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EAPCCT ABSTRACTS

Abstracts of the XXVIII International Congress of the European Association of Poison Centres and Clinical Toxicologists, May 6–9, 2008, Seville, Spain

1. Prevention of Poisoning Through Management of Chemical Risks in the Workplace

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Objective: To manage the occupational hazards associated with the production and use of numerous potentially toxic chemicals at the world's largest chemical site. *Method:* BASF has set up a comprehensive system to deal with the risk of injury or intoxication with chemical substances that includes accident prevention by means of plant design and process safety. The Occupational Medical and Health Protection Department and the Safety and Environmental Department work closely together in performing workplace risk assessment and education of the workers in the safe handling of hazardous substances. Every worker handling hazardous chemicals receives regular medical examination, including biomonitoring, when appropriate. For management of emergency exposures, immediate response is crucial. To this end, the following are available: trained first-aiders at each plant; an on-site medical emergency service; an emergency physician on duty 24/7; and a site clinic equipped with decontamination materials, antidotes and adequate personal protective equipment. Processes for immediate decontamination and treatment of intoxicated employees have been defined and are verified in regularly performed drills. Toxicological evaluations and specific treatment guidelines (Chemical Emergency Medical Guidelines) for chemicals are prepared to guarantee current medical treatment. The information management of public and media is the last step of our system. *Results:* Among a total number of 33,000 employees at the BASF Ludwigshafen site in 2006 there have been 1,375 accidents documented in the site clinic. Most of these accidents were mechanically caused and insignificant. 234 of the accidents were caused by chemicals (106 effects with systemic symptoms, 67 chemical burns, 61 irritations). The most frequent chemicals involved were: acrylic acid, sodium hydroxide, nitric acid, ammonia, sulfuric acid, hydrochloric acid, formaldehyde, phosgene, phthalic anhydride and chlorine. Only five patients were transferred to external specialist treatment, and only one was hospitalized. All others were treated in the site clinic. *Conclusion:* The BASF system of management of chemical risks is effective in the prevention of chemical poisoning and health sequelae. Regular updates of program, materials and training of staff are a prerequisite for the continuing effectiveness of this system.

2. Biological Monitoring in the Workplace

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Objective: To demonstrate the utility of biological monitoring as a tool to assess and help control occupational exposure to hazardous chemicals. *Methods:* Biological monitoring is based on the analysis of hazardous substances or their metabolites in biological fluids (usually urine, blood or breath). Biological monitoring gives a guide to the uptake or systemic exposure (as opposed to external exposure). It has a particular role for substances that can be absorbed through the skin, or where control of exposure relies on personal protective equipment (respirators or gloves) where air and surface monitoring alone may not give a complete guide to exposure. The only biological monitoring that is compulsory in the UK is for workers exposed to lead. Exposure to other hazardous substances comes under the Control of Substances Hazardous to Health Regulations. Biological monitoring has roles under regulation 10 (control of exposure) and regulation 11 (health surveillance). The Health and Safety Laboratory provides analytical support to the Health and Safety Executive, other Government Departments and private industry, in this area. Samples for biological monitoring come from industry occupational health providers and hygienists or from Medical Inspectors. Samples may be for regular monitoring of exposure and controls, or for investigations ranging from isolated incidents to industry-wide surveys. HSL has biological monitoring methods for over 100 different analyte matrix combinations based on published methods using GC-MS, LC-MS-MS or ICP-MS. All have internal quality assurance and, where available, external quality assurance schemes. *Results:* Workplace poisonings are, fortunately, rare but we have had a couple of incidents recently with workers becoming overcome by hydrogen sulphide in slurry pits. Exposure to hazardous substances has traditionally been controlled by occupational exposure limits (1–3). These are based on available evidence and where possible, are set at levels that workers could inhale 8 h/day, 5 days a week for a working life time without significant risk of ill-health. In the case of carcinogens, mutagens, respiratory sensitisers and substances with insufficient data to set a health-based limit, the exposure limits are not health-based and the onus on employers is to reduce exposure to as low as is reasonably practical. More recently, in the UK, there is a move towards controlling exposure based on good occupational hygiene practice rather than air monitoring. Globally, biological monitoring guidance values have been developed for around 100 substances found in the workplace (1–3). Most are health-based or based on the biological monitoring values found after inhalation of the occupational exposure limit for 8h. In the case of carcinogens, these guidance values are not health-based but are biological equivalents. In the UK an alternative approach based on good occupational hygiene practice has been developed based on the 90th percentile of data from workplaces with good control. A survey of 25 workplaces with potential exposure to polyaromatic hydrocarbons (PAHs) showed good relationships between: a) airborne exposure to 9 carcinogenic PAHs and benzo(a)pyrene (r-squared 0.97, n=220) and b) airborne exposure to benzo(a)pyrene and urinary 1-hydroxypyrene (r-squared 0.77, n=50). A guidance value of 4 micromol 1-hydroxypyrene/mol creatinine has been adopted based on the 90th percentile of data from workplaces with good control. Biological monitoring for the suspect human carcinogen MbOCA is based on measurement of urinary MbOCA and its labile metabolites. HSL has monitored workers exposure to MbOCA for over 30 years. The number of samples varies each year from 175–598 workers in 15–27 companies. In 1977 the 90% value for urinary MbOCA was 180 mmol/mol. This was reduced to 30 mmol/mol in 1983 (and became a 'Biological Action Limit'). Biological monitoring provides a feedback loop for control of exposure and by targeting action to those companies and workers exceeding the guidance value exposure can be gradually reduced. This approach enables employers to demonstrate good control of exposure and HSE to show an overall reduction in exposure and risk of ill-health. It is also reassuring to workers. The 90% value for MbOCA was further reduced to 15 mmol/mol in 1993 and renamed a Biological Monitoring Benchmark value. Since then the 90% value of biological monitoring data has been <10 mmol/mol but a recent survey showed that controls could be improved further. The most recent biological monitoring guidance value adopted by HSE is for exposure to isoycanates. Isocyanates are the biggest cause of occupational asthma in the UK. Spray painters using 2-pack isocyanate-based paints in vehicle repair are at particular risk. Paint spraying is carried out in spray booths or rooms to prevent exposure of other workers, and the sprayers themselves use air-fed masks. Biological monitoring based on the analysis of isocyanate-derived diamines in urine is a simple and practical way to establish if the controls are working and being used correctly. A biological monitoring guidance value based on the 90th percentile of isocyanate-derived diamines collected from over 1300 urine samples was 1 micromol isocyanate-derived diamine/mol creatinine. This has been promulgated across the industry as part of the information given in the HSE Safety and Health Awareness Days. Where biological monitoring results have exceeded the guidance value a second set of urine samples bottles was sent to the workers for a re-test after improving controls. The results from the second round show lower levels indicating improved controls. *Conclusion:* Biological monitoring is a useful tool for employers, occupational health professions and regulators to assess and help control exposure to hazardous substances in the workplace. *References:* 1. ACGIH. TLVs and BEIs Based on the documentation of the Threshold limit values for chemical substances and physical agents & Biological Exposure Indices. ACGIH Worldwide Cincinnati OH USA: 2006; ISBN 1-882417-62-3. 2. Deutsche Forschungsgemeinschaft. List of MAK and BAT values. Commission of the Investigation of Health Hazards of Chemical Compounds in the work area. Report 42. Wiley VCH, Verlag GmbH & Co KgaA: 2006. 3. HSE. EH40/2005 workplace exposure limits. HSE Books, 2005: ISBN 0 7176 2877 5.

3. Occupational Asthma in the Chemical Industry

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Occupational asthma (OA) is characterized by airway inflammation, bronchoconstriction, and airway hyperresponsiveness in response to workplace exposures. The development of OA results from a complex interaction between environmental factors and individual susceptibility. More than 300 agents have already been identified as causative agents in the development of OA. In the Czech Republic with a population of 10 million, 80 patients were acknowledged with OA in 2006. In developed countries, OA is among the most prevalent occupational lung diseases. The definition does not specify the mechanism of asthma induction, and therefore allergen-induced hypersensitivity reactions, pharmacological effects, and direct airway irritation can qualify as OA (1). The attributed proportion of asthma due to occupational exposures among all asthma cases may represent about 15%. Occupations using chemicals that contribute to asthma are found especially in the chemical industry (2), metal, rubber and plastic work, construction, printing and cleaning. Workplace exposure is an important cause not only of new-onset asthma, but also of exacerbations of pre-existing disease. The diagnosis of OA requires the highest level of evidence, because it has significant implications for both worker health and socioeconomic status. Two types of OA are distinguished, by whether they appear after a latent period of exposure necessary for the worker to acquire immunologically mediated sensitization to the causal agent (1). 1. Immunological OA (more than 90% of OA). It is characterized by a latent period between onset of exposure and symptoms that may vary from a few weeks to several years. It develops after repeated low exposures to vegetable and animal proteins, enzymes, industrial cleaning agents, persulfates, solder flux, metal dusts (e.g. cobalt, chromium, nickel, platinum salts), fumes, sensitizing drugs, etc. Nasal allergic symptoms usually precede and accompany immunological OA. The airway inflammation is characterized by the presence of eosinophils and neutrophils, and thickening of the reticular base membrane leads eventually to marked fibrosis and remodelling of the airways. 1.A. Immunologically mediated OA by IgE mechanism involves mostly high-molecular-weight agents (vegetable and animal allergens) and some low-molecular-weight agents (platinum salts, acid anhydrides, etc, acting as haptens and combining with a body protein to form functional antigens). All these agents induce mostly

early asthmatic reaction within the first minutes or hours after exposure in a sensitized person. Total and specific IgE serum levels (*in vitro*) and skin prick tests in the patient contribute to the diagnosis of OA IgE mediated. 1.B. Immunologically mediated OA where IgE mechanism has not been demonstrated - involves mostly low molecular-weight agents, such as diisocyanates, and acrylates. Asthmatic reaction shows frequently a late (after several hours) or biphasic (both early and late) asthmatic response in the sensitized subject. Otherwise, the clinical and pathologic features are no different from the first type. The diagnosis in both types of immunologically mediated OA may be supported by bronchial hyperreactivity in nonspecific bronchoprovocation test (with inhaled methacholine or histamine), and serial PEF (peak expiratory flow) measurement at least 4 times a day during several working weeks and at least 2 weeks off work. However, the main pitfall of serial PEF is patient compliance and possible malingering. Therefore, specific inhalation challenge tests are generally considered a "gold standard" to prove the cause of immunologically mediated OA. They are performed with suspected occupational allergens in the exposure chamber or at the workplace, and are accompanied by repeated measurements of lung functions. They should be used with caution as systemic allergic reactions may rarely occur. 2. Nonimmunological (Irritant-induced) OA. This type (about 6% of OA) is characterized by the absence of a latency period. It occurs after accidental exposure to high concentrations of a workplace irritant. The most definitive form of irritant-induced asthma is the reactive airway dysfunction syndrome (RADS) developing within 24 hours after a first exposure to high levels of an irritating vapor, fume, or smoke (3,4). Chemicals involved in this type of asthma include chlorine, sulfur dioxide, ammonia, combustion products, etc. Due to the initial injury the bronchial epithelium becomes denuded and loses its protective properties. Exposure of nerve endings leads finally to the tissue remodelling response. Diagnosis of nonimmunological OA is based on the typical history of the accident and non-specific bronchial hyperreactivity, which may persist for many years after initial exposure. Specific bronchoprovocation challenge test is not used. The assessment of exposures of OA always begins with a focused occupational history. Additional information can be gained from material safety data sheets of chemical products present at work. Industrial hygienists may help to clarify the presence of work sensitizers or irritants and to collect samples for the specific challenge tests. Early referral and medical evaluation is needed because the diagnosis may be very hard to establish in patients who have left work. The decision to leave a job is difficult given the implicit socioeconomic impact in most countries. However, the longer the duration of symptoms of OA before diagnosis, the poorer is the outcome (5,6). Patients with OA should always be transferred to a job where exposure to the causal allergen is excluded. In parallel, limiting exposure to environmental allergens and nonoccupational irritants, such as tobacco smoke, and optimizing antiasthma therapy is necessary. *References:* 1. Sastre J, Vandenplas O, Part HS. Pathogenesis of occupational asthma. *Eur Respir J* 2003; **22**: 364–373. 2. Klusackova P, Lebedova J, Pelclova D, *et al*. Occupational asthma and rhinitis in workers from a lasamide production line. *Scand J Work Environ Health* 2007; **33**: 74–78. 3. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS): persistent asthma syndrome after high level irritant exposures. *Chest* 1985; **88**: 376–384. 4. Nemery B. Late consequences of accidental exposure to inhaled irritants: RADS and the Bhopal disaster. *Eur Respir J* 1996; **9**: 1973–1976. 5. Park HW, Kim DI, Sohn SW, *et al*. Outcomes in occupational asthma caused by reactive dye after long-term avoidance. *Clin Exp Allergy* 2007; **37**: 225–230. 6. Klusackova P, Pelclova D, Lebedova J, *et al*. Occupational asthma after withdrawal from the occupational allergen exposure. *Ind Health* 2006; **44**: 629–38. *Acknowledgement:* MSM 0021620807.

4. Of Paradigms and Paradoxes: Unraveling the Basis of Chlorine Poisoning

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Introduction: An understanding of the pathophysiology of the toxicological effects of inhalant gases requires an awareness of the intimate interplay between toxicokinetics and chemistry. The former is dependent on aqueous solubility and has dominated the intellectual construct of the toxicological behavior of gases. Hence, the accepted paradigm to explain the anatomical loci of gases has a virtual sole reliance on solubility. The reason for the acceptance of this paradigm is that it generally explains most of the observations of adverse effects of gas exposure. For example, exposure to gaseous ammonia, which is highly water soluble, causes adverse manifestations primarily in the eyes, nose, and upper airways. In contrast, exposure to sufficient doses of the very slightly water soluble NOx causes little to no effect at these anatomical loci yet can cause substantial adverse effects at the alveolar level. This is explained by the low solubility of NOx, thus its passage through the upper airways without being absorbed by the moist mucosal surfaces over which it traverses. While solubility often provides an ample explanation of the effects of many gases, restricting the conceptualization of their toxicology to this parameter is too simplistic in certain circumstances. In cases where the solubility paradigm fails to explain gaseous behavior a *de rigueur* analysis generally identifies a superimposition of chemical properties of the molecule in question that alters its toxicokinetics. This is no mere theoretical obscurity; rather it explains the behavior of the singly most common potentially toxic gas exposure, both for individuals and in mass casualty scenarios – chlorine gas. There have been numerous descriptions of groups heavily exposed to chlorine. Generally, however, these are in the form of uncontrolled case series and rarely are there exposure or dose assessments. Almost never is there information provided about pre-exposure pulmonary function. Thus, the assessment of the literature on chlorine exposure and its aftermath is limited by these fundamental data deficiencies. Yet some information can still be gleaned from these data. From these it is possible to critically reach conclusions regarding the acute effects, and chronic sequelae, of chlorine exposure. *Acute presentation of chlorine exposure:* There have been numerous descriptions of the clinical picture of acute symptomatic chlorine exposure. The earliest major description derives from studies on chlorine-exposed soldiers from the release of this gas at Ypres, Belgium in 1915. (Berghoff 1919) However the large number of confounding factors and poor followup makes this information, despite impressive numbers of individuals involved, of limited utility. A description of the various effects of chlorine poisoning in more contemporary literature can be found, for example, in the work of Chasis 1947; Kaufman 1971; Hasan 1983; Charan 1985; Jones 1986; Ramachandran 1990; Schwartz 1990; Fleta 1986; Moulick 1992; Sexton 1998; Guloglu 2002; Horton 2002; LoVecchio 2005; and Ngo, 2007. Based on these studies it appears that the initial symptoms associated with chlorine gas inhalation, even if severe, are predominantly upper respiratory and associated with coughing. A small percentage of individuals will develop bronchospasm and minor eye symptoms are common. Indications on initial presentation of severe pulmonary injury are uncommon. *Chronic sequelae of chlorine exposure:* A number of studies have assessed individuals with acute chlorine exposure for subsequent sequelae. Several of these are: Chasis 1947; Joyner 1962; Kowitz 1967; Weill 1969; Sessa 1970; Kaufman 1971; Mustchin 1979; Hasan 1983; Barrett, 1984; Philipp 1985; Ramachandran 1990; Jones 1986; Abhyankar 1989; Schwartz 1990; Salisbury 1991; Moulick 1992; Sexton 1998; LoVecchio 2005; and Ngo 2007. An analysis of the data in the above allows for the following conclusions to be gleaned. Following very large exposures to chlorine there can be rapidly fatal acute pulmonary edema and necrotic tracheo-bronchitis. These tend to occur at concentrations over 1,000 ppm. In those individuals who survive an initial exposure pulmonary function tests may be initially abnormal. Multiple different patterns of abnormalities have been described. The most common, and most likely, abnormality described is an obstructive pattern which tends to resolve, typically within weeks to months. Although described in only nine cases (Evans, 2004), some individuals with a reactive pattern on their pulmonary function tests may also develop reactive airways dysfunction syndrome. *The chlorine paradox:* Being a relatively insoluble gas it would be expected that the primary clinical effect of a significant exposure would be at the level of the lungs, with large exposures causing alveolar damage. Yet empirical experience suggests that a consequential exposure tends to cause primarily upper respiratory effects with more distal damage being relatively rare and generally reversible. A solution to this paradox can be found in the work of Nodelman (1999), a study of volunteers who were exposed to chlorine; almost all of which was absorbed in the hypopharynx at low and in the upper airways at higher concentrations. Thus the clinical picture that is seen in chlorine exposure derives from the fact that it is absorbed at a much more proximal level of the respiratory system than would be predicted on the basis of its solubility. The reason for this can be found in its chemical reactivity. When chlorine gas comes in contact with the moisture of the airways it reacts with water to form the soluble hypochlorous acid. This reaction lies so far to the right that it effectively goes to completion with >100,000 times more hypochlorous acid than Cl2. Thus, despite its limited solubility, chlorine's toxicological behavior is that of a relatively soluble gas. *Selected references:* 1. Berghoff RS. The more common gases: their effect on the respiratory tract. *Arch Int Med* 1919; **24**: 678–84. 2. Kaufman J, Burkons D. Clinical, roentgenologic, and physiologic effects of acute chlorine exposure. *Arch Environ Health* 1971; **23**: 29–34. 3. Hasan FM, Gehshan A, Fuleihan FJ. 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Six month follow-up of fourteen victims with short-term exposure to chlorine gas. *J Soc Occup Med* 1989; **39**: 131–2.

5. Lead Exposure in the Workplace and its Management

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Introduction: Lead's high resistance to corrosion, its high ductility, malleability, relatively low melting point (327°C) and chemical stability explain why it is employed widely in industry. Lead is used in the manufacture of batteries, as a solder, in radiation shielding, in copper smelting, as a pigment in outdoor paints, as a rust proofing agent on steel structures, in lead shot for firearms, and in rubber and plastic manufacturing. Inhalation is the predominant route of occupational exposure, though exposure can occur via ingestion if hygiene is poor. Workers are most likely to be exposed to lead dust when abrading or burning lead-containing surfaces. However, working with lead does not necessarily pose a significant exposure risk. For example, hand-held soldering with a tin/lead solder should not result in substantial lead exposure because the temperature of the soldering iron is usually kept below 500°C so fume is not generated. *Surveillance:* Variable legislation exists across Europe to protect the health and safety of workers exposed to lead (1). In the UK, it is the responsibility of employers to undertake a risk assessment, which may include airborne lead concentration monitoring (2). The amount of lead fume or dust generated by a process must be minimised and local exhaust ventilation installed, if necessary. Additional measures, such as protective respiratory masks, may be required. Employers should provide adequate washing facilities and suitable places to store contaminated clothing to prevent lead transmission back to the home. Having established control measures, employers are required to confirm that they work. Lead in blood is considered to be the best indicator of the concentration of lead in soft tissues and hence of recent exposure. A blood lead concentration ≥35 μg/dL is the trigger value in the UK for an employee to be placed under regular medical surveillance; in 2005/6 8,618 workers were placed under surveillance. Employers are required to take action to investigate blood lead 50 μg/dL and to suspend a worker from lead work if the concentration is ≥ 60 μg/dL; the equivalent suspension value in Germany concentration is 40 μg/dL. Lower concentrations for action and suspension exist for women of reproductive capacity and those under 18 years of age. In the UK, 60 males and 1 female were suspended from work in 2005/6 because their blood lead concentrations exceeded 60 μg/100 mL and 30 μg/100 mL respectively (3). *Features following exposure:* Occupational lead poisoning is usually due to chronic exposure with a gradual increase in the body burden. In these cases, although blood lead concentrations are often in excess of 50 μg/dL, those exposed may have few symptoms or only non-specific complaints such as fatigue, headache, dizziness and abdominal pain, the clinical significance of which may be missed unless the possibility of the diagnosis is considered. In contrast, even short-term exposure to high concentrations of lead, for example, flame cutting of lead-painted metal structures without appropriate respiratory protection, can give rise to toxic blood lead concentrations within days so that symptoms are more readily linked to an occupational cause. For employees not undergoing periodic blood lead concentration monitoring, the diagnosis of lead

poisoning may be made only when a routine blood film reveals a normocytic, normochromic anaemia, possibly with basophilic stippling, features present only when the blood lead concentration exceeds 50 µg/dL. The need to reduce occupational exposure is supported by mounting evidence that blood lead concentrations <50 µg/dL can have deleterious health effects (4), such as reduction in peripheral nerve conduction velocity (5), proximal tubular damage (6) and reduced semen quality (7). *Management:* Strict hygiene regimens and removal from lead exposure are the most important aspects of management and are often all that is required. However, after removal from exposure, it is appropriate to offer chelation therapy to those with a blood lead concentration ≥ 50 µg/dL and symptoms compatible with lead poisoning. Oral succimer (DMSA) 30 mg/kg/day is of similar efficacy to intravenous sodium calcium edetate 75 mg/kg/day in enhancing urine lead excretion and reducing blood lead concentrations. Since succimer causes less zinc depletion than sodium calcium edetate, is not associated with renal toxicity and can be given orally, it is the chelating agent of choice in the treatment of occupational lead poisoning. *Conclusions:* Occupational lead poisoning is a preventable disease, if a risk assessment has been performed and appropriate hygiene arrangements are in place. Mounting evidence suggests strongly that blood lead concentrations below 50 µg/dL are deleterious to health and therefore that the present occupational suspension limits in many European countries should be reduced for toxicological reasons. *References:* 1. Taylor A, Angerer J, Arnaud J, *et al*. Differences in national legislation for the implementation of lead regulations included in the European Directive for the protection of the health and safety of workers with occupational exposure to chemical agents (98/24/EC). *Int Arch Occup Environ Health* 2007; **80**: 254–64. 2. Health and Safety Commission. Control of lead at work. Norwich, England: Her Majesty's Stationary Office, 1998. 3. Health and Safety Executive, 2007. HSE Statistics. http://www.hse.gov.uk/statistics/causedis/lead/index.htm. 4. National Institute for Occupational Safety and Health. Adult blood lead epidemiology and surveillance, 2007. http://www.cdc.gov/niosh/topics/ABLES /ables-description.html. 5. Araki S, Sato H, Yokoyama K, *et al*. Subclinical neurophysiological effects of lead: A review on peripheral, central and autonomic nervous system effects in lead workers. *Am J Ind Med* 2000; **37**: 193–204. 6. Pergande M, Jung K, Precht S, *et al*. Changed excretion of urinary proteins and enzymes by chronic exposure to lead. *Nephrol Dial Transplant* 1994; **9**: 613–18. 7. Telisman S, Cvitkovic P, Jurasovic J, *et al*. Semen quality and reproductive endocrine function in relation to biomarkers of lead, cadmium, zinc, and copper in men. *Environ Health Perspect* 2000; **108**: 45–53.

6. An Update on Selected Toxic Gases in Industry

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Despite improvements in industrial hygiene and occupational health measures, toxic gases continue to be the substances most often involved in hazardous materials releases resulting in human injury. This review will focus on five gases that pose substantial risks in industry due to their ubiquity and high inherent toxicity: carbon monoxide, cyanide, hydrogen sulfide, phosgene, and arsine. Carbon monoxide (CO) is the most common source of poisoning worldwide. Unlike many industrial toxicants for which the risk of lethal exposure has been all but eliminated in developed countries, carbon monoxide continues to kill at a rather alarming rate. Official statistics likely underestimate the death toll, due to both the vagaries of ICD-9 coding of causes of death and due to failure to diagnose CO poisoning as an underlying cause of death. A substantial portion of CO deaths occur in the workplace. This rate is likely many times higher in developing countries, where engineering controls and environmental monitoring are lacking, than in developed countries. Sources of CO and recent perspectives on the value of hyperbaric oxygen treatment will be examined. Cyanide continues to be used extensively in the mining, metallurgy, electroplating, and chemical synthesis, offering opportunity for accidental exposures. Cyanide may be diverted from industrial sources for illicit purposes such as suicide, homicide, or chemical terror. However, the greatest risk of cyanide poisoning is as a component of smoke inhalation. While the presence of cyanide in smoke has been recognized since the 1960's, its importance as a co-toxicant to carbon monoxide in the setting of smoke inhalation has only recently been widely accepted. Hydroxocobalamin, an antidote safe for use in the setting of smoke inhalation, has recently been approved for use in the US and is viewed as likely to be approved by the European Union (EMEA) at the writing of this abstract. Hydrogen sulfide (H_2S) is another deadly gas employed in the production of elemental sulfur and sulfuric acid and of heavy water. It is a by-product of decomposition of sulfur-containing organisms, and is thus found in the petroleum, tanning, smelting, fertilizer production, fishing, meat processing, and other industries. Only 6 deaths were reported in 2005 to the American Association of Poisons Centers. Occupational deaths due to H_2S are difficult to determine from available statistics. The treatment of H_2S poisoning remains primarily supportive; antidotal therapy successes are anecdotal. Recent data on the mechanisms of H_2S poisoning may lead to more effective antidote development strategies against the sulfides. Phosgene is frequently thought of as a chemical warfare agent, but it is widely employed in industry in the manufacture of plastics and resins, carbamate pesticides, herbicides, dyestuffs, isocyanates, polyurethane. In the US, only a handful of exposures to phosgene are reported annually in a new registry system set up by phosgene manufacturers and users. No cases were identified among fatal poisonings in the 2005 report of the National Poisoning and Exposure Database of the American Association of Poisons Centers. Treatment of phosgene exposure is supportive. Arsine is a gas whose importance has grown in recent years due to the explosive expansion of semiconductor and fiber optics production. It may be produced when strong mineral acids come in contact with arsenic salts. Fortunately, engineering controls have limited the number of accidents. When exposures occur, they may involve multiple victims. The treatment of arsine poisoning is generally supportive. Massive hemolysis may lead to requirement for urinary alkalinization, hemodialysis and transfusion. *Conclusion:* In summary, these five gases are of significant importance in industry due to the commonness of their presence in the workplace. Of the five, only carbon monoxide and cyanide (as a component of fire smoke) cause notable mortality in workplace incidents in developed countries, but all may pose a deadly threat when exposures occur.

7. Deliberate-Self Harm: Nature, Psychosocial Management and Prevention Strategies (With an Emphasis on Restriction of Access to Means)

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Deliberate self-harm (DSH; intentional self-poisoning or self-injury) is a substantial problem in most countries of the world. It is strongly associated with risk of subsequent suicide. Where methods of self-harm are particularly dangerous, such as consumption of pesticides as is common in developing countries, acts which are not intended to result in death may have a fatal outcome. The large numbers of deliberate self-harm patients presenting to emergency departments, estimated, for example, to be as many as 220,000 per year in England alone (1), presents huge demands for medical staff, and also for those responsible for psychosocial care. Because of the strong association between DSH and suicide, improved services and clinical management of DSH patients is a central focus of suicide prevention strategies in most countries (e.g. Department of Health 2002) (2). In this presentation an overview will be provided of the main factors that contribute to DSH, including psychiatric disorders, personality factors, life events and problems, and environmental influences, including access to means. The extent of the problem of DSH will be quantified, with a brief summary of its epidemiology. After a patient has arrived at the general hospital emergency department and physical treatment has been instigated, a careful psychosocial assessment is essential. Hospitals vary greatly in the quality of psychiatric services for DSH patients. In order to rectify this and improve individual care, guidelines have been produced in several countries to assist clinicians and service planners. In the UK, for example, the National Institute for Health and Clinical Excellence has produced a major guideline (National Collaborating Centre for Mental Health, 2004) (3). In spite of this, development of services remains patchy. Evidence from other countries suggests that this is a common phenomenon. The key components of a psychosocial assessment (4) include investigation of: life-events and problems preceding the act, suicidal intent, other motives for the act, psychiatric and personality characteristics, family history, alcohol and drug misuse, coping resources and supports, exposure to suicide and deliberate self-harm by others, and risk of repetition and of suicide. The assessment should where appropriate or feasible include interviews with key informants, such as relatives or friends, and gathering of information from other clinicians who know the patient. This should allow the clinical assessor to develop a management plan. A problem-orientated approach is particularly appropriate with most DSH patients. These components of the assessment will be elaborated further during the presentation. Aftercare arrangements will be based on the needs of patients, but also on what is available locally. Again, provision of aftercare varies greatly between services. In this presentation the current evidence regarding efficacy of specific types of treatment for DSH patients will be summarised, based on the findings of a Cochrane Collaboration Systematic Review. This has provided convincing evidence for the efficacy of psychological therapies. Prevention of DSH and suicide depends on implementation of a range of strategies. These include improved detection and treatment of people with the psychiatric disorders most associated with suicide (e.g. depression, alcohol abuse, schizophrenia and bipolar disorder), improved care for other key high risk groups (e.g. DSH patients, prisoners, persons in high risk occupational groups, and socially and economically deprived populations), screening of populations for at-risk individuals, mental health promotion, and promoting improved reporting and portrayal of suicidal behaviour in the media. However, restricting access to specific means for suicide is a further important approach (5), which is included in national suicide prevention strategies of all countries which have such programmes. This approach is based on the fact that large-scale restriction in the availability of means for suicide has been shown to not only reduce suicides involving that method, but also to have an overall impact on suicide rates by all means (e.g. Kreitman, 1976) (6). Also, periods of risk for suicide are often brief, during which access to means may be crucial in determining whether or not an act occurs and its outcome. Furthermore, survivors of serious suicide attempts have a surprisingly low subsequent suicide rate (7). A brief mention will be made of specific methods of suicidal behaviour for which there is some evidence that restricting access has or can be beneficial. However, such approaches are not without controversy, as will be highlighted during the presentation. *References:* 1. 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8. Prescription Naloxone: A Novel Approach to Opiate Overdose Prevention

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The mortality and morbidity from heroin overdoses have increased both in the United States and internationally in the last decade. The lipid solubility allows the rapid deposition of heroin and its metabolites into the central nervous system and accounts for both the "rush" experienced by users and the toxicity. Risk factors for fatal and non-fatal heroin overdoses such as recent abstinence, decreased opiate tolerance, and poly-drug use have been identified. Opiate substitution treatment such as methadone or buprenorphine is the only proven method of heroin overdose prevention. The mortality and morbidity from heroin overdoses increased both in the United States and internationally during the 1990's (1–3). Heroin related deaths have been implicated in 9.4% of the total mortality in all persons 15–39 years of age in that country and is the leading cause of death among men aged 25–54 years in Oregon (1,4). In San Francisco, heroin overdose deaths have represented the third leading cause of years of potential life lost (5). In 2002, the Drug Abuse Warning Network recorded 93,519 non-fatal heroin overdose related emergency departments visits in the United States representing a 34% increase from 1995 (6). Death from a heroin overdose most commonly occurs at home in the company of other people and most commonly occurs one to three hours after injection (7). Numerous communities have taken advantage of this opportunity for treatment by implementing overdose prevention education to active heroin users as well as prescribing naloxone for home use (8). Naloxone is a specific opiate antagonist with no agonist properties and no potential for abuse. It is inexpensive, non-scheduled and readily reverses the respiratory depression and sedation caused by heroin as well as causing transient withdrawal symptoms. Program implementation considerations, legal ramifications, and research needs for prescription naloxone will be discussed. The unique pharmacology of heroin makes it more likely than other opiates to cause

a serious overdose. Heroin and other opiates produce their effects as agonists on the mu, kappa, and delta receptors in the central nervous system. Mu1 receptors are responsible for most of the analgesic effects, and Mu2 receptors are responsible for respiratory depression, delayed gastrointestinal motility, miosis, euphoria, and physical dependence. Heroin is more lipid soluble than morphine and other opiates; it therefore crosses the blood-brain barrier within 15 to 20 seconds and achieves relatively high brain levels quickly. Sixty-eight percent of intravenous heroin is absorbed into the brain compared with less than 5% of intravenous morphine. This lipid solubility allows the rapid deposition of heroin and its metabolites in the central nervous system and accounts for both the "rush" experienced by users and the toxicity. *Implementation of a prescription naloxone program:* 1. Sites such as syringe exchange programs and jails are logical first steps for these programs. 2. Educational Points for Prescription Naloxone Education. 2A. The differentiation between the normal deep lethargy of opiate use (a deep nod) and an opiate overdose. The lack of a response to a sternal rub or other vigorous stimulation, blue lips, absent breathing are all signs of a significant overdose requiring further treatment. 2B. Rescue breathing should be taught and emphasized. The recovery position should be stressed if rescue breathing is not used. One study has demonstrated a modest decrease in hospitalization rates of non fatal opiate overdose patients when bystander CPR was performed. 2C. The use of other stimulation such as ice, milk, and amphetamines should be discouraged. 2D. The importance of contacting emergency medical services and the need for hospital evaluation after an overdose must be stressed because of the complications that can arise. 2E. The short half-life of naloxone in comparison to heroin and other opiates should be highlighted. The importance of not using more heroin or other opiates within a few hours of revival should be stressed. 2F. The proper dosing and administration of intramuscular naloxone. 3. The prescription should be provided by a licensed health care provider. 4. Medical records of the patient encounter and prescription need to be maintained. 5. Any prescribed medication must be properly labeled with the patients name and instructions for use. 6. A system for medication refills should be established. 7. Primary care providers can be instructed in the use of prescription naloxone for patients who are still actively using heroin. Local pharmacies can be involved in honoring these prescriptions. *References:* 1. Oxman G, Kowalski S, Drapela L, *et al*. Heroin Overdose Deaths – Multnomah County, Oregon, 1993–1999. *MMWR* 2000; **49**: 633–636. 2. Solet D, Hagan H, Nakagawara J, Plough A, Ball J. Unintentional Opiate Overdose Deaths - King County, Washington, 1990–1999. *MMWR* 2000; **49**: 636–640. 3. Gerostamoulos J, Staikos V, Drummer OH. Heroin-related deaths in Victoria: a review of cases for 1997 and 1998. *Drug Alcohol Depend* 2001; **61**: 123–127. 4. Hulse GK, English DR, Milne E, Holman CD. The quantification of mortality resulting from the regular use of illicit opiates. *Addiction* 1999; **94**: 221–229. 5. Seal KH, Downing M, Kral AH, *et al*. Attitudes about prescribing take-home naloxone to injection drug users for the management of heroin overdose: a survey of street-recruited injectors in the San Francisco Bay Area. *J Urban Health* 2003; **80**: 291–301. 6. Emergency Department Trends From DAWN: Final Estimates 1995–2002. March 2005; http://dawninfo.samhsa.gov/old_dawn/pubs_94_02/edpubs/2002final/ 7. Sporer KA. Acute heroin overdose. *Ann Intern Med* 1999; **130**: 584–590. 8. Sporer KA, Kral AH. Prescription naloxone: a novel approach to heroin overdose prevention. *Ann Emerg Med* 2007; **49**: 172–177.

9. Preventing Household Poisoning

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The unintentional human exposure to household chemicals still results in morbidity and mortality and the importance of prevention is becoming increasingly apparent. *General approach for prevention:* There are three levels of prevention. Primary prevention of poisoning includes actions on how to avoid the poisoning accident occurring. Secondary prevention includes initial steps to minimize the effects of the toxic exposure when an accident happens, the diagnosis and the first aid treatment. Tertiary prevention deals with diagnosis and treatment of the poisoned person to prevent death or permanent disability. We will focus here on primary prevention. Prerequisites for primary prevention are the identification of high risk circumstances which result in the identification of the need for prevention. It is followed by a search for options for prevention and must include the many different partners that have roles in the implementation, realization and evaluation of poisoning prevention programmes. Evaluating the impact of programmes is of crucial importance and must be part of the injury control programme. *Establishment of the need for a prevention programme:* Identification of a real household poisoning problem needs very careful analysis. Only precise information on the severity, the frequency of poisoning, the circumstances of occurrence (product, substance, situation) and the specific populations at risk enable proper identification of a real problem and need for prevention. This process starts before putting a household product on the market and it is the responsibility of the manufacturer to carry out a safety evaluation and to take appropriate measures in particular concerning product formulation and package labeling. Once the products are on the market, the post marketing surveillance and the epidemiological studies on acute poisonings are the main source of information concerning the high risk situations. Retrospective and prospective studies on poison centre inquiries, hospital based surveys and forensic medicine coroner reports give valuable information for identifying problems and needs. Although there has been scepticism about the value of poison centre data from inquiries for epidemiological studies because the methodological bias causes underreporting of severe /fatal cases, these data remain a major source of information to identify problems, to develop early warning surveillance systems and to study trends of toxic exposures (1). The main groups reported at highest risk are the very young and the very old and low income-low education population groups. Children without supervision and with previous poisoning have been reported to be at increased risk of poisoning (2). Due to illiteracy and inability to read and understand label instructions some adult groups have also been identified as at increased risk for poisoning (3). On the other hand high risk situations, include improper storage and disposal, mislabeling of products, inadequate warning and first aid instructions, unsafe packaging, and improper use of apparatus (2,4,5). *Preventive programmes:* Strategies to reduce unintentional household poisonings, may involve regulatory, educational or technological components. Regulatory or technological approaches require little or no individual action, and these so-called passive measures (safety features built in as a constant feature of the environment or product) are generally recognized as more effective in reducing accidents than as attempts to change people's behaviour. They include measures concerning the packaging, the labeling, the protective clothing and product formulation. Child resistant closures, warning/hazard symbols, safety phrases and instructions concerning storage, use and disposal are the most common. If the use of child-resistant packaging and labeling have become the basis for preventing unintentional exposures, some concern has been raised concerning the utility or quality of some of them (6,7). For example, the mandatory addition of denatonium benzoate to reduce unintentional ethylene glycol or methanol exposures in children has been questioned (8). *Educational approaches:* Educational approaches to effect behavioural change and modify hazards in the environment have been reported to be less effective immediately and more difficult to assess. However, they can be an efficient approach, in particular when risk management measures demonstrate some limits. For example, the education approach to enhance consumer perception of hazard is particularly needed for prevention of "in use" child poisoning when the safety closure is open and labeling or storage is not appropriate for "in use" (9). Therefore education and awareness are essential components of any poison prevention programme. Prevention programmes should be well targeted, the objectives should be specific and reasonable, and the opportunity for educating people is when they are most receptive. Finally, and difficult to implement, the evaluation of the effectiveness of the programme including the methods, the tools and results is important. Special attention has to be given to identification of key factors of success as well as of lack of success. *Conclusion:* Preventing household poisoning is a concern of many partners. While efforts have been made in the past with some good and less good results, there is still a need for prevention. In the future, better complementarity should be encouraged between technological risk management measures and educational programmes to develop better understanding of these measures. In this perspective, Poison Centres have a key role to play in the identification of high risk circumstances and the evaluation of effectiveness in the prevention of household poisoning. *References:* 1. Mathieu-Nolf M. Poison centres place and role in the health protection of the population: changes and perspectives. *Przeglad Lekarski* 2005; **62**: 543–546. 2. Soori H. Developmental risk factors for unintentional childhood poisoning. *Saudi Med J* 2001; **22**: 227–230. 3. Mrvos R, Dean BS, Krenzelok EP. Illiteracy: a contributing factor to poisoning. *Vet Hum Toxicol* 1993; **35**: 466–468. 4. Kaufman MM, Smolinske S, Keswick D. Assessing poisoning risks related to storage of household hazardous materials: using a focus group to improve a survey questionnaire. *Environ Health* 2005; **4**: 16. 5. 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10. Collective Poisoning Including One Death Due to Emission of Carbon Monoxide from Wood Pellets

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Objective: To describe a collective poisoning involving four men exposed to carbon monoxide released from wood pellets on a cargo ship, and to highlight this possibly neglected risk to crew members and stevedores. *Case series:* A crew member was found dead after entering the staircase leading to the cargo hold of a ship in harbour. A stevedore, coming to rescue him, lost consciousness and was pulseless when brought out after 10 minutes. He was ventilated with oxygen whereupon circulation and breathing stabilized. On admission to hospital COHb was 43.8%. He was treated with 100% oxygen and with hyperbaric oxygen (HBO). Four days post-exposure acute neurological symptoms supervened and the patient presented at hospital with central *facialis paresis* and dysarthria. One additional HBO treatment was given without any apparent effect. Magnetic resonance tomography showed infarcts in *corpus callosum* and *capsula interna sinistra*. The patient's condition deteriorated further with right-sided clonic, epileptic jerks followed by a spastic paresis of the right arm and leg. Also a period of unconsciousness occurred. Angiography showed occlusion of the left *arteria cerebri* media. One year after the accident, the patient is fully awake, but confined to his wheel chair. Finally, two rescue workers experienced mild symptoms (COHb 6.6% and 7.7% respectively) and were treated with 100% oxygen. It is known that CO emission from wood pellets occurs simultaneously with depletion of oxygen, presumably through auto-oxidation of fatty acids and other components in wood (1). In 2002 one man died in Rotterdam under similar circumstances. To our knowledge that accident has not been reported in the literature, but it further emphasizes the hazard associated with storage of wood pellets in closed spaces for a long time. *Conclusion:* This case series proves that storage of wood pellets in closed spaces may cause CO levels high enough to give serious and even lethal poisoning. Measurement of CO and oxygen levels should be mandatory before entry. *Reference:* 1. Svedberg U, Högberg HE, Högberg J, *et al*. Emission of hexanal and carbon monoxide from storage of wood pellets, a potential occupational and domestic health hazard. *Ann Occup Hyg* 2004; **4**: 339–49.

