptor. We performed comparisons using ANOVA for repeated measurements followed by Bonferroni post-tests. *Results:* Pre-treatment with intravenous naloxonazine (devoid of significant effects on arterial gases) significantly diminished the effects of morphine, fentanyl, and methadone on $PaCO_2$, PaO_2, and pH. This effect corresponded to a reduction in TI increase ($p<0.001$) and an inhibition of TE increase ($p<0.001$). By contrast, rat pre-treatment with Nor-BNI did not result in any significant modification of respiratory times. Furthermore, subcutaneous naloxonazine significantly diminished the opioid-related effects on $PaCO_2$ and pH, and regarding fentanyl, on PaO_2. This effect corresponded to a reduction (partial effect) in TI increase ($p<0.05$) and to an inhibition (full effect) of TE increase ($p<0.001$). By contrast, rat pre-treatment with Nor-BNI and naltrindole did not result in any significant modification of blood gases parameters and respiratory times. *Conclusion:* Mechanisms of respiratory depression in relation to toxic doses of opioids is not uniform, depending on the molecule. Our results clearly suggest different control patterns of $PaCO_2$ and PaO_2 as well as inspiratory and expiratory times by opioid receptors. Opioid-related hypercapnia, respiratory acidosis, and TE increase are mediated by mu-1 receptors.

300. A Comparative Study in Mice of Tolerance to Morphine Analgesic and Respiratory Effects

Tardy F,[1] Mégarbane B,[1,2] Noble F,[1] Risède P,[1] Mohammed W,[1] Baud FJ.[1,2]
[1]*INSERM U705, University Paris-Diderot, Paris;* [2]*Réanimation Médicale et Toxicologique, Hôpital Lariboisière, Paris, France*

Objective: Morphine may be responsible for severe poisonings. Morphine toxicity was attributed, in chronically treated patients, to the development of a weaker tolerance for its respiratory effects in comparison to its analgesic effects. Our objective was to test this hypothesis. *Methods:* Experimental study in Swiss mice with intraperitoneal morphine administration and comparison of both analgesic (using hot plate, N=10/group) and respiratory effects (using plethysmography under 4%-$FiCO_2$, N=8/group); determination of a protocol inducing acute and chronic tolerance; calculation of the 50%-effective dose (ED50); *in vitro* study of 3H-DAMGO binding on 2 brain structures (periaqueductal grey region and brain-stem); comparisons using ANOVA for repeated measurements followed by Bonferroni post-test. *Results:* Morphine analgesic effects were dose-dependent. Tolerance to morphine was reached with a repeated 2.5 mg/kg/day administration during 10 days, with a 13-time increase in ED50. Kinetics of morphine-related respiratory effects were parallel to the analgesic effects with a significant increase in inspiratory time (TI) at 30 and 40 min after injection ($p<0.01$), without any significant modification in the total volume. Mice pre-treatment with a huge dose of morphine (100 mg/kg, subcutaneously) one day before resulted in a significant reduction of 2.5 mg/kg morphine-related effects on the expiratory time (TE) ($p < 0.05$). Using the same protocol, we observed in mice only a limited tolerance at day 10 in comparison to day 1 without a significant modification in the ED50 of the respiratory effects. Tolerance intensity to the analgesic effects was more important than tolerance to the respiratory effects at day 10. This difference was not accompanied by any significant modification in membrane expression of mu-opioid receptors based on differences in 3H-DAMGO binding between the periaqueductal and brainstem regions. *Conclusion:* Tolerance to morphine respiratory effects was more limited than to its analgesic effects at day 10 of repeated administration. Consequently, this model supports the hypothesis that attributes morphine toxicity to the development of a weaker tolerance to its respiratory effects. However, other mechanisms of toxicity should be considered to explain the variability of respiratory depression.