11. Prevention of Poisoning – Safe Storage of Pesticides in Developing Countries

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Introduction: Causing around 300,000 deaths per year, self-poisoning with pesticides is a major public health problem in many middle and low income countries. This problem is related to the easy availability and widespread use of pesticides at community level in agrarian areas in these countries. Self-poisoning with pesticides as a problem has been best documented in the Asian region. However, as agriculture production intensifies, and changes in cropping patterns take place in Africa, it is feared that pesticide poisoning may develop into a significant disease burden in the African continent and in other developing regions of the world. The impulsive nature of self-poisoning makes it important to restrict the availability of pesticides in the domestic environment, and at community level in general, and several strategies have been developed to achieve this. Restricting the availability of the most toxic pesticides and those most difficult to manage by the health care services in low and middle income countries must take precedence in any policy aimed at reducing deaths following self-poisonings. The aim of such policy should be the almost immediate phasing out of all WHO class I and II products, followed by strict enforcement. An additional benefit of such a policy will be the reduction in mortality following accidental and occupational poisonings. Further, national agricultural policies must focus on limiting the overall use of pesticides through either the support to

Table 1. Utilization of safe storage devices among households in Sri Lanka using pesticides at the time of survey specified for the different design options made available to the households. All devices were provided with a strong padlock (based upon Weerasinghe et al paper in press)

Type of device	No. of households with device	No. of households using pesticides at the time of survey		No. of locked devices		No. of unlocked devices	
		After 7 months	After 24 months	After 7 months	After 24 months	After 7 months	After 24 months
Large device made of mango wood	39	32	32	25 (78%)	20 (63%)	7 (22%)	12 (37%)
Small device made of mango wood	100	84	74	70 (83%)	42 (57%)	14 (17%)	31 (43%)
Device made of pinewood	56	53	*	38 (72%)	*	15 (28%)	*
Device made of metal	61	56	56	46 (82%)	27 (48%)	10 (18%)	29 (52%)
Device made of concrete	112	103	*	68 (66%)	*	35 (34%)	*

*Survey not done.

economic incentive programs for pesticide free produce, the promotion of integrated pest management strategies or the introduction of pesticide resistant strains of plants. Reducing the overall use of pesticides will lessen the proportion of rural households with access to pesticides. This, in turn, will have a positive impact on the incidence of pesticide self-poisoning and other episodes of pesticide poisonings. Restricting the sale of pesticides by local agricultural dealers to individuals with suicidal tendencies has also been proposed but inadequate field evaluations make it difficult to assess the feasibility of such an approach. *Methods:* Literature review. *Results:* Systematic research into the possibilities of reducing access to pesticides at community level through safe storage of pesticides has received increasing attention over the past five years. As part of this effort safe storage devices have been distributed among agricultural communities in a partnership among national authorities, development agencies and manufacturers of plant protection products in both Asia and Latin America. To assess community acceptability and use of community safe storage devices, the most in-depth research, as part of a series of pilot studies, was undertaken in Sri Lanka. This included studies by the charitable organization Sumithrayo in the North Western and Southern parts of the island (3) and projects in the north-central part of Sri Lanka by the South Asian Clinical Toxicology Research Collaboration (SACTRC) and partners (1,2). The SACTRC studies (Table 1) documented a high interest in using the gratis safe storage devices, with some variation to the specific storage design introduced with up to 83% (70 out of 84) of the households storing pesticides exclusively in the provided locked device seven months after its distribution. This was a major shift from the (approximate) two percent of the households storing pesticides under lock and key before the introduction of the safe storage device. However, a gradual decline was found among the households that were followed for 24 months where, in some villages, only less than half the households used the locked device after two years. The preferred design was influenced by a number of occupational factors such as land size, crop patterns and types and the quantity of pesticides used and it was clear that a single design would not suit all farmers. Environmental factors, such as termites and house structure, also influenced the material used for the manufacture of the device and its location. The introduction of storage devices designed for domestic use significantly reduced the storage of pesticides hidden in the field. This resulted in pesticides being stored either in or near the house giving rise to concerns among both community members and the researchers that this shift may increase its availability among vulnerable individuals. The device that was meant for in-field storage was insufficiently developed to convince farmers that it would prevent theft. The studies conducted by SACTRC also revealed that it was difficult to keep the key to the device hidden from children; and that the person in charge of the key was very vulnerable to ingesting the stored poison, indicating that further studies are needed to develop an appropriate design. *Conclusions:* Hand in hand with a policy for restricting the use and availability of pesticides, national preventive or health services and development agencies must also address the underlying factors that make people at risk for self-harm. These include domestic violence, alcohol and drug addiction, emotional distress, depression, physical handicaps, social isolation and financial hardship. Unfortunately, we still lack research in low and middle income countries to fully understand the risk factors of self-harm and the help-seeking and coping strategies among people with suicidal thoughts, making research a priority before we can formulate a targeted strategy. Similarly, research and further investments are needed for upgrading the curative health services to reduce deaths following attempts of self-poisoning with pesticides. *References:* 1. Konradsen F, Dawson AH, Eddleston M, *et al*. Pesticide self-poisoning thinking outside the box. *Lancet* 2007; **369**: 169–170. 2. Konradsen F, Pieris R, Weerasinghe M, *et al*. Community uptake of safe storage boxes to reduce self-poisoning from pesticides in rural Sri Lanka. *BMC Public Health* 2007; **7**: 13. 3. Ratnayeke L. Secure storage of pesticides: pilot study 1. Presentation at the WHO-IASP meeting on community access to pesticides: safer interventions. Geneva, Switzerland.

12. Epidemiological Aspects of Pediatric Poisonings at School

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Objective: To determine the circumstances of poisoning at school that can be used in prevention. *Methods:* A retrospective review of paediatric intoxications at school from January 1991 to October 2007 in the Spanish Poison Control Centre. Data included patient age and gender, route and reason of exposure, and management site. *Results:* Of the total of intoxications at schools, 84.6% (N=1,505) were in individuals less than 19 years of age. The main age ranges were between 6 and 10 (21.4%) and 11 to 14 years (22.5%). The vast majority (92.9%) of exposures were unintentional; suicidal attempts corresponded to 2.6% of cases. Therapeutic errors accounted for 2.3%, of which 91.2% involved dosing errors. Drug abuse were detected in 15 cases, malicious in 7 (mouthwash plus shampoo, fire extinguisher, household cleaner, defence sprays, rodenticide in drinking water); homicide in one. Thirty-seven episodes involved multiple victims (5–60 children): accidental inhalation (including propane, tetrahydrothiofen, turpentine, stain remover, chlorine, fire extinguisher, metal fume fever, benzocaine, fumigants), contaminated fruits with organophosphates, and a degreaser confused with mouthwash. Therapeutic drugs were given by one child to the others in 3 episodes. Special settings: the school laboratory (7 episodes); teacher´s medication (3). Oral was the route of exposure in 66.9% of cases, followed in frequency by buccal 10.4%, inhalation 6.4%, ocular 4.5%, dermal 4.1%, several routes 7.7%. Household products were the first class of substances (31.7 %) - mainly pen/ink (32.7% of these) and typewriter correction fluid (26.4%) - followed by pharmaceuticals 23.5%; industrial chemicals (13.5%); cleaning products (10.9%); cosmetics (7%); pesticides (4.9%); plants (3%); mushrooms and bites/stings (0.7%). When the enquiry was made from the school (75% of cases), most of them (64.4%) were managed on site. On the other hand, 24.6% were referred to a health care facility of whom 43.8% had minor or no symptoms. *Conclusion:* Due to the fact that the majority of accidents in children tend to occur at home, there is a lack of knowledge of epidemiological aspects of poisoning at school. This study can help to prevent them and avoid the saturation of emergency health services since many episodes are mild or can affect multiple victims.

13. Preventing Poisoning in Children

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Objective: The purpose of this presentation is to provide data regarding evidenced-based poison prevention strategies that may be directed towards children. *Methods:* A search of published peer-reviewed medical and scientific studies was done using Medline and Embase with level of evidence assessed by Cochrane criteria. *Results:* Ten characteristics of effective primary prevention programs are: 1. based upon sound scientific theory and research in their content, structure and implementation, 2. have a clearly defined purpose and goals, 3. adopt a multi-level approach that attends to multiple pathways of development, 4. attend carefully to dosage as well as boosters or follow-up to achieve and sustain desired outcomes, 5. consider existing strengths and competence as well as risks and difficulties of individuals and systems, 6. sensitive to target population in content, structure and implementation, 7. incorporate high quality evaluation and monitoring into program design, 8. structured and packaged so as to be transferable and translatable, 9. attend to diverse resource needs, and 10. characterized by socio-political sensitivity (1). Involvement of key stakeholders (parents, teachers, schools, community leaders, product manufacturers, government agencies, advertisers/newspapers/radio/TV) will create a broader base of skills, knowledge, commitment and resources, and the actual process of collaboration generates enhanced skills, knowledge, commitment and resources among the stakeholders themselves. Use of the Haddon Matrix incorporates timing of exposure/poisoning, human host factors (e.g. infant, toddler, child, teenager), and the agent/vector/poison as well as pre-exposure/pre-existing, exposure and post-exposure characteristics – all of which are critical parameters to incorporate into pediatric poison prevention strategies (2). Causes of and risks for poisoning/exposure often are related to a child's developmental stage (infancy (birth-one year), toddler-preschool (1–4 years), early school age (5–9 years), middle childhood (10–14 years), adolescence (15–19)). Infants have total dependence on adults; toddlers have concrete thinking and a high degree of exploratory behavior; early school age children have less fear and judgment than older children; children 10–14 years old are beginning to develop abstract thinking; and adolescents have an idealistic and self-centered mode of thinking and a sense of personal immortality (3). These characteristics require that pediatric poison prevention education strategies are adapted to different age behaviors. Selected poison prevention education programs have demonstrated improvement between pre-test and post-test knowledge and behavior, e.g. 9.4% to 13% and 5.7% to 24%, respectively, for physicians (4). Exposure-corrected risk estimates may detect higher risk rates, especially for younger children, than uncorrected risk estimates (5). Examples of pediatric poisoning prevention include safety packaging of drugs (6) and education of public health nurses regarding iron poisoning risk in children (7). *Conclusion:* Published evidence provides a basis for the design and implementation of pediatric poison prevention approaches that may enhance their effectiveness and outcome. *References:* 1. Bond LA, Carmola-Hauf AM. Taking stock and putting stock in primary prevention: characteristics of effective programs. *J Primary Prevention* 2004; **24**: 199–221. 2. Prevention and Public Education. In: Forging a Poison Prevention and Control System, Institute of Medicine, National Academy of Sciences, Washington DC, NAP Press, 2004; 201–268. 3. Sewell KH, Gaines SK. A developmental approach to childhood safety education. *Pediatr Nursing* 1993; **19**: 464–466. 4. Polivka BJ, Casavant MJ, Malis E, *et al*. Evaluation of the be poison smart poison prevention intervention. *Clin Toxicol* 2006; **44**: 109–114. 5. Senturia YD, Binns HJ, Christoffel KK, *et al*. Exposure-corrected risk estimates for childhood product related injuries. *Accid Anal Prevent* 1993; **25**: 473–477. 6. Walton WW. An evaluation of the poison prevention packaging act. *Pediatr* 1982; **69**: 363–370. 7. Broderick M, Dodd-Butera T, Wahl P. A program to prevent iron poisoning using public health nurses in a county health department. *Public Health Nursing* 2002; **19**: 179–183.

14. Characterization of Pediatric Fatalities Related to Over-The-Counter Cough and Cold Medications

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Objective: To characterize pediatric deaths related to OTC cough and cold medications. *Methods:* An independent consensus panel of eight experts (pediatric, toxicology, emergency medicine, forensic, pathology) reviewed all available fatalities from three sources: (1) English language medical literature (1949–2007), (2) National Poison Data System of the American Association of Poison Control Centers (1983–2007) and (3) safety records from manufacturers (1980–2007). Inclusion criteria were age <12 years, outcome of death and mention of cough and cold ingredient (brompheniramine, chlorpheniramine, dextromethorphan, diphenhydramine, doxylamine, guaifenesin, phenylephrine, pseudoephedrine). Fatalities were abstracted independently by two trained abstractors that were not involved in the consensus process. The panel assessed causal relationship between exposure to cough and cold medicine and death using explicit definitions (definitely related, likely related, possibly related, unlikely related, definitely not related). The panel also determined dose (therapeutic/supratherapeutic), intent of administration and potential contributing factors. *Results:* Of 227 fatalities, the panel excluded 36 cases (10 duplicates, 26 did not meet inclusion criteria) and judged 49 cases as not related to a cough and cold drug. Of the remaining 142 deaths, 20 reported inadequate information to determine causality, leaving 122 deaths related to a drug of interest. Of these, 86 cases involved non-prescription drugs only, 21 involved non-prescription plus a prescription drug, and 15 involved a prescription medication alone. Of the 107 non-prescription cases, 80 (75%) occurred in children <2 years old. Exposures in children <2 years occurred in the child's home in 30 cases, daycare facility or babysitter's home in 13 cases, health care facility in 2 cases and unknown in 35 cases. Of 92 cases in which a dose could be determined, all were judged to involve a supratherapeutic dose. There were no fatalities judged to involve a therapeutic dose. Contributing factors involved in overdose: attempts to sedate or harm the child, use of inappropriate products, use of inappropriate administration technique or the use of two products containing the same active ingredient. *Conclusions:* The vast majority of deaths related to OTC cough and cold medications occurred in children <2 years of age and were caused by intentional or accidental overdose.

15. Pre-Hospital Use of Antidote in Acute Poisoning

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Objective: To discuss the place of antidotes in pre-hospital care. In some countries, pre-hospital medical emergency care units (MECU) take care of critically ill patients, including severely poisoned patients, as early as possible to stabilize them before and during transport to the most appropriate hospital. Although antidotes are only available for a small number of poisons, they may be an essential part of the treatment in some life-threatening situations. *Methods:* Medical literature and some national or regional expertise were taken into account. *Results:* Few data are available about the epidemiology of acute poisoning-related MECU activity: as much as 5 to 10% has been reported by some centres, but many interventions involved non life-threatening situations. The main point is to define which treatment should be started in the pre-hospital phase and which other should be restricted to in-hospital care. In most acute poisoning conditions, primary care of the patient is mainly supportive with special attention to neurological, respiratory and cardio-circulatory conditions. Besides these non-specific measures, early intervention of the MECU also gives the opportunity to start more specific treatments including decontamination and administration of antidotes. Antidotes may be classified according to their mechanism of action, but a classification based on their availability in due time is more useful. Such recommendations have been produced by the International Program on Chemical Safety, the American College of Emergency Physician, or the British Association for Emergency Medicine and Guy's Hospital Poison Unit (1). In these guidelines, agents are commonly classified in 3 groups: those that need to be immediately available in the emergency department; those that should be available in the hospital for delivering within 1 to 4 hours; and those that can be stocked at a regional level. However no recommendations specifically apply to pre-hospital emergency care. It seems sensible to consider that antidotes that need to be carried in MECU vehicles are a subset of those that may be immediately required in the emergency department (2). Besides the potentially life-saving value of an agent, several other criteria should be taken into account when deciding to carry antidotes: - Mechanism of action: only antidotes with a toxicodynamic effect are likely to be required in the pre-hospital setting, especially if the time interval before hospital admission is short; - Distance and time interval to the hospital; - Clinical situation: as the antidote use is likely to be based on clinical features, agents directed against toxidromes rather than specific poisons seem preferable: - Probability of use, depending on local epidemiology and industrial activities; - Ease and safety of use, possible side-effects; - Storage condition and shelf life; - Cost/benefit assessment, including waste of unused or outdated products; - Particular risks of mass casualties (chemical disasters, threat of terrorist attacks): the need for strategic stocks must be considered; - Qualification and skill level of the pre-hospital emergency personnel as well as the quality of the first call medical assessment (physicians, nurses, paramedics). Very few data are available regarding the actual use of antidotes in the pre-hospital setting, but it seems reasonable to recommend carrying the following substances - Oxygen: 100% oxygen is especially required in carbon monoxide, cyanide or hydrogen sulphide intoxication; Hypertonic glucose: correction of hypoglycemia due to insulin, oral antidiabetic or others; Naloxone: pre-hospital administration of naloxone is especially useful to patients with opiate or opioid overdose found with bradypnea. In those with overdose complicated by severe hypoxemia (inhalation or respiratory arrest) or hypothermia, intubation, respiratory support and copious oxygenation is preferable. Rules for safe use of naloxone include dilution, titration and close continuous observation of the patient because of possible adverse effects and short lasting action. Recently, intranasal instillation of naloxone has been reported as a valuable pre-hospital alternative to IM injection in patients with difficult venous access. Flumazenil: although usually not life-threatening, benzodiazepine (or analogues) intoxication is very common. As for naloxone, careful titrated administration is recommended; Hydroxocobalamin: patients exposed to smoke from fires may suffer direct injury from hot and irritant gases, and soot, but also from poisoning by carbon monoxide and cyanide. Significant cyanide poisoning is more likely in those with cardiac arrest, unconsciousness, hemodynamic compromise or severe dyspnea at the scene, and cyanide antidotes may be needed. Although expensive, hydroxocobalamin undoubtedly appears as the safest cyanide antidote in the pre-hospital context as it does not promote hemodynamic instability or impairment of oxygen transport. EDTA-dicobalt has known side-effects but is much cheaper and might be considered in collective poisoning. Atropine: it is an essential part of moderate to severe intoxication with anticholinesterase insecticides or nerve agents that could be involved in terrorist attacks. This agent is commonly available in MECU vehicles for other purposes, but high doses may be needed during the first half hour until pulmonary muscarinic signs and symptoms are alleviated, so that conventional amounts transported by the MECU may be rapidly depleted, especially when facing multiple causalities. Oxime administration must only be started after atropinization and reoxygenation: it is usually not required at the scene and may be delayed until hospital admission; pre-hospital use must be considered in the field in multiple casualty incidents when hospital admission is delayed by field triage and stabilization before transport. Diazepam has been shown to decrease neurocognitive dysfunction after anticholinesterase poisoning but this agent is commonly available in MECU. Sodium bicarbonate or lactate: it is indicated in poisoning by membrane stabilizing effect agents. The primary end-point is the narrowing of the QRS complex, but bicarbonate infusion may also improve blood pressure. *Conclusion:* Only a few antidotes are of life-saving importance in the pre-hospital setting. Medical teams should be trained to use these agents properly. For some agents, "strategic storage" should be available when facing multiple casualties. *References:* 1. BAEM – Clinical Effectiveness Committee Current Guidelines. Antidote availability and treatment guideline. http://www.emergencymed. org.uk/BAEM/CEC%20 (audit%20guidelines%20standards%20publications)/ CEC%20Guidelines.asp 2. Danel V, Tournoud C, Lheureux P, *et al*. Antidotes. EMC (Elsevier Masson SAS, Paris), Médecine d'urgence, 25-030-A-30, 2007.

16. Pressure-Immobilization Bandages Increase Survival in a Porcine Model of Rattlesnake Envenomations

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Objective: Pressure-immobilization bandages sequester venom from snakebites in extremities and are recommended for neurotoxic snakebites without local toxicity. For severe snakebites with local and systemic toxicity without readily available antivenin, pressure-immobilization bandages might delay potential lethal systemic toxicity, but with increased toxicity to the extremity. This study analyzes pressure-immobilization bandages in an anesthetized swine model of severe rattlesnake envenomations. *Methods:* Six swine were sedated with Xylazine, 1 mg/kg and Telazol, 5–6 mg/kg, and intubated. Ear vein and external jugular vein catheters were placed. PT, INR, CBC, electrolytes, and CK were measured every two hours for eight hours, and then daily or for signs of distress. Freeze-dried *Crotalus atrox* (Western diamond-back rattlesnake) venom (Natural Toxins Research Center, Kingsville, TX) was suspended in sterile water at 200 mg/1 mL. 200 mg was injected subcutaneously in a distal hind leg at a depth of 3 mm. One minute after injection, pigs were randomized to receive either a pressure-immobilization bandage (3 pigs) or not (3 pigs). General anesthesia was maintained for 6 hours, then analgesia was maintained with fentanyl and morphine sulfate. Pigs surviving to 24 hours received antivenin treatment with an Fab2 antivenin for North American Crotalid snakes (Instituto Bioclon, Mexico). After antivenin administration, pressure-immobilization bandages were removed. Protocols were approved by the institutional animal care and use committee. Pigs were observed for 7 days for recovery from the local toxicity. Chi-square analysis was used to compare survival at 24 hours. *Results:* The three pigs who received the pressure-immobilization survived for 7 days, and were walking on the affected extremity by 7 days. The three pigs who did not receive a pressure-immobilization bandage died before receiving antivenin, with time to death 13.68+3.42 hours. The difference in survival was significant with chi-square p value=0.014. *Conclusions:* In this model of pressure-immobilization bandages for a crotalid envenomation with severe local and systemic toxicity and a 24 hour delay to treatment, survival was improved by use of a pressure-immobilization bandage. Though local toxicity was marked, the pigs who received the pressure-immobilization bandage recovered from an otherwise fatal envenomation with use of the extremity.

17. 4-Aminopyridine Derivatives for Calcium Channel Blocker Poisonings

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Pharmacodynamics: 4-Aminopyridine is an antagonist to voltage-dependent potassium channel K1 in cytoplasm side. Blocking potassium channel causes an increase in intracellular calcium concentration by increasing calcium inflow across the L-type voltage-dependent calcium channel in the sarcoplasmic reticulum. Several compounds were shown to promote calcium entry including 4-aminopyridine, Bay K 8644, and CGP 28932. 4-Aminopyridine facilitates neurotransmitter release in both cholinergic and sympathetic transmissions, and promotes the release of a number of hormones, including insulin (Bowman 1981, 1982). *Experimental studies:* In the first experimental study, 4-aminopyridine failed to protect verapamil-poisoned rabbits (Wesseling *et al.* 1983). However, animals did not receive artificial ventilation. Therefore, in a subsequent study, Agoston *et al.* (1984) administered verapamil in mechanically ventilated cats until there was an 80% drop in mean arterial blood pressure (MABP) or an 80% drop in HR or a complete atrioventricular block. Thereafter, 4-aminopyridine was administered 0.5 mg/kg i.v. twice, 5 min apart. All the 4-aminopyridinetreated animals survived. In contrast, 4 of the 6 control animals died. 4-Aminopyridine improved both HR and MABP. Significant improvement occurred within 10 min after 4-aminopyridine administration. However, the authors did not measure cardiac output (CO). They assumed that the hemodynamic improvement resulted from an increase in peripheral resistance. Gay *et al*. (1986) provided further data on the action of 4-aminopyridine in spontaneously breathing dogs poisoned with verapamil. Verapamil induced

a decrease in HR, CO, and MABP. However, in this dog model there was no significant effect of toxic doses of verapamil on the total systemic resistance. Gay *et al.* compared the effects of different treatments. In brief, atropine and calcium were partially effective. All catecholamines were effective. 4-Aminopyridine, 0.5 mg/kg i.v. administered as a bolus, twice, 5 min apart, resulted in significant increase in MABP, HR, and CO. The authors concluded that although 4-aminopyridine improved all hemodynamic parameters, there was no statistical significant difference when comparing the effects induced by 4-aminopyridine with the effects of the other drugs. Unfortunately, this study did not address the hemodynamic effects of the combination of drugs. Thereafter, Korstanje *et al.* (1987) compared the effects of Bay K 8644, CGP 28932, and 4-aminopyridine in verapamil-poisoned rabbits. Animals were spontaneously breathing. All the three drugs improved verapamil-induced effects on atrioventricular conduction. However, Bay K 8644 was more efficient than 4-aminopyridine; 4-aminopyridine resulted in only partial and with lower rate of recovery. In the search for more potent drugs, Plewa *et al.* (1994) investigated the effects of 3, 4-diaminopyridine in a model of mechanically ventilated swine poisoned with verapamil. 3,4-Diaminopyridine was reported to be six times more potent in enhancing neuromuscular transmission than 4-aminopyridine and may have fewer side effects secondary to its diminished blood-brain barrier penetration (Lemeignan 1984). 3, 4-Diaminopyridine (14+5.6 mg/kg) reversed the decrease in MABP, HR, and CO induced by verapamil. However, it failed to improve survival and resulted in several complications including muscle twitching, tachycardia, and hypertension. However, the dose effect relationship of 3, 4-diaminopyridine in verapamil poisoning was not assessed. Thus, overdose with 3, 4-diaminopyridine cannot be excluded. Tuncok *et al.* (1998) assessed the dose-effect relationship of 4-aminopyridine in spontaneously breathing rats poisoned with verapamil. They showed that a 2 mg/kg/h but not a 1 mg/kg/h dose of 4-aminopyridine was efficient to improve the MABP and HR. However the 2 mg/kg/h dose induced side-effects, including seizures, secretions, and fasciculation. Magdalan (2003) showed in rats that the combination of a 1 mg/kg bolus dose associated with a 2 mg/kg/h infusion of 4-aminopyridine, stopped when conduction disturbances were corrected, appears more efficient than calcium or epinephrine treatment. However, in two animals, seizures occurred several minutes after 4-aminopyridine withdrawal. Clinical studies: ter Wee *et al*. (1985) had to cope with a 67 year-old man overdosed with verapamil while being on chronic intermittent haemodialysis. He presented with low blood pressure, bradycardia and complete atrioventricular block. He received a 10 mg dose of 4-aminopyridine slowly infused and repeated 5 min later. Approximately 90 min after 4-aminopyridine administration, the patient became normotensive and sinus rhythm was restored. The patient complained of dizziness after 4-aminopyridine infusion which lasted 24 hours. Magdalan *et al.* (2003) reported a 51 year-old man severely poisoned with felodipine, a dihydropyridine derivative, and theophylline with refractory cardiovascular hypotension refractory to vasopressor and calcium therapy. The addition of 4-aminopyridine resulted in fast reversal of shock and metabolic acidosis. Magdalan *et al.* (2003) reported further three cases of severe verapamil poisonings with shock and second-degree atrioventricular block in one case, refractory to atropine, calcium, and catecholamines. In addition to this treatment, the 3 patients were treated with 4-aminopyridine. There was a reversal of cardiovascular shock and conduction disturbance. *Discussion and conclusion:* In spite of improvement of supportive as well specific treatment, acute calcium channel blocker poisonings still remain a cause of severe shock and even death. There is a need for further antidotes. Aminopyridine derivatives appear promising drugs against the toxicity of CCB. 4-Aminopyridine appears efficient to counteract the toxic effects of the two major classes of CCB, verapamil and dihydropyridine, including arterial vasodilation, conduction disturbances and cardiogenic shock. The respective contribution of the different pharmacological effects to the antidotal effect remains to be determined. Indeed, 4-minopyridine may act by direct effects of heart cells as well as indirect effects including catecholamine and insulin release. However, the experimental and human toxicities of 4-aminopyridine may question further development. 3,4-Diaminopyridine is a more potent derivative. Some clinical experience exists with chronic treatment with 3,4-diaminopyridine in neurological diseases. The dosage regimens may, however, be quite different. Anyway, severe CCB overdose, refractory to optimal conventional treatment, is waiting for an efficient antidote. However, the development of clinical trials of new drugs in CCB overdose refractory to optimal conventional treatment is hampered by the lack of knowledge of CCB-specific prognostic factors.

18. Differences Between Human and Animal Poisonings

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Objective: To give an overview of differences between human and animal poisonings. *Key points:* There are significant differences between human and animal poisonings. One of the main reasons for this is the differences between species regarding physiology, anatomy and behavior. Each species is unique, and caution is warranted when extrapolating toxicological data from one species to another. Information on the species in question is necessary, but not always available, so basic knowledge of veterinary physiology and toxicological mechanisms must be applied. The differences between animal species can be as profound as or even greater than the differences between animals and humans, but there are behavioral differences that have toxicological significance. Animals do not commit suicide or abuse drugs, but they will often lick their coat when something has been spilled on it. Furthermore, as most animals do not have hands, they are more prone to use the mouth for exploring their environment and this is an important route of exposure. But there are differences between the species in this regard; cats are more careful, dogs have indiscriminate eating habits and ferrets are extremely inquisitive and fearless. The causes of poisonings also vary somewhat between humans and animals due to different exposure patterns and susceptibility. For instance, raisins, chocolate and macadamia nuts can be dangerous for dogs, and eating lilies (*Liliaceae*) can be deadly for cats. On the other hand, methanol is much less dangerous for most animals than for humans (e.g. primates). Poisonous plants rarely cause significant intoxications in humans, at least in the European setting, while moderate, severe and even fatal plant poisonings occur from time to time in grazing animals. When it happens it often affects more than one individual, becoming more like an epizootic disease. Although communication and cooperation with patients can be challenging for doctors regardless of species, veterinary medicine is very different from human medicine on this point. Perhaps the most obvious reason for this is that the patient does not talk. Adding to the challenge is that each species has to be handled according to its ethological requirements. Furthermore, biting, kicking and scratching are normal behavior for animal patients. Simple examinations such as inspection of the oral cavity will often require sedation or even anaesthesia. On the other hand, large bore nasogastric tubes are easily placed in horses. Another important cause of differences is economy. The importance of economy on therapeutic decisions varies considerably between continents and countries. In Norway, medical care for humans is a public service and thus very inexpensive whereas veterinary treatment is very costly. Even though more and more pets are insured, the willingness and ability of the owner to pay for the treatment has to be taken into account and this limits both what treatments are feasible and how technically advanced veterinary clinics are. While it is the feelings and solvency of the owner that are important when it comes to companion animals, the situation is quite different in case of poisoning of livestock. Investigation and prophylaxis is often more important than treatment of the individual animal and it can sometimes be better not to treat. There are also some treatment options that veterinarians have, that are not used in human medicine, for example euthanasia. *Conclusion:* There are numerous large and small differences between animal and human poisonings.

19. Improving Telephone Advice for Poisonings in Veterinary Practice – The Impact of Species and Breed Differences

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Introduction: Many poisons centres answer telephone enquiries from veterinarians and pet owners. Few attract dedicated funding for such activity, and consequently may not devote many resources to amassing veterinary specific material for such enquiries. Providing advice based on human experience, whilst tempting and understandable, may ultimately lead to sub-optimal advice for these callers and care of the animals in their charge. This review highlights why species and breed differences are important in this regard, and why these may impact on potential treatment recommendations, particularly with regard to use of medicines. *Discussion:* Physiology makes a difference. Every toxicologist knows why canaries were early carbon monoxide detectors in coal mines because of the particular sensitivity of their haemoglobin to the gas. Feline haemoglobin, characterised by presence of 8 prominent sulphydryl groups, is peculiarly susceptible to oxidation. This is one reason why cats are badly affected by paracetamol, developing both methaemoglobinaemia and Heinz body anaemia. Limited hepatic glutathione increases their risk. Worse, cats have low levels of glucuronyl transferase and thus limited glucuronidation, and a capacity-limited sulphation pathway. These limited biotransformation routes render them susceptible not only to paracetamol, but increase their apparent susceptibility to other agents such as pyrethroids and benzoic acid. Canine erythrocytes have oddities too. Dogs develop haemolytic anaemia after ingestion of onions or other *Allium spp*, but some have erythrocytes with inherited high sodium-potassium ATPase activity, high potassium and low sodium concentrations which dramatically speed the development of anaemia and induces methaemoglobin formation in these animals (1,2). The antiparasitic agents Ivermectin, Milbemycin and Moxidectin are particularly toxic to collie, Sheltie and Australian shepherd dog breeds owing to an enhanced penetration of the CNS that occurs as a result of a genetic variation (3,4). An inherited autosomal recessive trait in Bedlington terriers causes young and middle aged specimens of this breed to develop chronic hepatitis owing to retention of copper in hepatocytes. Other dog and cat breeds have particular sensitivities to drugs which have not been fully elucidated. Examples include griseofulvin in Abyssinian and Himalayan cats, sulphonamides in Dobermans and Schnauzers, thiopentone in Greyhounds, Salukis and Whippets, and acepromazine in Boxers. These latter two drugs might occasionally be considered for use in the management of various intoxications, and knowledge of their contraindication in these breeds is important. Similarly, other drugs have less breed-specific toxicity in some species: propionic acid and arylacetic acid derived NSAIDs, Vitamin D compounds, and methylxanthines such as theobromine and caffeine in canines for example. Some plants affect certain species, e.g. the hepatotoxicity of *Senecio spp* in equines, the nephrotoxic effects of *Hemerocalis spp* and *Lilium spp* in cats as well as *Vitis vinifera* in dogs. The same may be true of food additives. In the USA the 5-carbon sugar alcohol Xylitol has been used as a sweetener in baking products for years. It is now seeing increasing use in sweets and even human medicines (nicotine replacement therapies) in the UK. Unfortunately Xylitol is a potent stimulator of insulin release in dogs, and accidental ingestion causes a rapid and dose-dependent hypoglycaemia, with as little as 0.9 mg/kg causing this effect (5, 6). Even chemicals can have differing effects – ethylene glycol is toxic to both dogs and cats, but particularly to the latter as they have a comparatively high resting oxalic acid production. Prescribing legislation, with regard to veterinary medicines and their licensed use, may affect management guidance offered by a poisons centre. One cannot simply recommend protocols based on human experience as drugs may not be available for veterinarians or appropriately licensed. Recent UK legislation, the Veterinary Medicines Regulations of 2005 and 2006, prevents veterinarians prescribing generically similar human medicines for conditions if a licensed veterinary medicine for that condition is available. Additionally, if a veterinary medicine is licensed for a particular indication in one species, then it should also be used in other animal species for that indication in preference to a human licensed drug. The recent launch of a veterinary anti-emetic Maropitant citrate (Cerenia®, (Pfizer)), licensed for use in dogs, has effectively meant that metoclopramide, formerly the anti-emetic of choice for veterinarians, cannot be recommended in animals. This is despite the fact that no regimens currently exist for use of Maropitant in cats and other species, and that veterinarians have more experience with the older compound. Such legislation may vary from country to country, and poisons centres should keep abreast of requirements and ensure their recommendations to their users are compliant. Thus, centres offering veterinary advice will need to devote resources to educating and training their staff appropriately. *Conclusions:* As with human enquiries, providing as specific advice as possible for each case on its own merits is important, both in terms of information about effects of poisons but also management advice. Staff of poisons centres that provide advice for veterinarians should be careful to elicit as much data on the animals about which referrals are made, particularly when collecting data on past cases, as inevitably there will be further interesting and unusual examples of toxicity variation to be discovered in years to come. *References:* 1. Kobayashi K. The hemolytic effect of onions on canine erythrocytes associated with inherited high Na, K-ATPase activity. *Japan J Vet Res* 1987; **35**: 137. 2. Yamoto O, Maede Y. Susceptibility to onion-induced hemolysis in dogs with heredity high erythrocyte reduced glutathione and potassium concentrations. *Am J Vet Res* 1992; **53**: 134–137. 3. Paul AJ, *et al*. Clinical observations in Collies given ivermectin orally. *Am J Vet Res* 1987; **48**: 684–685. 4. Mealey KL, *et al*. Ivermectin sensitivity in collies is associated with a deletion mutation of the mdr 1 gene. *Pharmacogenetics* 2001; **11**: 727–733. 5. Foss TS. 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20. How Poison Centres can Help in Animal Welfare Campaigns

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Introduction: The Feline Advisory Bureau (FAB), which incorporates the European Society of Feline Medicine, is a charity which provides information on the care of cats in a wide range of markets, from veterinarians through to cat owners. FAB also funds veterinarians to specialise in feline medicine at several UK veterinary schools. Cats, though less prone to eating poisonous substances than dogs, have metabolic differences that render them more susceptible to poisoning by some common household products and drugs. They are also compelled to groom contaminants off the coat and paws and may therefore ingest substances they would normally avoid. FAB can draw on huge expertise in medicine and surgery but lacks depth in the area of toxicology. FAB is represented on a British Veterinary Association Advisory Panel on Poisoning to which the Veterinary Poisons Information Service (VPIS) reports annually. FAB only provides information based on sound scientific basis. Data on animal poisonings are not available elsewhere in the UK and FAB looks to VPIS to give us reliable information to a) understand the scale of poisoning problems in cats, b) recognise new poisons or potential risks to cats, c) provide advice on management and prevention, d) monitor feedback and incidence after campaigns etc., e) provide answers to questions raised by vets and owners on an occasional basis. *Collaboration:* Two examples of FAB / VPIS collaboration are detailed here. 1) FAB's Cat Friendly Practice Campaign. During 2006 and 2007 FAB has undertaken a campaign to make veterinary practice friendlier for cats and their owners and improve the care cats get in practice. Information was provided for veterinary practices and alongside this a series of nine leaflets were produced for vets to give their clients. One of these was on six of the most common (and potentially lethal) poisonings in cats, and contained advice about prevention and first-aid. The text and advice was written by VPIS and the leaflets produced under the imprint of both organisations. These leaflets have proved popular in practices. 2) Permethrin Spot-on products campaign. Over the years there have been many letters in the UK veterinary press from individuals, and reports from the Veterinary Medicines Directorate about the dangers of pet owners mistakenly using canine spot-on preparations containing permethrin on their cats. The dog dose provided in the pipettes contains potentially lethal doses for cats and many deaths have occurred. However, the scale of the problem was unknown. The problem is exacerbated because a) owners are not aware of the dangers, b) cheap permethrin spot-on products for dogs are available through supermarkets and other outlets making them an easy buy without any consultation or advice, c) poor labelling has meant that many owners do not notice the warnings, d) veterinarians have not been aware of the extent of, and have therefore probably been underdiagnosing, the problem, e) many veterinarians have not known how best to treat affected cats, f) some medications needed for optimum management of these cases are not readily available to veterinarians. The result has been that many cats have been severely poisoned, requiring several days of intensive treatment at considerable financial and emotional cost to owners. FAB and VPIS met to discuss how this could be tackled. As a result VPIS reviewed past cases retrospectively and submitted a detailed paper which was submitted, peer-reviewed and accepted for publication in the Journal of Feline Medicine and Surgery (1). On its publication a joint VPIS/ FAB PR campaign was launched in veterinary, pet and national press referring to the paper. Information was produced for owners explaining the different types of flea treatments available, also highlighting the dangers of using dog products on cats. This was made available on the FAB website (www.fabcats.org) (2). An article on recognising and treating permethrin poisoning in cats, written by a specialist in veterinary critical care, appeared in several publications to bring veterinarians up to date (3). Information was disseminated to the Cat Group – a collaboration of rescue, welfare, scientific and breeding organisations that make feline information available to their contacts. Regulatory bodies were contacted to try and make better labelling of packaging mandatory and to develop a recognisable graphic to warn owners the product is potentially dangerous for cats. Contact was made with veterinary pharmaceutical companies to try and improve the availability of the drugs used by veterinarians to treat these cases. Reporting following the campaign was monitored. *Outcome:* To date results have been a) widespread coverage in veterinary press bringing increased recognition of the problem, b) substantially increased reporting of cases, both serious and fatal, from veterinarians to both FAB and VPIS, c) raised awareness and interest within the regulatory authorities and ongoing discussions about how packaging, labelling and promotion can be tightened, d) some improvement in awareness of owners, although uptake of the press releases by the national press was poor, e) improved collaboration with other veterinary groups, f) raised awareness of the activities of both FAB and the VPIS. *Conclusion:* The collaboration between VPIS and FAB generated a statistical and scientific analysis of the scale and severity of a particular problem in veterinary practice, which although known about was previously underappreciated. Careful coordination of activity at the time of publication of the report allowed dissemination of information to a range of organisations and owners that would not have been possible by either organisation alone. Poisons centre data can prove invaluable for veterinary welfare campaigns. *References:* 1. Sutton NM, Bates N, Campbell A. Clinical effects and outcome of feline permethrin spot-on poisonings reported to the Veterinary Poisons Information Service (VPIS) London. *J Feline Med Surg* 2007; **9**: 335–340. 2. http://www.fabcats.org/owners/fleas/info.html 3. Boag A. Permethrin flea treatments: often not spot-on for felines. *Vet Times* 2007; **37**: 10.

21. Neuroadaptations Caused by Drugs of Abuse – The Leaky Cauldron

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Objective: Neuroadaptations (an environmental or genetic influence that causes a compensatory physiologic response) may occur following a single exposure or multiple exposures to a drug of abuse. Neuroadaptations include changes in gene expression; molecular and cellular function; brain anatomy; release of neurotransmitters (NT), their transporters and receptors; and neurocircuits. The objective is to review the neuroadaptations that occur following use of selected drugs of abuse. *Methods:* Review of the international literature. *Results:* Selected neuroadaptations and specific drug-related neuroadaptations are discussed. *Molecular and cellular targets:* Within hours of use, some drugs of abuse activate Immediate Early Genes (IEG) which initiates plastic remodelling of neurons. IEG regulate transcription factors which are proteins that bind to regulatory regions and modify downstream gene expression. IEGs also change neuronal cell functions (e.g. intracellular signalling and synaptic modification of structure or metabolism) and subsequently change neural circuits. Brain imaging is providing insight into changes in nuerocircuits, NT transporters and receptors (1). *Neurocircuit Nueroadaptations*: Activation of the opioid receptor (coupled to the G-protein which initiates cellular effects) recruits many NT systems. The dopaminergic (DA) system is one of the most frequently recruited. In turn, DA interacts with other NT such as glutamate (involved in molecular changes) and GABA (main NT in DA projections). With repeated drug administration, neuroadaptations in glutamatergic and GABAergic circuits increase their influence on the brain's response to drugs of abuse. Changes in receptor number and function represent neuroadaptation at a cellular level. During development, each type of nerve is programmed to expect a certain level of input from each NT to which it can respond. If a nerve receives too few impulses via a specific NT, it responds by increasing the number of receptor proteins for this NT. Conversely, too many impulses cause a decrease in receptor proteins (downregulation). Exogenous drug of abuse administration can cause a change (neuruoadaptation) in the number or function of receptors. *Cocaine:* The number of DA receptors appears to be genetically-predetermined and influences susceptibility to drug use. An innate paucity in number of D2 receptors predisposes monkeys to greater cocaine self-administration than monkeys with more D2 receptors. In monkeys who self-administer cocaine, D2 receptor density decreases (neuroadaptation). Social rank also changes the number of D2 receptors. When monkeys are housed together, D2 receptor density increases in monkeys that become dominant-a neurobiological adaptation induced by attainment of dominant rank. When both dominant and subordinate monkeys are allowed to self-administer cocaine, subordinate monkeys have a significantly higher intake and choose cocaine over food (presumably due to relatively fewer D2 receptors). Recovery in number of D2 receptors is variable when these monkeys are subsequently maintained cocaine abstinent. Environmental and social variables can change receptor density and vulnerability to self-administration of drugs (2,3). *Methamphetamine (Meth)*: Neuroadaptations involving DA, serotonin (5-HT), glucose metabolism, neruometabolite levels and gross structural abnormalities have been demonstrated in humans who used Meth. Changes are most pronounced in basal ganglia which have the highest densities of DA synapses. Basal ganglia enlargement in recent Meth users may be due to Meth-induced inflammation or reactive gliosis. Decrease in basal ganglia volumes in chronic meth users suggests volume loss with continued use. Chronic D1 or D2 receptor occupancy may cause neuroadaptations, although how the receptors cause morphological changes remain unclear (4). *MDMA:* There is evidence that the substituted amphetamine 3.4-methylenedioxymethamphetamine (MDMA) destroys 5-HT axons and axon terminals. Although axons can undergo regenerative sprouting, the reinnervation pattern is abnormal. However, MDMA does not cause damage to 5-HT neurons when injected directly into the brain, suggesting that metabolic activation is necessary for the development of neurotoxicity. (N-7) MDMA also causes lasting decreases in 5-HT transport proteins (SERT). In knock-out animals that do not have SERT, metabolic changes are induced. Could axonal degeneration be a result of neuroadaptive metabolic changes secondary to loss of SERT (5,6)? *Conclusion:* Neuroadaptations alter physiologic responses to subsequent drug exposure. Imaging studies allow us to gain a better understanding of the neuroadaptations. The future challenge is the discovery of the correlative clinical manifestations. *References:* 1. Kubic S, Miyashita T, Guzowski J. Using immediate-early genes to map hippocampal subregional functions. *Learning & Memory* 2007; **14**: 758–770. 2. Volkow N, Wang G, Fowler J *et al*. Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D2 receptor levels. *Am J Psychiatry* 1999; **159**: 1440–1443. 3. Morgan D, Grant K, Gage D, *et al*. Social dominance in monkeys: dopamine D2 receptors and cocaine self-administration. Nature Neuroscience 2002; **5**:169–174. 4. Thompson P, Hayashi K, Simon S, *et al*. Structural abnormalities in the brains of human subjects who use methamphetamine. *J Neuroscience* 2004; **26**:6028–6036. 5. Fischer C, Hatzidimitriou G, Wlos J, *et al.* Reorganization of ascending 5-HT axon projections in animals previously exposed to recreational MDMA. *J Neuroscience* 1995; **15**: 5476–5485. 6. Xie T, Tong L, McLane MW, *et al*. Loss of serotonin transporter protein after MDMA and other ring-substituted amphetamines. *Neuropsychopharmacology* 2006; **31**:2639–2651.

22. How Effective are Public Information Programs in Preventing Poisoning?

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Introduction: Poisoning is a major cause of morbidity and mortality. The majority of poisonings are unintentional and seemingly, they should be preventable or 'controllable' events as the term 'poison control' implies. The epidemiological model (victim [human/animal]+agent [poison]+environment [conducive setting to bring the victim and agent together]=injury [poisoning]) requires that three parameters or conditions must be met for a poisoning to occur. Any strategy that interferes with the interaction between or among the three parameters should result in successful poison prevention. Primary poison prevention education promotes avoidance of risk by eliminating the poison or the conducive environment that brings the victim into contact with the poison. Secondary education assumes that a poisoning exposure has occurred and seeks to reduce morbidity and mortality by utilizing the services of a poison center. Most poison prevention programs combine aspects of both primary and secondary education. In other words, the general purpose of 'public information programs in preventing poisoning' is to create avoidance of exposure to poisons and enhance awareness of the poison center in the event that an exposure has occurred. How effective are these efforts? While there is evidence that temporary behavior changes can occur following directed poison prevention education activities, there is no evidence that demonstrates that primary education is effective. *Discussion:* Theoretically, primary education should be effective, but does it change outcomes and is that measurable? Poison avoidance would be a good indicator of primary education and reduced poison center exposure call volume might be a reflection of effectiveness. Conversely, increased call volume may be an indicator of the success of secondary poison prevention education strategies. Since most poison prevention education endeavors combine both primary and secondary education messages, the specific effectiveness of primary education cannot be measured. Ultimately, improved patient outcome is the desired goal. However, there is no evidence that public education programs result in improved patient outcome. A review of the American Association of Poison Control Centers National Poison Data System for the last five years failed to reveal any changes in patient outcome (positive or negative). The data also show a pattern of slow but continued growth in the number of exposure calls and precipitous growth in the volume of information calls (a reflection of the effectiveness of secondary education?). While the effectiveness of primary education cannot be validated, the impact of secondary education on

enhancing the awareness of the poison centers is impressive. As evidence, the national toll-free Poison Help telephone number (800–222–1222) was implemented in January, 2002. Calling the universal number will connect the caller with the nearest regional poison center in the United States and US territories. From October, 2006 through September, 2007 3,448,412 exposure and information calls were directed to US regional poison centers via the national toll-free Poison Help telephone number—from no calls at inception to over three million calls in 6.5 years! An estimated 80% of the calls now originate on the Poison Help toll-free number. It is evident that poison center awareness education (secondary education) has been successful, but the question still remains: is primary education effective? According to the Haddon Matrix which goes beyond the traditional epidemiological model, injury prevention can be achieved only through a multifaceted approach that includes both voluntary (e.g. public poison prevention education) and involuntary initiatives. The integral components of effective programs incorporate six elements: education, environmental/engineering modifications, enactment/enforcement, economic incentives, empowerment and evaluation. Poison centers can educate and empower the public with regard to poison prevention within their service region. With the exception of demonstrating enhanced poison center awareness through secondary education, poison center evaluation of the effectiveness of primary education is nearly nonexistent. The most significant poison prevention measure to date in the United States was not a primary education strategy but an involuntary intervention that incorporated the engineering, enactment and enforcement components of Haddon's Matrix. In 1970 the Poison Prevention Packaging Act was passed to protect children from unintentional poisoning due to prescription and nonprescription medications as well as chemicals such as methanol and corrosives. Following implementation of the PPPA, pediatric fatalities plummeted. Poison centers reinforce the importance of utilizing child-resistant closures properly in their primary education programs. However, it is clear that the PPPA, an involuntary measure, has had the greatest impact on preventing morbidity and mortality due to poisoning in children. *Conclusions:* Primary poison prevention is time-consuming, expensive and has not been validated. The 2004 Institute of Medicine report on Forging a Poison Prevention and Control System reported that " . . . public education efforts are necessary but not sufficient to accomplish primary or secondary prevention of poisoning." Furthermore, the IOM report recommended that the primary and secondary poison prevention education efforts should be separated so that the evaluation of primary education initiatives can occur. It is incumbent upon poison centers to examine the cost-effectiveness of education programs and invest in those aspects that produce the greatest benefit. Poison center awareness activities are successful. While primary education interventions have theoretical benefit and emotional justification, emphasis on poison center awareness (secondary education) may be the most appropriate public education strategy until there is evidence to support the value of education that stresses primary prevention. Primary poison prevention efforts have focused on the pediatric population where most exposures have minimal consequences. Poison prevention education should be refocused to address the impact of interventions that target high risk groups (and that can be evaluated) such as senior citizens and those at risk of being exposed to highly toxic agents instead of expending a disproportionate amount of resources to address pediatric exposures.

23. The Role of Medicines Regulation in Prevention of Serious Poisoning

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The regulation of medicines has become increasingly centralised within a European framework. Licensing is now primarily carried out by the EMEA with contribution from drug regulatory authorities within individual member states. Availability of medicines is restricted primarily by source of supply. Drugs are available as prescription only when first marketed, and much safety data is now needed before they are available without prescription as pharmacy or over-the-counter sales. Assessment now includes the potential for abuse and overdose. This was not the case in the past when licensing concentrated on quality, safety and efficacy. Within this framework efficacy and safety were considered in the context of normal therapeutic use. Potential for abuse, as in for example with opioids or central stimulants, was managed by controlling supply, and restriction of the prescription conditions necessary before a patient could receive a drug in the out of hospital setting. Within hospitals systems for recording drug usage are used to prevent illicit supply. License variation has long been used a means of limiting toxicity in therapeutic use, with revocation the ultimate sanction. More recently concerns about drug safety in overdose, and likelihood of contributing to behaviour that would increase overdose behaviour has focused interest on the use of legislative tools as a way of limiting the risks in overdose. Pharmaceutical supply is influenced by legislation and the content of the product SPC. Limitation of supply can be in a variety of ways. The most extreme is used in opioid dependency programmes whereby a patient may be required to be observed to take their daily dose of long-acting opioid substitute (methadone) to reduce self harm and trafficking. The more usual approaches rely on limitation of availability at sale, ultimately revocation of a marketing authorisation. Recent examples in Europe include thioridazine, removed because of concerns about QT prolongation. This was frequently prescribed to patients with behavioural disorders and frequently associated with admission secondary to self-harm. Revocation affected the prescription pattern of other antipsychotics drugs, and thus had implications for particular groups of patients who are at risk of self-harm. In the UK there were rapid changes in prescription and overdose patterns (1). In order to properly assess risk in overdose for licensing data sets reflecting patterns and toxicity in overdose need to be collected. In contrast to routine pharmacovigilance, information on overdose, either while taking a product, or use of the product in overdose, is generally not systematically acquired by regulators or manufacturers. Poisons Centers are often approached for such data, although much of the data is acquired from call data, reducing its value for the purposes needed. 30 years ago aspirin was a common cause of poisoning and death in overdose in the UK. The recognition that Reye's syndrome was linked to aspirin use in young children (2) led to it only being advised for children over the age of 12 years. The gastric irritant properties, and the introduction of over-the-counter non-steroidal anti-inflammatory agents (ibuprofen) also affected use of aspirin. Its value in myocardial protection and as a treatment for thromboembolic disease at low doses also changed the size of tablets used. Taken together the pattern of serious aspirin poisoning in the UK was changed fundamentally, and serious aspirin poisoning is now hardly ever seen, thus illustrating the potential impact of adjustments to an over-the-counter availability of a product. Following extensive consultation the UK licensing body changed the availability of pack sizes for over-the-counter sale of paracetamol. A maximum of 32 tablets, 16 grams, of paracetamol was allowed in pharmacies with smaller amounts suggested in non-pharmacy outlets. Initially trends in poisoning presentations involving paracetamol suggested a benefit of the legislation. Subsequent data from Scotland, where rates of self-harm may be higher than other parts of the UK, showed a reverse in the trend with a significant deterioration in health outcomes from paracetamol overdose (3). These findings have raised questions on the approach used to limit availability. It is generally considered that alternatives to paracetamol, such as ibuprofen, would create a different, but equally important health problem (4). Patients buy paracetamol in a planned manner from a variety of outlets prior to their overdose and implications for future legislation are unclear. Although not all outlets have strictly adhered to the policy, it is unlikely that this non-adherence accounts for the observed effects. In contrast restrictions in the licenses of prescription drugs are far more effective in limiting availability. It is important to balance any perceived danger in overdose with potential loss of clinical benefit if patients were to be denied an effective therapy. In the case of co-proxamol (dextropropoxyphene 32.5 mg and paracetamol 325 mg) these arguments were played out in a very public arena within the UK. It was possible to show a clear excess mortality and death that occurred early after overdose prior to potential hospital care. Furthermore manufacturers of the drug were unable to demonstrate a therapeutic benefit against paracetamol alone. Scottish data clearly show a marked effect. Whether in future more information on the effects of drugs in overdose will be used more strategically remains uncertain. The differential toxicology of antidepressants and SSRIs in overdose is well known. Using this data to alter licensing restrictions is challenging. Thus the excess mortality associated with dosulepin has been known for 20 years, and yet no formal attempt has yet been made to restrict use. Many challenges remain for clinical toxicology in poisons prevention and there is an enormous potential for clinical toxicologists and poisons centres to contribute public safety in this area. *References:* 1. Good AM, *et al. Br J Clin Pharm* 2002; **53**: 416P-417P. 2. Mortimer EA. *JAMA* 1987; **257**: 941. 3. Bateman DN, *et al. Br J Clin Pharm* 2006; **62**: 573–581. 4. Sheen CL, *et al. Pharmacoepimiol Drug Safety* 2002; **11**: 329–331. 5. Afshari R, *et al. Br J Clin Pharm* 2005; **60**: 444–447. 6. Sandilands E, *et al*. EAPCCT Congress, 2008.

24. Toxicokinetics in Senior Patients: Lessons from Therapeutic Drug Monitoring

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Objective: Senior patients have an increased risk of poisoning by dosage errors or mix-up with medication in comparison to younger adults. In these cases centrally acting agents are often involved (e.g. analgesics, neuroleptics or antidepressants). Although excretion of many substances is supposed to be altered in aged patients, subsequent measurement of blood concentrations during the course of an acute intoxication is not commonly performed. In addition, precise information on the ingested amount, time of exposure and body weight is often unavailable. In order to evaluate age-specific factors influencing the excretion of substances in intoxicated senior patients, data from therapeutic drug monitoring (TDM) covering ten different centrally acting agents were analyzed for individual kinetic parameters of aged patients and compared to those obtained from younger adults. *Methods:* (a) The number of inquiries regarding intoxications with olanzapine, clozapine, carbamazepine, lamotrigine, valproic acid, gabapentin, risperidone, pregabalin, amisulpride, and amitriptyline in the Berlin Poison Information Centre between 2002 and 2006 with patient age > 60 years (n=5,468) were compared with those of age between 15 and 60 years (n=46,360). (b) Data from TDM of patients receiving these substances with documented dosage and lean body weight were used to compute individual clearances in steady-state. Individual clearances were grouped by age (n=1040 / 103) according to (a) and unpaired t-tests were used to detect significant differences between both groups. *Results:* (a) Inquiries for all substances enrolled in this study had lower relative frequencies in old patients (> 60 years) when compared to the control group (aged 15 to 60 years). Minimum value was found for amisulpride (0.28) followed by olanzapine (0.38) and risperidone (0.66). Maxima were obtained for clozapine (0.86) and amitriptyline (0.98). (b) When compared to younger patients, in older patients significantly ($p<0.01$) reduced individual clearances were found for clozapine (5.03±2.44 / 7.14±3.97 $ml*min^{-1}*kg^{-1}$) and gabapentin (0.41±0,32 / 2.97±1.08 $ml*min^{-1}*kg^{-1}$). Clearance of the other substances appeared not to be significantly affected by age. This remains to be further analyzed, as a reduced oral bioavailability could mask a simultaneous decline in excretion. *Conclusion:* Data from TDM appear to be useful in gaining additional information on age-specific effects in the excretion kinetics of substances involved in intoxications of seniors. The knowledge of the patient's individual clearance is valuable in estimating the duration of symptoms, uncovering age-dependent risks of complication and might facilitate the individualisation of therapeutic management of the poisoned patient.

25. Withdrawn

26. The European Database on New Drugs (EDND) – An Early Warning System for Novel Psychoactive Substances

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Objective: Inquiries to the Swedish Poisons Information Centre regarding new psychoactive drugs have increased rapidly during recent years. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has set up a database (EDND) designed as an information source of recreational drugs and an early warning system, and since 1997 all EU-countries are obliged to report the discovery of new psychoactive substances to EMCDDA. To facilitate detection of new drugs and to ensure correct reporting routines, the Swedish National Institute of Public Health established a specialised network in the year 2000. This network includes experts from the police, customs, poisons centre and forensic laboratories. The following survey was performed by using the EDND to investigate occurrence and frequency of new drugs of abuse in Europe, with special focus on Sweden. *Methods:* Data from EDND were compiled and evaluated. *Results:* During the period 1998-Oct 2007, 46 different drugs divided into five groups were reported to EMCDDA. Phenethylamines (18/46), indolalkylamines (11/46), piperazine derivates (8/46), cathinones (2/46) and others (7/46). In our opinion, seven of these substances should be excluded because they may rather be classified as old drugs, medical products or impurities after synthesis. The majority of the substances have been reported from United Kingdom (23), Finland and Sweden (22 each), while three countries have not delivered any

reports. First time occurrence of a specific drug was reported most commonly from Sweden (16/39) followed by United Kingdom (11/39) and Finland (7/39). If yet unregistered Swedish reports were included, 33 new drugs have been discovered in Sweden during the past decade. *Conclusion:* The high frequency of first substance detection in Sweden suggests a relatively easy access to these synthetic drugs in our country and a preference among drug dealers for this market. However, more probable explanations are the existence of a specialised network in Sweden ensuring reliable reporting routines in combination with efficient forensic laboratories. The European Database on New Drugs (EDND) could be a most useful tool in detecting and exchanging information regarding new psychoactive substances. Therefore it is important that poisons centres and clinical toxicologists in Europe contribute with their experience.

27. Medication Safety: The Role of Poison Centers

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Objective: Patient safety, including medication safety has become a health priority in the United States. Pursuing safety in general has involved a paradigm shift from a focus on practitioner knowledge and individual responsibility to a system focus with shared responsibility, multi-party empowerment and system processes to prevent error. Poison centers are playing an increasing role in this system 1) as sources of information for patients, 2) as sources of information for practitioners, 3) as assimilators/evaluators of the errors of others and 4) as self-critical identifiers of safety issues in their own practice. Expansion and modification of these non-traditional roles may allow greater efficacy in reaching societal goals. *Discussion:* As an example, our Drug and Poison Information Center staff of pharmacists and nurses takes over 170,000 calls per year from health professionals and the public. Approximately 45,000 involve exposures (traditional poison center role) and 108,000 involve medication identification (57% from the public concerning drugs with abuse potential—answered as part of a harm reduction strategy). Another 10,000 involve questions directly related to answering public concerns about the specific indications for the use of the medication, side effects, risk for medication interaction and dosage—part of empowering patients so that they can participate effectively in the medication safety system. Practitioners also call about medication interactions and about appropriate use of rarely used drugs—another safety issue. These information resource roles could be expanded and advertised, particularly in poison centers with significant pharmacist staff. We, with other poison centers, have recently accessed the AAPCC database to review reports of therapeutic errors in children resulting in severe adverse effect or death. Reviewing 240 cases over 5 years we noted that the majority of reports involved medications administered at home (including OTC products). Unsurprisingly dosing errors were the most common mechanism, but other patterns emerged. In many cases poison center charts did not have sufficient information to discern the root cause of the event. Helpful information was gleaned, but the substance distribution, home bias (hospitals are reluctant to call and reveal potential legal problems) and incomplete nature of the reports limits the use of past data. Anticipating these cases with a focused data collection tool could improve this. It may be particularly suitable for a poison centre in a more centrally organized country to be assigned the task of national investigator and repository of medication error information. Lastly our center identified an area in which poison centers are uniquely susceptible to contributing to medication error. We have discovered occasions where the DPIC advice recorded on the hospital patient chart does not match the poison center audio record of the medication advice given in the call. We have also recently experienced a "near miss" sound alike medication error (omeprazole for fomepizole) and communicated this to our peers. Poison centers need to incorporate procedural safeguards such as write down-read back and spelling medication names into their function. *Summary:* Poison centers are currently playing a role in addressing societal medication safety goals and ought to be more intentional by explicitly describing their actions, evaluating their utility and refining them accordingly.

28. The 2007 United States Pet Food Recall

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Objective: The purpose of this abstract is to describe the 2007 United States pet food recall, including the chronology of events, subsequent investigation, and legislative and regulatory outcome. What was learned? *Case report:* Menu Foods, headquartered in Canada, reported complaints alleging sickness in pets related to consumption of company products in February 2007. At the same time a laboratory under Menu Foods contract reportedly initiated a routine feline palatability study designed to compare desirability of side by side diets. Twenty cats were offered diets over a four-day period. Seven cats died and nine more were affected. Two additional cats from a second group also died. Histopathology indicated acute renal tubular necrosis. Many surviving animals had elevated blood urea nitrogen and creatinine values. Dogs offered suspect diet reportedly refused consumption. On March 13, a pet food company veterinarian managed a consumer call involving seven cats in one household allegedly sickened from consumption of a diet manufactured by Menu Foods. Two additional cases were identified from recent calls involving the same lot number. This information was provided to Menu Foods. Menu Foods informed the US FDA on March 15 and announced the recall on March 16, 2007. The initial recall involved 60 million containers spanning 100 brands of "cuts and gravy" style canned cat and dog food manufactured in the US from December 03 to March 06. On March 23, the New York State Department of Agriculture and Markets announced the isolation of aminopertin, a folic acid antagonist known to have anti-neoplastic properties similar to methotrexate, from pet food. Toxicity of aminopterin or methotrexate is manifested by gastrointestinal upset and bone marrow suppression resulting from damage to rapidly dividing cells. On Mar 27, the ASPCA Animal Poison Control Center released a statement based on call data suggesting reported signs were inconsistent with aminopertin toxicosis. On March 30, the US FDA announced detection of up to 6.6% melamine in wheat gluten from China and halted imports. Xuzhou Anying Biologic Technology Development Co. Ltd was identified as a source. Although confirmed by separate laboratories, the connection between melamine and renal failure was unclear. Melamine alone is moderately toxic with crystaluria reported (1). On April 03 ChemNutra recalled 792 metric tons of wheat gluten. Scientists at a US-based consumer products company produced renal failure in a rodent model resulting from melamine-cyanuric acid crystaluria. Such crystal formation was previously demonstrated *in vitro* (2). Melamine cyanurate appears to cause mechanical injury to renal tubular cells resulting in renal damage. On April 05, Menu Foods extended the recall back to November 08, 2006 and on April 10 expanded the recall to include pet food manufactured in a Canadian facility. On April 06 Dr. Stephen Sundlof of the US FDA stated melamine was added to wheat gluten to boost non-protein nitrogen analysis used to estimate protein equivalent for ruminants. Cattle rumen microbes combine NPN with carbohydrates to generate proteins. Monograstrics are unable to use this pathway. On April 12, the US Senate called for improved regulation and inspection, central reporting and a single food safety agency. To further complicate matters, Natural Balance announced a recall of pet foods containing rice protein supplements tainted with melamine. Cases of pets developing renal failure following consumption of contaminated diets were reported to the US FDA, www.PetConnection.com, www.VIN.com, the ASPCA Animal Poison Control Center, and veterinary diagnostic and university laboratories. The US FDA received thousands of consumer complaints. Following the outbreak, the American Association of Veterinary Laboratory Diagnosticians developed a voluntary study of accredited laboratories in North America. As of June 06, 2007, 347 cases met the defined criteria as a confirmed case. Of these 68% were cats and 32% were dogs. Case criteria included history of ingestion, consistent histopathologic renal lesions and detection of melamine in tissues or urine. Only a small number of cases had significant pre-existing disease (3). Analysis of data collected by the Veterinary Information Network from veterinarians indicated 20% of affected animals died or were euthanized with an average treatment cost of US$1000 (4). No age, breed or sex predilection was identified by either retrospective study. *Conclusion:* Wheat gluten and rice protein supplements from Chinese suppliers contained melamine, cyanuric acid and related compounds. In China these compounds are used to raise the NPN equivalent of low quality feed for use by ruminants, although with variable safety (5). The apparent reason for the addition of these compounds was to fraudulently increase the value of low quality raw food ingredients. Early detection of intentional or accidental adulteration of food is challenging. In this case adulteration was intentional, although apparently not malicious. A similar outbreak occurred in 2004 in Korea (6). In September 2007, US President George Bush signed into law an act attached to PDUFA requiring pet food processing and ingredient standards and an early warning surveillance system to identify contamination. Ingredient, processing and label standards must be developed within two years and an early warning surveillance system within one. Labels will clearly identify ingredients and countries of origin. Additionally, pet food companies voluntarily increased oversight of imports and testing. In the end, intentional or accidental contamination may be difficult to prevent, but rapid response may greatly reduce morbidity and mortality. *References:* 1. Hammond B, Barbee S, Inoue T, *et al*. A review of toxicology studies on cyanurate and its chlorinated derivatives. *Env Health Perspect* 1986; **69**: 287–292. 2. Arduini M, Crego-Calama M, Timmerman P, *et al*. A novel type of hydrogen-bonded assemblies based on the melamine-cyanuric acid motif. *J Org Chem* 2003; **68**: 1097–1106. 3. Rumbeiha W, Agnew D, Maxie G, *et al*. AAVLD survey of pet food-induced nephrotoxicity in North America, April to June 2007. *AAVLD Annual Conference Proceedings* 2007: 29. 4. Gwaltney-Brant S. 2007 PFR Demographics: results of an online survey of veterinarians. AAVCT Annual Meeting, Reno, NV, 2007. 5. Clark R. Melamine crystaluria in sheep. *J S Afr Vet Med Ass* 1966; **37**: 349–351. 6. Brown C, Jeong K, Poppenga R, *et al*. Brief Communications: Outbreaks of renal failure associated with melamine and cyanuric acid in dogs and cats in 2004 and 2007. *J Vet Diagn Invest* 2007; **19**: 525–531.

29. Veterinary Medicines – Potential Toxicity and Pharmacovigilance

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Introduction: Veterinary medicines are widely used both domestically and for commercial purposes. Human exposures occur either through eating meat from animals receiving treatment, through deliberate misuse and as a result of unintentional exposure. Within the EU there is strict legislation regulating the licensing of veterinary medicines. However, regulations in other parts of the world differ. *Animal toxicity:* Animal toxicity from veterinary medicines may occur as a result of predictable or idiosyncratic reactions. Incorrect dosing, use for an incorrect indication, or in an inappropriate species may produce toxicity. For example, the inappropriate application of a fipronil-containing ectoparasiticide licensed for use in dogs may produce severe side effects or mortality if used on cats. *Inadvertent exposure:* Human exposure to veterinary medicines is often associated with attempts to administer the medicine to the animal. Administration may be difficult and result in inadvertent operator exposure. For example, a large animal may need appropriate restraint if operator safety is to be ensured. Each year there are numerous accidental needle-stick injections and the farming and veterinary professions need to be made aware of the possible hazards (1). Potential hazards arise from exposure to biological infection – either to zoonoses, from biological contamination arising from use of a needle which has been used on multiple occasions, or from the constituents of the product itself. Pressure injuries may occur from automatic injection devices, though these generally inject a fixed volume, unlike injuries occurring from other high pressure devices. Veterinary medicines intended for intramuscular injection may contain mineral oil adjuvants. These can produce local granulomas or severe tissue damage, particularly if injected into confined spaces, for example a finger (2). Although early symptoms may be mild, prompt medical attention should be sought if severe damage is to be avoided. Occasionally amputation of a digit is necessary (3). Animals often receive treatments for ectoparasiticides and in some countries treatment has been compulsory. Inadvertent exposure to sheep dips may occur, either from handling concentrate, from splashing during the dipping process itself or from contact with sheep which have been dipped recently. In the United Kingdom concern about possible adverse human health effects led to the temporary suspension of marketing authorisations for organophosphorus–containing sheep dips and the subsequent introduction of closed transfer systems intended to reduce operator exposure. The phenomenon of apparent acute or chronic ill-health associated with dipping sheep has become a concern (4,5) and research is currently being undertaken to determine the nature and frequency of ill health associated with dipping. Substitution of alternative medicines to organophosphorus dips is not without its own problems. Synthetic pyrethroids may also be used to treat ectoparasites. However, whilst of low mammalian toxicity, they are particularly toxic to aquatic life and their use is associated with aquatic environmental incidents. When licensing veterinary medicines it is necessary to consider their environmental fate in addition to their toxicity in the target species (6). *Intentional misuse:* A number of veterinary medicines may be anticipated to have a predictably high human toxicity. For example, large-animal euthanizing agents would be expected to be potentially fatal in humans and have been used to commit suicide. However, other products, which might not be perceived to be toxic by the user, have an apparently unexpected human toxicity. An example of this is the cardiotoxicity and occasional human deaths associated with the accidental injection of small quantities of the antibiotic

tilmicosin (7). *Adverse reactions:* Pharmacovigilance schemes exist to monitor adverse reactions to veterinary medicines, in both animals and humans. These schemes provide the basis for improved animal and human safety. However, they generally rely on the voluntary reporting of adverse reactions to manufacturers and national reporting bodies and suffer from substantial underreporting. For example, the United Kingdom's National Poisons Information Service receives more enquiries about veterinary needle stick injuries than are reported to the United Kingdom's Appraisal Panel for Human Suspect Adverse Reactions to veterinary medicines. Despite this, these schemes are powerful enough to be able to detect unusual adverse events and to generate hypotheses concerning toxicity. This information is then used to improve product safety and to strengthen the marketing authorisation process for future products. *Conclusion:* Veterinary medicines contribute greatly to animal welfare, and to the commercial aspects of farming. The do however, have the potential to cause animal, human and environmental toxicity and must be regulated and used carefully. *References:* 1. Skilton D, Thompson J. Needlestick injuries. *Vet Rec* 2005; **156**: 522. 2. Jones DP. Accidental self inoculation with oil based veterinary vaccines. *N Z Med J* 1996; **109**: 363–5. 3. O'Neill JK, Richards SW, Ricketts DM, Patterson, MH. The effects of injection of bovine vaccine into a human digit: a case report. *Environ Health* 2005; **4**: 21. 4. Solomon C, Poole J, Palmer KT, Peveler R, Coggon D. Neuropsychiatric symptoms in past users of sheep dip and other pesticides. *Occup Environ Med* 2007; **64**: 259–66. 5. Rees H. Exposure to sheep dip and the incidence of acute symptoms in a group of Welsh sheep farmers. *Occup Environ Med* 1996; **53**: 258–63. 6. Boxall AB, Fogg LA, Blackwell PA, Kay P, Pemberton EJ, Croxford A. Veterinary medicines in the environment. *Rev Environ Contam Toxicol* 2004; **180**: 1–91. 7. Veenhuizen MF, Wright TJ, McManus RF, Owens JG. Analysis of reports of human exposure to Micotil 300 (tilmicosin injection). *J Am Vet Med Assoc* 2006 1; 229: 1737–42.

30. Outcome of Pregnancy After Maternal Treatment with Lithium

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Objective: There is evidence that exposure to therapeutic doses of lithium in pregnancy can cause teratogenic and other toxic effects in the fetus and neonate (1). In addition, there is accumulating evidence that inadequately treated psychiatric illness can adversely affect pregnancy outcome (2). This on-going prospective case series aims to collect data and assess the potential fetotoxic effects of lithium during pregnancy. *Method:* Using standardised procedures, NTIS has provided fetal risk assessment and collected prospective outcome data on 71 pregnancies exposed to maternal lithium therapy. *Results:* Results are shown in the table. Therapeutic use occurred in 71 pregnancies including 1 set of twins. Of the live born infants exposed to lithium during pregnancy, 3/43 (7.0% 95% CI 1.8, 20.1) had malformations. The malformations in the 3 infants were reported as (1) valproate syndrome with an absent left thumb (associated with concurrent maternal exposure to valproate), (2) macrosomic polyhydramnios, (3) tricuspid regurgitation associated with valve dysplasia. All 3 infants were exposed to polytherapy. *Conclusions:* A slight increased rate of congenital malformations was observed following exposure to lithium, but this is not statistically significant and no specific pattern of malformations was seen. Confounders (e.g. polytherapy, maternal illness and age) preclude establishment of a causal relationship with lithium. More data are required for this on-going series. *References:* 1. Jacobson SJ, Jones K, Johnson K, *et al*. Prospective multi-centre study of pregnancy outcome after lithium exposure during the first trimester. *Lancet* 1992; **339**: 530–3. 2. Cott AD, Wisner KL. Psychiatric disorders during pregnancy. *Intl Rev Psychiatry* 2003; **15**: 217–30.

Table: Outcome of pregnancy after maternal treatment with lithium

Trimester	Total pregnancies / total live born	Normal healthy	CM	NP	ETOP	SA
1st	32/19	14	1	4	10	3
3rd	1/1	0	0	1	0	0
1st/2nd	2/2	0	0	2	0	0
1st/3rd	8/5	3	1	1	1	2
Unknown	29/16	13	1	2	7	6
Total	72/43	30	3	10	18	11

CM=congenital malformation, NP=neonatal problem, ETOP=elective termination of pregnancy, SA=spontaneous abortion.

31. Pregnancy Outcomes After Exposure to Lead During Pregnancy

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Objective: Small numbers of case reports have suggested an increase in the incidence of minor congenital anomalies following maternal exposure to lead during pregnancy. However, a causal relationship has not been established and there is no compelling evidence that there is an increased risk of major congenital malformations, although third trimester exposure to high lead concentrations has been associated with macrocephaly. This on-going prospective case series aims to collect data and assess the potential fetotoxic effects of lead exposure during pregnancy. *Method:* Using standardised procedures NTIS has provided fetal risk assessment and collected outcome data on a prospective case series of 71 women exposed to lead in pregnancy. *Results:* Pregnancy outcomes are shown in the table. Of the 71 pregnancy outcomes, 27 women were reported to have been exposed to other chemicals or therapeutic medications during pregnancy. Of the live born infants exposed to lead during pregnancy, 3/65 (4.6%, 95% CI 1.2, 13.7) had malformations. The malformations reported in the 3 infants were (1) positional talipes with a slight degree of plagiocephaly and motor delay associated with hypotonia (2) a ventricular septal defect with poor feeding and jaundice (3) a left *calcaneal valgus*. *Conclusions:* The rate of congenital malformations was a little higher than expected, although this is not statistically significant and no specific pattern of malformations was observed. Further collection of data is warranted to investigate any possible association between lead exposure during pregnancy and the incidence of congenital malformations.

Table: Pregnancy outcomes after exposure to lead during pregnancy

Trimester of exposure	Total pregnancies / total live born	Normal healthy	CM	NP	SA	ETOP
1st	19/16	15	1	0	2	1
2nd	8/8	7	0	1	0	0
1st & 2nd	9/9	7	1	1	0	0
3rd	6/6	5	0	1	0	0
Throughout	5/5	5	0	0	0	0
Unknown	24/21	19	1	1	3	0
Total	71/65	58	3	4	5	1

CM=congenital malformation, NP=neonatal problem, ETOP=elective termination of pregnancy, SA=spontaneous abortiono.

32. Preliminary Data on Exposure to Statins During Pregnancy

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Objective: There are several conflicting reports of adverse human pregnancy outcome after *in utero* exposure to statins. However, interpretation of the studies is difficult due to a lack of data on concomitant medication and maternal disorders such as diabetes or hypertension. Decreased cholesterol synthesis may disrupt embryo-fetogenesis. A number of malformations such as holoprosencephaly, neural tube defects and VACTERL defects have been reported after exposure to lipophilic stains during pregnancy. This on-going prospective case series aims to collect data and assess the potential fetotoxic effects of both lipophilic and hydrophilic statins during pregnancy. *Method:* Using standardised procedures, NTIS has provided fetal risk assessment and collected outcome data on a prospective case series of 25 women exposed to statins in pregnancy. *Results:* Pregnancy outcomes are shown in the table. Of the 25 pregnancies, 22 (88%) were first trimester exposures and only 7 (28%) of the 25 mothers were on monotherapy. Of the live born infants exposed to statins during pregnancy, 4/18 (22.2%, 95% CI 7.4, 48.1) had malformations. The 4 congenital malformations reported included 2 after exposure to atorvastatin (a missing middle phalanx on right ring finger and a unilateral dilated renal pelvis) and 2 after exposure to simvastatin (a sacral pit with IUGR and mild positional talipes). *Conclusions:* The results of this small series are consistent with those of other published data and suggest an increased rate of congenital malformations after exposure to lipophilic statins. Until further data are available, the use of any statin during pregnancy should be avoided.

Table: Pregnancy outcomes after exposure to statins in pregnancy

Exposure	Total pregnancies/ total live born	Normal healthy	NP	CM	SA	ETOP
Atorvastatin	7/5	3	0	2	1	1
Simvastatin	14/9	5	2	2	4	1
Pravastatin	4/4	4	0	0	0	0
Total	25/18	12	2	4	5	2

CM=congenital malformation, NP=neonatal problem, ETOP=elective termination of pregnancy, SA=spontaneous abortion.

33. Maternal Toxicity Following Intra-Amniotic Digoxin Administration

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Objective: Although digoxin has been used as an abortifacient since the early 1990s, information about the complications of this route of administration is sparse. Because the total dose administered is usually small and presumed to be sequestered in the fetus, maternal toxicity is unexpected. We report maternal symptoms of digoxin toxicity following intra-amniotic digoxin administration. *Case report:* A 22-year old, 23-week pregnant woman was sent to the ED from a local family planning center for evaluation after noticing a first-degree atrioventricular heart block on her rhythm strip. The patient was undergoing cardiac monitoring during a termination of pregnancy procedure that involved a 1 mg intra-amniotic injection of digoxin. A pre-procedure ECG was not obtained. In the ED, she was asymptomatic and in no distress. Vital signs were: BP, 102/54 mmHg; pulse, 78/minute; respirations, 16/minute; temperature, 37°C (98.6°F); and pulse oximetry, 97% on room air. Her physical examination was significant only for a gravid uterus, and a formal 12-lead ECG in the ED did not demonstrate any conduction delay or dysrhythmia. Her serum digoxin concentration (SDC) was 0.3 nmol/L (0.4 ng/mL). She was observed for 6 hours in the ED and never developed any conduction delays or dysrhythmias on her subsequent rhythm strips. *Conclusion:* Intra-amniotic and intra-fetal digoxin crosses the human placenta (1,2) and has been associated with occasional atrioventricular conduction delays and PVCs (1). Although this patient's SDC was not life threatening, the use of digoxin in late-second trimester abortions should be recognized as a potential source of poisoning. *References:* 1. Drey EA, Thomas LJ, Benowitz NL, *et al*. Safety of intra-amniotic digoxin administration before late second-trimester abortion by dilation and evacuation. *Am J Obstet Gynecol* 2000; **182**: 1063–1066. 2. Jackson RA, Teplin VL, Drey EA, *et al*. Digoxin to facilitate late second-trimester abortion: a randomized, masked, placebo-controlled trial. *Obstet Gynecol* 2001; **97**: 471–476.

34. Varenicline (Chantix®) Overdose in an Adolescent Female

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Objective: Varenicline (Chantix®) is a partial agonist of the α4β2 subtype of the nicotinic acetylcholine receptor that was approved by the United States Food and Drug Administration in February 2006 for aid in smoking cessation. We describe a large, laboratory-confirmed, intentional overdose of varenicline in an adolescent female. *Case report:* A 14-year-old female presented to an emergency department (ED) after confessing to her grandmother that she had ingested 21 of her mother's varenicline 1 mg tablets in a suicide attempt. The mother's pill count subsequently confirmed 21 tablets missing. Although the patient's grandmother described her as "lethargic", there is no medical documentation of altered mental status. She was given 50 grams of activated charcoal PO and laboratory samples were obtained. The patient was transferred to our pediatric ED for further management. On arrival, 5 hours after ingestion, her vital signs included temperature 36.3°C, heart rate 80/minute, respiratory rate 24/minute and blood pressure 114/77 mmHg. Her examination was remarkable only for dilated, briskly reactive pupils at 5 mm. She was alert and oriented with a normal neurological examination. Her laboratory results included a negative urine pregnancy test, acetaminophen level <10 mg/dL and salicylate level <4 mg/dL. Her urine drugs of abuse screen was negative, but a comprehensive urine drug screen revealed caffeine, dextromethorphan, and varenicline. All other laboratory data were normal. The patient was admitted for observation. She remained stable with no evidence of toxicity. Psychiatry diagnosed the patient with major depressive disorder and severe post-traumatic stress disorder secondary to previous sexual and physical abuse. She was medically cleared after 12 hours and transferred to an inpatient psychiatric facility for further treatment. *Conclusion:* Varenicline overdose has not been reported in the literature and very little is known about its toxic effects. This patient only exhibited minor toxicity despite her history of ingesting 21 tablets with qualitative confirmation of her ingestion via the comprehensive urine drug screen. Her only symptom was lethargy as described by a family member. By the time she arrived to our institution, she was asymptomatic. Further post-marketing surveillance is needed to determine varenicline's toxicity in overdose.

35. Mortality and Complication Associated with Acute Tramadol Intoxication

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Objective: During a 12 month retrospective study in Tehran, tramadol exposure occurred in more than 15% of all hospitalized intoxicated patients aged >12 years (1). The present study was carried out to evaluate the complications of tramadol intoxications. *Methods:* During a 4-month period in 2007, all consecutive hospitalized tramadol intoxicated patients were prospectively assessed. A questionnaire was used and age, sex, dose, etiology of exposure, complications, abuse and psychiatric history and outcome of each poisoned patient were collected. Data were computerised and statistical analysis by chi-square test was performed using SPSS 15. *Results:* In total 427 individuals was entered into the study. Mean age was 22.7±6 years (range 14–61) and 92% were less than 30 years. 72.1% were male, 77.6% have took tramadol deliberately. The complications are summarized in Table 1. Less than 12.9% of all patients had a history of convulsions. 35.2%, 31.7% and 9.7% of patients who had evidence of seizures had a history of convulsions, a history of tramadol abuse and a history of substance abuse respectively (p=ns). History of tramadol abuse was claimed in 29.1% while 9.5% were substance dependent. Mean ingested dose of Tramadol was 2000±1850 mg (range 200–10,000). There was significant correlation between ingested dose and complications including respiratory depression and apnoea (P<0.001). There was significant correlation between history of tramadol abuse and non deliberate self poisonings and history of substance abuse, (P<0.001). Also there was significant correlation between history of tramadol/substance abuse and history of psychiatric illness (P<0.001). *Conclusion:* Abuse liability and high occurrence of complications particularly seizures and death should be taken into consideration for tramadol as an analgesic. *Reference:* 1. H Hassanian-Moghaddam, AA Kolahi. Tramadol intoxication /abuse: a new issue on high-access population. 6th Annual Congress of Asia Pacific Association of Medical Toxicology; 2007; 12–14 December, Bangkok, Thailand.

Table 1: Complications associated with tramadol in 427 acute poisoned patients*

	No	%
Dizziness	310	73.8
Nausea	244	58.1
Dry mouth	183	43.6
Seizure	152	36.2
Drowsiness	143	34
Vomiting	67	16
Respiratory depression	62	14.8
Apnea	19	3.6
Head & neck trauma	12	2.9
Coma	10	2.4
Tiredness	7	1.7
Death	7	1.7
Shoulder dislocation	3	0.7
Headache	3	0.7
Lethargy	2	0.5
Chest pain	1	0.2

*We couldn't complete all data for the deceased.

36. Amlodipine: Collection and Analysis of Case Data in the Society of Clinical Toxicology of German Speaking Countries (GfKT)

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Objective: In recent years the GfKT created a working group which collects and analyzes experiences about drug overdose to provide drug monographs. We developed an exchange format for case data together with another GfKT working group. The example of amlodipine is used to demonstrate how case data can be exchanged and which conclusions can be drawn from the collected data sets. *Methods:* The participating centers were asked to send data of all cases which met the following criteria: 1: Monointoxication 2: Uncertainty in the dose less than 10 percent. 3: Follow up for at least 12 hours. The centers were encouraged to send additional cases not meeting these criteria if they consider them useful to describe special aspects of amlodipine toxicity. Centers were to use the developed spreadsheet format if possible. Information implied in other fields (e.g. free text remarks) was used to improve incomplete data sets. *Results:* 5 of 10 centers sent a total of 88 cases. All but one provided information in the developed spreadsheet format. 52 cases fitted the criteria 1 to 3. Main symptoms were arterial hypotonia, tachycardia, and drowsiness. First symptoms occurred within 1.5 to 3 hours, moderate or severe symptoms after 3 hours or later. Of 26 children all but one ingested less than 1 mg/kg. All children developed no or minor symptoms. 7 of 26 patients over 14 years had moderate or severe symptoms after ingestion of 100 mg or more. One of these 26 patients died (70 years old, cardiovascular depression, asystole after 500 mg). Another fatality was found in the additional cases which did not meet the mentioned criteria for complete analysis (75 years old, known coronary heart disease, bradycardia, shock, multiorgan failure after an unknown dose plus alcohol). *Conclusion:* After less then 1 mg/kg (children) or 100 mg (adults) only minor symptoms occurred. The main problem is cardiovascular depression. The exchange data format is useful to exchange case data and to draw conclusions relevant for the daily work in poison information centers. The centers should strive for higher follow up rates and further harmonization of the poisons centers' documentation.

37. Delirium from Promethazine Poisoning – A Case Series

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Objective: There is limited information on promethazine overdose despite it being available for decades and its ongoing use for multiple common medical conditions. The aim of this study was to describe the clinical effects of promethazine in overdose. *Methods:* Promethazine poisonings were identified from a prospective database of poisoning admissions to a regional toxicology service. Data were extracted including demographics, details of ingestion, clinical features including delirium, complications and medical outcomes (length of stay and ICU admission rate). A fully Bayesian approach using logistic regression was undertaken to investigate the relationship between predictor variables and the occurrence of delirium. *Results:* There were 182 patients with 215 presentations with a known ingested dose of promethazine. There were 42 patients with 44 promethazine alone presentations. The median age of the patients ingesting promethazine alone was 20 years (inter-quartile range [IQR]:16–31), 32 of which were female (73%). The median ingested dose was 600 mg (IQR: 250–1000 mg; Range 25–2500 mg) and this was similar to the group as a whole. Median length of stay was 17 hours (IQR 11–26 hours) and 5 cases were admitted to the ICU of which 3 were ventilated. Two patients had myoclonus and there were no seizures, arrhythmias or deaths. Tachycardia (HR>100) occurred on 24 occasions (55%) and hypotensive (systolic blood pressure <90 mmHg) occurred once. Delirium occurred on 23 of the 44 promethazine alone presentations (52%) and 71 of 215 all promethazine presentations (33%). The median time to delirium was 3.8 hours (IQR 2.8–6.1 hours; Range 0.4–9.8 hrs) from ingestion for the 44 cases. Logistic regression demonstrated that only dose predicted whether patients developed delirium, irrespective of whether coingestants were taken. The administration of charcoal did not decrease the probability of delirium occurring. A nomogram for the probability that a patient will develop delirium based on dose was constructed which showed the probability of delirium for 500 mg was 43% and for 1 g was 81% for promethazine alone overdoses. *Conclusion:* The main feature of promethazine toxicity was delirium and the probability of this occurring can be predicted from dose ingested. ICU admission, coma and seizure activity are uncommon and no severe cardiovascular effects occur.

38. Comparison of Toxicity Following Escitalopram and Citalopram Overdoses

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Introduction: Clinical toxicity following overdoses of citalopram, an SSRI marketed in the US for 10 years, includes seizures and QTc prolongation. There is less overdose experience with the more recently marketed drug escitalopram, the active S-enantiomer. The purpose of this study was to compare clinical effects, including the frequency of seizures after overdoses of these drugs, and to correlate seizure risk with doses ingested. *Methods:* A retrospective review of single substance overdoses with citalopram and escitalopram reported to a poison center between 2002 and 2005 was performed. Only patients treated in a hospital were included. Data were analyzed for patient demographics, dose, clinical effects and outcome. *Results:* There were 62 citalopram and 103 escitalopram cases that met inclusion criteria. For citalopram there were 41 (66%) females and ages ranged from 17 months to 74 years (median, 17 years). For escitalopram there were 79 (77%) females and ages ranged from 19 months to 70 years (median, 18 years). There were no symptoms for 34 (55%) citalopram cases and 58 (56%) escitalopram cases. There were no major effects or deaths. Most frequently reported clinical effects with citalopram compared with escitalopram were drowsiness/lethargy [9 (15%) vs. 17 (17%)], tachycardia [12 (19%) vs. 25 (24%)], hypertension [4 (6%) vs. 6 (6%)], agitation/irritability [5 (8%) vs. 2 (2%)], vomiting [2 (3%) vs. 8 (8%)], and seizures [3 (5%) vs. 0]. The 3 patients with seizures ingested 440 mg, 500 mg and 1000 mg of citalopram. Of 22 children < 4 years old, only one child who

ingested 30 mg of escitalopram developed symptoms. In patients > 12 years of age, doses ranged from 80–2000 mg for citalopram and 40–600 mg for escitalopram. Median doses in asymptomatic and symptomatic patients > 12 years of age were not significantly different for either citalopram (330 mg vs. 370 mg; p=0.229) or escitalopram (140 mg vs. 170 mg; p=0.328). *Conclusions:* Frequency of clinical toxicity is similar after overdoses of citalopram and escitalopram. A multi-center study is planned to confirm these findings with a larger number of patients.

39. Obtundation and Seizure Following Accidental Overdose of Ondansetron in an Infant

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Introduction: We report a case of a 12-month-old infant who ingested eight tablets of his mother's ondansetron and subsequently developed significant multisystem toxicity requiring endotracheal intubation and intensive care unit admission. To our knowledge, this is the first report of significant toxicity secondary to ondansetron overdose in an infant. *Case report:* A 12-month-old male was transferred to our facility after ingesting approximately eight tablets of his mother's 8 mg ondansetron. He was found to be somnolent, tachycardic, and had stridorous breathing, horizontal nystagmus, and myoclonic movements. AST and ALT levels were 93 U/L and 127 U/L, respectively. Upon transfer, a brief tonic-clonic seizure and a diffuse erythematous rash were also reported. At our hospital, the examination showed a heart rate of 175 beats per minute, hyperreflexia, and lower extremity clonus. The initial QTc was 461 milliseconds. During his ICU admission, he developed a fever of 38.4C. The next day, he was successfully extubated and had an uneventful hospital stay with subsequent resolution of his abnormalities. *Discussion:* Ondansetron, a 5-HT3 antagonist, is an increasingly used antiemetic with a favorable safety profile. Seizures and cardiotoxicity have been reported with their use (1,2). Ondansetron has been shown to prolong the QTc interval when compared to placebo (2). Furthermore, our patient's constellation of symptoms was consistent with that observed in a serotonin syndrome. Authors reporting this phenomenon have speculated that the antagonism at the 5-HT3 receptor subtype increases the synaptic levels of serotonin (3). Up to two percent of patients using this agent for chemotherapy-induced nausea suffered rises in their hepatic enzymes. Given the increasing use of ondansetron in both inpatient and outpatient settings, this case report illustrates the potential for major toxicity in young children. *References:* 1. Sargent AI, *et al*. Seizure associated with ondansetron. *Clin Pharm* 1993; **12**: 613–15. 2. Boike SC, *et al*. Cardiovascular effects of intravenous granisetron at two administration rates and of ondansetron in healthy adults. *Am J Health-Syst Pharm* 1997; **54**: 1172–1176. 3. Turkel SB, *et al*. Possible serotonin syndrome in association with 5-HT3 antagonist agents. *Psychosomatics* 2001; **42**: 258–60.

40. How Dangerous are Pediatric Ingestions of Fixed Combinations of Hydrochlorothiazide and Angiotensin-Receptor-Blockers?

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Objectives: The antihypertensive Angiotensin-II receptor blockers (ARB) are often prescribed in a fixed drug combination with hydrochlorothiazide (HCT). No data about toxicity of this combination are available. *Case series:* Retrospective analysis of pediatric overdoses of fixed combinations of HCT and ARB was done in a cooperation of the Poison Centers Berlin (1/1996–10/2007) and Freiburg (5/2000–10/2007). Inclusion criteria were: Age 0–13 years, known ingestion and dose, follow-up information available. Dose was reported as defined daily dose (DDD) referring to normal adult dose. The DDD of ARB and of HCT were added together. *Results:* 28 children, age 1–9 years (Median 2), DDD 0.75–12 (Median 1). Children were observed in health care facility (27) or at home (1). ARB ingested were candesartan (9), irbesartan (4), losartan (5), telmisartan (1), valsartan (9). After ingestion of less than 2 DDD no child developed symptoms (10). Severity of poisoning was minor (3) or asymptomatic (15) after ingestion of 2 or more DDD. One child developed an increase in diuresis and 2 children developed transient hypotension. *Conclusions:* Only mild symptoms were reported after ingestion of ARB/HCT in a fixed combination. Frequency of symptoms was slightly higher than after ingestion of ARB's alone (11% vs. 10%) (1). Thus HCT doesn't seem to aggravate symptoms of accidental ARB-ingestions. Children who ingested less than 2 DDD (smallest dose of ARB/HCT in a fixed-combination in 1 tablet) can safely be observed at home because no child developed symptoms after ingestion of less than 1 tablet. *Reference:* 1. Balit CR, Gilmore S, Isbister GK. Paediatric ingestion of angiotensin converting enzymes inhibitors and angiotensin II blockers. *J Paed Child Health* 2007; **43**: 686–688.

41. Severe Pediatric Tolperisone Poisoning

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Objective: Tolperisone, a centrally acting muscle relaxant, has been used in European countries for more than 40 years. Site of action is believed to be the voltage-dependent sodium channel. Up to now, information on pediatric overdose in the literature has not been available. We present a review of cases with tolperisone intoxication in toddlers reported to the national Poisons Centre between 1966 and 2007, including one case of severe intoxication with precipitous development of life-threatening symptoms and persistent neurological sequelae. *Case series:* 39 cases fulfilled the inclusion criteria: children <5 years of age with monointoxication of tolperisone, written follow-up by a physician and sufficient causality between symptoms and exposure. Severity was assessed according to the Poisoning Severity Score (1). Thirty-four patients showed no or mild symptoms, 2 moderate and 3 severe (table). Decontamination within one hour was performed in 19 cases with no or mild symptoms, in one with moderate and in none with severe symptoms. The case with the most serious intoxication, a 2 yo girl, had ingested 2700 mg. Half an hour post ingestion she had a self-limited seizure. A few minutes later she rapidly deteriorated from respiratory insufficiency to circulatory arrest. Circulation was re-established only after prolonged resuscitation. After 9 months of rehabilitation the girl continued to have serious developmental impairments. The serum level of tolperisone 14 hours after ingestion was 0.72 mg/L. *Conclusion:* Tolperisone may lead to rapidly developing life-threatening symptoms after ingestion of large doses in toddlers. *References:* 1. Persson H, *et al. Clin Tox* 1998; **36**: 205–13.

Table: Poisoning Severity Score for tolperisone poisoned patients

	No symptoms (n = 23)	Mild symptoms (n = 11)	Moderate symptoms (n = 2)	Severe symptoms (n = 3)
Age [months]	14–48	23–38	18–36	15–20
Dose [mg]	50–max. 1200	150–600	400–max. 1500	1500–2700
Symptoms		vomiting (3), somnolence (6), mydriasis (2)	agitation (2), tachypnoea (1)	coma (3), metabolic acidosis (3), mydriasis (3), convulsions (3)

42. Being Vigilant about Provigil: Texas Poison Center Network Experience with Adult Modafinil Exposures

Givens MG,[1] Hellums J,[1] Borys D,[2] Morgan D.[2] *[1]Carl R Darnall Army Medical Center, Fort Hood; [2]Central Texas Poison Center, Temple, US.*

Objective: Modafinil is a novel medication with growing indications to include narcolepsy, shift work sleep disorder, and attention deficit disorder. The objective of this study is to describe adult modafinil exposures reported to the Texas Poison Center Network. There are no previous studies in the literature exploring toxic exposures to modafinil and few case reports to describe toxicity (1,2). *Methods:* A retrospective chart review was conducted on all calls to the Texas Poison Center Network from January 2004 through August 2007 that listed modafinil as an exposure. Patients with co-ingestants were excluded to better identify the unique effects of modafinil. *Results:* Of the 105 reported modafinil exposures that occurred in the study timeframe, 48 were single exposures. Nineteen of the single exposures were seen at a health care facility. Agitation was the most commonly reported symptom, seen in 6 patients, followed by tachycardia (5), sedation (3), neurologic symptoms (3) and hypertension (2) with exposure ranges from 200–8400 mg. Six patient were admitted of which 2 were asymptomatic. The only intervention reported included I.V. fluids in 7 patients and benzodiazepines in 2 patients. The largest reported ingestion was 8400 mg and the patient was described as drowsy. The patient was intubated but also received sedation with a benzodiazepine. A 6000 mg ingestion was reported as causing drowsiness with no interventions required. *Conclusion:* Modafinil exposures reported to the Texas Poison Center Network resulted in minor symptoms amenable to basic supportive care. As indications for this medication expand, surveillance should continue to further describe modafinil's effects in overdose. *References:* 1. Lyons TJ, French J. Modafinil: the unique properties of a new stimulant. *Aviat Space Environ Med* 1991; **62**: 432–435. 2. Oskooilar N. A case of premature ventricular contractions with modafinil. *Am J Psychiatr* 2005; **162**: 1983–1984.

43. Quantitative Confirmation of a Hydroxychloroquine Overdose

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Objective: Serious ingestion of hydroxychloroquine is uncommon. Although rarely reported, few cases have confirmatory levels. We report a characteristic case with confirmatory testing to help appreciate the toxicodynamic/toxicokinetic relationship. *Case report:* A 45 year old man with sarcoidosis and gout was found lethargic on a park bench. He admitted to attempting suicide by ingesting a bottle of his medications with ethanol approximately 1.5 hours prior to arrival but couldn't remember which medication. He took prednisone, colchicine and hydroxychloroquine at unknown doses. Initial vital signs were: temperature, 98.6 F; pulse, 80/min; respirations, 18/min; blood pressure, 148/94 mmHg; and pulse oximetry, 97% on room air. He was somnolent, but arousable and answered questions appropriately. The physical examination was unremarkable. Electrocardiography revealed a sinus rhythm. The QRS interval was 128 msec and the QTc was 576 msec. T-wave flattening in leads v3-v4, I and avL with T-wave inversion in leads V5- V6, II, III and avF were noted. Laboratory results included: sodium, 145 mEq/L; potassium, 2.6 mEq/L; chloride, 104 mEq/L; bicarbonate, 18 mEq/L; blood urea nitrogen, 15 mg/dL; creatinine, 0.115 mmol/L; glucose, 2.94 mmol/L; calcium, 2.2 mmol/L; and magnesium, 2.1 mEq/L. Aspirin and paracetamol levels were negative, but ethanol was 1.71 g/L. The patient was treated with potassium and glucose. His somnolence resolved over several hours. He remained without complaints during his hospital stay. Since his presentation was inconsistent with prednisone or colchicine toxicity a hydroxychloroquine concentration was drawn approximately nine hours post-ingestion. It was 2.0 mcg/mL (therapeutic 0.1–1.0 mcg/mL). On hospital day two, the patient was hemodynamically stable. His ECG returned to normal and he was transferred to psychiatry. *Conclusion:* Hypokalemia and hypoglycemia with ECG changes is suggestive of hydroxychloroquine poisoning. Serious hydroxychloroquine poisoning resembles chloroquine poisoning with rapid cardiovascular collapse. There is insufficient data to prognosticate patients based on dose or levels. This case suggests that a level twice the upper limit of therapeutic is well tolerated. We encourage obtaining blood levels to help better define the toxicokinetic/toxicodynamic relationship.

44. Focal Seizure Activity Following Intentional Isoniazid Overdose

Charlton N, Holstege CP. *Division of Medical Toxicology, University of Virginia, Charlottesville, US.*

Introduction: Seizures induced by isoniazid (INH) are described as generalized, tonic-clonic seizures. We report a case focal seizure activity following an acute INH overdose. *Case report:* A 15 year old Burmese female presented with three focal seizures within a 30 minute time span. She had no history of past medical problems. She had been behaving normally until just prior to her reported seizures at home. On arrival her pulse was 156 beats per minute and her respiratory rate 38 breaths per minute. She did not respond to verbal stimuli. She was hyperreflexic. The

remainder of her physical examination was unremarkable. During this initial assessment and stabilization, the patient seized and was witnessed by the emergency department personnel and a board certified neurologist. The seizure duration was 2 minutes and characterized by focal tonic-clonic activity of the right upper extremity with simultaneous tonic deviation of her eyes to the right. There was no motor activity of her left arm or either leg. She received 4 mg of intravenous lorazepam with cessation of tonic-clonic activity but continued with altered mental status. Initial laboratory evaluation and head CT were unremarkable. It was discovered that she had a history of a positive PPD for which she had been taking INH. Pyridoxine, 5 grams, was infused and she developed no further seizures and her mental status improved. The patient later admitted that she overdosed on all of her INH. She made a full recovery. Subsequent MRI imaging of her brain and an EEG were negative. *Discussion:* A review of the literature reveals that the seizures associated with INH toxicity are always described as generalized in nature, without focal signs. The patient presented in this case clearly demonstrated seizure focality with an altered level of consciousness. The presentation of focal seizures in this patient initially dissuaded the medical team away from INH toxicity as the etiology of the seizures. This case illustrates INH toxicity from an intentional overdosage causing focal seizures.

45. Texas Poison Center Network Experience with Pediatric Exposures to Modafinil

Givens MG,[1] Hellums J,[1] Borys D,[2] Morgan D.[2] *[1]Carl R. Darnall Army Medical Center, Fort Hood; [2]Central Texas Poison Center, Temple, US.*

Objective: Modafinil is a relatively new medication used for narcolepsy, shift work sleep disorder, and is being studied for use in other conditions to include attention deficit disorder. The objective of this study is to describe pediatric modafinil exposures reported to the Texas Poison Center Network. There are no previous studies in the literature exploring pediatric unintentional exposures to modafinil and few case reports to describe toxicity (1,2). *Methods:* A retrospective chart review was conducted on all calls to the Texas Poison Center Network from January 2004 through August 2007 that listed modafinil as an exposure. *Results:* Thirty ingestions occurred in children less than 6 years of age (range 1–5 years) of which 22 were single exposures. Seven of these single exposures were seen at a health care facility with ingestion amounts ranging from 100–200 mg. Six of these patients were asymptomatic and discharged. One patient was admitted for observation but remained asymptomatic. Seven of the remaining 8 unknown or combined exposures were seen at health care facilities with exposure dose ranging from 100–200 mg with 2 unknown amounts. Drowsiness was the only reported symptom in one child who ingested 200 mg. Of the 16 cases not seen at a health care facility, 6 received telephone follow-up and all remained asymptomatic other then 1 episode of diarrhea in a child who ingested 200 mg. *Conclusion:* Pediatric ingestion of modafinil at doses less than 200 mg is not associated with significant symptoms as reported to Texas Poison Control Centers. *References:* 1. Lyons TJ, French J. Modafinil: the unique properties of a new stimulant. *Aviat Space Environ Med* 1991; **62**: 432–435. 2. Oskooilar N. A case of premature ventricular contractions with modafinil. *Am J Psychiatr* 2005; **162**: 1983–1984.

46. Lacosamide Overdose Induced Status Epilepticus Treated with Hemodialysis

Charlton N, Holstege CP. *Division of Medical Toxicology, University of Virginia, Charlottesville, US.*

Objective: Lacosamide is an investigation drug for use as adjunctive treatment in epilepsy and diabetic neuropathic pain(1). This case report describes the first reported overdose of lacosamide resulting in status epilepticus requiring hemodialysis. *Case report:* A 47 year old female involved in an investigational study for a novel anti-epileptic medication presented with tonic-clonic seizures. The patient had a past medical history of epilepsy and treated with Zonegran, with an average of one seizure per month. She recently was entered into a study utilizing lacosamide as an antiepileptic. Family witnessed the patient taking a "large handful" of the lacosamide. About thirty minutes later the patient had a witnessed tonic-clonic seizure at which point emergency services were called. The patient took between 3 grams and 10 grams in overdose (average therapeutic daily dose is 600 mg). In the emergency department continued seizure activity was noted and the patient was given 17 mg of intravenous midazolam to stop tonic/clonic activity and begun on a midazolam continuous infusion. Initial laboratory values were only significant for a metabolic acidosis. Despite treatment, the patient continued to have intermittent seizure activity with declining mental status requiring intubation and mechanical ventilation. From personal communication with study coordinators the drug was noted to be dialyzable. A single four hour run of standard hemodialysis was completed. Over the next 24 hours sedation was weaned and the patient was extubated. Evaluation by the neurology service showed no focal or cognitive deficits. Drug levels of lacosamide and Zonegran are pending. *Conclusion:* Lacosamide is a novel drug currently under investigation as adjunctive therapy in epilepsy. Mechanisms of action include enhancement of voltage gated sodium channel slow inactivation and modulation of collapsing response mediator protein-2 (2). This is in contrast to other sodium channel modulators including carbamazepine, phenytoin and lamotrigine which block fast inactivation of voltage gated sodium channels (3). In this patient, overdose was associated with *status epilepticus* which was treated with dialysis and benzodiazepines. *References:* 1. Doty P, *et al*. Lacosamide. *Neurotherapeutics* 2007; **4**: 145–148. 2. Ben-Menachem E, *et al*. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. *Epilepsia* 2007; **48**: 1308–1317. 3. Errington AC, *et al*. The investigational anticonvulsant lacosamide selectively enhances slow inactivation of voltage-gated sodium channels. *Mol Pharmacol* 2008; **73**: 157–69. Epub 2007.

47. Atenolol Massive Ingestion without Poisoning

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At therapeutic doses, atenolol is a selective beta-1-receptor-blocker without intrinsic agonist activity and membrane stabilizing activity, and with low lipid solubility. It's half-life is 5–9 hours and the therapeutic blood concentration range is 0.2–1 micrograms/ml. Severe hemodynamic and respiratory alterations have been described with atenolol blood levels from 5.6 up to 250 micrograms/ml (1,2). *Objective:* To describe and discuss a case of massive atenolol overdose documented by laboratory analysis in which the patient remained asymptomatic. *Case report:* A 43 year-old woman (60 kg bw) was brought to the emergency department 12 hours after ingestion of an estimated amount of 5–10 g of atenolol (assumed not to be usual therapy), promazine 100 mg, lorazepam 10 mg and clonazepam 25 mg. At admission the woman was awake and oriented with no signs of respiratory failure nor bronchial obstruction; the ECG was normal, HR 72 bpm and BP 90/60 mmHg; blood sugar was 92 mg/dl. Monitoring of cardiac parameters was started and gastric decontamination was performed in case of a more recent ingestion. At admission atenolol blood level was 42 micrograms/ml. During the following hours the patient remained asymptomatic with HR 70 bpm and a SBP ranging between 100 and 110 mmHg. No antidotal treatment was necessary. Atenolol blood levels at 36 and 60 hours after ingestion were 9.8 and 0.38 micrograms/ml respectively. The patient was discharged to a psychiatric department three days after admission. *Conclusions:* A poor correlation between beta-blockers blood levels and their toxic effect has already been observed, perhaps related to interindividual variability in pharmacokinetics and pharmacodynamics (3). However to our knowledge no cases of asymptomatic patients with such high atenolol levels have been reported before. Anamnesis, clinical presentation, BP and ECG monitoring are the most important parameters to consider in taking the proper decisions about treatment. Nonetheless in patients with toxic atenolol blood concentrations a non-invasive monitoring could be appropriate until normalization of atenolol levels even if asymptomatic. *References:* 1. Montgomery AB, Stager MA, Schoene RB. Marked suppression of ventilation while awake following massive ingestion of atenolol. *Chest* 1985; **88**: 920–921. 2. Hagemann K. [Atenolol poisoning] *Dtsch Med Wochenschr* 1986; **111**: 1523–5. 3. Love JN. Beta-blocker toxicity: a clinical diagnosis. *Am J Emerg Med* 1994; **12**: 356–7.

48. Skin Rash as a Clue to an Unsuspected Calcium Channel Antagonist Exposure in a Pediatric Patient

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Objective: The objective of this case report is to highlight dermatologic clues to calcium channel blocker poisoning in pediatric patients. Cutaneous reactions can occur in up to 48% of exposures to calcium channel blockers and provide an important clinical clue to otherwise unsuspected poisoning. *Case report:* A 20 month-old male presented to the Emergency Department (ED) with a chief complaint of rash. The child was otherwise asymptomatic and had no significant past medical history and was taking no medications. His vital signs were as follows: heart rate 175 beats per minute, blood pressure 131/66 mmHg, respirations 32 breaths per minute, and afebrile. His physical examination was remarkable for a blanchable, erythematous, macular rash originating on his posterior legs and buttocks with extension to a confluent rash involving his anterior legs, abdomen and bilateral arms during his ED stay. Only after extensive investigation into the child's history were providers able to uncover that the patient had been playing with his grandfather's pillbox containing felodipine on the morning of presentation. The child received whole bowel irrigation with polyethylene glycol solution and was transferred to the pediatric intensive care unit for monitoring. His lowest recorded blood pressure was a systolic of 100 mmHg and diastolic of 45 mmHg on day 2 of hospitalization. His lowest heart rate was 85 bpm. He was maintained on intravenous fluids and a calcium gluconate drip that was discontinued on hospital day 2. The rash waxed and waned over the course of 48 hours but gradually resolved over the course of the 3 days leading up to his hospital discharge. *Conclusion:* Dermatologic changes may be an early important clue in otherwise asymptomatic pediatric patients with unsuspected toxic exposures to calcium channel antagonists. *References:* 1. Ioulios P, Charalampos M, Efrossini T. The spectrum of cutaneous reactions associated with calcium channel antagonists: A review of the literature and the possible etiopathic mechanisms. *Dermatol Online J* 2003; **9**: 6. 2. Stern R, Khalsa JH. Cutaneous adverse reactions associated with calcium channel blockers. *Arch Int Med* 1989; **149**: 829–32.

49. Pediatric Ingestion of Angiotensin II Receptor Antagonists: What's the Risk?

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Objectives: Angiotensin-II receptor blockers (ARB) prevent the binding of angiotensin II to the AT1 receptor subtype. The antihypertensive effect of the different sartans seems to be relatively comparable. Only few data are available about toxicity in childhood (1). *Case series:* Retrospective analysis of pediatric ingestions was done in a cooperation of the poison centers GIZ-Berlin (1/1996–10/2007) and VIZ-Freiburg (5/2000–10/2007). Inclusion criteria were: age 0–13 years, known ingestion and dose, follow-up information available. Dose was reported as defined daily dose (DDD) to express equipotent doses of the different ARB's referring to normal adult dose. Severity of poisoning was rated according to PSS (2). *Results:* 81 children, age 0.8 - 13 years (median 2), DDD 0.25 – 26 (median 1). Children were observed in health care facility (73) or at home (8). Substances ingested were candesartan (39), eprosartan (2), irbesartan (8), losartan (9), olmesartan (6), telmisartan (7), valsartan (10). After ingestion of less than 1 DDD no child developed symptoms (21). Severity of poisoning was minor (2) or asymptomatic (43) after ingestion of 1–2 DDD. 15 children ingested more than 2 DDD. 5 of them developed minor symptoms. Hypotension requiring therapy was reported in one case (6 DDD). Latency between onset of symptoms and ingestion was <6 h (7) or unknown (1). *Conclusions:* Symptomatic pediatric ingestions were reported in 8 of 81 exposures (10%). Similar rates of symptoms were reported before in a prospective case series of 10 patients (transient hypotension in one child). With exception of one child who ingested 6 DDD and developed hypotension requiring treatment all symptoms were mild and transient. Children who ingested less than 1 DDD can safely be managed at home. Asymptomatic children should be observed at home for at least 6 hours. *References:* 1. Balit CR, Gilmore S, Isbister GK. Paediatric ingestion of angiotensin converting enzymes inhibitors and angiotensin II blockers. *J Paed Child Health* 2007; **43**: 686–688. 2. Persson H,

Sjöberg GK, Haines JA, et al. Poisoning Severity Score. Grade of acute poisoning. *J Toxicol Clin Toxicol* 1998; **36**: 205–13.

50. Prevalence of Risk Factors for Paracetamol Hepatotoxicity in Patients Presenting with Overdose in Northern England

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Objective: Paracetamol (acetaminophen) poisoning is common with the drug involved in over 40% of UK overdoses. Although evidence is inconclusive, the risk of hepatotoxicity may be increased by hepatic enzyme induction (e.g. by chronic alcohol consumption or drug treatment) or by starvation. UK guidelines advocate lower antidote treatment thresholds for such patients. This study measured the prevalence of these risk factors in patients presenting with paracetamol overdose in the North of England. *Methods:* Data was obtained from all patients admitted with paracetamol poisoning in Newcastle over 1 year from December 2005, including information on demographics, medical history and alcohol or medicines use. *Results:* There were 374 episodes of paracetamol overdose during the study period involving 339 patients (60% female, median age 32.3 y). Of these, 356 (95%) cases were intentional, 6 (1.6%) accidental and in 12 (3.2%) the aetiology was unknown. Doses reported were at least 7.5 g or at least 12 g in 272 (72%) and 190 (51%) episodes respectively. Data on chronic alcohol use was available for 306 (90%) patients at first presentation; 43 (14%) did not drink at all, 142 (46%) drank more than UK recommended limits (Females -14 units, Males - 21 units weekly) and 75 (25%) drank more than 60 units weekly or had drinking habits recorded as "high - amount unknown". Four patients (1.3%) were taking enzyme-inducing drug therapy and 4 (1.3%) had anorexia nervosa. Of 122 patients with weight recorded, 14 (11%) weighed less than 50 kg. Of the 339 first presentations, 43 (13%) had paracetamol concentrations above the usual (200 mg/L at 4 h) treatment line and 68 (20%) between the usual and 'high risk (100 mg/L at 4 h) treatment line. Of the latter group, 43 (63%) were treated with acetylcysteine; 28 of these drank excess alcohol, 3 had anorexia and 2 weighed less than 50 kg. The reasons for treatment in the other 10 were not recorded. *Conclusions:* Presumed risk factors for paracetamol hepatotoxicity are common, especially chronic excess alcohol consumption, so many patients with concentrations below the usual treatment threshold receive acetylcysteine. More information is needed on the relationship between the amount of alcohol consumed and the increase in risk of paracetamol hepatotoxicity.

51. Irreversible Lithium-Induced Brain Toxicity: Observations in a Clinical Toxicology Unit

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Objectives: Lithium overdosage (both acute and chronic) is characterized by motor and mental symptoms which in some cases do not fade. Cases of severe lithium-induced permanent brain damage have been repeatedly described in detail and a clinical entity named "silent syndrome" (syndrome of irreversible lithium-effectuated neurotoxicity (1)) has been proposed. *Methods:* We examined the clinical records of lithium intoxicated patients admitted to the Clinical Toxicology Unit, Florence University Hospital, between 1997 and 2007. *Results:* 63 patients had blood lithium levels above 1.5 mM and 4 of them (6.3%) had severe brain impairment with movement and mental disorders which did not fade when blood lithium levels returned to therapeutic values. The four patients were admitted to our Unit because of blood lithium concentration above therapeutic range, leucocytosis, increased creatinine values, rigidity, dysarthria and tremors. They had been treated with lithium (and other psychoactive agents) for several years because of a bipolar disorder and the actual presence of elevated blood lithium levels was ascribed to fever or dehydration. All immediately received intensive supportive therapy, which included sodium chloride solution (approximately 4/liters per day), benzodiazepines and antibiotics. Two of the four patients had cranial magnetic resonance imaging (MRI) showing the presence of cerebellar and pallidal damage. All had neurological sequelae for at least two months after lithium cessation. *Conclusion:* Irreversible lithium-induced brain toxicity (SILENT) is a relatively rare clinical condition associated with chronic lithium treatment. Acute renal impairment, leucocytosis and motor symptoms in patients treated with lithium and other psychoactive agents are key features of the syndrome. To limit the brain damage and the consequent neurological disabilities, a prompt diagnosis and a proper therapy aimed at rapidly reducing blood lithium concentrations associated to benzodiazepines are probably useful procedures. *Reference:* 1. Adityanjee, Munshi KR, Thampy A. The syndrome of irreversible lithium-effectuated neurotoxicity. *Clin Neuropharmacol* 2005; **28**: 38–49.

52. Deliberate Self-poisoning with Panadol Extend® Results in Delayed Peak Serum Concentrations and Prolonged Absorption of Paracetamol

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Background: Panadol Extend® (PE®) is an extended-release paracetamol formulation available in Australia (665 mg/caplet, 2/3 extended-release, 1/3 immediate-release). To date, there have been no cases of deliberate self-poisoning reported with PE®. A volunteer model of simulated overdose revealed peak serum [paracetamol] was significantly delayed (3 vs 1 hour) and 60% lower with Panadol Extend® than with immediate-release (IR) paracetamol. Area-under-the-time-concentration curve was also 30% less with PE® (1). We report the first documented case of PE® overdose in Australia. *Case report:* A 64 yo female (65 kg) presented with GCS 8 two hours post-ingestion of 24 grams PE® and 250 mg diazepam. She was intubated and activated charcoal was administered on arrival. She remained haemodynamically stable throughout her admission. Serum [paracetamol] peaked at 967 micromole/litre, 4.5 hours post-ingestion and remained persistently above the 1000 micromole/L at 4 hours, Rumack-Matthews nomogram line for 12 hours. Intravenous N-acetylcysteine was administered. Liver function remained normal during admission. The elimination half-life was calculated as 3.8 hours. *Conclusion:* Overdose with Panadol Extend® resulted in delayed peak paracetamol concentrations around 4 hours post-ingestion. This parallels simulated overdose observations (1). A slower rate of paracetamol release from PE® may result in delayed absorption and simultaneous hepatic metabolism of paracetamol with lower peak serum [paracetamol] than when comparable doses of IR-paracetamol are ingested. The prolonged elimination half-life of paracetamol probably also reflects on-going paracetamol absorption rather than impaired hepatic metabolism. *Reference:* 1. Tan C, Graudins A. Comparative pharmacokinetics of Panadol Extend and immediate-release paracetamol in a simulated overdose model. *Emerg Med Australasia* 2006; **18**: 398.

Table: Panadol Extend® overdose serum levels versus time

Time post-ingestion (Hours)	Serum Paracetamol concentration (micromole/L)
2.5 h	928
4.5 h	967
7.5 h	744
10 h	651
12.5 h	414
15.5 h	259
18 h	115
22.5 h	54
27 h	33

53. QT Prolongation after Acute Amisulpride Poisoning

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Objective: To present a case of massive amisulpride poisoning. *Case report:* A 53 year old woman presented to the emergency department claiming to have ingested 24 g of amisulpride six hours previously. On examination she was conscious, with a Glasgow Coma Score of 15, had normal reactive pupils, a heart rate of 80 bpm, blood pressure of 100/60. An EKG presented a sinus rhythm with frequent atrial extrasystoles, at 64 bpm, normal QRS complex and a QTc of 608 ms. Initial blood tests showed a creatinine of 1.33 mg/dl and arterial blood gas with pH 7.460, pCO_2 33.6mmHg, pO2 130.8 mmHg. HCO_3 23.6 and amisulpride concentration of 4671 mg/L. The patient was monitored, and 50 g of activated charcoal was administered. Further blood tests showed creatinine 1.17 mg/dL, Potassium 3.4 mmol/L and normal calcium and magnesium levels. Saline solution with potassium supplements and sodium bicarbonate were administered. Serial EKGs revealed continued QTc prolongation with bifid T waves and isolated ventricular ectopy with a normal QRS complex until 33 h after ingestion when amisulpride concentration was found at 209 mg/L. Serial amisulpride measurement by HPLC (at 10, 15 and 33 h after ingestion) allowed calculating the amisulpride concentration (C0) and biological half life (t1/2). C0 was 18034 mg/L and t1/2 was 5.1 h. She was admitted to the psychiatric ward and discharged after 30 days. *Conclusion:* This case shows QT prolongation after amisulpride poisoning with extremely high serum levels. *References:* 1. Isbister GK, Murray L, John S, *et al.* Amisulpride deliberate self-poisoning causing severe cardiac toxicity including QT prolongation and torsade de pointes. *Med J Aust* 2006; **184**: 354–356. 2. Ward I. Two cases of amisulpride overdose: A cause for prolonged QT syndrome. *Emerg Med Australas* 2005; **17**: 274–6.

54. Spectrum of Toxicity Due to Varenicline (Chantix®) Exposure

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Objective: Our objective is to describe the spectrum of toxicity related to varenicline (Chantix®), a partial agonist of the $\alpha 4\beta 2$ nicotinic acetylcholine receptor. This medication was approved in February 2006 by the United States Food and Drug Administration for smoking cessation therapy. Safety and efficacy data from clinical trials have been previously reported but no overdose data have been published. *Methods:* The Texas Poison Center Network database was searched for the key words varenicline and Chantix® in 2007; 33 human exposures were identified. Fourteen cases were excluded because they were not followed to conclusion by the Poison Center. The remaining 19 cases were included for discussion in this report. *Results:* Of the 19 cases of varenicline exposure in this case series, (Table) 2 distinct groups were identified: (1) Age < 5 years, unintentional ingestion, n=10. The average age was 2 years; 50% were female; estimated range of exposure was 1–10 mg; all outcomes were self limited with minor or no effect (vomiting, sedation) according to the American Association of Poison Control Centers' annual report definitions.(2) Age > 13 years, intentional ingestion, n=9. The average age was 36 years; 78% were female; estimated range of exposure was 0.5–21 mg in 6 known cases and unknown in 3 cases; outcome ranged from no effect to major effect. In the 2 cases with major effects (coma requiring intubation, hypotension, tachycardia), the ingested varenicline dose was unknown, but other drugs were co-ingested that could account for the observed effects (cocaine, benzodiazepines, valproic acid, quetiapine). In cases where varenicline was the only drug ingested, outcome was no effect or minor effect (vomiting, sedation). *Conclusion:* Varenicline ingestion alone did not result in severe toxicity in this case series. However, a larger study is needed to confirm these observations.

55. Tretinoin Overdose: A First Case Report

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Tretinoin (Vesanoid) is a retinoid that has a different spectrum of toxicity from Vitamin A (1). To date, there have been several case reports on overdose with its isomer isotretinoin, but none involving overdose of tretinoin. We report the first known case of a patient who ingested

Table: Unintential and intentional varenicline overdoses

Age(yrs)	Sex	Substance and Quantity	Reason	Clinical Effects	Therapy	Labs	Medical Outcome
Group 1:							
1	M	Varenicline 4 mg, Escitalopram 20 mg	U	Emesis, Lethargy, Ataxia	AC	None	Minor
1	F	Varenicline 1 mg	U	None	None	None	No Effect
1	M	Varenicline 1 mg	U	None	None	None	No Effect
2	M	Varenicline 1 mg	U	None	None	None	No Effect
2	M	Varenicline 2 mg	U	None	None	None	No Effect
3	F	Varenicline 4 mg, Escitalopram 20 mg	U	Emesis, Lethargy, Ataxia	AC	None	Minor
3	F	Varenicline 10 mg	U	None	None	None	No Effect
3	F	Varenicline 1 mg	U	Emesis, Lethargy	None	None	Minor
3	M	Varenicline 4 mg	U	Abd. Pain	AC	None	Minor
4	F	Varenicline 1 mg	U	None	None	None	No Effect
Group 2:							
14	F	Varenicline 21 mg	I	Lethargy	AC	UDS: caffeine, dextro-methorphan, varenicline	Minor
19	F	Varenicline 7.5 mg	I	None	None	None	No Effect
20	F	Varenicline 9 mg	I	None	None	None	No Effect
36	F	Varenicline unknown mg	I	Nausea, Dizziness, Coma	Intubation supportive care	UDS: cocaine, benzodiazepines	Major
43	F	Varenicline unknown mg, Valproic Acid unknown mg, Quetiapine unknown mg	I	Hypotension, Tachycardia, Coma	IVF, OGL, AC, Flumazenil, Intubation, Supportive Care	VPA peak 350 mcg/mL	Major
46	F	Varenicline 1 mg Verapamil unknown mg, Lisinopril unknown mg, Lamotrigine 1.2 mg	I	Lethargy	Supportive Care	ETOH 30 mg/dL	Minor
54	M	Varenicline unknown mg, Metoprolol 250 mg, Amlodipine unknown mg, lisinopril 200 mg, theophylline unknown mg	I	Lethargy, Bradycardia	Supportive Care	Theophylline 36.7 mcg/mL	Minor
57	M	Varenicline 0.5 mg	AR	Weakness,Dizziness	None	None	Minor
NK	F	Varenicline 0.5 mg	U	Emesis	None	None	Minor

U - Unintentional, I - Intentional, AR - Adverse Reaction.

an overdose of tretinoin. *Case report:* In a suicidal attempt, a 31 year old man with a history of acquired immunodeficiency syndrome (AIDS) and acute promyelocytic leukaemia in remission ingested 100 pills of Vesanoid® (10 mg each). He sought Emergency care within an hour of the ingestion. Given the rapid time to peak concentration of 1 hour (1) a significant amount of drug was believed to be absorbed into the systemic circulation. Although there has been no experience with acute overdose in humans, the maximal tolerated dose in patients was 195 mg/m^2/day (1), which makes his overdose about 3 times higher. The patient developed non-bloody diarrhea but was otherwise asymptomatic. His vital signs were normal and his clinical examination was unremarkable. He was given an oral dose of activated charcoal and he was hydrated with normal saline in dextrose 5%. Toxicology studies were negative. He was noted to have a baseline creatinine level of 3–3.5 mg/dl due to his underlying renal insufficiency from a congenital single kidney. He had an unexplained drop in his hemoglobin level from 12.2 g/dL to 10.2 g/dL. There was no evidence of gastrointestinal blood loss, nor were tests done to rule out hemolysis in this patient. However, the hemoglobin level remained stable (10.3 g/dL) when repeated on the third day after admission and the initial drop was thought to be secondary to dilution from the fluids that the patient had received. He did not have complaints after his diarrhea rapidly resolved. The patient's blood results did not show any deterioration on the third consecutive day. After psychotherapy, the patient was discharged on the third day. *Conclusion:* We believe this to be the first case report of ingestion of a large intentional oral overdose of tretinoin. The patient had only minor immediate effects of diarrhea, but was otherwise asymptomatic. *Reference:* 1. Product information Vesanoid®, tretinoin, 1995.

56. Ranolazine Overdose

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Objectives: Ranolazine (Ranexa®) is an antianginal agent with anti-ischemic effects (1). To date, there have been no case reports on overdose with ranolazine in literature. We report a case of a patient who accidentally ingested an overdose of ranolazine. *Case report:* A 52 year old man with a history of ischemic heart disease, diabetes mellitus, chronic pain syndrome, hypertension and hyperlipidemia mistakenly took 7 tablets of ranolazine 500 mg. He presented with altered mental status and labored breathing. Other than bilateral pitting edema to the mid-shins, the rest of the patient's clinical examination was essentially unremarkable. In the emergency department, the patient was noted to have hypoglycemia with a glucose level of 39 mg/dL. Although this was treated, he developed hypotension with a blood pressure of 65/50 mmHg and desaturated, requiring intubation and ventilatory support. His electrocardiogram (EKG) showed a normal sinus rhythm with a right bundle branch block pattern and a prolonged QTc of 531 milliseconds. Prolongation of the QTc interval is consistent with dose and concentration-related increases in patients taking the drug therapeutically (2). He was managed with intravenous fluids, antibiotics and vasopressors. The patient's QTc interval gradually normalized over the next 2 days (472 milliseconds). He had a troponin leak although the EKG continued to show no evidence of myocardial injury. Echocardiography showed a left ventricular ejection fraction of 50% with mildly decreased left ventricular systolic function but there were no focal wall motion abnormalities. His hypotension persisted for 4 days, possibly contributed by sepsis from lung aspiration. He continued to improve gradually and was discharged home on the 7th day after admission. *Conclusion:* We believe this to be the first case report of an overdose of ranolazine. Hypotension, hypoglycaemia and prolonged QTc were seen in our patient. In the event of overdose, general supportive measures should be initiated. Baseline and follow-up EKGs should be obtained to evaluate effects on QT interval. *References:* 1. Product information Ranolazine (Ranexa™) 2006. 2. Siddiqui MA, Keam SJ. Ranolazine: a review of its use in chronic stable angina pectoris. *Drugs* 2006; **66**: 693–710.

57. Enoxaparin-Associated Intracranial Hemorrhage Treated with Activated Factor VII

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Objective: No specific agent exists to reverse hemorrhage in the setting of anticoagulation with low-molecular weight heparins (LMWH). Protamine is a specific antidote for heparin, but only partially effective for reversal of anticoagulation with LMWH. rFVIIa reverses anticoagulation with LMWH *in vitro* (1), but this application has not been studied *in vivo*. We report a case of life-threatening intracranial hemorrhage in a patient taking enoxaparin that was treated with recombinant activated factor VII (rFVIIa). *Case report:* A 62 year old woman with a history of breast cancer presented to the emergency department with sudden-onset of right-sided weakness. One week prior to presentation she was started on enoxaparin for the treatment of multiple thromboses related to therapy with bevacizumab, an antiangiogenesis adjunctive chemotherapy that increases the risk of both thromboembolic and hemorrhagic events. On presentation the patient was alert and without speech or cognitive deficits. Physical examination was unremarkable except for a dense right hemiparesis. CT of the brain demonstrated a left parietal mass with central bleeding. Immediate treatment included upright positioning and protamine sulfate 50 mg infused intravenously. Within hours the patient began to vomit and became somnolent. MRI of the brain revealed increased bleeding with extension into the ventricles along with mid-line shift. The patient was given 4.8 mg rFVIIa and had surgical resection of the mass. No further bleeding was diagnosed post-operatively, and the patient was restarted on enoxaparin on post-operative day four. *Conclusion:* The utility of LMWH for patients at increased risk of hemorrhage is mitigated by a lack of effective reversal agents. rFVII may be considered with caution for the management of life-threatening bleeding in patients anticoagulated with LMWH if protamine and supportive measures fail. Further research is needed to determine the safety of this strategy, particularly in patients with complex hematologic disorders that may independently increase the risk of thrombotic complications. *Reference:* 1. Young G, Yonekawa KE, Nakagawa PA, *et al.* Recombinant activated factor VII effectively reverses the anticoagulant effects of heparin, enoxaparin, fondaparinux, argatroban, and bivalirudin *ex vivo* as measured using thromboelastography. *Blood Coag Fibrin* 2007; **18**: 547–553.

58. Guanfacine Poisoning and Munchausen's Syndrome by Proxy

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Objective: To describe the value of collaboration between clinicians and the toxicology laboratory when standard testing does not confirm a clinical diagnosis suspected from history and physical examination. *Case report:* A 4 y/o male with history of asthma and atypical absence seizures presented to an outside hospital after one day of intermittent lethargy. The child was evaluated for similar symptoms one-year prior, an extensive work-up was negative, and the child was placed on valproate for presumptive absence seizures and clonidine for insomnia. On examination at the outside hospital, the patient was somnolent but otherwise normal. Laboratory studies and an EEG were also normal. The patient was transferred to a tertiary care center and admitted to the pediatric neurology service. Extensive additional diagnostic testing was normal with the exception of an increased ammonia level (100 mg/dL) likely associated with valproate therapy. Clonidine

and valproate were both discontinued, however the patient's somnolence persisted with periods of mild hypotension, bradycardia and miosis. A toxicology consultation (hospital day 4) identified a toxidrome consistent with the alpha-2 agonist properties of clonidine, but an analysis of urine using GC/MS was negative. Additional history revealed that the patient's sibling was prescribed guanfacine for ADHD, and hospital staff noticed an association between the mother's presence and the recurrence of the patient's symptoms. With this new development and the lack of a commercially available test, our clinical toxicology laboratory developed an assay that detected guanfacine in the patient's urine. Serial testing correlated positive guanfacine levels with recurring symptoms. This heightened suspicions of Munchausen's Syndrome by Proxy, however the mother denied complicity. During the subsequent Child Abuse Team investigation, the mother confessed to giving the patient guanfacine for over a year, including periods during this hospitalization. With parent-child interaction restricted, the patient fully recovered and was placed in foster care upon discharge. *Conclusion:* Munchausen's Syndrome by Proxy is a difficult diagnosis. In this case, guanfacine was administered to a child for over a year, resulting in unnecessary diagnostic testing and drug therapy. This case illustrates the value of combining clinical and analytical toxicologists' efforts in diagnosing occult poisoning.

59. Accidental Chloroquine Poisoning in a Child

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Objective: Since 2004, the Poisons Information Centre (PIC) in Norway has received only 9 inquiries regarding possible chloroquine poisonings, of which 2 were children (1). Chloroquine has a low margin of safety. In overdose, severe symptoms can occur within one hour. Major clinical manifestations include coma, respiratory depression, convulsions, hypokalemia and cardiovascular collapse. We want to report a non fatal case of chloroquine poisoning in a child, including the PIC management. *Case report:* A 22 month old girl ingested 1–2 tablets of chloroquine phosphate 250 mg (24.3–48.5 mg/kg) at her home. The parents brought the child to the local physician, who contacted the PIC. The dose ingested indicated a potentially serious poisoning and we recommended hospital admission as quickly as possible. Due to the risk of rapid onset of severe symptoms, we recommended a physician to be present during the transportation. Since chloroquine poisonings are unusual, we immediately contacted the hospital and our clinician on call gave treatment guidelines to the pediatrician. The patient arrived at the hospital 15–20 minutes later, approximately one hour post ingestion. At admission, the child was awake and in good general condition. ECG showed no QRS prolongation, normal QTc interval and increased U-waves. Serum potassium was normal (3.7 mmol/l). A gastric lavage was performed followed by activated charcoal. Tablet residues where seen in the lavage fluid. The patient was intubated and mechanically ventilated. She was given diazepam (2 mg/kg over 30 min followed by 1 mg/hour) and adrenaline infusion (2). Blood pressure was 86/25 at the lowest. Hypokalemia (2.7 mmol/l) developed within 2 hours, and was corrected. No further symptoms developed and she was discharged 44 hours post ingestion with a normal ECG. *Conclusion:* Rapid information flow and cooperation between PIC, emergency phones and other health care personnel are essential to ensure early and optimal management of such cases. *References:* 1. Statistics 2004-Nov 2007, PIC Norway, 2. Riou B, Barriot P, Rimailho A, *et al.* Treatment of severe chloroquine poisoning. *N Engl J Med* 1988; **318**: 1–6.

60. A Case Report of Chronic Bupivacaine Toxicity

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Objective: Lethal cardiac dysrrhythmias from inadvertent intravenous injection of bupivicaine is well described. Toxicity from a continuous perineural bupivacaine infusion is unreported. We report a case of CNS and respiratory depression resulting from a continuous bupivacaine perineural infusion. *Case report:* A 73 year-old woman underwent a radical left arm amputation due to invasive carcinoma. Post operatively, she was given a brachial plexus block for pain control, which continuously infused bupivacaine (0.25% at a rate of 8 ml/hr day 1, then 6 ml/hr day 2, then 4 ml/hr day 3). On post-operation day 3, the patient was noted by nursing to have increasing somnolence, respiratory difficulty and hypopnea with a normal respiratory rate of 18, requiring Bipap assisted ventilation. She became unresponsive to verbal and painful stimuli. Her pupils were 3 mm and reactive. Her heart rhythm was regular with a rate in the 80s and a blood pressure of 129/81 mmHg. Her lung sounds were slightly diminished on the left side but were otherwise normal and chest wall excursion was diminished but equal bilaterally. The rest of her examination was normal. The bupivacaine was discontinued due to concern for systemic toxicity. Her labs from post-operation day 3 included a bupivacaine concentration of 4.2 mcg/mL, well above the generally accepted level for continuous blocks (0.5–1.1 mcg/ml) (1,2). With supportive care and discontinuation of the bupivacaine, the patient slowly became more arousable. By day 6 she was alert, oriented and her need for respiratory assistance ended. *Conclusion:* Continuous infusion of perineural bupivacaine can result in CNS depression and respiratory depression without evidence of cardiac toxicity such as dysrhythmias or seizures. *References:* 1. Tuominen M, Pitkanen M, Rosenberg PH. Postoperative pain relief and bupivacaine plasma levels during continuous interscalene brachial plexus block. *Acta Anaesthesiol Scand* 1987; **31**: 276–8. 2. Tuominen M, Haasio J, Hekali R *et al.* Continuous interscalene brachial plexus block: clinical efficacy, technical problems and bupivacaine plasma concentrations. *Acta Anaesthesiol Scand* 1989; **33**: 84–88.

61. Prolonged Severe Toxicity Following Verapamil Ingestion

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Objective: Verapamil is a calcium-channel blocking agent used in treatment of cardiac arrhythmias, angina and hypertension. Amongst the calcium-channel blockers, verapamil has the most potent effect on the cardiac conduction system. The case report below follows a patient's severe intoxication with sustained-release (SR) verapamil. *Case report:* 79-year-old patient with a pre-existing atrial fibrillation on rate control therapy and a psychiatric disorder presented unconscious to ICU 1.5 hours after ingestion of 6.0–7.2 g of verapamil SR and an unknown amount of digoxin. He recovered en-route. On admission vital signs were: BP 120/70 mmHg, HR 95/min, he was awake and conversant. Gastric lavage was performed, activated charcoal administered. Simultaneously insulin with glucose, and calcium treatment was started. Due to a slow but progressive decline in BP 82/56 mmHg and HR 60/min 6.5 hours after exposure norepinephrine therapy was initiated, and during the next five hours the dose of catecholamine had to be progressively increased to maintain adequate BP. Verapamil plasma level of 3600 ng/mL confirmed a potentially lethal dose ingested. Digoxin plasma level was found below therapeutic range (0.70 nmol/L). Due to progressive rate disturbance (junctional bradycardia of 30 beats/min) responding neither to atropine nor catecholamine 18.5 hours after poisoning intracardiac pacing was initiated, the patient then went into a coma (GCS of 6). On day 3 a profound decline in BP was observed (sBP 60 mmHg). Massive crystalloid support and large doses of catecholamine were continued to be administered regardless that patient's condition was considered terminal (GCS of 3); although oliguric no extracorporeal elimination method was used. Surprisingly the need for catecholamine support decreased later on the 3rd day. Catecholamines were stopped and on 5th day a spontaneous heart activity (atrial fibrillation (120/min)) was observed. The patient experienced several complications (acute renal failure, aspiration bronchopneumonia). He was transferred on 9th day to a standard department demonstrating a stable BP 160/90 mmHg. He was referred to psychiatric department on 21st day to treat the underlying chronic schizophrenia. *Conclusion:* Presentation of junctional rhythm is a significant ECG parameter in verapamil intoxication. Even if the prognosis of the patient looks desperate the condition can improve when the drug is eliminated.

62. Therapeutic Lithium Intoxication – An Increasing Problem in Sweden

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Objective: During recent years the Swedish poisons centre has noticed an increase in inquiries concerning therapeutic lithium intoxication. The aim of this study was to investigate the circumstances of these therapeutic misadventures and to find out if this tendency correlated with an increase in the use of lithium. *Methods:* Information recorded in connection with all hospital calls regarding therapeutic lithium intoxication during the period 2001–2006 was studied retrospectively. *Results:* During the study period the poisons centre received the following number of inquiries annually concerning patients with therapeutic lithium intoxication 12-13-15-17-28-31 respectively. In total 116 patients. During the same period the amount of lithium sold by Swedish pharmacies increased by 17% only, so additional explanations must be sought. Patients were middle-aged or elderly, females dominated. Concerning the circumstances, a remarkable finding was that many patients stayed at home despite rather pronounced symptoms, which delayed diagnosis and treatment. At least 19 patients (16%) had symptoms for 1–2 weeks, and 12 patients (10%) had symptoms for 3–4 weeks or more before medical care was sought. Initially at least 20% of the cases were observed at a psychiatric clinic, and diagnosis was further delayed. Intake of lithium sometimes continued. In several cases stroke or other diagnosis were suspected. Serum lithium concentrations were available to the study group in 101 cases. 52 cases had 2.0–5.6 mmol/L, 32 had 1.5–1.9 mmol/L and in 17 cases the S-Li was below 1.5 mmol/L. Frequently recorded symptoms were confusion and other changes in mental status, tremor, GI-symptoms, dehydration and impaired renal function. Several patients had deteriorated nutritional status. Coma and bradycardia occurred occasionally. Hemodialysis were recommended by the poisons centre in 22 cases and discussed in another 14. *Conclusion:* The increasing number of therapeutic lithium intoxications could not be explained only by a certain increase in the use of the drug. A considerable diagnostic delay was evident, both a patient's and a doctor's delay. Preventive information about these alarming findings will be spread among clinicians in Sweden. Beside routine S-Li controls, additional check-ups are imperative in cases with unclear psychiatric or somatic symptoms.

63. Serotonin Syndrome Following Lamotrigine Overdose

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Objective: To present the first reported case of serotonin syndrome associated with overdose of lamotrigine and to discuss the mechanism for the presentation. *Case report:* A 23 year old Caucasian lady was admitted following an overdose of lamotrigine. A few hours after admission she developed pyrexia, generalised rigidity, myoclonus of her jaw and unconsciousness, symptoms consistent with serotonin syndrome (1). She recovered completely with diazepam, dantrolene and general ITU care. *Method:* We searched three main sources and there were no cases reported in the literature on serotonin syndrome with lamotrigine overdose. The three main sources were 1) Leading reference textbooks 2) Web-based databases, and 3) Journal articles with the following MEDLINE (1950 to Oct 2007) search strategy: "Anticonvulsants/or lamotrigine.mp" [limit (humans and English language)]: with "serotonin syndrome.mp.or * Serotonin Syndrome". *Results:* Our searches found no case reports which were relevant to our objective. *Conclusions:* Lamotrigine is a newer anti-epileptic drug used more frequently than previous anti-epileptic drugs because it has a favourable side effect profile. It can cause serotonin syndrome in overdose, which can be explained by its pharmacological actions (2,3,4). *References:* 1. Radomski JW, Dursun SM, Reveley MA *et al*. An exploratory approach to the serotonin syndrome: an update of clinical phenomenology and revised diagnostic criteria. *Med Hypotheses* 2000; **55**: 218–224. 2. Southam E, Kirkby D, Higgins GA *et al.* Lamotrigine inhibits monoamine uptake *in vitro* and modulates 5-hydroxytryptamine uptake in rats. *Eur J Pharmacol* 1998; **358**: 19–24. 3. Bourin M, Masse F, Hascoët M. Evidence for the activity of lamotrigine at 5-HT 1A receptors in the mouse forced swimming test. *J Psychiatry Neurosci* 30: 275–282. 4. Vinod KY, Subhash MN. Lamotrigine induced selective changes in 5-HT 1A receptor mediated response in rat brain. *Neurochem Int* 2002; **40**: 315–319.

64. Benzodiazepines Overdoses. Is there Anything to Do About It?

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Background: Benzodiazepines are the main agents implicated in acute overdoses of pharmaceuticals in Spain. The conventional treatment has been based on gastric decontamination and the well known antidote Flumazenil. The broad experience in these kinds of situations allows us nowadays to decide if it is worth taking particular measures or whether just to observe the evolution for a few hours. *Methods:* We have studied prospectively all overdoses with benzodiazepines alone, attending our ED for a one year period. We have evaluated the epidemiological

profile, the delay between overdose and treatment, clinical picture, analytical results, treatment and outcome. We have evaluated the indications for decontamination and antidotal treatment. We have discarded the more frequent cases presenting with benzodiazepines associated with other drugs. We have compared the results with those obtained in a previous study ten years ago. *Results:* Of a total of 1452 acute poisonings attending our ED 112 had taken an overdose of benzodiazepines alone, 39 males and 73 females, with a mean age of 37 years, most of them (85 cases) suicidal attempts. Thirty nine cases were asymptomatic. The more frequent clinical picture was coma (10.2%), (only one under GCS8). The time since ingestion was known in 41 cases and only in 12 of them was it less than 1 hour. Decontamination was used in 29 cases (26%) and only in seven of them was the time since ingestion less than 1 hour. The antidote was used in 27 cases (24%) but, only in two cases was there a clinical indication. All cases were discharged in less than 24 hours. In comparison with a previous study between the years 1995–2004 we can verify a clear diminution in decontamination treatment from 50% to 26% *Conclusions:* The lack of risk in overdoses of benzodiazepines allows us to discard the indication for decontamination procedures taking into account that in the exceedingly improbable case of presentation of some complication you have an antidote that, as a matter of fact, is usually overused.

65. Three Percent Hypertonic Saline as a Therapy in Reversal of the Cardio Toxic Effects Induced by Tricyclic Antidepressants

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Introduction: Hypertonic saline has been shown to be of therapeutic value in cardiotoxicity induced by tricyclic antidepressants (TCA). 7.5% hypertonic saline has been used in the past to counter the cardio toxicity induced by TCAs. We used 3% hypertonic saline which is described first time in the literature. *Case report:* A 54 year old woman was admitted to the Intensive care unit (ICU) after massive imipramine overdose. She was intubated at the scene where she was found unresponsive. Her initial QRS at the time of presentation was 168 milliseconds and her systolic blood pressure was 80 mmHg. Sodium bicarbonate therapy was initiated. After 24 hours of this therapy, the serum pH was 7.6 and the QRS was still in the range of 140–150 milliseconds. Patient's clinical status continued to worsen, systolic BP of 80 and requiring pressor support. In addition, the patient was still hypotensive. At this juncture, 300 cc of 3% hypertonic saline (4 cc per kilogram) was started with immediate result of QRS narrowing to 100 milliseconds (both in the monitor and EKG). The patient received more doses of 3% hypertonic saline boluses, mainly intended for pressor support. *Discussion:* TCA induced cardio toxicity is predominantly caused by blockade of cardiac fast inward sodium channels, especially in His-Purkinje system and ventricular muscle. Sodium loading and alkalization reduces this effect, which could be achieved by administering sodium bicarbonate. Prolonged bicarbonate therapy could result in iatrogenic alkalemia which has a negative effect on myocardium, CNS and skeletal muscle. Approximately 150 meq of sodium was infused by administering 300 cc of 3% hypertonic saline which was given over 20 minutes. In resuscitation scenario, by using the usual 200 cc of 7.5% hypertonic saline, the sodium infused is approximately 250 meq. The above same dose has been used in TCA induced cardiotoxicity with significant positive therapeutic effect, as described by previous case reports. To date there are no case reports which portrays 3% hypertonic saline as a therapy in cardiotoxicity induced by TCA. *Conclusion:* 3% hypertonic saline could be considered along with other treatments in TCA induced cardiotoxicity.

66. Digoxin Toxicity in the Modern Era

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Objective: To evaluate the frequency, severity, and treatment of digoxin toxicity in contemporary practice. *Methods:* A retrospective review of digoxin exposures reported to the Illinois Poison Centers between July 1, 2001 and June 30, 2006 was conducted. *Results:* During the study period 438 exposures were reported, representing 0.1% of all exposures called into the Illinois Poison Center. Two distinct patterns of toxicity were identified: patients with minimal-no toxicity (332 exposures, 75.8%) and patients with moderate-severe toxicity (106 exposures, 24.2%). Patients with minimal-no toxicity were young, mean age 41.6 years, and female, 63.3%, while those with moderate-severe toxicity were older, mean age 66.6 years, and male, 63%. Acute exposures occurred more frequently in patients with minimal-no toxicity compared to patients with moderate-severe toxicity, 92.2% *vs*. 35.9%. Mean serum digoxin concentrations were higher in patients with moderate-severe toxicity compared to patients with minimal-no toxicity, 4.5 ng/mL (range <0.3–22.6 ng/mL) and 3.4 ng/mL (range <0.3–25 ng/mL). Overall 284 (64.8%) patients were asymptomatic after exposure and had minimal-no toxicity. Bradycardia or AV node dysfunction occurred in 50% and hyperkalemia occurred in 29.2% of patients with moderate-severe toxicity while hypotension and gastrointestinal symptoms occurred in 21.7% and 17.9% respectively. In patients with minimal-no toxicity, 225 (67.7%) were managed at home by the poison center. In patients with moderate-severe toxicity, 53 (50%) received fluid resuscitation, 23 (21.7%) received vasopressors, 12 (11.3%) received atropine, and 8 (7.5%) were paced. Overall 66 patients (15.1%) received digoxin immune Fab; 61 (57.5%) patients with moderate-severe toxicity received digoxin immune Fab. Patients with moderate-severe toxicity received a mean dose of 3.4 vials of digoxin immune Fab. Death occurred in 5 (4.7%) of patients with moderate-severe toxicity. *Conclusion:* The incidence and severity of digoxin toxicity reported to the Illinois Poison Center was low during the five year study period. Digoxin immune Fab may have been under utilized in some patients with moderate-severe toxicity. Prompt recognition of serious signs and symptoms and timely treatment, including administration of digoxin immune Fab, is crucial to patient survival.

67. Cardiotoxic Agent Poisonings. What are We Doing Wrong?

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Objective: To review clinical actions when confronted with cardiotoxic agent poisonings and identify noncompliers. *Methods:* All intoxicated patients treated during 2007 were reviewed. Those poisoned with cardiotoxic agents were analyzed to detect EKG or cardiac monitoring along with other variables: type of drug, main clinical symptoms, the shift and day of the week. *Results:* In the first semester of 2007: 503 poisonings were treated (1.11% of total emergencies). 137 cases were identified as poisoned by a cardiotoxic agent for which EKG or continuous cardiac monitoring were deemed necessary. In 34 (24.81%) of these cases, no EKG or cardiac monitoring was performed or registered in the clinical history. By substance type, 17 cases of cocaine (50%) followed by anticonvulsants, tricyclic antidepressants and antihistamines, with three cases each (8.8%), were noncompliers. The primary symptoms in noncompliant cases were neurologic, (n=22, 64.7%) e.g. diminished level of consciousness, headache or convulsions, psychiatric (n=10, 29.4%), e.g. agitation, anxiety or psychosis, and digestive (n=5, 14.7%). 23 cases (67.6%) were treated during the night shift and seven (20%) were in the evening. 17 (50%) noncomplier cases were treated on public holidays. *Conclusion:* Non-cardiovascular symptoms may condition attending physicians to overlook potential cardiac toxicity. More noncomplier cases were treated on evening or night shifts and on holidays with less emergency department staff physicians present. Awareness of possible cardiotoxicity among attending physicians should be reinforced even if not evident in the clinical symptoms. Poisoning treatment protocols recognition should be reinforced among attending physicians other than emergency department staff. *References:* 1. Brent J. Cardiovascular instability caused by drugs or chemicals. In: Ford MD, Delaney KA, Ling LJ, Erickson T eds. T. Clinical Toxicology. Philadelphia, WB Saunders Company; 2001: 177–183. 2. Nogue S, Puiguriguer J, Amigo M. [CALITOX-2006: Quality indicators in emergency assistance for acute poisonings] Asociación Española de Toxicología, Sección de Toxicología Clínica. www.aetox.es/Grupos/clinica/CALITOX-AETOX-30-04-2006.pdf

68. Withdrawn

69. Lithium Induced ST-Elevation Myocardial Infarction Without Coronary Artery Disease

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Introduction: Several pharmacological agents have been identified as potential triggers of coronary spasm that can result in acute myocardial infarction. (AMI). This has rarely been reported with acute lithium intoxication. We report a case of intentional lithium overdose in a patient who developed ST-elevation myocardial infarction without angiographic evidence of coronary artery disease. *Case report:* A 51-year-old male with bipolar disorder was found down with bottles of Depakote ER and Lithium ER around him. On physical examination he was responsive to verbal stimuli and protecting his airway. His vitals were heart rate, 116 beats per minute, blood pressure, 106/70 mm Hg, oxygen saturation on room air, 92%, and respirations 24 breaths per minute. The patient's condition worsened. He was started on dopamine for hypotension and intubated for airway protection. EKG revealed sinus tachycardia at a rate of 114 beats per minute, without any acute changes. Initial lithium and valproic acid level were greater than 5 mEq/L, and 154 mcg/mL. Repeat levels were 9.39 mEq/L and 188 mcg/mL. The patient was hemodialysed and then switched to CVVHD because of persistent hypotension requiring norepinephrine. A troponin I checked on the first hospital day, was elevated at 33.79 ng/mL (normal < 0.1 ng/mL). A repeat EKG at then time revealed ST segment elevation in leads V3-V6, as well as leads I and aVL consistent with lateral wall myocardial infarction. Emergent cardiac catheterization showed normal coronary vessels. The patient was treated supportively and continued on CVVHD till his lithium level was < 1 mEq/L. He did well and was discharged to a psychiatric facility. *Conclusion:* We report a case of lithium-induced ST- elevation MI in a patient with acute lithium overdose. The exact pathogenesis of lithium-induced myocardial infarction is unknown. However, a possible mechanism includes lithium-induced prolonged coronary artery spasm.

70. Lithium-Induced Encephalopathy: Nonconvulsive Status Epilepticus or Triphasic Encephalopathy?

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Introduction: Triphasic waves (TWs) are a distinctive but nonspecific electroencephalographic (EEG) pattern. TWs are often interpreted as generalized periodic patterns, slow spike-wave complexes, or rhythmic sharp waves. Such patterns are usually associated with nonconvulsive *status epilepticus* (NCSE) and raise the possibility of over interpretation of some EEG patterns as NCSE. We report a case of chronic lithium induced encephalopathy with TWs initially thought to be NCSE on EEG. *Case report:* A 77-year-old male with a history of bipolar disorder was admitted with disorientation, confusion and shuffling gate. The patient was on lithium and was recently started on valsartan, a specific angiotensin II antagonist. His physical examination revealed him to be confused to self, to time, and to place. His vitals were: heart rate, 68 beats per minute; blood pressure, 120/70 mm Hg; and respiratory rate, 16 breaths per minute. His neurological examination revealed a festinant gait without hyperreflexia or clonus. The lithium level was 2.52 mEq/L and the initial creatinine was 1.9 mg/dl. The patient became increasingly confused and combative in the hospital. A 22 channel digital EEG performed was initially thought to show seizure-like activity but was finally read as generalized triphasic waves. The patient was treated conservatively with saline hydration and his lithium levels normalized three days later. The patient was discharged to a nursing home. *Discussion:* Triphasic waves (TWs) and generalized nonconvulsive *status epilepticus* (GNCSE) share morphological features that may create diagnostic ambiguity. Triphasic waves are a nonspecific finding for a variety of diffuse CNS disorders including toxic-metabolic as well as diffuse parenchymal disorders. They are not felt to represent an ictal state. *Conclusion:* Lithium toxicity poses significant diagnostic challenges from EEG and clinical perspectives. EEG changes of TWs may be suggestive of electrographic status epilepticus. However, caution is needed before making an assumption of *status epilepticus*.

71. Intravenous Hypertonic Sodium Bicarbonate Infusion Reverses Flecainide-Induced Ventricular Cardiac Conduction Delay

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Background: Flecainide is a class 1c anti-arrhythmic agent which acts on the fast inward Na^+-channel during phase 0 of the cardiac action potential. Acute flecainide poisoning can cause cardiovascular collapse, ventricular conduction delays from Na^+-channel blockade and ventricular arrhythmias due to proarrhythmic effects from inhibition of repolarization K^+-conductance. We report a case of staggered flecainide ingestion resulting in QRS prolongation. *Case report:* A 59 year old, 80 kg lady presented with a history of dizziness, and palpitations. She had a past history of paroxysmal atrial fibrillation. Her medications included regular atenolol and prn flecainide. The night before presentation, she developed palpitations and took a total of 1200 mg of flecainide over the next 12 hours (200 mg q2h). On arrival to the Emergency Department, she was alert, with a heart rate of 40 bpm and systolic BP of 120 mmHg. Her ECG showed slow atrial fibrillation with QRS prolongation (222 msec) and a corrected QT interval of 512 msec. Her biochemical profile showed a sodium of 126 mmol/l and normal creatinine. She was given 200 ml of 8.4% sodium bicarbonate intravenously as intermittent 50 ml boluses over 30 minutes and had complete resolution of her ECG changes. The QRS duration remained within normal limits for the rest of her admission. She remained stable until discharge next day and had reverted to sinus rhythm on discharge. *Conclusion:* Although flecainide-induced QRS widening has been reported following acute poisoning with this medication, we report significant conduction delay following staggered ingestion over 12 hours. Hyponatraemia in our patient may have exacerbated her risk of developing QRS conduction delay. *In vitro* studies have shown that extracellular Na^+ concentration modulates flecainide's interaction with the Na^+ channel in cardiac conduction tissue. Administration of hypertonic sodium bicarbonate was associated with a persistent reduction in QRS widening in our patient. This case adds further support to previous reports that hypertonic Na-bicarbonate therapy may be useful in reversal of flecainide-induced conduction delay. *References:* 1. Devin R, Garrett P, Anstey C. *Emerg Med Australasia* 2007; **19**: 155–159. 2. Lovecchio F. Berlin R. Brubacher JR. Sholar JB. *Am J Emerg* Med 1998; **16**: 534–7.

72. Spontaneous Subdural Hematoma Associated with Sildenafil Use

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Objective: Sildenafil has been associated with strokes/transient ischemic strokes and intracerebral hemorrhage. However there are no reported cases of spontaneous subdural hemorrhages associated with sildenafil. *Case report:* A 60 year old male with a past medical history of diabetes was transferred to the emergency department for a spontaneous subdural hemorrhage revealed by way of CT scan secondary to the patient's complaints of headache post sildenafil use. The patient denied any history of trauma or falls. Home medications included glyburide 10 mg twice daily, metformin 850 mg daily, and sildenafil 100 mg as needed. On exam, the patient was arousable and followed commands. His pupils were equal and reactive. He moved all extremities appropriately. His repeat CT showed a moderate sized right subacute subdural hematoma and was taken to surgery the following day for evacuation of the hematoma. *Conclusion:* Sildenafil is a phosphodiesterase inhibitor, specifically type 5 (PDE5) which is found in the *corpus cavernosum* smooth muscle. In lower concentrations PDE5 is also found in other tissues such as platelets, vascular and visceral smooth muscle, and skeletal muscle. The inhibition of PDE5 in these tissues by sildenafil may explain the enhanced platelet antiaggregatory activity of nitric oxide that is observed *in vitro*, as well as the inhibition of platelet thrombus formation *in vivo* and peripheral arterial-venous dilatation *in vivo*. This mechanism may explain the effects observed in this patient. *References:* 1. Habek M, Petravic D. Stroke – an adverse reaction to sildenafil. *Clin Neuropharmacol* 2006; **29**: 165–7. 2. Egan RA, Pomeranz H. Transient Ischemic attack a stroke associated with sildenafil use. *Neurology* 2002; **59**: 293. 3. Morgan JC, Albatou M, Oberlies J, *et al*. Transient ischemic attack and stroke associated with sildenafil use. *Neurology* 2001; **57**: 1730–1. 4. Buxton N, Flannery T, Wild D, et al. Sildenafil induced spontaneous intracerebral hemorrhage. *Br J Neurosurg* 2001; **15**: 347–9. 5. Monastero R, Pipia C, Camada LK, *et al*. Intracerebral hemorrhage associated with sildenafil citrate. *J Neurol* 2001; **248**: 141–2.

73. Dystonia Secondary to Escitalopram Use After a Dosage Change

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Objective: Dystonia is a neurological movement disorder in which sustained muscle contractions cause twitching and repetitive movements. Dystonias can occur secondary to neuroleptics and rarely secondary to selective serotonin reuptake inhibitors (SSRIs). Here we report a case of dystonia secondary to an increase in dosage in one SSRI, but not another. *Case report:* A 39 year old female presented to the emergency department complaining of increased anxiety, tremor, paraspinal neck stiffness, jerking head movements with pain, and perioral twitching. The patient stated that she has had a worsening depressed mood in recent months. Past medical history significant for depression and anxiety. Medications included alprazolam 0.5 mg as needed and escitalopram 20 mg daily. In the emergency department her twitching and head jerking was witnessed and was consistent with dystonias. She was given diphenhydramine 50 mg orally and the movements resolved. She was discharged from the emergency department with a prescription for lorazepam and diphenhydramine as needed, a script for paroxetine 10 mg daily, and instructions to discontinue further escitalopram. *Conclusion:* We present a case of cervical dystonia secondary to escitalopram after a dosage change. Two other cases have been reported, one case which was an oculogyric dystonic reaction and the other was a paroxysmal dystonic reaction. The patient had been stable on the drug for 3 months. Once her dose was increased from 10 mg to 20 mg, the patient developed dystonias. Her symptoms resolved with diphenhydramine and discontinuation of the drug. All other causes of dystonias were ruled out. The patient a month later was stable with the use of paroxetine with no further episodes. *References:* 1. Garcia Ruiz, PJ, Cabo I, Bermejo PG. Escitaloparm-induced paroxysmal dystonia. *Clin Neuropharmacol* 2007; **30**: 124–6. 2. Patel OP, Simon MR. Oculogyric dystonic reaction to escitalopram with features of anaphylaxis including response to epinephrine. *Int Arch Allergy Immunol* 2006; **140**: 27–9.

74. Haemodialysis Clearance of Baclofen

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Objective: Baclofen is a centrally acting gamma-aminobutyric acid agonist used for spasticity of spinal origin and mainly excreted unchanged by the kidneys with an elimination half-life of 6.8 h. We report a combined baclofen serum and dialysate concentration measurement during haemodialysis in a patient with baclofen-related encephalopathy and acute renal failure followed by the calculation of haemodialysis clearance, haemodialysis removal rate constant and total amount of removed baclofen. *Case report:* A 60-year-old man with spastic tetraplegia on chronic baclofen therapy was admitted due to pneumonia and acute renal failure. The patient became comatose and baclofen concentration was found in the toxic range (0.70 mg/L) since baclofen dosage was left unchanged despite a deterioration of renal failure due to hypotension. During a 4-hour-long bicarbonate haemodialysis the patient woke up and became completely orientated and cooperative. Baclofen therapy was afterwards stopped and the patient remained conscious. The total amount of baclofen recovered in dialysate during the 4-hour-long haemodialysis was only 13.5 mg, which represented 18% of the daily dose and 37% of the active drug present in the patient prior to haemodialysis. The pharmacokinetics calculations revealed baclofen elimination half-life during haemodialysis 3.7 hours, baclofen haemodialysis removal rate constant 0.152 1/h and haemodialysis clearance 2.14 mL/s. *Conclusion:* Patients on a stable baclofen regime can develop baclofen toxicity due to acute renal failure. Haemodialysis removes baclofen as effectively as normal kidneys and it seems reasonable to use haemodialysis as a treatment modality in patients with accidental baclofen overdose due to acute renal failure.

75. Tramadol Overdose Induced CPK Rise, Haemodynamic and Electocardiographic Changes and Seizure

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Introduction: Overdose with tramadol, an opioid with unique structure, shows a variety of complications (1). This study aimed to evaluate the clinical findings related to this overdose and determine if evaluated CPK in these cases are related to seizure. *Methods:* All cases admitted with suspected tramadol overdose from 1st September 2006 to 31st August 2007 were included prospectively. The patients with known previous seizure, cardiac or kidney problems were excluded. *Results:* Tramadol overdose accounted for 151 cases (1.2% of all cases). A male predominance (63%) was found. Mean (SD) age was 22.6 (7.4) years. Four cases were referred to the nephrology department, one case referred to ICU. The most common ECG finding was sinus tachycardia. Heart rate was 94 (± 24) bpm on admission. PR interval was 151 (± 26) msec, QRS duration was 83 (± 18) msec, and QTc was 428 (± 38) msec. When patients were discharged, these indices were heart rate 78 (± 15), PR 147 (± 28), QRS 81 (± 13) QTc 321 (± 27). A ratio was derived by dividing R wave to S wave in aVR Lead. It was positively associated with QTc on admission ($r=0.457$, $P<0.001$). This relationship disappeared by the time of discharge. 15% experienced at least one episode of seizure. Patients with seizure had a higher heart rate at admission ($P=0.024$), but not when discharged. They also showed a high CPK of 557 (± 656) which was not significantly higher than patients with no seizure. WBC was slightly higher 11535 (± 11934). Other laboratory findings were in the normal range. *Conclusion:* Tramadol overdose commonly induces tachycardia and raised CPK and to a lesser extend seizure. It may also rarely lead to acute renal failure. CPK is raised in this overdose even in the absence of clinically reported seizure. Tachycardia and QTc prolongation are controlled in the period of admission. These patients need cardiac and laboratory monitoring. To our knowledge, this is the largest study in regard to tramadol overdose, and the only one which relates the ECG, CPK and seizure. *Reference:* 1. Spiller HA *et al*. Prospective multicenter evaluation of tramadol exposure. *J Toxicol Clin Toxicol.* 1997; **35**: 361–4.

76. Chemical and Product Type Categorisation of Product Ingredients in Poisons Centre Data Processes

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Objective: Classification systems play an important role in generating reports and statistics. Therapeutic substances are classified using the ATC (or similar) system, and non-therapeutic substances by product type, or chemical classification where a chemical or chemical class is the primary toxicant. A comprehensive chemical classification system for ingredients in multi-ingredient products is lacking, and retrieval of cases where a substance or group of substances is a minor (but toxic) component is often not possible. *Methods:* MSDS-sourced ingredient names were extracted from the TOXINZ database into an Excel spreadsheet. Each substance was assigned a chemical classification, based on the IUPAC guidelines. Some compromise was necessary due to the variable nature of information sources. Polymers were classified by chemical characteristic (acrylic, epoxy etc) and proteins by form or function (biological, hydrolysate etc). Identification of substances and their synonyms was based on the CAS number, if available. The information is stored in a Java-based relational database. *Results:* Each substance has four classifications: CAS number, synonyms, chemical classification and product type. The chemical classification and product type categories allow for multiple classifications. Currently the system contains 3,410 substances, with 8,671 synonyms, and 60 product type groups. There are 16 primary level and 566 secondary level classifications: acyclics (147), alicyclics (33), aromatics (66), carbohydrates (14), heterocyclics (69), inorganics (111), lipids (21), petroleum distillates (7), polycyclics (11), polymers (30), proteins (8), steroids (7), terpenes (8), miscellaneous (10), unknowns (19) and (currently) unclassified (5). *Conclusions:* The classification system and its associated data is not only a stand-alone information resource that integrates MSDS-based ingredient information of variable quality and specificity, but can also be integrated with other information resources. For example, we are currently using the system to group ingredients according to their specific product type (e.g. cyanoacrylate adhesives, brake fluids, industrial disinfectants), thereby facilitating quick, accurate and consistent data entry into product information documents in the TOXINZ database. The system also has the potential

to be the basis of a harmonised chemical classification system, with sufficient flexibility to accommodate more substances and classes as necessary, based on local requirements.

77. ASHT Project: Poisons Centre Attitudes to an EU-Wide Database of Enquiries

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Objective: To investigate the attitudes of poisons centres in the EU to pooling data into an EU-wide database of poisons centre enquiries, as part of a feasibility study conducted for the EU Public Health Project 'Development of an Alerting System and Criteria for Development of a Health Surveillance System for the Deliberate Release of Chemicals by Terrorists' (ASHT). *Methods:* A questionnaire was developed, which included questions about attitudes to different aspects of data pooling. Respondents were presented with a series of statements and asked to indicate the extent to which they agreed or disagreed with them. The questionnaire was emailed to the Directors of poisons centres in EU Member States and in Candidate countries. The centres were identified from EAPCCT and WHO directories. Two reminders were sent to non responders. *Results:* Poisons centres were identified in 26 countries and questionnaires were sent to 68 poisons centres for which contact details could be found. Replies were received from 33 poisons centres (48.5%) representing 22 countries (84.6%). Only the results concerning attitudes are presented here. 79% of respondents either agreed or strongly agreed that the database would yield useful public health data and 88% that it would be a valuable surveillance tool. 85% of respondents would be prepared, in principle, to submit data and 82% thought that this should be linked to funding. There was stronger support for the database to be hosted by the EAPCCT (82% agreed or strongly agreed) rather than the EU (26%), or by a body set up for the purpose (41%). 94% of respondents felt that contributing poisons centres should have a say in how the compiled data could be used, and 92% thought that contributing centres should be able to search the entire database. *Conclusions:* Overall there was a positive attitude to an EU pooled database of poisons centre enquiries, and a view that responsibility for the database should rest with the EAPCCT. There are many technical issues to consider before such a database could be built and the continuing work of the EAPCCT Monitor and ASHT projects aims to identify ways to overcome these.

78. Methanol Outbreak in Italy: Role of the Poison Centre Rapid Alert System and the Syndromic Surveillance

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Outbreaks of methanol poisoning may occur in every country causing a medical and public health emergency. The most recent and severe reported outbreak in Italy occurred in 1986. *Objective:* To describe an outbreak of methanol poisoning occurring in Sicily in 2006–2007, and the role of the Poison Centre in the Rapid-Alert and syndromic-surveillance (SS) systems. *Methods:* All Sicilian cases of methanol poisoning referred to the Pavia Poison Centre (P-PC) in the considered period were analysed for PSS, time for analytical confirmation, treatment, outcome and influence of the alert/surveillance systems in the amelioration of identification of poisoned cases. *Results:* Ten cases occurred from Aug-2006 (first alert) to Oct-2007. Four additional cases from Feb-2003 to Apr-2006 were identified retrospectively. A total of fourteen cases were identified. PSS at admission was 1, 2 and 3 in 1, 1 and 12 cases respectively. The most frequent clinical features were mydriasis (14/14), metabolic acidosis (12/14), coma (11/14), shock (9/14), respiratory failure (9/14). Serum methanol was assessed in 10/11 cases, ranging from 10 to 420 mg/dL; one case had urinary confirmation. Time required for laboratory confirmation ranged from 6 to 60 hours. Supportive, antidotal and dialysis treatment was performed in 14/14, 13/14 and 11/14 patients respectively. Eleven patients died, one patient was lost at follow-up. The population involved is mainly composed of eastern European young women (8/14) living in Italy as caregivers. Nine rapid-alerts were subsequently forwarded by P-PC to all Italian PC and to National and Regional authorities: a specific SS system was implemented. *Conclusions:* The outbreak mortality is high, mainly because of late diagnosis and treatment. Laboratory support has been essential in identifying new cases. The alert and SS systems activated by the P-PC according to the Ministry of Health and the Regional authorities seems to ameliorate the EDs recognition of methanol intoxications. Specific preventative measures have also been activated by the Ministry of Health and the Sicilian regional authorities. The source of the methanol remains still unknown, even though the habit of adding denatured alcohol to vodka might have a role due to an erroneous use of high concentration commercial methanol products in Sicily.

79. The Leonardo Da Vinci Programme – Evaluation of Exchange Experiences Between Five European Poisons Centres

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Objective: The Leonardo Da Vinci Programme was adopted in 1994 with the aim to improve vocational education and experiences by collaboration between European countries, e.g. exchange visits, creation of networks and development of training and educational systems (1). Grants from this programme enabled visits between poisons centres in five different countries during 2006–2007. Only two centres (in Sweden and Slovakia) accomplished a bilateral exchange. Refusals by the National Agencies in the other countries resulted in unilateral visits from Sweden to Bulgaria, Lithuania and Romania. Each stay was 1–2 weeks long and the host country elaborated a suitable programme for the visitors. Specially requested presentations were held, e.g. on treatment strategies, methods for collection of data and management of antidotes. A survey was performed to evaluate the experiences. *Methods:* An evaluation form with 13 questions was sent to each participating country with a four graded answering scale. Staff members at the five poisons centres, involved in the Da Vinci activities, were asked to answer the questions. *Results:* We collected 25 anonymous answers. The most important results are as follows. The aim for the exchange and the duration of the visits were judged to be adequate by most of the respondents (16/25) but only half of them (11/25) thought that the time for planning was enough. Only a few participants had been involved in writing the Da Vinci application form and they thought that this work was time-consuming, "bureaucratic" and barely relevant. A majority agreed completely that their experience and knowledge in clinical toxicology were enhanced as well as improved language skills and cultural understanding (19/25). Two participants claimed that their work was not disturbed, but most persons daily routines were affected in various degrees. The participants felt encouraged to further collaboration (23/25) and recommended others to take part in similar projects (24/25). Comments expressed the opinion that bilateral exchange was desirable. *Conclusion:* The Leonardo Da Vinci Programme enables a great opportunity to exchange experiences with colleagues at poisons centres in other EU-countries. However, to optimise the outcome of the visits, bilateral exchange is to be preferred. *Reference:* 1. http://ec.europa.eu/education/programmes/llp/structure/leonardo_en.html

80. Singapore Drug and Poison Information Service: User Satisfaction After 3 Years

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Introduction: The Drug & Poison Information Centre (DPIC) in Singapore was set up in April 2004 by the Department of Emergency Medicine at the Singapore General Hospital and funded by the Ministry of Health's Health Service Development Program. *Objectives:* A survey was conducted to evaluate the satisfaction of callers who used the service of DPIC. It aimed to determine the quality of service provided by the DPIC as well as to collect information on caller needs and expectations; to identify perceived and potential problems that need improvement or changes. *Methods:* A prospective study of 100 callers to the DPIC was performed. A telephone questionnaire survey was developed based on a customer satisfaction survey (1) and modified accordingly. A trained interviewer conducted the telephone interview over 20 minutes about 1 week after their initial consult. Scales were created with response categories of "excellent to poor." Items scored included ease of access, staff knowledge and overall satisfaction with the service provided. *Results:* All the calls were perceived to be an emergency by the caller following a potential poisoning exposure. 94% of the calls were answered immediately. 92% of callers found the staff to be knowledgeable. 82% of callers rated their overall experience with DPIC good, 10% fair and 8% rated it excellent. 86% found the instructions given clear and easy to follow. The following information was offered: signs and symptoms to look for (100%), time frame of manifestation of signs and symptoms (85%), need to seek care in the Emergency Department (63%). 74% of callers found the information very useful, 26% found it somewhat useful and all the callers replied that they will call again for a future poisoning question or problem and will recommend the service to their relatives and friends. 43% felt willing to pay for the services provided, of which 81% would pay on a per call basis while 19% prefer a monthly subscription. All felt that the government should fund the service. If the DPIC was non-existent, the callers would call an ambulance (15%), call their primary physician (13%), visit their primary physician (28%), visit the Emergency department (26%), search the internet for information (10%) or do nothing (8%). *Conclusion:* The DPIC was highly regarded for its speed, competence and applicability, facilitating better treatment and unnecessary emergency visits. There was overall satisfaction with the service provided by DPIC. *Reference:* 1. SurveyShare Resource Center. http://www.surveyshare.com/resources/

81. "Nano" Sealing Sprays Health Impairments in Germany

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Background: In Germany a series of rapidly developing and sometimes severe cases of health impairment were observed after the correct use of "nano" sealing sprays intended for the treatment of glass and ceramic surfaces in March 2006. *Results:* Based on rapid and complete documentation of about 160 cases in collaboration with the German Poison Centres, the BfR, as an independent federal institute, immediately initiated a recall of the hazardous products. The public, as well as authorities and ministries, were informed by timely publication of press releases based on BfR and EU expert meetings. Investigations into the composition of the product were complicated considerably, because some of the supplier companies of the products' components were located in different German federal Länder and the basic component of the nanofluid had been produced in Luxembourg. The BfR expert meeting at the end of May 2006 and different analysis measures arrived at the result that the products concerned did not contain any nano-sized particles. Due to unexpected chemical changes during the processing to produce the aerosol sprays, the active silicon compounds in the active substances had obviously disappeared to a large extent. The hazardous manifestations associated with nano sealing sprays were very similar to the health problems documented in a number of earlier case clusters associated with leather and impregnating sprays (Germany, USA, Netherlands, Denmark, Switzerland). *Perspectives:* Currently, in research projects, the BfR has analysed the "nano" case series - pattern of signs and symptoms and reviewed the case series reported from other countries to find out the similarities to the "waterproofing sprays syndrome". In parallel, a chemical analysis of the aerosols has been performed and animal studies have been carried out to examine the respirable components of the aerosol fractions in the sprays that caused the health impairments reported.

82. Value of Formal Stakeholder Questionnaire Feedback of Telephone Enquiry Answering by Poisons Centres in the United Kingdom

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Objectives: It is important for poisons centres to collect information on user satisfaction in a systematic way to provide evidence of good practice and to identify areas where services should

be improved. To achieve this, the United Kingdom National Poisons Information Service (NPIS) has performed a formal stakeholder feedback exercise of its telephone enquiry service for health professionals on 4 occasions since 2002. *Methods:* Standard questionnaires were sent out by post to a random sample of callers by the NPIS units in Edinburgh, Cardiff, Newcastle and Birmingham. The questionnaires sought information on a variety of issues including use of other poisons information sources prior to the enquiry, ease of access to the service, value and relevance of information provided and the politeness of the staff member responding to the enquiry. An overall satisfaction score ranging from 1 to 6 is also requested, as well as free text comments. The exercise was conducted on 4 occasions: in the calendar year 2002 and the fiscal years 2004/5, 2005/6 and 2006/7. *Results:* Over the 4 exercises 7,965 questionnaires were sent out and 3,616 returned (response rate 45%). Designations of responders matched the profile of callers to NPIS. Overall quality scores were high over all 4 years of study, with the proportion of responders scoring 5 or 6 out of a maximum possible 6 being 96.0%, 94.9%, 95.7% and 95.7% in the exercises conducted in 2002, 2004/5, 2005/6 and 2006/7 respectively. Highest scores were obtained for politeness of the staff member (96.2%) and relevance of the reply (94.9%), while the lowest scores were for the speed at which information was passed on during the telephone conversation (76.7%). Between 2002 and 2006/7, scores for speed of access to the service improved, reflecting improvements to the way telephone calls are routed to units with lines available. There were no significant differences in quality scores between the 4 units in any of the 4 years studied or overall. *Conclusions:* Postal questionnaires can provide valuable information about user satisfaction with services and can detect improvements associated with service reorganisation. Use of common methodology by different poisons centres allows their results to be compared.

83. Establishment of the Estonian Poison Information Centre

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Objective: To describe the development leading to opening of the service of the Estonian Poison Information Centre (EPIC). Initiating an EPIC had been discussed for the last 10 years. In 2006 in Estonia 392 persons died in poisonings (28/100,000 inhabitants) and 57,500 persons required medical attention (4,104/100,000 inhabitants) for an estimated total cost of 753,000 EUR. *Method:* Due to ongoing health reforms it would have been impossible to start the PIC as a part of a medical institution, so it was decided that the PIC should be established within the Ministry of Social Affairs (MSA) as a part of CNC. In hindsight, the establishment under the Ministry was crucial for data and information exchange to key decision makers. By 2005 the necessary knowledge to build a concrete plan to set up the operations had been acquired in collaboration with the Finnish and other Nordic PICs. Two emergency medicine specialists were recruited in summer 2006 with a mission to initiate the center and develop appropriate documentation. They participated in the 4-week training by the Finnish PIC. These specialists put together the EPIC vision statement and developed a 5-year plan, including budgets. Brainstorming and discussion of concepts was started with leaders in intensive care, MSA and hospitals. A consensus was reached that the EPIC needs to be open 24/7, and answer calls both from medical personnel and the public. The EPIC was donated a copy of the poison information monographs of the Finnish PIC. In 2007 the monographs were translated into Estonian, and updated with local information about natural poisons, chemicals, drugs etc. Quality assurance processes and documentation were developed. The EPIC is now ready to announce a governmental call for expressions of interest to choose the best hospital that could host the new center. Up till now the total costs have been 127,742 EUR, and the next 5 year's total budget has been set at 806,400 EUR. *Conclusion:* The EPIC starts working in the summer of 2008.

84. Establishing an Antidote Network in Slovenia

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Objective: Presently many countries and regions have established systems for antidote stocking and distribution. The Poison Control Unit in the University Medical Centre Ljubljana is the only one of its kind in Slovenia. It provides for a population of 1.96 million in an area of 20,073 square kilometers. A country with comparatively small urban centres interspersed within mainly rural areas and with a good traffic infrastructure provided us with a challenge for establishing our own centralized antidote network. *Methods:* In accordance with WHO's guidelines for poison control (1), published data of other Poison centres rationales for antidote stocking (2) and our PCU's statistical data on acute poisonings and their regional distribution derived from our information service for health care providers, and together with the help of European Union experts, we established a web of 14 acute hospitals and 5 psychiatric hospitals dealing with acute poisoning cases. Within them we identified contact persons and performed a survey of their existing antidotes stocks. Also we established contacts with other state services (e.g. military) possibly presenting a reserve antidote pool. *Results:* A strategy for additional antidote purchase and a network for their distribution were devised and is currently being implemented at a national level. *Conclusion:* An operational antidote network is being set up in Slovenia with the aim of providing a dependable service for all its users. *References:* 1. www.who.int/ipcs/publications/training_poisons/guidelines_poison_control/en/index.html. 2. Dart RC, Goldfrank LR *et al*. Combined evidence- based literature analysis and consensus guidelines for stocking of emergency antidotes in the United States. *Ann Emerg Med* 2000; **36**:126–32.

85. Poisoning in the Very Young and Old

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Objective: To investigate the pattern of serious cases referred to a poisons service concerning the very young and old. *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 June 2006 to 31 August 2007 were reviewed for age, agents taken and reason for referral, to determine the pattern of referrals. *Results:* Between 1 June 2006 and 31 August 2007 there were 1388 referrals to these consultants involving 1319 patients. 2.4% of patients concerned were aged <1 year and 15.4% were aged 60 and over. For those aged <1 year (31 patients) 14 referrals were due to therapeutic errors. Three neonates had high levels of lithium (2) and magnesium (1) from high maternal levels at birth. The remainder concerned exposures to drugs (8), household products (2), others (2) and unknown (2). For patients aged 60 years or over there were 203 patients. 170 (83.7%) incidents involved drugs with 21.2% (43) of these being digoxin, followed by paracetamol (14.8%, 30) and aspirin (7.4 %, 15). The most common reasons for referral were specific management advice on treatment, general management advice and diagnosis. For digoxin 43 patients required consultant advice (1–4 referrals/patient) compared with only 3 patients aged under 60 years. In those digoxin patients aged 60 and over there were 21 cases of chronic accumulation, 9 acute on chronic poisoning, 4 intentional overdoses, 4 therapeutic errors and 5 uncertain. Patients had bradycardia/complete heart block (28), tachycardia (3), renal impairment/failure (22), and hyperkalaemia (17). Most referrals involved advice on the use of digoxin antibodies. *Conclusions:* Therapeutic errors are a common cause of referral in the very young. Digoxin toxicity is a particular problem in the UK in the over 60s. *Acknowledgement:* NPIS consultants and staff for the data.

86. Withdrawn

87. A Toxic Event Surveillance System in the Emergency Department of Spanish Hospitals

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Objective: To maintain an updated profile of the toxic incidents caused by chemical products that reach the Emergency Departments of Spanish Hospitals, in the frame of a collaborative program developed by the Health Ministry and the section of Clinical Toxicology of the Spanish Association of Toxicology since 1999. *Methods:* Data are submitted by members of the emergency department staff. The clinical data for each patient include: sex, age, symptoms, treatment and outcome and product identification, exposure cause, exposure place and exposure route. We present here the results of the first 8 years of the program. *Results:* There are 24 participant hospitals, which have reported a total of 4664 cases. Admission has been required in 1324 (28.39%). Mean age is 37 years. Males represent 49.80% and females 50.20%. Reason for the exposure has been domestic accidents in 3092 cases (66.29%), suicidal in 572 (12.26%), occupational 801 (17.17%), other 168 (3.60%). The main families of chemical compounds have been classified as: toxic gases 1812 cases (38.85%), caustics 1308 (28.04%), solvents 439 (9.41%), detergents 304 (6.52%), pesticides 446 (9.56%), metals 53 (1.14%), other 314 (6.48%). The route of exposure has been oral in 1771 cases, respiratory in 2046, cutaneous in 212 and ocular in 712, some of them associated. 4050 (86.83%) cases have had some symptoms: neurologic 1149, respiratory 1034, digestive 1426, cutaneous 165 and ocular 719, renal 7, cardiovascular 111, others 81. Some treatment has been used in 3863 cases: gastric decontamination in 363, cutaneous or ocular decontamination in 505, antidotes in 1221, enhanced elimination in 49 and symptomatic measures in 2609 cases. Mean time in hospital was 49 hours. There have been 81 deaths (1.74%), caused by methanol (9), paraquat and other pesticides (30), HCl (21), CO (14) and others (7). Most of the non lethal cases have had a good outcome. *Conclusion:* This program is useful to maintain an updated profile of poisoning by chemical products. The data show a homogeneity along the years that allows identifying the most dangerous compounds and families and contributing to develop preventive strategies to avoid the most frequent or dangerous exposures.

88. Inquiries about Drug Poisoning to the Danish Poison Information Centre, Adherence to the Advice Given and Quality of the Discharge Diagnoses

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Objective: To determine the degree of adherence to advice given by the Danish Poison Information Centre (DPIC). Secondly to determine the quality of the registration of the discharge poison diagnoses. *Methods:* Cross-sectional study of multiple drug poisoned patients that DPIC was involved in over a 12-month period (23/10/06 - 22/10/07). Only cases with available discharge letters or medical records were included. Multiple drug poisoning was defined as at least 2 drugs or at least 1 drug and 1 or more drug of abuse. The given treatment (activated charcoal, antidotes, aspiration) and observation level (intensive care unit, special care unit, ordinary care ward or emergency ward) were compared with the advice given by DPIC. The discharge diagnoses were compared with the diagnoses given by DPIC. The drug poisoning diagnoses were based on the ICD10 classification and the ATC codes for the involved drugs. *Results:* A discharge letter or a medical record were available in 59 out of 632 cases. The average intake was 3.2 drugs per case. Suicide attempt accounted for 68% of the cases (40/59), while drug abuse accounted for 10% (6/59). The treatment advice was followed in 87% of the cases (45/52) and in 86% the observation advice was followed (51/58). Telemetry observation was followed in 92% of the cases (30/32) where it was recommended. The ICD10 poison diagnoses were correct in 35% of the cases (19/54) while the diagnoses were entirely wrong in 37% of the cases (20/54). All the ATC codes were correct in 27% of the cases (15/54) while all were missing in 41% of the cases (22/54). Both the ICD10 diagnoses and ATC codes were correct in 9% of the cases (5/54). *Conclusion:* The given advice was followed in the majority of the cases. In only in one third of the cases, was there a correct ICD10 diagnosis or ATC code for all the drugs taken. This could endanger correct extraction of data from register-based studies about multiple drug poisonings and may indicate a need for simplifying the poisoning diagnoses.

89. Acute Quetiapine Overdose in Adults: A Five-year Poison Control Center Experience

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Objective: Quetiapine is widely used for the treatment of depression, bipolar disorder, and schizophrenia. The aim of this study was to review the clinical effects of quetiapine after overdose in adults as reported to a large regional poison control system. *Methods:* A retrospective

cohort study was performed by chart review of the California Poison Control System (CPCS) database for cases from 2002 to 2006. Inclusion criteria included adult patients with acute ingestion of quetiapine. Patients with coingestants were excluded. Symptoms, signs and outcomes were extracted from the database and also by direct chart review for some variables (e.g. QT interval). *Results:* A total of 1062 cases of acute adult quetiapine ingestion (without coingestants) were reported to the CPCS. Intentional ingestants accounted for 87% of cases while intent was unknown in 12.5% cases. Less than 1% were due to adverse reactions. 50% of the cases involved patient aged 18 to 35 and 5% occurred in patients older than 55 years. 54% of the patients were female. Clinical outcomes were reported as minor or none in 38%, moderate in 40% and major in 4%. There were three deaths and they all presented with coma, tachycardia and respiratory depression requiring ventilatory support. Central nervous system effects included drowsiness (75.6%), slurred speech (80%), agitation (5.4%) and confusion (2.3%). Tachycardia occurred in 54.5%, hypotension in 16.4% and respiratory depression in 4.6% of cases. 2.4% of patients had documented electrocardiographic changes or conduction disturbances. Two patients had episodes of ventricular tachycardia, but there were no reports of torsade de pointes. In eletrocardiographic findings noted in the CPCS medical record, 10 patients (1%) had QRS prolongation and 28 (2.6%) had QTc prolongation. There were 19 reports of seizures, but in 3 of these patients the toxicology screen was positive for amphetamines. Symptoms generally lasted for less than 3 days (only 4% lasted 3 days or more). More than a third of patients (37.7%) were managed in an intensive care unit, and 15% were endotracheally intubated. *Conclusion:* Quetiapine is a common drug involved in acute intentional overdose. Drowsiness, tachycardia, and hypotension are common but QRS and QT interval prolongation was rare. There were no reports of torsade de pointes. Death was rare.

90. On-Line Poisons Information Sources for the Public (Sweden)

Carlvik B, Lindberg H, Persson H. *Swedish Poisons Information Centre, Stockholm, Sweden.*

Objective: Description of the development, contents, design, use and future of the Swedish Poisons Information web page. *Results:* The web page – www.giftinformation.se - started in 1998 and in 2005 was subject to an extended revision. The page is designed for the public. The on-line information source intended for medical professionals – www.giftinfo.se - is not dealt with here. The web page for the public informs about risks, symptoms and first aid in poisoning accidents and it highlights when admittance to hospital is indicated. The information concentrates on poisoning accidents in children. There are two extensive sections - on chemical products and plants (including pictures) - each containing around 300 items where symptoms and relevant treatment is indicated. The page also stores information related to accidental and deliberate poisonings in adults and drug abuse. Information is also available on snake bite, stings, poisonous fungi (with pictures), contact with marine animals, toxic algae etc. Furthermore, prophylactic aspects constitute a key issue. This kind of information was earlier found in brochures, books and posters. The information is now easier to retrieve, it will reach far more people and it can be up-dated at any time and adapted to the season. The web page also informs manufacturers and suppliers of chemical products on how to submit information on product composition to the centre (electronically, special forms etc.) The availability of a comprehensive web page might also reduce the number of calls to the centre. After years of continuous increase, the number of calls from the public has declined since the new page was released. The number of visits is at the moment around 8000/week. To date only part of the web page is translated into English, but plans are at hand to extend the section in English. *Conclusion:* The web page has been available for ten years. After a complete revision in 2005, providing a user-friendly and comprehensive home page, there has been a steep rise of web page visits and a slight fall of telephone queries from the public.

91. Increase in Fatal Outcomes Reported to the NPIS (Cardiff) over a Three Year Period

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Objective: To identify changes in numbers of calls with fatal outcomes regarding cases dealt with by the NPIS (Cardiff) in recent years. *Method:* Call records and follow-up data between years 2004 – 2006 were interrogated to determine total number of calls and fatal outcomes to calculate changes in the percentage of cases resulting in death. *Results:* In 2004 the unit received 26,164 calls - seven of these known to result in fatalities (0.027%). In 2005 the figures were 26,029 calls and 17 fatalities (0.065%). 2006 saw 21,786 calls with 22 fatalities (0.101%). The types of drug most commonly involved in the fatal cases were: Calcium channel blockers – four; cardiac glycosides – nine (all digoxin); beta blockers – three; benzodiazepines – three; analgesics – six; anticonvulsants – three; antidepressants – five. 24 deaths followed intentional overdoses, nine chronic accumulation, three adverse drug reactions and one therapeutic error. The remainder were unknown or due to other causes. Notably, digoxin was involved in nine of the fatal cases (two deaths in 2004 and 2005 and five deaths in 2006). These were all elderly patients (aged 76–91) who died following complications due to chronic digoxin accumulation. Inquiries to the Office of National Statistics indicate that digoxin was mentioned in the death certificates of between 4 and 12 fatalities annually between 1996 and 2005 where the cause of death was recorded as being a result of drug abuse/dependence, intentional self-harm, assault, and self-poisoning of undetermined intent. *Conclusion:* The results show although call numbers to the unit have fallen there has been a rise in the number of deaths known to us. Digoxin deaths are significantly greater than those relating to any other drug, it was also the only drug linked to deaths from chronic accumulation. Further studies could look at the effectiveness of therapeutic monitoring and changes in prescribing practice. It should also be determined if there have been changes in the way in the NPIS is used, with the telephone service perhaps being used more for serious cases.

92. Clinical Toxicology Research in Spain (1991–2005)

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Objective: Clinical toxicology is a branch of toxicology that studies the clinical repercussions of human poisonings, their diagnosis, prognosis and treatment. This care-based activity may be accompanied by a research component. This study analyzes the characteristics of Spanish scientific research in the field of clinical toxicology. *Methods:* The Web of Knowledge of the Institute for Science Information (ISI) was used as the bibliometric search tool and the Science Citation Index (SCI)-Expanded programme as the data base. The study period was 1991 to 2005. Documents produced by Spanish toxicologists in the field of clinical toxicology were sought using the following search strategy. In the field Address the word Spain plus any expression that identified a Service, Unit or Department of Toxicology, were entered. Of the documents retrieved, those related to clinical toxicology were selected. *Results:* A total of 173 documents were identified as produced by Spanish toxicologists in the field of clinical toxicology (11.5 documents per year). They came from 8 Spanish autonomous communities, of which the most productive were Catalonia, Andalusia and Valencia. The most-productive individual centre was the Hospital Clinic of Barcelona (n=34). The Spanish journal Medicina Clínica published the largest number of these articles (20). The number of articles published each year increased slightly year-on-year, although the growth was not statistically-significant at any time in the study period. Studies on toxicological epidemiology in the emergency department (n=14) were more common than those in the intensive care unit (n=6). The most-studied clinical repercussions of poisonings were neurological (n=49), digestive, hepatic, renal, muscular and respiratory. There were more studies on antidotes (n=19) than on gut decontamination (n=3) and extra-renal purification techniques (n=2). There were 90 articles on complementary toxicological tests, 52 on the repercussions of poisonings in general tests and 27 articles on mortality. *Conclusion:* There has been a steadily rising trend in the number of articles published on clinical toxicology in Spain during the last fifteen years. The analytical and clinical repercussions of poisonings are the principal subjects treated in these articles.

93. Gastrointestinal Bleeding and Massive Liver Damage in Neuroleptic Malignant Syndrome

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Objectives: Neuroleptic malignant syndrome (NMS) is a rare side effect of antipsychotic therapy characterized by fever, muscular rigidity, altered mental status, increased level of serum creatinine phosphokinase, and increased number of white blood cells. The mortality rate of patients with NMS remains elevated. *Methods:* We examined the clinical records of patients diagnosed with severe NMS admitted to the Clinical Toxicology Unit, Florence University Hospital, between 1990 and 2004. *Results:* Eight patients presented with this neurological disorder. All were treated with supportive therapy, which included dantrolene, levodopa/benserazide, benzodiazepines, metamizole and/or paracetamol, and antibiotics. Five survived and three died. Of the three deceased, two had large hemorrhages in the gastrointestinal tract and one had massive liver damage and diffuse hemorrhages throughout the body. *Conclusion:* Our results suggest that gastrointestinal bleeding is a frequent cause of death in NMS patients. Bleeding may occur as a consequence of commonly accepted medical treatments (especially the use of cyclooxygenase inhibitors as antipyretic agents) and of NMS-induced changes in blood coagulation status. To increase the survival rate of these patients, it is necessary to avoid using drugs that may facilitate gastrointestinal lesions and to utilize procedures known to decrease the risk of bleeding.

94. Epidemiology of Hospital-Acquired Pulmonary Infections in Acutely Poisoned Patients Admitted to an Intensive Care Unit in Paris, France

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Objective: Hospital-acquired pneumonia may be responsible for significant morbidities in poisoned patients admitted to the intensive care unit (ICU). Our objectives were to investigate toxicants that may facilitate these infections and to determine the sensitivity to antibiotics of the causative bacteria, in order to choose the best therapeutic strategy. *Methods:* Inclusion of all the patients admitted to our ICU during a 6-month period for a severe poisoning resulting in a hospital-acquired pneumonia (onset >48h after admission); prospective data collection, including pulmonary microbiology (cultures of sputum, protected specimen brush samples, and bronchoalveolar lavage as well as their corresponding antibiograms); descriptive analysis (median [10%, 90%-percentiles]). *Results:* Fifty-eight poisoned patients (18F/40M, 42 years [38–61], SAPS II 62 [37–79], ICU stay duration: 25 days [7–81]) were included. Toxicants were either psychotropic drugs (57%; antipsychotic 15/58, sedatives 9/58, antidepressants 6/58, opioids 3/58) or cardiotropic drugs (41%; chloroquine 13/58, beta-blockers 9/58, calcium-channel blockers 1/58, anti-arrhythmic drugs 1/58) or smoke inhalation (1/58). Fifty-six patients were mechanically ventilated (duration: 24 days [5–47]) at time of diagnosis. Among these patients, 41/58 had already received antibiotics for aspiration pneumonia and 14/58 had been re-intubated. Causative bacteria were the following: *Pseudomonas aeruginosa* (24/58), enterobacteriae (15/58), *Haemophilus influenza* (5/58), *Staphylococcus aureus* (8/58), *Acinetobacter baumanii* (2/58), *Streptococcus pneumoniae* (2/58), and *Stenotrophomonas maltophilia* (1/58). Based on antibiograms, the best choices of antibiotics were the combination of piperacillin/tazobactam+amikacine or cefepime+ciprofloxacin. Vancomycin appeared necessary only if the onset was >7 days, due to potential methicillin-resistant *Staphylococcus aureus* (3/8). *Conclusions:* Mechanically-ventilated poisoned patients in ICU may suffer from hospital-acquired pneumonia resulting in significant morbidity. Both psychotropic and cardiotropic drugs were associated with the onset of pneumonia. In poisoned patients, optimal management should include the characterization of local bacterial ecology to guide the appropriate antibiotic treatments.

95. Calcifications in Eye Burns Related to Phosphate Buffers in First Aid Treatment

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Introduction: For years it has been recommended that first aid for eye burns be performed with water, saline or phosphate buffer. Although phosphate is not present in the corneal stroma we found a multitude of corneal calcifications after first aid rinsing with phosphate buffers in non-calciferous corneal burns. *Methods:* Results from the ACTO database on eye burns were

evaluated retrospectively. A clear correlation of corneal calcification with initial rinsing or therapy with phosphate containing fluids was identified. In *ex vivo* eye irritation testing (EVEIT) we could identify corneal calcification in simulation of phosphate rinsing of mechanically abraded corneas. A clinical case of severe eye burns was treated with phosphate buffer containing eye drops due to incipient perforation and resulted in total corneal calcification saving the eye from perforation. *Results:* There is a clear effect of phosphate buffers administered to the epithelial damaged cornea, which is consistently associated with corneal calcification ($p < 0.05$ in humans, $p < 0.001$ in animals). Even a single dose application after eye burns resulted in dramatically increased phosphate in the corneal stroma measured by EDX analysis in 5 rabbit corneas, freshly burnt. The effect of corneal calcification was seen experimentally by us (1). We could trace this in humans and *ex vivo* experiments as well as *in vivo* experiments. *Conclusion:* Eye rinsing with phosphate buffer in the first aid situation should be avoided. Unless buffering is weak a corneal calcification with visual impairment is a probable severe adverse event. *Reference:* 1. Schrage NF, Schlossmacher B, Aschenbrenner W, *et al*. Phosphate buffer in alkali eye burns as an inducer of experimental corneal calcification. *Burns* 2001; **27**: 459–64.

96. Caustic Soda and H_2SO_4 Decontamination of the Cornea *Ex Vivo* Demonstrated via OCT

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Objective: Efficacy of rinsing substances in case of caustic soda burn of the eye is up to now estimated to be similar for water and amphoteric solutions. *Methods:* By means of high resolution OCT we are able to demonstrate penetration of caustic soda (2 molar) and H_2SO_4 (1 molar) into the excised rabbit's animal cornea derived from a slaughter house. Thus our interest was to demonstrate corneal decontamination with two different types of rinsing solutions recommended for this purpose: water and diphoterine. *Results:* We found penetration of both substances for untreated corneal burns of 20 sec duration. Rinsing with water showed deep penetration of the caustic substance and dilution compared to non rinsed corneas. In case of diphoterine rinsing for 15 min we found cessation of the penetration in the middle of the cornea and no penetration into deep stroma for acid and alkali up to 60 minutes of observation whereas in water rinsing the deep stroma was affected after the rinsing therapy stopped. *Conclusion:* There are considerable differences in quality and quantity of decontamination achieved by means of amphoteric hyperosmolar rinsing of the burnt cornea with diphoterine compared to water. By this experiment we are able to give an indication of increased therapeutic possibilities in case of caustic damage of the eye by use of appropriate decontamination systems. *Reference:* Spoler F, Forst M, Kurz H, *et al*. Dynamic analysis of chemical eye burns using high-resolution optical coherence tomography. *J Biomed Opt* 2007; **12**: 041203.

97. Experience of Providing Fomepizole (4-Methylpyrazole, 4-MP) to Manage Toxic Alcohol Exposures in the UK

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Objective: Fomepizole (4-methylpyrazole, 4-MP) is an effective antidote for toxic alcohol poisoning (1), particularly as there are often difficulties associated with safe administration and monitoring of the alternative antidote, ethanol. We undertook prospective monitoring of the use of fomepizole, particularly looking at adverse events associated with its use and logistical problems in supply and/or administration. *Methods:* Our protocol for patients with a strong history of ingestion and/or clinical/biochemical features consistent with toxic alcohol ingestion, is to supply fomepizole to the treating hospital until the result of a confirmatory blood toxic alcohol concentration is available, with continuation of fomepizole where indicated. Cases meeting these criteria since the introduction of Fomepizole OPi in the UK (November 2004-October 2007) were reviewed. *Results:* There were 73 possible toxic alcohol cases. Laboratory analysis confirmed the ingestion of ethylene glycol in 31 (43%) cases, methanol in 4 (6%); neither in 30 (41%) and there was no result in 8 (11%). 34 (47%) had initial treatment with ethanol prior to fomepizole, either due to the distance between the poisons unit and the treating hospital or delays in contacting the poisons unit. Fomepizole was administered in 66 cases, it was supplied in the remaining 7 cases but not used. In 3 (4%) cases there were difficulties with fomepizole administration: it was mislaid in 2 hospitals following delivery and there was 1 dosing error. No clinical adverse events relating to the use of fomepizole were reported. *Conclusions:* The use of fomepizole in this large cohort of presumed toxic alcohol cases was not associated with any significant clinical adverse events. The only problems were logistical and related to receipt and dosing of the fomepizole. This supports the use of fomepizole in the management of presumed toxic alcohol poisoning, and also more widespread availability to prevent delays in administration. *Reference:* 1. Mégarbane B, Borron SW, Baud FJ. Current recommendations for treatment of severe toxic alcohol poisonings. *Intens Care Med* 2005; **31**: 189–195.

98. Acute Renal Failure Alters the Kinetics of Pralidoxime in Rats

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Objective: Pralidoxime (PX), the antidote to organophosphate poisoning, is eliminated unchanged by the renal route. This study assessed the effect of acute renal failure (ARF) on the kinetics of PX. *Methods:* In male Sprague-Dawley rats ARF was induced by potassium bichromate. PX (50 $mg.Kg^{-1}$ as PX base) was administered intramuscularly. Control rats received isotonic sodium chloride solution. Plasma PX concentrations were measured by HPLC, urine concentrations using capillary electrophoresis. Results are expressed as mean +/– SEM. Statistical analyses were performed using non-parametric tests. *Results:* Maximal plasma creatinine levels occurred 48 hours following bichromate injection (22.4 +/– 1.8 $\mu mol.L^{-1}$ control vs 169.6 +/– 26.5 $\mu mol.L^{-1}$ ARF). No significant difference was observed regarding the Cmax (24.4 +/–1.1 vs 35.2 +/– 4.9 mg/l). In contrast, the areas under the curve (AUC) in the ARF group were about 3 times greater than in the control group ($p < 0.01$). The volumes of distribution were not modified. The total clearances were significantly reduced in ARF (1.5 +/– 0.2 vs 3.1 +/– 0.1 $l.kg^{-1}.h^{-1}$; $p< 0.01$) resulting in a significant increase in the elimination half-life (102.8 +/– 7.9 ARF vs 44.0 +/– 1.1 min control; $p< 0.01$). A positive correlation ($r^2= 0.7665$) existed between the AUCs and the plasma creatinine values. *Conclusion:* The kinetics are significantly different between control and ARF groups. Acute renal failure did not modify PX distribution but decreased significantly elimination from plasma. PX kinetics was correlated with creatinine clearance. From a clinical viewpoint, our data suggest that the dosage regimen of PX should be modified in patients with severe acute renal failure. Further investigations are required to determine whether the antidotal efficacy of PX is modified in ARF.

99. Antidotes - How Often Did We Use Them?

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Objective: The aim of the study was to assess the rate of antidote use in the treatment of poisoning cases. *Material and methods:* Retrospective analysis of all cases treated between 1999 and 2006 was performed. The total number of patients was 10,965; for further analysis 8,772 acute poisoned patients were included (acute poisoning with ethanol in addicted patients and withdrawal syndromes were excluded). In the study population 66.2% patients were poisoned with medicines or medicines together with ethanol, 20.7% with carbon monoxide and 13.1% with other chemicals. The use of following antidotes was studied: N-acetylcysteine, atropine, ethanol, flumazenil, physostigmine, naloxone, methylene blue, glucagon, oximes and chelating agents. *Results:* During the study period antidotes were applied in the treatment of 524 patients (5.97%), with no significant difference in the rate in the successive years. The most frequently used was N-acetylcysteine (38.9%), followed by physostigmine (23.9%), atropine (9.0%), naloxone (7.4%), flumazenil (3.8%). The remaining antidotes (16.0%) were used in single cases. *Discussion:* Antidote use is determined by the kind of poison involved. The rate of paracetamol poisoning (20–30 cases per year) meant that N-acetylcysteine was used frequently to prevent hepatotoxicity. Central anticholinergic syndrome (agitation and agitated delirium) was the indication for physostigmine treatment. No complications were observed. The small number of poisonings with organophosphate pesticides was the reason for rare oxime use, in contrast to poisonings with carbamates, in which atropine was the only antidote. *Conclusion:* Antidotes were used in a small number of cases, but in particular poisonings they were essential.

100. Preparing for Chemical Terrorism: A Study of the Stability of Expired 2-PAM

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Objective: Oximes such as pralidoxime (2-PAM) are essential antidotes for life-threatening organophosphate poisoning. Unfortunately, oximes are expensive, have limited use, and short shelf-lives. As such, maintaining large stockpiles to prepare for terrorism is not always possible. Previously, we demonstrated that atropine is stable well beyond its labeled shelf-life (1). Additionally, we demonstrated that recently expired 2-PAM was clinically efficacious in a series of poisoned patients (2). Since 2-PAM is dosed empirically, clinical improvement does not guarantee pharmacological stability. We therefore chose to analyze the chemical stability of expired 2-PAM. *Methods:* Samples of lyophylized 2-PAM (Protopam Chloride, Ayest Laboratories, INC) were maintained according to the manufactures recommendations for 20 years beyond the published shelf-life. Additionally, we studied MARK I autoinjector 2-PAM that was stored properly for 3 years beyond its expiration. Analysis used an Agilent LC/MSD 1100 with DAD detector, and an Agilent, Sorbax SB–C-18, 4.6x150 mm, 5 um, column with the following solvent system: water with 0.01% TFA (A) and methanol with 0.01% TFA (B). Fresh reagent grade 2-PAM (Sigma) was used as a standard. Results were repeated for consistency. *Results:* Lyophylized 2-PAM was a white powder that was clear and colorless in solution. LC was identical to the standard and resulted in two isolated peaks with identical mass spectra suggesting that they are stereoisomers. The autoinjector discharged a clear, yellow-colored solution. In addition to the two peaks identified for lyophylized 2-PAM, a very small third peak was identified with a mass spectra corresponding to the reported N-Methyl pyridinium carboxaldehyde degradation product. *Conclusions:* When properly stored, lyophylized 2-PAM is chemically stable well beyond its expiration date. Although the relative amount of degradation product found in solubilized (autoinjector) 2-PAM was small, it is unclear if this could be potentially toxic and therefore is of concern. In the event of an emergency, and only after in-date supplies are exhausted, in might be reasonable to consider using lyophylized out-of-date 2-PAM. *References:* 1. Schier JG, *et al*. Preparing for chemical terrorism: stability of injectable atropine sulfate. *Acad Emerg Med* 2004; **11**: 329–34. 2. Bouchard NC, *et al.* Expired 2-PAM effectively reverses cholinergic crisis in humans. *J Toxicol Clin Toxicol* 2004; **5**: 742.

101. Treatment of Severe Calcium-Channel Blocker Poisonings with Hyperinsulinemia/ Euglycemia Therapy: A Study of Feasibility and Safety in Intensive Care Unit

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Objective: Calcium-channel blocker (CCB) poisonings represent the first cause of cardiotoxic death in the US. Management includes high-dose catecholamines. Several antidotes have been proposed; however, they were disappointing. Hyperinsulinemia/euglycemia therapy (HIET) seems more promising, although no controlled study has established its benefit. Our objective was to study HIET safety in Intensive Care Unit (ICU). *Methods:* Observational prospective study including all CCB-poisoned patients treated with HIET in 2003–2007; data collection, including doses of insulin and glucose, as well as HIET-attributable side-effects; descriptive analysis (median [extremes]). *Results:* Thirteen CCB-poisoned patients (6F/7M, 40 years [17–95]) received HIET. Patients ingested elevated doses of verapamil (6/13, dose: 8.4 g [1.6–14.5]), diltiazem (3/16), nicardipine (2/16), nifedipine (1/13), and amlodipine (1/13). Several had a past history of cardiac disease (8/13) or suicide attempt (8/13). HIET was started in ICU 9 hours [2–26] after CCB ingestion. Systolic blood pressure was 88 mmHg [67–126] before and 115 mmHg [64–28], 2 hours after HIET. Concomitant catecholamine infusion rate was 8 mg/hour [1–50] for norepinephrine and 6 mg/hour [1–15] for epinephrine. HIET modalities were the

following: continuous 0.5 UI/kg/hour [0.1–0.5]-insulin infusion during a 18.5 hours [4–81]-period associated with hypertonic glucose at a maximal rate of 9.5 g/hour [2–27]. Catecholamines were weaned in none of the patients. HIET-related side-effects included hypokalemia (12/13, 2.6 mmol/l [2.1–3.3], with a favourable response to potassium infusion) and hypoglycemia (3/13, 2.5, 2.7 and 3.3 mmol/l with a favourable response to glucose infusion). General complications of poisonings were the following: cardiac arrest (2/13), high-degree atrioventricular block (2/13), sepsis (8/13), acute renal failure (7/13, including one case requiring hemodialysis), acute respiratory distress syndrome (4/13), and death (4/13). The final benefit of HIET remained however difficult to analyse, due to the variety of the ingested CCBs and the concomitant supportive therapies. However, in one case, the premature interruption of HIET resulted in the immediate reintroduction of elevated doses of catecholamines which were significantly reduced as soon as HIET was restarted. *Conclusions:* HIET (0.5–1 UI/kg/hour) used to treat CCB-induced cardiovascular toxicity is safe, but requires close monitoring of potassium and glucose concentrations. When correctly monitored, HIET side-effects are mild. However, the final HIET benefit remains to be demonstrated.

102. How to Develop Cost-Effective Antidote Logistics – A Comparison Between Slovakia and Sweden

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Objective: Fast and cost-effective antidote distribution is important to guarantee efficacy in treatment of some acute poisonings. Antidote recommendations are mainly based upon poisoning panorama, geographical conditions, national treatment regimens and economical aspects. This survey was performed to study antidote logistics in Slovakia and Sweden, two countries with different socioeconomic means (1). *Results:* Poisons centres in both countries regularly elaborate and publish national antidote recommendations (mandatory to follow in Slovakia but optional in Sweden) which include e.g. type of antidotes and stock quantities. Both countries have three different levels of antidote storage: 1. Local, in all hospitals – antidotes intended for immediate access and/or commonly used. 2. Regional, in larger hospitals – often expensive antidotes which can preferably be co-ordinated within the region. 3. National, with 24-hours service - very expensive and/or rarely used antidotes. Group 1 and 2 antidotes are kept mostly in hospital pharmacies in Slovakia and in an emergency department (ED) or intensive care unit (ICU) in Sweden. The Slovak national storage is handled by the poisons centre and emergency transport is operated by ambulances or delivery firms. In Sweden this is managed by the only 24-hours open pharmacy and the SOS organisation (responsible for 112 emergency calls and coordination of rescue work). The costs of antidote use and distribution, in Slovakia, are divided between the Ministry of Health and the hospitals but in Sweden these expenses are paid by the hospitals only. Both countries have established a national data base covering present information about types and quantities of antidotes and locations of storage in the hospitals (e.g. ED, ICU and hospital pharmacy). This information is updated continuously by the poisons centres in close cooperation with the hospital pharmacies. *Conclusion:* Despite differences in economical welfare many similarities in antidote distribution were found when comparing Slovakia and Sweden. Development of a national coordinated system, including antidote recommendations and establishment of a database, has enhanced the cost-effectiveness of antidote logistics, but improvements can still be made to optimize antidote efficiency. *Reference:* 1. GNI per capita 2006, Atlas method and PPP. World Development Indicators database, World Bank, 14 September 2007.

103. To Give or not to Give Antidote – A Case of Iron Poisoning Requiring Liver Transplantation

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Objective: To raise discussion of appropriate recommendations for antidotal treatment in iron poisonings. *Case report:* A 17 year old girl took 6 g ferrous sulphate depot tablets (100 mg/kg), 8 mg tizanidine and alcohol. She was brought rapidly to the health centre. On arrival she was conscious, alcometer 0.8%. She vomited some tablets, was given activated charcoal and transferred to a secondary level hospital. At arrival there, approximately 4 hours after ingestion, her status was unchanged, and she had only a mild metabolic acidosis. Gastric lavage was performed and WBI started. Plasma iron (fP-Fe) at that time was 72.2 micro-mol/l. The next fP-Fe was determined the following day and then once daily with all values lower than the first. No antidote was administered. Liver enzymes increases indicating liver toxicity appeared. The Poison Information Centre was consulted after 3 days recommending deferoxamine treatment with a lower dose due to the impaired liver function. The antidote was administered without problems but increasing signs of deteriorating liver function became apparent. After transfer to the Liver Transplantation Unit MARS treatment was performed during next four days, N-acetylcysteine and deferoxamine were given. At day 10 liver transplantation was performed. *Discussion:* Our criteria for deferoxamine treatment which include either significant symptoms or a fP-Fe ≥ 90 micromol/l at 3–6 hours after ingestion were not met. Only one case has been published with acute liver failure after iron poisoning and comparable iron levels (1) *Conclusion:* Single value fP-Fe decision criteria are problematic for medicines available in formulations with varying rates of absorption including slow-release formulations, when a patient has mild symptoms at the beginning. Peak fP-Fe value may have been missed in this case. *Reference:* 1. Daram SR, Hayashi PH. Acute liver failure due to iron overdose in an adult. *South Med J* 2005; **98**: 241–4.

104. Does N-Acetylcysteine Alter Prothrombin Index in Acetaminophen Poisoned Patients Admitted to the Intensive Care Unit without Hepatocellular Injury?

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Objective: N-acetylcysteine (NAC) reduces the severity of acetaminophen poisoning-related liver damage. However, it may interact with clotting factors containing disulphide bonds. Our objective was to study the effect of NAC on prothrombin index (PI) in NAC-treated poisoned patients. *Methods:* Retrospective data collection, including PI, V-factor, and liver enzymes, measured before and during NAC administration; descriptive analysis (median [25%, 75%-percentiles]); comparison of paired data using Wilcoxon tests. *Results:* During a 10 year-period, 171 patients (123F/48M, 28 years [21–41]) were admitted to our ICU for acetaminophen poisoning and treated with intravenous NAC (150 mg/kg in 1 h followed by 50 mg/kg in 4 h, 100 mg/kg in 16 h and, if necessary in case of liver damage, by 300 mg/kg/day). Acetaminophen concentration was 317 µmol/l [149–708] with a 9 h [5–14]-delay from ingestion. Nine patients suffered from previous liver disease. Eighty percent were multidrug ingestions, mainly including propoxyphene and codeine. On admission, PI was 75 % [64–90], V-factor 66 % [45–82], AST 22 IU/l [16–44], ALT 20 IU/l [12–33], alkaline phosphatase 55 IU/l [39–70], bilirubin 8 µmol/l [6–13], and creatinine 66 µmol/l [56–81]. The following complications were observed: cytolytic hepatitis (ALT>50 IU/l, 26%), acute liver failure (4%), acute renal failure (1%), and multiorgan failure (2%, leading to death). In patients without hepatocellular injury (ALT <50 IU/l and PI >60%, N=115), there was a significant decrease in PI under NAC (82% [72–92] before versus 73 % [66–79] at 11 h [10–19] following NAC administration, p<0.001) without significant modification in AST (19 IU/l [15–28] versus 18 IU/l [15–24], p=0.9) and ALT (15 IU/l [10–22] versus 17 IU/l [13–23], p=0.1) measured at the same time. In these patients, no clinical consequences in relation to PT decrease were observed. *Conclusions:* Admission to ICU for acetaminophen poisoning remains frequent. Significant morbidity may be observed in case of co-ingestions or significant delay to antidote administration. Clinicians should be aware that NAC may significantly reduce PI, in the absence of previous liver or clotting abnormalities. Decrease in PI does not result in any significant alteration of liver enzymes or clinical consequences. However, the molecular mechanism of NAC interaction with PI remains to be determined.

105. Characteristics of Ocular Hydrofluoric Acid Burns Decontaminated with Water, Calcium Gluconate 2% and Anti-HF, by OCT Examination

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Introduction: It is now possible to follow up in real time ocular burns via high resolution OCT technique. Therefore we evaluated HF burns treated and untreated to learn the efficacy of the decontamination fluids usually recommended for HF burns. *Methods: Ex vivo* eyes of slaughtered rabbits were exposed to 25 ul of 1.25 mol HF filter paper. After removing the filter no rinsing or immediate rinsing with water, calcium gluconate 2% or Anti HF solution from Prevor was started for 15 min., continuous OCT observation was done during 75 min. *Results:* There was total penetration of the untreated corneas within 15 min, water rinsing resulted in deep stromal changes with less severity, calcium gluconate showed initial stopping of the burn but later progression. Anti HF solution proved to stop the burn without any progression after 75 min. There was corneal opacity for water, calcium gluconate and no treatment, only Anti HF corneas remained clear (1). *Conclusion:* There is significant difference in decontamination of HF from ocular tissue dependent on the type of rinsing fluid. Rinsing with water is better than no treatment, significant improvement is achieved by calcium gluconate rinsing but best results were found with Anti HF solution. The mechanism of decontamination is now directly accessible via OCT and comparisons of rinsing fluids are possible. *Reference:* 1. Spoler F, Frentz M, Forst M, *et al*. Analysis of hydrofluoric acid penetration and decontamination of the eye by means of time-resolved optical coherence tomography. *Burns* 2007 Sep 13; Epub ahead of print.

106. Use of Pralidoxime without Atropine in Carbamate Toxicity: A Case Report

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Objective: Some experimental models demonstrate pralidoxime therapy of carbamate toxicity to be deleterious. Pretreatment with atropine minimizes the adverse effect of pralidoxime in such cases, but concerns continue. We present a unique case of carbamate toxicity treated successfully with pralidoxime alone. *Case report:* An 80 year-old woman with Alzheimer's dementia presented to the ED with 3–4 days of lightheadedness, vomiting, diarrhea, and bilateral lower extremity muscle pain. Extensive review of systems was otherwise negative. Her vital signs were: BP, 207/85 mmHg; pulse, 101 beats/minute; rectal temperature, 36.6°C; respirations, 18/minute; and SpO_2 95% breathing room air. Her bedside glucose measurement was 6.7 mmol/L. Physical examination revealed a confused, diaphoretic, ill-appearing female with miosis and fasciculations of the tongue, eyelids, gastrocnemius, and quadriceps bilaterally. The neurologic, heart, lung, abdominal, and head, eyes, ears, nose, throat examinations were otherwise unremarkable. Nine 5-cm^2 rivastigmine patches (9.5 mg/24-hour) were found adherent to her torso and lower extremities. The patches were immediately removed and underlying skin cleansed with soap and water. Laboratory values of blood count, basic metabolic panel, calcium, magnesium, phosphorus, troponin, coagulation studies, and urinalysis were unremarkable. Due to minimal muscarinic findings no atropine was administered. However, 1 g of pralidoxime was administered intravenously over 30 minutes to treat fasciculations. Within 30 minutes of this treatment there was significant improvement in symptoms and resolution of fasciculations. She was admitted to the hospital, required no further pralidoxime therapy, and was discharged after 3 days. *Conclusion:* Rivastigmine is a reversible (carbamate) cholinesterase inhibitor used to treat dementia. In overdose, cholinergic crisis is expected and in this case was precipitated by patch overuse. We believe there was a causal relationship between pralidoxime administration and the prompt resolution of symptoms and fasciculations. This case of apparently safe and effective pralidoxime use without concomitant atropine administration for carbamate toxicity reinforces recent data demonstrating the potential safety of pralidoxime in carbamate toxicity (1). Clinicians should be aware of the potential for transdermal rivastigmine overdose and how it might safely be treated. *Reference:* 1. Mercurio-Zappala M, Hack JB, Salvador A, *et al.* Pralidoxime in carbaryl poisoning: an animal model. *Hum Exp Toxicol* 2007; **26**: 125–9.

107. Successful Treatment of Shock Induced by Propafenone Overdose with Insulin Infusion

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Objective: Propafenone is a Vaughan Williams Class Ic antidysrhythmic agent (1). This agent blocks fast inward sodium channels, is an L-type calcium channel blocker, and is a weak

beta-adrenergic antagonist (1). The conventional therapy of hypotension induced by propafenone overdose includes fluid resuscitation and sodium bicarbonate followed by inotropic support, if needed (2). We report a case of successful insulin therapy for propafenone-induced hypotension unresponsive to other inotropics and sodium bicarbonate. *Case report:* A 41-year-old woman with a prior medical history of atrial fibrillation presented to the emergency department complaining of chest discomfort after ingesting 4500 mg of propafenone in total. On examination, she was alert and her vital signs and laboratory studies were normal. Fifteen minutes later, her electrocardiogram revealed ventricular fibrillation. We gave her atropine and electrical shock of 200J for defibrillation. When CPR was stopped, her blood pressure was 70/40 mmHg, and her heart rate was 68 beats/min with wide QRS complex. Normal saline was administered rapidly, and dopamine, dobutamine, norepinephrine and glucagons were injected to improve hypotension. And we also injected sodium bicarbonate. But, her blood pressure was not improved. Refractory to the conventional therapy for sodium channel blocker toxicity, we administered short-acting insulin of 0.5 IU/kg as a loading dose followed by 1.0 IU/kg/h continuously, considering the properties of propafenone, which also has calcium channel blocking effect. Her blood glucose level was kept euglycemic by continuous 5% dextrose infusions. Her blood pressure was increased gradually. Thirty minutes after we administered insulin, her systolic blood pressure was checked at 100 mmHg. Her blood pressure was maintained and we could taper the other inotropics successfully. She was discharged 8 days post-ingestion without further cardiac complications. *Conclusion:* Physicians should be familiar with the properties of propafenone and recognize the important role of insulin therapy in the case of extremely severe hypotension unresponsive to conventional therapy for sodium channel blocker overdose. *References:* 1. Faber TS, Camm AJ. The difference of propafenone from other class Ic agents. *Eur J Clin Pharmacol* 1996; **51**: 199–208. 2. Brubacher J. Bicarbonate therapy for unstable propafenone-induced wide complex tachycardia. *CJEM* 2004; **6**: 349–356.

108. Glucarpidase for Methotrexate Poisoning

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Background: High-dose Methotrexate therapy (HDMTX) is a key treatment component in a variety of malignancies, including acute lymphoblastic leukaemia, lymphoma and osteosarcoma. The doses of Methotrexate (MTX) used in HDMTX protocols for leukaemia and lymphoma typically exceed 1 g per square meter body surface area and are even higher than 10 g in osteosarcoma treatment schedules. Following a 4 to 24 hour MTX infusion, together with vigorous hydration and urine alkalinisation to enhance the solubility of MTX, plasma MTX levels are expected to be less than 1 microM/L at 42 hours after start of HDMTX. Pharmacologically guided Leucovorin (LV) rescue is always necessary to restore the intracellular pool of reduced folates. Using these supportive care measures, HDMTX can safely be administered in the majority of patients. However, precipitation of MTX in renal tissue could cause renal failure resulting in prolonged exposure to toxic MTX blood concentrations and consequently life-threatening toxicity. *Extracorporeal removal of Methotrexate:* Renal replacement therapies (e.g. hemodialysis, hemofiltration) have limited effects in lowering MTX blood levels with frequent rebound increases upon termination. High-flux hemodialysis allows a more effective MTX removal, but requires high blood flow-rates and published experiences are limited to few patients (1). Moreover, techniques for extracorporeal removal of MTX are not always readily available, require an invasive access and repeat administration is usually necessary. *Properties and development of Glucarpidase:* Glucarpidase (formerly termed Carboxypeptidase G2) is an 83kDa enzyme, which cleaves the glutamate residue from various folates, including MTX. Interestingly, the resulting metabolite from MTX cleavage, 2,4-diamino-N10-methylpteroic acid (DAMPA), exhibits no cytotoxicity *in vitro* (2). Glucarpidase is derived from Pseudomonas strain RS-16 and its gene was introduced into E. coli allowing the production of sufficient amounts of this enzyme for therapeutic purposes (3,4). *Pharmacological and clinical effects of Glucarpidase detoxification:* Experiences with Glucarpidase have been reported from 1 US and 2 European studies evaluating patients with renal failure and delayed MTX elimination after HDMTX therapy (5–7). In the US study, a subset of patients additionally received thymidine, but this rescue agent is no longer available (8). A single injection of Glucarpidase (scheduled dose: 50 units per kg body weight) resulted always in a >95% decline of MTX blood levels within a median of 15 minutes (5,7). The amounts of MTX, recovered from the urine as the enzyme-induced metabolite DAMPA, ranged up to 35% and were higher in patients with early intervention, high levels of circulating MTX and continued optimal hydration (7). Lethal MTX toxicity was significantly associated with late intervention with Glucarpidase in an updated report from the US intervention study (8). In the majority of study patients, Glucarpidase was tolerated without any side effects. Only 8 of 145 study patients experienced drug-related events, which were occasionally treated with steroids or diphenhydramine and always resolved without sequelae (5–7). It is noteworthy, that immunoassays greatly overestimate MTX blood levels after Glucarpidase treatment due to interference with the DAMPA metabolite (5,7). DAMPA is less soluble than MTX, which potentially could result in further renal toxicity. However, the time periods until normalisation of serum creatinine values in patients treated with Glucarpidase are similar to those in patients receiving dialysis-based treatment (1). Furthermore, complete recovery from renal failure was reported in 5 patients with renal failure and MTX blood levels exceeding 100 microM/L (9). Intrathecal Glucarpidase treatment has also been given to patients with accidental intrathecal MTX overdoses. Following cerebrospinal fluid (CSF) exchange in 4 patients, the CSF MTX levels declined by >98% in all 7 patients. All patients fully recovered, except for 2 patients who had persisting memory impairments (10). *Conclusion:* Glucarpidase is easy to administer, carries a low risk of treatment-related adverse events and rapidly and effectively removes MTX from circulation. As Glucarpidase does not hydrolyse intracellular MTX, continuation of LV rescue is still required after Glucarpidase intervention. LV is also a substrate for Glucarpidase, although with lower affinity compared to MTX, and the efficacy of LV rescue may be reduced after Glucarpidase intervention. Thus, the optimal dosage and schedule of LV in patients receiving Glucarpidase should be evaluated in future studies. *References:* 1. Widemann BC, Adamson PC. Understanding and managing methotrexate nephrotoxicity. *Oncologist* 2006; **11**: 694–703. 2. Widemann BC, Sung E, Anderson L, *et al*. Pharmacokinetics and metabolism of the methotrexate metabolite 2,4-diamino-N10-methylpteroic acid. *J Pharmacol Exp Ther* 2000; **294**: 894–901. 3. Minton NP, Atkinson T, Sherwood RF. Molecular cloning of the Pseudomonas carboxypeptidase G2 gene and its expression in *Escherichia coli* and *Pseudomonas putida*. *J Bacteriol* 1983; **156**: 1222–1227. 4. Sherwood RF, Melton RG, Alwan SM, *et al*. Purification and properties of carboxypeptidase G2 from Pseudomonas sp. strain RS-16. 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109. Cardiotropic Effects of Insulin

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Background: Insulin exerts multiple effects on the heart that collectively have a beneficial effect on myocardial substrate metabolism and cardiac function. The objective of this review is to present fundamental data concerning insulin signalling and regulation of myocardial glucose metabolism (1). Most of the available data were obtained from ischemia-reperfusion models. Nevertheless, acute poisoning by some substances may also be complicated by myocardial insulin resistance and disturbed myocardial glucose uptake (2). Insulin will therefore appear as a key regulator of cardiac substrate metabolism and function. *Insulin signalling:* Insulin action is initiated by the binding of insulin to a specific receptor at the plasma membrane. This will result in the activation of the intracellular tyrosine kinase domain. In addition, another important substrate, the insulin receptor substrate 1 (IRS1), becomes tyrosine phosphorylated and this will lead to the activation of the lipid kinase phosphatidylinositol 3'kinase (PI3K). The next step will be the activation of the protein kinase B (PKB/Akt). The activation of the PI3K/PKB/Akt pathway is likely the key to the regulation of fatty acids and glucose metabolism. Subsequent substrates of PKB/Akt (eNOS, AS160, GSK3, FOXO, PRAS40, S6) have been involved in several aspects: vasodilation, glucose uptake, glycogen synthesis, gene expression, anti-apoptosis, protein synthesis. *Regulation of myocardial substrate metabolism by insulin:* Insulin regulates myocardial energy metabolism by stimulating the uptake of both glucose and fatty acids via the translocation of GLUT4, the specific glucose transporter, and CD36, the specific transporter of long-chain fatty acids. Glucose enters cardiomyocytes through two types of glucose transporters: the most abundant is the GLUT1 type, and the type GLUT4 which is insulin-regulated. After insulin stimulation, GLUT4 translocates to various domains of the plasma membrane and plays a central role in adaptive glucose metabolism (3). Insulin is also promoting the dephosphorylation of glycogen synthase and is stimulating the glycogen synthesis (4). Insulin stimulates glycolysis not only by enhancing GLUT4-mediated glucose uptake, but also by increasing the intracellular levels of fructose 2,6-biphosphate through inactivation of 6-phosphofructo-2-kinase (PFK-2) (5). Regarding fatty-acids metabolism, insulin enhances the rate of uptake of long-chain fatty acids by cardiomyocytes. This action is mediated by a translocation of CD36 transporters. The long-chain fatty acids taken up in response to insulin are not oxidized but are diverted into triacylglycerols. Under normal conditions (unstressed and aerobic state), myocardial metabolic energy is derived from the oxidation of long-chain fatty acids (60–70%) rather than from glucose (30–40%) or lactate (10%). In pathological conditions, the preference for a specific substrate will be modified. In experimental models of ischemia-reperfusion, it has been well documented that glucose is the preferred substrate. In case of stress related to poisoning by some substances (e.g. beta-blockers, calcium channel antagonists), cells are also forced to become carbohydrate dependent. At the same time, fatty-acid excretion is reduced and insulin-stimulated glucose uptake is impeded in myocardial and peripheral cells. This metabolic disturbance will be amplified by other factors. The blockade of L-type calcium channels will inhibit the calcium-mediated pancreatic insulin secretion. The peripheral utilization of glucose may also be impaired by the effects of counter-regulatory hormones, such as endogenous catecholamines and glucocorticoids. Finally, glucose delivery or glycolysis may also be affected by hemodynamic conditions, with low tissue perfusion. In summary, insulin is actively stimulating myocardial glucose metabolism, while inhibiting fatty-acid metabolism. In addition, insulin accelerates myocardial lactate oxidation through an induction of pyruvate dehydrogenase activity (6). *Regulation of contractile force development and calcium metabolism by insulin:* The positive inotropic effect of insulin has been demonstrated in several *in vitro* and *in vivo* models. It is not precisely known how insulin exerts its inotropic action. It seems that the pharmacological inhibition of PI3K activity could prevent the positive insulin-dependent inotropic effect. Apparently, there is a relationship with glucose utilization as inhibition of glycolysis partially blocks the insulin-dependent inotropic effect. In rat hearts, but also in human cardiac muscle preparations, insulin could mediate an increase in intracellular [Ca^{2+}]. There are at least two potential intracellular targets for insulin: 1) insulin via the activation of the PI3K pathway could reduce the Ca^{2+} extrusion by the trans-sarcolemmal Na^{+}/ Ca^{2+}exchanger (NCX); 2) insulin via the IRS-1/2 pathway could reduce the Ca^{2+} re-uptake by the sarcoplasmic reticulum. Beneficial effects on inotropy may also be partly related to insulin-induced hypokalaemia, resulting into a facilitation of intracellular calcium entrance during systole and protective membrane stabilising effect due to intracellular loading of potassium in excitable cells. *Effects of insulin on myocardial blood flow:* In addition to its direct effect on glucose uptake, insulin could also mediate an increase in myocardial blood flow leading to a better glucose disposal. This action seems to be mediated by the phosphorylation of endothelial nitric oxide synthase (eNOS) by PKB/Akt (7). *Conclusions:* Insulin may have a potential benefit in optimizing myocardial metabolism under stress conditions. This could be particularly helpful when insulin secretion is decreased or when systemic insulin resistance is increased following some drug overdoses. *References:* 1. Ouwens DM, Diamant M. 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110. Six-year Follow-up After the 2001 Methanol Outbreak in Estonia

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Introduction: Mass poisonings with methanol are seen and reported regularly. Data from the time of the poisoning is therefore available, but follow up-data is scarce. We therefore conducted a six-year follow up study after the large methanol outbreak in Estonia in September 2001 (1), where methanol was verified in more than 150 patients. This is to our knowledge the first reported follow-up study of methanol poisoned patients. *Method:* Surviving victims from the outbreak six years ago were contacted, and invited to an interview and clinical evaluation by an ophthalmologist and physician. The patients that failed to respond were searched for in the Estonian Register of Population. *Results:* During the outbreak in 2001, 86/111 hospitalized survived: of those, 66 survived without sequelae (Group I) and 20 with sequelae (Group II). Six years later, 27 (31%) of these 86 patients was tracked and examined, 26 (30%) were dead, and 33 (38%) were lost to follow-up: 22/66 of the patients in Group I, and 5/20 in Group II were found and examined: 4/5 of the examined patients had visual disturbances at discharge six years earlier; and this was still present in all of them. Among the 26 dead, 19 were from Group I, and seven were from Group II. Alcohol intoxication was the most frequent cause of death (7/26). Few patients drinking alcohol on a regular basis reduced their drinking habits after the incident. *Conclusion:* Methanol poisoning has a high mortality and morbidity: In this study, all four patients who were discharged with visual disturbances still had impairments six years later, suggesting that these is irreversible damage. 7/20 (35%) and 19/66 (29%) of the patients discharged with or without sequelae, respectively, were dead five years later (no significant difference between the groups). The most frequent reason for death during these six years was alcohol intoxication. The methanol poisoning six years earlier therefore did not seem to change their drinking habits. *Reference:* 1. Paasma R, Hovda KE, Tikkerberi A, *et al.* Methanol mass poisoning in Estonia: Outbreak in 154 patients. *Clin Toxicol* 2007; **45**: 152–157.

111. Benzodiazepines – More than Just Sedatives

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Objective: Benzodiazepines are among the most widely used therapies in poisoned patients. Their sedative properties are invaluable in the treatment of patients with agitated delirium that results from a broad variety of poisonings such as sympathomimetics, anticholinergics and hallucinogens. Additionally, because of a wide therapeutic index and minimal cost, benzodiazepines have become the mainstay of therapy in patients with alcohol and sedative hypnotic withdrawal. Moreover, because of their ability to rapidly terminate seizures, benzodiazepines have gained acceptance as the first-line anticonvulsant in virtually any poison-related seizure. All of these benefits can be attributed to well-described interactions between benzodiazepines and the GABAA chloride channel resulting in hyperpolarization and sedation. The purpose of this presentation is to review other possible benefits of benzodiazepines and suggest a different mechanism of action that may act in concert with GABA-related sedative effects. *Methods:* Review of existing literature *Results:* Two clinical scenarios suggest additional effects of benzodiazepines. Chloroquine poisoning is associated with seizures, dysrhythmias and cardiovascular collapse. Recommended therapy consists of early endotracheal intubation, epinephrine and high-dose benzodiazepines. This therapy is supported by experimental evidence where benzodiazepines alone protected pigs against chloroquine-induced cardiovascular toxicity. Under anesthesia, which would prevent either agitation or seizures, chloroquine produced hypotension and QRS widening that was reversed with diazepam (1). Corroborative evidence can be found in studies using rats and dogs, and in a clinical case series in humans (2,3). Similarly, patients who use cocaine often present with chest pain that is suggestive of myocardial ischemia and infarction. At the time of their presentation, most patients lack the typical findings of a sympathomimetic toxic syndrome. Despite the absence of psychomotor agitation, diazepam was at least as effective as nitroglycerin in relieving chest pain in two blinded and controlled human trials (4,5). These non-sedative, beneficial effects of benzodiazepines could result from their interaction with what are commonly referred to as "peripheral benzodiazepine receptors" (PBRs). The term "peripheral benzodiazepine receptors" was originally used in the 1970s to describe high affinity binding sites for benzodiazepines that were found outside of the central nervous system. Because this receptor demonstrates high affinity binding for compounds that are structurally dissimilar to benzodiazepines and can also be found on microglia of the central nervous system, the term PBR is now considered to be archaic. Currently the proposed name for this receptor is "translocator protein (18 kDa)", although PBR will still be used for this discussion (6). The PBR complex is a heterotrimer that is composed of an isoquinoline binding protein (which is the actual 18 kDa receptor), a voltage-dependent anion channel (VDAC); and an adenine nucleotide transporter (ANT) (7). PBRs are highly conserved in nature and found in many tissues, especially the brain, heart, kidney as well as diffusely in mitochondria. In mitochondria, the PBR is linked to the mitochondrial permeability transition pore (PTP). When opened, the PTP destroys the electrochemical gradient that is essential for mitochondrial function leading to swelling and the subsequent release of apoptogenic factors. PBR ligands such as 4-chlorodiazepam (CDZ) protect mitochondria from ischemic injury and limit the size of myocardial infarction following coronary artery ligation (8,9). In cardiac tissue, the PBR is linked to a voltage-dependent calcium channel (7). PBR ligands alter cardiac conduction and contraction. Finally, in various tissues, the PBR is linked to steroid synthesis that might modulate stress responses. *Conclusion:* In summary, it is possible that the beneficial effects of benzodiazepines in a variety of toxic and non-toxic stresses result not only from sedation, but from protection against oxidative and ischemic injury and myocardial dysfunction. The use of non-benzodiazepine PBR ligands should be studied in models of poisoning such as chloroquine and cocaine. *References:* 1. Riou B. Protective cardiovascular effects of diazepam in experimental acute chloroquine poisoning. *Intens Care Med* 1988; **14**: 610–6. 2. Riou B. Treatment of severe chloroquine poisoning. 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112. Antidote Supply and Stocking Issues

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Objective: The evidence demonstrating the toll of medication errors has grown inexorably. Most studies of medication errors focus on acts of commission, where the wrong drug or the wrong dose is administered. A relatively unrecognized problem is an act of omission; for example, the lack of an antidote to treat a poisoned patient. To be useful, an antidote must be available within an appropriate time period, stocked in adequate amounts, and the health care provider must recognize the need for it. Poison centers and toxicologists often encounter the issue of lack of antidote availability. Why should poison centers and toxicologists care about this issue? For many poisons, an antidote must be administered promptly to prevent injury. Time is Tissue. For example, delayed administration of crotaline snake antivenom allows local injury to worsen. In the case of elapid snakes, delayed administration of antivenom may allow irreversible paralysis to develop. Adverse effects of delayed pyridoxine administration have been reported. *Results:* At least 18 studies over the past 25 years have documented the lack of antidote availability around the world. Most research has focused on the lack of availability due to antidote nonstocking. While naloxone is stocked reliably in nearly all hospitals, insufficient stocking has been shown to exceed 50% for antidotes such as cyanide antidotes and digoxin immune Fab. Factors associated with poor stocking of antidotes include small hospital size, rare use of antidotes by the facility, lack of a formal review process for antidotes, and cost, among others. One method of guiding clinical practice is the consensus guideline. A combined evidence-based review of the existing literature with a modified Delphi consensus method to create guidelines for hospital stocking of emergency antidotes in the United States was developed. It has been distributed widely, but its impact on antidote stocking is unclear. More recent consensus recommendations are being developed currently. Another potential solution is regulatory intervention to require hospitals to stock appropriate antidotes for their service area. Even when antidotes are available, practitioners may not realize they are available. To address this issue, some facilities have created charts listing antidotes and their location within that hospital while others have created a special area in the pharmacy specifically for the stocking of antidotes and still others have created a poisoning cart similar to a code cart. It is recommended that each facility ensure that the place of storage, as well as the amount of each antidote stocked, is known and immediately accessible to all hospital personnel providing patient care. *Conclusion:* Renewed efforts are needed to document the toll of antidote nonstocking and mechanisms to correct the problem. *References:* 1. Burda AM, Sigg T, Haque D, *et al*. Inadequate pyridoxine stock and its effect on patient outcome. *Am J Ther* 2007; **14**: 262–264. 2. Aguilar Salmeron R, Soy Muner D, Nogue Xarau S. [Antidotes availability in health services of Catalonia, Spain]. *Medicina Clinica* 2006; **127**: 770–773. 3. Wiens MO, Zed PJ, Lepik KJ, *et al*. Adequacy of antidote stocking in British Columbia hospitals: the 2005 Antidote Stocking Study. *Can J Emerg Med Care* 2006; **8**: 409–416. 4. Locatelli C, Petrolini V, Lonati D, *et al*. [Antidotes availability in Emergency Departments of the Italian National Health System and development of a national data-bank on antidotes]. [Italian] *Annali Dell'Istituto Superiore di Sanita* 2006; **42**: 298–309. 5. Bailey B, Bussieres JF, Dumont M. Availability of antidotes in Quebec hospitals before and after dissemination of guidelines. *Am J Health-System Pharmacy* 2003; **60**: 2345–2349. 6. Solheim L, Andrew E, Jacobsen D. [Antidote availability in Norway]. [Norwegian] *Tidsskrift for Den Norske Laegeforening* 2002; **122**: 1111–1113. 7. Juurlink DN, McGuigan MA, Paton TW, *et al*. Availability of antidotes at acute care hospitals in Ontario. *Can Med Assoc J* 2001; **165**: 27–30. 8. Plataki M, Anatoliotakis N, Tzanakis N, *et al*. Availability of antidotes in hospital pharmacies in Greece. *Vet Human Toxicol* 2001; **43**: 103–105. 9. Ong HC, Yang CC, Deng JF. Inadequate stocking of antidotes in Taiwan: is it a serious problem? *J Toxicol Clin Toxicol* 2000; **38**: 21–28. 10. Dart RC, Stark Y, Fulton B, et al. Insufficient stocking of poisoning antidotes in hospital pharmacies. *JAMA* 1996; **276**: 1508–1510. 11. Krenzelok EP, Drake T, Dean BS. The poison center as a reservoir for antidotes for veterinary poisoning emergencies. *Vet Human Toxicol* 1992; **34**: 168–169.

113. Antidotes for Mass Alcohol Poisoning

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The typical feature of a mass outbreak of a poisoning is that it overwhelms the available resources and number of beds, and in particular the ICU capacity. Triage in these situations is important and should be based on an easy and fast diagnostic approach, evaluation of the prognostic features for priority levels, and treatment initiated as early as possible. Methanol poisoning is one of the most common toxicants in mass poisoning, and in spite of modern diagnostics and treatment, morbidity and mortality remains high. Major pitfalls causing this are late diagnosis and late initiation of treatment. Obtaining diagnosis is often difficult, and even when the diagnosis is established, there may be difficulties in getting hold of the necessary buffer, antidote, and hemodialysis equipment: The outbreaks of mass alcohol poisonings often occurs in poor countries or rural areas, and even if the diagnosis is established, the availability of antidotes, especially fomepizole, is often limited (1). Bureaucracy has also been an obstacle in some situations, where days can be lost before the transport of the necessary antidotes is allowed to pass the borders. The established treatment includes the use of antidote (2), and fomepizole is generally considered the antidote of

choice (3). Fomepizole is expensive itself, but has several advantages over ethanol: It binds 500–1000 times more strongly to the alcohol dehydrogenase enzyme than does ethanol, hence it is more efficient. The dosing is easy; one iv or po dose every 12 hrs is sufficient (every 4 hrs during hemodialysis), and unlike ethanol, no S-monitoring is necessary. The patients are sober; hence treatment is clearly simpler from a treating and nursing perspective. Fomepizole is not CNS-depressive, and can imply an important reduced need for ICU beds. Hemodialysis can also in many cases be postponed or avoided (4), and patients can safely be transported to dialysis facilities. Therefore, the cost-benefit analysis should also account for the reduced need for ICU, and the potential for changing triage because of the new dialysis indications (4). Distribution of fomepizole to countries with fewer resources has already been suggested and also tried, but given that the outbreaks have already occurred, it has certain obstacles: 1) Getting hold of sufficient amounts of antidote including funding for such takes time, but time is the limiting factor for improving the prognosis. 2) Bureaucracy can make it a very time consuming effort to get the antidotes through the customs at the borders. Therefore, a satellite distribution of antidote worldwide will have several benefits: Fomepizole has a relatively limited shelf-life, hence central stockpiling will be economically beneficial; the physical distance of transporting the antidote will be shorter, and will eventually save valuable time; having stocks available will potentially increase knowledge on the use of the antidote, but also the general treatment of these poisonings; establishing contacts with the different governments in advance will determine where the bureaucratic process will be an obstacle, and subsequently hopefully open a gateway to the countries before the outbreaks are a fact; each stock should preferably be administrated by a poison control center or a hospital, and not by a politically run administration. They should also contribute with a locally adapted triage for the handling of such an incident, and a short turn-around time for distribution of the antidote; Infrastructure varies, and should be adapted to each region: Private and governmental airplanes, the military or similar, should be implemented in such a plan; The same stockpiles can also be used for other types of antidotes, as well as medicines and equipment for epidemics or disasters; stockpiles of ethanol should also be considered in conjunction with the fomepizole stores: For the less severely poisoned patients and in the lack of availability, ethanol will potentially save the fomepizole for the ones who are in most need. This will in turn make the antidote stores last longer; the economic aspect should be considered a joint effort from the developed world, suggesting that the producers of antidotes will make a distinction in price for these markets, compared with the rest; key players should be global organizations such as WHO and PAHO, the toxicological associations in each continent, the antidote producers, and potential external fundraisers. *Conclusion:* Mass outbreaks of poisonings are situations where resources are often overwhelmed, and time and triage plays an important role. Satellite stockpiling of antidotes can help overcome many of the difficulties for the developing countries where mass poisonings most often appear: availability increases, bureaucratic obstacles may be solved in advance, and the use of infrastructure can be optimized. Finally, this is the most cost-beneficial way to distribute fomepizole in areas where the local health care systems are unable to deal with the costs of purchase. *References:* 1. Paasma R, Hovda KE, Tikkerberi A, *et al*. Methanol mass poisoning in Estonia: Outbreak in 154 patients. *Clin Toxicol* 2007; **45**: 152–157. 2. Jacobsen D, McMartin KE. Antidotes for methanol and ethylene glycol poisoning. *J Toxicol Clin Toxicol* 1997; **35**: 127–143. 3. Brent J, McMartin K, Phillips S, *et al*. Fomepizole for the treatment of methanol poisoning. *N Engl J Med* 2001; **344**: 424–429. 4. Hovda KE, Froyshov S, Gudmundsdottir H, *et al*. Fomepizole may change the indication for HD in methanol poisoning: Prospective study in 7 cases. *Clin Nephrol* 2005; **64**: 190–197.

114. Comparison of Silibinin Monotherapy with Combination Therapy of Silibinin and Penicillin in Amatoxin Poisoning in 388 Patients

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Objective: The current concept in the treatment of amatoxin poisoning includes the administration of silibinin and penicillin singly or in combination. The aim of the following study is to compare silibinin monotherapy with the combination of silibinin and penicillin in the treatment of amatoxin poisoning. *Methods:* Data from 604 patients with the diagnosis of amatoxin poisoning treated from 1957 to 2005 were retrospectively collected. 216 patients were excluded due to incomplete data or treatment which did not use silibinin. Of the remaining 388 patients 258 received silibinin in combination with penicillin and 130 patients obtained silibinin alone. For statistical analyses univariate comparisons of event rates between patient groups were performed using Fisher's exact test. *Results:* Of the 258 patients who received the combination of silibinin and penicillin 21 patients died and 1 patient obtained liver transplantation; of the 130 patients, who received silibinin alone 1 patient died and 5 patients were transplanted. This implies that in the combination therapy group the proportion of patients who died or received liver transplantation was nearly twice as high as in the monotherapy group: combination therapy 8.53% [90%CI 5.84–11.95] versus monotherapy 4.62% [90%CI 2.03–8.91]. The p value of this comparison (0.21) does not prove superiority of monotherapy, however inferiority of monotherapy can be excluded based on a 0.5% equivalence level, since the difference between the upper limit of 90% CI in the monotherapy group (8.91) and the expected value in the combination therapy (8.53%) is 0.4%. *Conclusion:* In amatoxin poisoning the monotherapy with silibinin is not inferior to the combination with silibinin and penicillin suggesting that the additional application of penicillin with its potential side effects should be avoided.

115. New Approaches in Therapy of Poisoning with Organophosphorus Compounds

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Poisoning by organophosphorus compounds (OP) is a challenge to clinical toxicologists. While the group of pesticides exhibit usually moderate toxicity, the group of nerve agents belongs to synthetic compounds with the highest toxic potency. The most important common mechanism of OP-poisoning is the inhibition of acetylcholinesterase (AChE) resulting in cholinergic crisis and finally death due to respiratory arrest. Besides routine supportive care, e.g. artificial ventilation, restoration of cardiovascular insufficiency, fluid and electrolyte balance (e.g. sodium bicarbonate administration), specific antidotes, antimuscarinics and oximes, are available. Furthermore, neuroprotectives such as benzodiazepines are required to cope with seizures and long-lasting brain damage in nerve agent poisoning. Consensus regards atropine as the cornerstone in the treatment of OP-poisoning. The drug is able to antagonize competitively acetylcholine at muscarine receptors. Generally, titration according to clinical effects is recommended. The use of oximes, however, is a matter of debate and subject of extensive investigations. Both potency and efficacy of oximes to induce reactivation of AChE is dependent on both the specific OP-compound and the oxime. In general, AChE inhibited by the most widely used pesticides can be reactivated with the clinically used oximes pralidoxime and obidoxime with the latter generally needing lower concentrations for a comparable rate of reactivation. In recent years, substantial research in civilian organisations was directed at appropriate administration protocols. Oximes should be given continuously, at appropriate doses and as long as reactivation can be expected. However, the clinically used oximes reach their limits in poisoning by most nerve agents, e.g. VR, cyclosarin, tabun and soman, as well as with some pesticides, e.g. fenamiphos. Due to these gaps, extensive research programs have been initiated over the last decades and are still ongoing to identify more effective oximes. First of all, the main scope was directed at reactivation of soman-inhibited AChE. Meanwhile, broad spectrum oximes, with special regard to nerve agents, are in the focus. Among some possible candidates, e.g. MMB 4 and TMB 4, the two Hagedorn oximes HI 6 and HLö 7 are regarded as promising compounds. In the meantime, substantial data on HI 6 safety and efficacy are available enabling military services of several countries to aim for licensing of HI 6 autoinjectors. Unfortunately, HI 6 is quite ineffective in reactivation of AChE inhibited by most pesticides and tabun. Alternative strategies, primarily supported by military forces, were developed. The pre-inhibition of AChE by carbamates was shown to be effective in several animal models up to some 5 LD_{50} of nerve agents. At present, pyridostigmine is licensed by the FDA for pre-treatment of soman poisoning. In Europe, a patch containing the centrally acting physostimine/hyoscyamine is under advanced development. Another, also primarily military approach, is the pre-treatment with scavengers in order to neutralize the nerve agent before it reaches its target. Since the eighties in the last century a variety of proteins, e.g. human carboxylesterase, fetal bovine serum derived acetylcholinesterase, and human butyrylcholinesterase (HuBuChe), have been under investigation. Plasma derived and recombinant forms of HuBuChE were selected for advanced development and transition to clinical trials. These scavengers bind OP stoichiometrically. The prerequisite of sufficient scavenging function is high affinity and a low poison load. Since BuChE has a high molecular weight (about 86 kDa) a comparatively large quantity is required to neutralize an equimolar amount of nerve agent. Therapeutic effectiveness in suicidal pesticide poisoning cannot be expected. The scavenging capacity of native human blood BuChE (36 pmol/ml) and AChE (3 pmol/ml blood) does not play any role in pesticide poisoning where several mmol of OP are ingested. However, the detoxification rate may be increased dramatically when a combination of AChE and oxime is used. For rapid detoxification A-esterases, such as paraoxonase type 1 (PON1) are under investigation. The velocity of the naturally occurring human serum enzyme appears to be too slow to afford significant protection. Thus, efforts are directed to modification of the active centre by site directed mutations in order to improve catalytic properties. Stability as well as stereoselectivity of these enzymes are a matter of fundamental research. The same holds true for AChE. Using comparable techniques, a more detailed knowledge of the relevant reactions at a molecular level should be attained and contribute to developing a scavenger that in combination with a nucleophile, e.g. an oxime, could provide rapid and broad spectrum detoxification. Other experimental studies are directed to interfering with different receptor systems potentially involved in OP poisoning, e.g. adenosine receptors or nicotine receptors. Furthermore, so called direct effects of high oxime concentrations were assumed to contribute to their effectiveness in animal experiments. However, these basic experimental approaches are not yet relevant for broad clinical use.

116. On-Line Poisons Information Sources for Medical Professionals (Sweden)

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Objective: The Swedish Poisons Information Centre web page designed for the public - www.giftinformation.se – will be discussed elsewhere in this meeting. In 2006 the centre released an additional on-line poisons information service, intended solely for use by medical professionals – www.giftinfo.se (password: intox). This presentation will discuss background, relevance, contents, design, use, future and costs of this new information source. *Background:* There is an increasing tendency to look for information of all kinds on the Internet. As for poisonings, information retrieved that way is not always well validated, nor suited for local conditions and treatment traditions. Therefore, the poisons centre decided to create a practical, user-friendly on-line information source, designed for medical professionals. *Methods:* A document structure was developed with the ambition to make the information easy to grasp. Headings of the sections are: Summary/characteristics; Symptoms/signs; Analyses/clinical investigations; Monitoring/treatment; Toxicity/concentrations; Occurrence/names. The documents are kept short and concise, in most cases 1–2 pages in total. For antidotes and other important medication exact doses are given. Whenever uncertainties about treatment may arise, the reader is encouraged, through a standard phrase, to contact the poisons centre. Around 200 substances - pharmaceuticals, chemicals and natural toxins - were selected for inclusion as a first step. Inclusion was based on incidence or severity of the poisonings - common, less toxic agents e.g. benzodiazepines and NSAIDs, as well as rare but nasty ones such as amatoxins and mercury were included. A continuous input is planned. The physicians of the centre wrote the documents individually, whereupon they were subject to peer review by a group of three physicians. The documents were then also scrutinized by a pharmacist. Soft-ware was developed by an IT-consultant in close collaboration with the physicians involved. The basis for compiling the documents is the substance monographs of the poisons centre, and up-dating is co-ordinated with the regular up-dating process of the centre. Changes can be made instantly in the documents. Costs for initial technical support were SEK 160,000 (≈ € 18,000) and costs for running the system are around SEK 10,000 (≈ € 1,100) annually. The cost for the writing the documents has not been calculated. *Results:* Time from start until release of the database was around one year. It was made available on the Internet in May 2006. Information was given through letters sent to all emergency hospitals in Sweden and through one of the medical journals. The physicians made site visits to a number of hospitals to demonstrate the data-base, and it was displayed at the annual meeting of the Swedish Society of Medicine. The number of web-site hits has increased steadily since the start and amounted in September 2007 to 1621 visits during that month. This new tool for poisons information has been received with enthusiasm in Sweden and Scandinavia. The number of inquiries to the poisons centre from the public has decreased

slightly over the last few years, mainly because of changes in switchboard priorities. Instead, the number of calls from medical professionals has increased since the new database was introduced. *Conclusion:* The introduction of an on-line information source for the medical profession seems to be an adequate way of adapting to modern times. It is important, however, to do this in such a way that the direct contact between treating physicians and the poisons centre concerning complicated cases will not be replaced by a computer. In our experience, the computerized on-line information source will remain a useful complement to the telephone service and provide a basis for the treating physicians in discussing severe cases. Having said this, many cases might certainly be treated adequately guided by the "giftinfo" documents alone.

117. On-Line Poisons Information in New Zealand. Current Status and Future Challenges

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The New Zealand National Poisons Centre has developed its own Internet accessible poisons information database, TOXINZ (www.toxin.com). This resource currently contains information regarding some 164,000 chemicals, pharmaceuticals, plants and hazardous creatures (including synonyms). In New Zealand it is used by all major hospitals and currently accounts for 59.5% (44,729) of annual enquiries to the New Zealand National Poisons Centre, representing a penetrance of 10.9 per 1,000 population. The 'traditional' telephone system answers 40.5% (30,471) of enquiries.) Currently TOXINZ is available to overseas Poisons Information Centres and is utilised by some 33 Centres in 27 countries. Overall, this project has proven to be highly effective at delivering quality poisons information. However, we are now facing a series of challenges due to the popularity and size of the database, coupled with increasing user expectations. Due to the ever changing nature of medical – and particularly toxicology – information, there is a constant requirement to update treatment recommendations. With a small database it is reasonably easy to incorporate change on an ongoing basis. However, as a database grows it will reach a point where all available resources can be consumed by the requirement to maintain existing information – no new data can be added and the database will not continue to grow. Or, conversely, the information contained will not keep pace with change, and degrade. Another challenge is globalisation and associated: ever broadening international trade of chemical and pharmaceutical products, increasing range of trade-names, and international movement of hazardous plants and creatures. There is a mounting need to access accurate toxicology information describing these substances, poisons and venoms. Such realities are increasing the requirement for a truly international poisons information repository. Yet, such a database would be large and expensive, and would need some form of international co-operation. Furthermore, such a resource should preferably meet the requirements of a wide range of countries taking into account differing levels of funding, antidotes, and treatment methodologies. While TOXINZ has gone some way to address this need, such an initiative will need novel information technology solutions to be practicable and cost effective; and a methodology to fund such a project will need to be developed, coupled with a genuine international desire to contribute. While international co-operation is an appealing notion to most, there are fundamental hurdles to its practical application. Such are the future challenges of online poisons information.

118. On-Line Poisons Information Services in the Netherlands

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Introduction: The Dutch Poisons Information Centre (PIC) provides a 24-hour telephone information service for medical professionals. The number of calls to the centre has gradually increased by 3–5% per year in the past five years, to a total of 37,000 telephone calls in 2006. As a consequence, the necessary staff and thus the costs simultaneously increased. To comply with new government policy on reducing the costs of this service, an internet access to the toxicological information was developed. The resulting Vergiftigingen.info website allows medical professionals to perform a risk analysis of acute intoxications ('Vergiftigingen'), thereby (hopefully) reducing the number of routine telephone requests to the Dutch PIC. Via Vergiftigingen.info only medical professionals have access to our database, registration is required. The registered user has direct access to substance monographs. However, unique in this website is that a risk assessment is provided based on the calculated dose(s) of the toxic substance(s) involved. This results in a presentation of expected symptoms with their grade of seriousness (expressed as slight, moderate, serious) as well as the relevant diagnostic procedures to establish the diagnosis. The provided therapies are based on the seriousness of the intoxication. Because the internet user misses the guiding of the PIC information specialist during a telephone inquiry, special care was taken to present all necessary information in a structured and understandable way. First patient and product information has to be entered into the system and checked by the user. The user is also asked to notify if the present case is just for orientation or a real intoxication. In the next step, for each toxic substance, the user is informed on possible special patient conditions that should be taken into account when interpreting the symptoms provided by the website. Then, in the following step, the expected symptoms with their grade of seriousness are presented. Next, in a similar manner, suggested diagnostic procedures and possible therapies are presented. In the final step, extensive information of each toxic substance can be evaluated in a substance monograph. The internet user receives a report in pdf format of the analysed case by e-mail, with all the information provided by the system in this particular case. *Results:* In the first half year, around 8750 users registered themselves. In the first month there was a high registration rate of 280 a day. After a half year, this has declined to 11 a day. Seventy percent of the registrants have never used the telephone service of the PIC before. In the first half year, 6500 cases were registered. This occurred at a rate of 104 cases a day in the first month and dropped to 18 a day in the last month. In the beginning, users indicated they predominantly used Vergiftigingen.info for orientation purposes. In the last month the use for orientation equals the use for real intoxications. Recent analysis of the data gave some first insight into the profession of the users and the product information consulted. Vergiftigingen.info is most popular with hospital physicians, as they are responsible for 40% of the internet cases as compared to 25% of the telephone cases. In contrast, primary care physicians, responsible for 55% of the telephone cases, create only 25% of the internet cases. Pharmacists are responsible for another 16% of the internet cases and 2% of the telephone cases. Pharmacists clearly indicate that they use Vergiftigingen. info mostly for orientation purposes, whereas the hospital physicians mostly analyse real intoxications. The top three of the main product categories used is the same for the internet cases and the telephone cases: medicines, household and do-it-yourself products, and drugs and drinks. These products represent 90% of the internet cases (60%, 15%, 15% respectively) as compared to 73% of the telephone cases (47%, 17%, 9% respectively). *Discussion:* Vergiftigingen.info provides medical professionals with poisons information in a structured manner in order to rapidly perform a suitable risk assessment for the poisoned patient and to evaluate the treatment needed. Compared to other on-line poisons information services, like TOXBASE in the UK (1) and TOXINZ in New Zealand (2), this website provides the physicians with a risk assessment. Other internet tools provide the user with monographs of the substances present in the chosen products. Each substance monograph needs to be separately evaluated for the effects, diagnostics and therapy. Here, the user himself needs to combine this information to perform a risk assessment. It is too early to see an effect on the number of telephone calls that remained stable at around 100 calls per day in this first half year. The introduction of TOXBASE to the internet reduced, after a slow start, the number of telephone cases in the UK over a period of five years by more than half (1). Within 2 years TOXBASE was more accessed for poisons information than the telephone service. *Conclusion:* Although the use of Vergiftigingen.info has not yet stabilised, analysis of the results in the first half year after launching showed that primary care physicians seem to prefer the telephone service, whereas hospital physicians make more use of the internet service. *References:* 1. Bateman DN, Good AM. Five years of poisons information on the internet: the UK experience of TOXBASE. *Emerg Med J* 2006; **23**: 614–617. 2. Fountain, J. TOXINZ: internet poisons information database. *Clin Toxicol* 2005; **43**: 416–417.

119. TOXBASE - Advantages and Challenges of an On-Line Poisons Database

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Background: TOXBASE, the on-line poisons database of the UK National Poisons Information Service (NPIS), began in 1983 with a few Scottish users and spread to 500 UK National Health Service (NHS) users by the mid 1990s. Changes were then required due to: UK NHS requiring uniform cost-effective provision of poisons information within limited budgets; the European working time directive limiting on-call time for doctors; the Internet becoming the usual method of on-line access to information; and new Public Health Information lines being introduced. TOXBASE transferred to the Internet in 1999. Rapid expansion occurred with >6000 hospital departments and other units now registered, UK and worldwide. Since 2000 the number of telephone enquiries/year to the NPIS has decreased from almost 250,000 to 57,000 while the number of TOXBASE sessions increased from 102,500 to 443,000 (1,2,3). Those referred are often more complex. The database currently uses custom written software based on Access. It is being transferred to a system using Episerver. There are two commercial servers with separate IP addresses on separate sites for resilience. *Funding:* Originally funding came from the UK Departments of Health. This was recently transferred to the Health Protection Agency in England, which collects a contribution from Scotland and Wales. A small amount of funding comes from subscription sales and contracts with national governments. Annual running costs include server hosting and maintenance and staff costs. Regular updating of software is required to take advantage of developments in technology. *Coverage:* TOXBASE is provided free to UK NHS users and European poisons centres. Pharmaceutical companies, non-European poisons centres and overseas hospitals pay an annual fee. A contract with the Republic of Ireland is in place which provides TOXBASE to Irish Emergency department users and adds Irish products to the database. Unlike most countries the UK NPIS only provides information to medical professionals. In the early days the main users of TOXBASE were Emergency departments. The new Public Health Information lines, staffed by specially trained nurse advisors, use TOXBASE to answer poisons enquiries for the public. TOXBASE is being modified to provide them with simple advice for triage. In 2006–7 the main users were hospitals (68%), Public Health Information lines (27%), others (5%; ambulance services, emergency chemical services, primary care) (1). Currently TOXBASE takes more than 1 million hits/year on product information (1). Content: There are about 14,000 product monographs, including pharmaceuticals (both generic and tradenames), chemicals (household, agricultural and industrial), plants and animals. The market for household products is particularly changeable and it is a challenge to keep the database up to date. Often minor differences in formulation or name occur and this is dealt with by having generic entries for particular types of household product. Monographs do not attempt to include all information on a particular product. The information is aimed at poisons centre staff answering poisons enquiries, emergency department staff dealing with immediate care of the patient and primary care and public information access service staff deciding on whether the patient needs to go to hospital. Each monograph includes the type of product, ingredients, toxicity (often with a treatment dose in mg/kg), features after poisoning and treatment. Clear, direct, accurate, concise, clinically relevant information in an easily understood and accessible form is what is required. There is a standard framework for output with printable advice summaries for case notes and a user response service. A poisons database does not need to be large to be useful. Ideally every product should be included but this is not practicable. In the UK one monograph (paracetamol) would answer 9% of TOXBASE enquiries, 10 monographs would answer 22%, 100 51 % and 1000 91%. The information requirement rises exponentially. TOXBASE hosts monographs from the National Teratology Information Service in Newcastle to provide information on drugs and chemicals in pregnancy. TOXBASE also acts as a store for documents for expert users, monographs in preparation for review, and national rotas and operating policies for the NPIS, available only to NPIS users. Peer review: There is a clinical governance structure in place. Monographs are written by staff (scientists and clinicians) of the NPIS or other involved centres and are reviewed by all NPIS units under a structured review scheme. This is backed by an HPA/NPIS TOXBASE group which meets 3 times a year to discuss policy and the Clinical Standards group of the NPIS (directors). These ensure the use of agreed and prioritised therapies and drive agreed national guidelines. Entries include the evidence base and references and a simple consistent structure and navigation is used. User group feedback is encouraged. Users can comment by e-mail if they have problems with an entry or have a suggestion for an addition. Problems are dealt with immediately if urgent or at weekly TOXBASE meetings in Edinburgh if non-urgent. A NPIS stakeholder meeting is to be held in January 2008. Future plans: It is intended to move to a 4 year rolling review of all entries. Planned improvements include output tailored to the type of user e.g. public information, particularly for non-toxic substances with general advice; simple triage information for primary care and public access services; more in depth information for emergency departments and intensive care units. There is

already an alerting system for pesticides as part of a project to improve the reporting of pesticide related incidents. A pilot project has been carried out for some chemicals, particularly those that might be used in terrorist attacks. Web based TOXBASE training is already available and a toxicology module is being added. *Conclusions:* On-line poisons information can reduce the need for telephone enquiries. Maintenance of a large poisons database requires intensive effort to keep it current. Usage rates indicate high user satisfaction. 1. National Poisons Information Service Annual report 2006–7 http://www.hpa.org.uk/publications/PublicationDisplay.asp?PublicationID=103 2. Bateman DN, Good AM, Kelly CA, Laing WJ. Delivery of poisons information to health professionals: telephone or internet? The Scottish experience. *J Toxicol Clin Toxicol* 2002; **40**: 567–9. 3. Bateman DN, Good AM. Five years of poisons information on the internet: the UK experience of TOXBASE. *Emerg Med J* 2006; **23**: 614–7.

120. Propagation of Evidence: Wikitox, Internet Based Opensource Curriculum in Clinical Toxicology

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Background: Evidenced based clinical practice of toxicology has been hampered by the boutique nature of the speciality and consequent lack of general advocacy. Propagation of expert opinion with well constructed position statements generally published in difficult to access journals are poorly cited. Even if incorporated into policy such guidelines often fail to alter clinical practices especially in the developing world. We sought to assess a novel approach to propagate existing information. *Methods:* In August 2006 we initiated an opensource toxicology curriculum project (www.wikitox.org). The basic principle is that clinicians could use the site as a repository to donate existing or new teaching material (such as Powerpoint presentations) which can be used by other clinicians. The site is open to all and can be edited easily online by any registered user. Contributors are encouraged to use material already created, examples include EAPCCT lectures. This material is supported by monographs. The purpose of the wiki is to provide a free resource for selfstudy and teachers. This source can be utilised online or offline. An offline version is distributed by widernet.org to Africa. The content is also being used to support a Masters distance learning course. *Results:* The wiki was examined for the number and type of contributions. Despite an inital core group of 20 people 95% of the contributions came from 3 people. Another 8 people donated extensive material indirectly through a project officer but without any direct editing of the wiki site. 469 pages were created and 258 files with teaching material uploaded. Topic areas of pharmaceutical and agrochemical poisoning were most extensively covered. Usage had increased dramatically from June 2007 with a large increase in visitors from 5 per day to over 75 per day from more than 109 countries. 13.8% of pages viewed were for educational resources, the remainder were for toxicology monographs. *Conclusion:* Clinical toxicology's underdeveloped evidence base is one of the most compelling reasons for toxicologists to promote and facilitate education. A wiki has the potential to provide teaching tools at low cost but requires expanded involvement.

121. Norwegian Poisons Information Centre - Information Distributed Through the Norwegian Electronic Health Library

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Objective: To introduce the Norwegian Electronic Health Library (NEHL) web site as the distribution channel for information from the Norwegian Poisons Information Centre (NPIC) to health care professionals, as a topic library on toxicology. Contents of the topic library and synergism by choosing NEHL for the publishing are pointed out. *Methods:* NPIC wanted to establish an electronic information channel towards health care professionals. NEHL was chosen mainly because it was assumed to reach the main target group. In addition it had suitable content and planned content and established technical solutions. In 2006 collaboration with NEHL through planning and development of the topic library on toxicology started. *Results:* NEHL's vision is to improve health care quality by providing free access for health personnel to useful and reliable knowledge. The NEHL web site was launched in June 2006. It is owned by the Directorate for Health and Social Affairs and the Regional Health Authorities and hosted by the Norwegian Knowledge Centre for the Health Services. NPIC is organized as a department within the Directorate for Health and Social Affairs. The topic library on toxicology was launched in 2007 and mainly consists of treatment guidelines for acute intoxications. Earlier this information was distributed as written documents, and on need faxed or e-mailed to treating physicians. The topic library guidelines include more than 100 different toxic agents/groups of agents, as well as general information on antidotes and methods for elimination. In addition, the topic library includes actualities on toxicology, relevant literature and journals extracted from the resources provided by NEHL. Examples of resources (free): Evidence based reviews, national and local guidelines, patient information, > 1500 medical journals (BMJ, JAMA, Annals of Internal Medicine, The New England Journal of Medicine, The Lancet etc.), bibliographic databases, PubMed, Clinical Evidence, Cochrane Library, EMBASE, MEDLINE, CINAHL, links to open access resources and important national medical resources. *Conclusion:* NEHL is increasingly used by health care professionals. Gains for NPIC: updated information always available, quality assessed information/guidelines, free resources, several other topic libraries available or in progress: mental health, public health, pharmaceuticals, cancer. *Reference:* www.helsebiblioteket.no (the NEHL web page).

122. On-Line Poison Information in the United States

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Background: The first United States poison center (PC) opened in Chicago, IL in 1953. A standardized poison information system for PCs did not exist. In 1974, Micromedex (Thomson Healthcare, Denver, CO, USA) launched Poisindex® a microfiche based system for poison centers. The system consists of continuously updated pharmaceutical and non-pharmaceutical product index and medical toxicological managements targeted to the active product ingredients. Now CD-ROM and internet based, all 61 US PCs use this system which interfaces directly with their local computer data entry software and provides a common upload to the US National Poison Data System (NPDS). Uploads of cases from poison centers occur continuously and allow for near real-time surveillance with alerts sent to a 24 hour monitoring team. Because of the detailed coding, data can also be examined for any combination of time period, location, region, or product. The AAPCC database (NPDS) documents over 2.4 million exposures and over 1.5 million information calls annually as published in the AAPCC Annual Report. *Objective:* Characterize the features of the US on-line poison information system. *Methods:* PCs respond daily to a variety of questions from the public and health care professionals. Poisindex® lists over 350,000 pharmaceutical and non-pharmaceutical products. All are identified by a unique product identification number and are categorized into one of 922 American Association of Poison Control Centers (AAPCC) generic codes. Product information is obtained directly from the manufacturers using either the Material Safety Data Sheet (MSDS) in the case of non-pharmaceutical products or the Package Insert (PI) for drugs. Product information includes: active ingredients, excipients, form, packaging, company contact information and in some cases inert ingredients. Product information also includes US EPA regulatory numbers, NDC codes, and Chemical Abstract Service (CAS) numbers. This data allows for the precise linking of one or more clinical toxicology managements to each product. Toxicology managements are written by in-house medical and clinical toxicologists with review by external toxicologists. This process insures accurate up-to date information. With the advent of the personal computer, the data system was transitioned to a CD-ROM format. In the last several years, the system has transitioned to the internet. This allows for weekly system updates. Managements and products can be entered weekly and provides the infrastructure for new or products associated with public health events to be added in a day. *Discussion:* Paramount to the provision of accurate management of PC calls is the correct identification of the products involved in the exposures. Poisindex® allows for near real-time product and toxicological treatment information entry. Future possible enhancements include: user independent notification of products not in the system, automated product information feeds to permit the system to have all licensed pesticides and updates as soon as they are released, and date time stamping of information access, and enhanced auto-population of PC case records. The products database also provides the foundation to aid global harmonization for diverse regulatory codes and reporting as it contains a wide variety of identifiers and synonyms. Since this product and management information is available electronically to PCs, centers can assist industry and regulatory agencies in post marketing surveillance; work in collaboration for new product launches, and assist with events of public health significance. Rapid trending and identification of unexpected outcomes of exposures to new or existing products helps minimize risk and liability and improve the public health. *Conclusion:* Data collection and product surveillance are core competencies of PCs. NPDS, operated by the AAPCC allows US PCs to have rapid access to exposure management and product data. Through this system, Poisindex® can work with manufacturers to provide accurate, timely product information that also permits companies to support their product stewardship functions. The Poisindex® - poison center relationship is a unique example of a public private partnership that works.

123. Sleeping Beauty Disease – An Outbreak of a Neurological Illness of Unknown Aetiology in Luanda Province, Angola

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Case series: A crisis intervention team from WHO was called in by the Angolan Ministry of Health due to an outbreak of an acute neurological disease. Symptoms reported included drowsiness, weakness, ataxia and coma. Most of the patients were directed to the hospital of Cacuaco. Patients who had improved a little were sent home again. Food supply was brought from home to the hospital. Blood, urine and food samples were taken and send to Munich and London. Between October 18th and November 15th, 371 patients were admitted to Cacuaco hospital between 5 and 25 per day. The clinical examination in 30 patients showed the following: central nervous system depression with a GCS ranging from 7–14 points. Mostly children were severely affected, they woke up to painful stimuli but fell back asleep. Muscle tone was extremely weak. There were no signs of peripheral neuropathy. When patients had woken up they hardly could prop themselves up. They could not walk alone. They could not stand or hop on one leg. Blood pressure and heart rate were normal. Respiration rate was slightly decreased. It was impossible to spot the food responsible by cluster evaluation. It became clear that the symptoms observed fitted best with the uptake of an unknown GABA-ercig sedative. Drowsiness, ataxia, fatigue, hypotonic musculature, duration of coma seemed to be more pronounced than seen in benzodiazepine or GHB poisoning. Urine samples which were send to Munich didn't show any organic compounds in GC-MS. In four of the five blood samples bromide levels between 1002 mg/l and 2451 mg/l (normal – 50 mg/l) were measured. In 5 other samples similar results were affirmed by a second laboratory. Salt samples consisted of sodium bromide. *Conclusion:* A so far unknown mass poisoning is described. Modern analytical measurements failed to detect the origin. Clinical observation helped to make the right diagnosis of a disease that reminded us of the fairy tale of the sleeping beauty.

124. Bromo-Dragonfly, a Life Threatening Designer Drug

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Objective: The hallucinogenic drug Bromo-Dragonfly (BDF) is an amphetamine derivative first synthesized in the late 1990s. We report pronounced and previously unknown severe vasoconstrictor effects of this new dangerous drug of abuse. *Case 1:* A 20-year-old male drug addict ingested 5–6 blotters soaked with 0.5 mg BDF each. Initial hallucinogenic effects were experienced but two days later cyanosis of peripheral parts of the limbs ensued. Six days after using the drug he sought medical care presenting cyanotic, pulseless and aching extremities. Laboratory signs of rhabdomyolysis were recorded. Initial treatment with nifedipine had some beneficial effects but nitroglycerine was also needed to prevent tissue necrosis. The treatment could be terminated after another four days and the patient was discharged without sequelae. *Case 2:* A 34-year-old man bought BDF via the Internet and tested an undetermined dose together with a friend. Shortly afterwards both collapsed and the friend died instantly. After 17 hours the dazed survivor was found by his brother. At hospital the patient displayed severely impaired peripheral circulation and acute renal failure. No method of vasodilatation therapy, including nifedipine, captopril and sympathetic blockade with guanethidine, was particularly effective. Neither was infusion of nitroglycerine, nitroprusside and iloprost. After nine days the spasm abated but the patient lost several distal phalanges of his fingers. The presence of BDF in

the urine was confirmed. *Discussion:* At least one more person in Sweden and one in Norway have been found dead after using BDF. Laboratory analyses established the presence of BDF in both of these cases. This psychoactive substance which has exceptionally strong 5-HT2A agonistic properties is a hallucinogen with structural similarities to other phenethylamine derivatives. It apparently exercises a potent long lasting vasoconstrictor capacity, which possibly also affects the coronary arteries, hypothetically explaining the sudden deaths. The first Swedish reports of its use came during 2006, and up to October 2007 SPIC has been contacted regarding 22 different cases. In most patients symptoms such as anxiety, agitation, visual hallucinations, tachycardia and mydriasis dominated. *Conclusion:* BDF is a new extremely hazardous drug of abuse that can cause severe vasoconstriction leading to tissue necrosis or even sudden death.

125. Withdrawn

126. Causality Assessment in Poisoning: An Essential Part of Data Quality

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As long as prospective randomized and controlled trials are not available for many aspects in clinical toxicology, Poisons Centre data remain an important and sometimes unique source of information on human poisoning, particularly with rare toxins. It is therefore an obligation of clinical toxicologists in Poisons Centres to collect data on such cases accurately, carefully, and as completely as possible. Data must be accurate if they are reported, published or used in epidemiology (e.g. to estimate the prior probability in the Bayesian approach of the diagnostic process (1)). As in the assessment of adverse drug reactions (ADR), the establishment of a causal relationship between exposure and clinical effects is crucial also in poisoning. The accuracy of the information on exposure and on clinical symptoms/findings must be known in order to be able to evaluate the case data appropriately. In Poisons Centres most clinical information is not at first hand because it is collected via the telephone. Moreover, exposure information is invariably taken from the patient history and therefore never proven. When using human data from Poisons Centres for risk assessment in acute toxicity, for toxicovigilance, and for data exchange, a quantitative measure of the accuracy of the data enhances data quality considerably. The situation is similar to the spontaneous reporting of adverse drug reactions in pharmacovigilance. Guidelines and rules for the evaluation of ADR have been set up in the 1970s and 1980s (2–6). Bayesian-based and algorithm-based systems are used. Criteria for the causality assessment in algorithm-based systems are chronology (temporality), symptomatology, contributing factors and differential diagnoses (exclusivity), and the consequences of dechallenge-rechallenge. Most of these systems are highly specific but have a relatively low sensitivity. The concordance between such systems is generally poor (7), and the inter-rater variability is high if no guidelines are applied. To increase reproducibility of these processes they have to follow a harmonized and standardized protocol (8) which decreases ambiguity of the data, facilitates data exchange, and prevents erroneous conclusions by following, at least in part, the viewpoints on causation by A.B. Hill (9). The assessment of causality in acute poisoning may be similar but not identical to that in ADR. There are important differences in the clinical setting between poisoning and ADR: Rechallenge is ethically not feasible. In addition, the setting of asymptomatic exposure does not exist in ADR but is frequent in toxic exposure, and, other than in the assessment of poisoning, it is always assumed in ADR that exposure has taken place. And finally the history of exposure is more difficult to obtain in poisoning than in ADR due to frequently altered mental status. Therefore, if a system similar to that in ADR reporting should be used, modifications are needed. Here, a dual system is proposed consisting of an assessment of the likelihood of exposure, and a causality assessment (causal relationship between exposure and clinical effect). Likelihood of exposure can be graded into four levels: 1) confirmed exposure with analytical detection of a substance in body fluids or tissue, 2) likely exposure with reliable observation of exposure by bystanders, 3) reliable history taken from the patient, 4) possible exposure with indirect evidence of exposure, 5) unlikely exposure with no evidence of exposure, and 6) the exclusion of exposure by a negative analytical test. Causality can be graded into three levels: 1) likely (probable) causality with symptoms occurring in a timely fashion after exposure according to the pharmacokinetic properties of the substance in question and the underlying mechanism of action, typical (expected/described) symptoms, and no other cause or explanation for the occurrence of the symptoms; 2) possible causality with symptoms occurring in a timely fashion after the exposure, with untypical symptoms but no other cause or explanation for the occurrence of the symptom, or with typical symptoms but other possible causes; and 3) unlikely causality with symptoms not occurring in a timely fashion after the exposure and/or symptoms not typical and with the presence of other causes or explanations for the occurrence of the symptoms. In asymptomatic patients and in cases with unusual symptoms, the likelihood of exposure is particularly important, whereas causality has higher priority in symptomatic cases. Only cases with a high likelihood of exposure and with high causality should be included in reports (10). The number of cases with poor causality may be significant (e.g. 12.5% in the STIC in 2006). However, the scientific value of these causality scoring systems is limited because they are difficult to validate (11). The assessment of exposure and causality can be performed by the Poisons Centre staff at any time during the course of poisoning. The result of this assessment can change with time depending on the information available. A final assessment can be done only after the course of illness is terminated and the maximum of information is available; routine follow-up is required to capture all symptoms including delayed effects. *References:* 1. Buckley NA, *et al*. *J Toxicol Clin Toxicol* 2002; **40**: 213–22. 2. Karch FE, Lasagna L. *Clin Pharmacol Ther* 1977; **21**: 247–54. 3. Begaud B, *et al. Thérapie* 1985; **40**: 111–8. 4. Moore N, *et al*. Lancet 1985; ii: 1056–8. 5. Jones JK. *Clin Pharm* 1982; **1**: 554–5. 6. Naranjo CA, *et al*. Clin Pharmacol Ther 1981; **30**: 239–45. 7. Benahmed S, *et al*. *Eur J Clin Pharmacol* 2005; **61**: 537–41. 8. Arimone Y, *et al. Eur J Clin Pharmacol* 2005; **61**: 169–73. 9. Hill AB. *Proc Roy Soc Med* 1965; **58**: 295–300. 10. Kelly WN, *et al*. Drug Saf 2007; **30**: 367–73. 11. Meyboom RHB, *et al. Drug Saf* 1997; **17**: 374–89.

127. The Effect of Single Dose Activated Charcoal on Drug Absorption During the First 6 Hours After Drug Ingestion - A Metaanalysis

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Objective: To estimate the effect of activated charcoal (AC) on drug absorption during the first 6 hours after drug intake and evaluate the influence of physical and pharmacological drug properties and charcoal/drug-ratio. *Methods:* 43 placebo-controlled studies (111 comparisons, 39 drugs, 1527 healthy volunteers) were included. The percentage reduction of drug absorption of AC treated volunteers compared with placebo treated volunteers was calculated at 5, 30, 60, 120, 180 and 360 minutes after drug ingestion. The influence of pKa, molecular weight (MW), volume of distribution (Vd) and charcoal/drug-ratio was analysed using a Spearmann-correlation. *Results:* The effect of AC was significant during the first six hours after drug ingestion (Table). The percentage reduction of drug absorption was correlated with the charcoal/drug-ratio ($R = 0.68$, $p < 0.0001$). A correlation was also demonstrated for MW ($R = 0.54$, $p = 0.0001$) and Vd ($R = 0.43$, $p = 0.0002$). *Conclusion:* AC is most effective when given immediately after drug ingestion. However, 25% of the participants achieved at least a 30% reduction of drug absorption up to 6 hours after drug intake, especially when AC was given with large charcoal/drug-ratio. AC appears to be most effective in drugs with large MW and Vd, where other treatment options, including dialysis, are limited and should be considered in poisoned patients, even when presented late to medical care. *Reference:* Position paper: single-dose activated charcoal. *Clin Toxicol* 2005; **43**: 61–87.

128. A Randomised Controlled Trial of Multiple Dose Activated Charcoal in Acute Self-Poisoning

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Objective: The case-fatality for intentional self-poisoning in the rural developing world is 10–50 fold higher than industrialised countries, due mostly to the use of highly toxic pesticides and plants. We aimed to determine whether routine therapy with multiple dose activated charcoal to interrupt enterovascular or enterohepatic circulations offers benefit, compared to no charcoal, in such an environment. The RCT was registered as ISRCTN02920054. *Methods:* We conducted an open-label parallel group randomised controlled trial of six 50 g doses at four hourly intervals vs no charcoal vs a single 50 g dose of activated charcoal in three Sri Lankan hospitals. Mortality was the primary outcome. *Results:* 4632 patients were randomised to receive no charcoal (1554), a single dose of charcoal (1545), or six doses of charcoal (1533); outcomes were available for 4629. 2338 (50.5%) had ingested pesticides whilst 1647 (35.6%) had ingested yellow oleander seeds. Mortality did not differ significantly between the groups. 97 of 1531 (6.3%) participants in the multiple dose group died, compared with 105 of 1554 (6.8%) in the no charcoal group (adjusted odds ratio [OR] 0.96, 95% confidence interval [CI] 0.70–1.33). 439 patients were admitted within two hours of poison ingestion and allocated to either MDAC (n=214) or SDAC (n=225). Comparing these 439 patients with 225 who were admitted within two hours of poison ingestion and allocated to no charcoal, there was no evidence of benefit on deaths of early charcoal administration (34/439 vs 15/225; OR 1.18 [exact 95% CI 0.61–2.38]; test of interaction P=0.5). In addition, there was no evidence of an interaction between early charcoal administration and any of the secondary outcomes. No significant differences were noted for patients who took particular poisons, or were more severely ill on admission. *Conclusion:* We found no benefit from routine administration of multiple dose activated charcoal, nor from early administration of charcoal, for patients poisoned by plants or pesticides in resource-poor rural developing world district hospitals. We cannot recommend the routine use of activated charcoal in rural Asia-Pacific; while further studies of early charcoal administration may be useful, effective affordable treatments are urgently required.

Table: The effect of AC at 5–360 mins after drug ingestion

Time to AC after drug intake	Reduction of drug absorption (%)						
	5 min	30 min	60 min	120 min	180 min	240 min	360 min
Median	89	54	30	23	25	27	15
25–75% percentile	64–97	40–64	25–59	12–33	11–40	21–32	9–32
Studies	62	5	18	8	4	4	3
Participants	767	56	266	145	74	71	40
Test for overall effect: Z	23.50	3.87	8.88	4.46	3.69	3.42	1.99
p	<0.00001	0.0001	<0.00001	<0.00001	0.0002	0.0006	0.05

129. Overview of Herbal and Complementary Medicines

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Several traditions of herbal medicine have developed in parts of the World and some still continue to be important to the public and to patients as a possible therapeutic option. In Europe, many herbal medicines are generally used for minor or self-limiting conditions, without the need to be prescribed by a medical practitioner. However some Western herbal traditions (e.g. anthroposophic medicine) are still practised by registered medical practitioners with training in the discipline. Other herbal medicines traditions such as traditional Chinese herbal medicine, Ayurvedic medicine (South-East Asia) and Kampo (Japan) are also practised in Europe. Herbal medicines may contain a range of biologically active compounds in the same preparation, and some of these compounds have been used as constituents of conventional products. Other complementary approaches involving the use of chemical substances include aromatherapy and homeopathy. Herbal and other complementary medicines may also sometimes be associated with toxicity (1). This may be related to Type A (dose-related) or Type B (idiosyncratic) toxicity caused by one or more of the agents contained within the medicine. Occasionally, toxicity may be associated with adulteration (deliberate or accidental) with other potentially toxic products, including other herbs, minerals (sometimes including heavy metals), animal products or even conventional medicines or their analogues. Microbial contamination has also been reported. In some circumstances, herbs may induce or inhibit the elimination of other medicines and result in herb-drug interactions. Because prescribers of conventional medicines do not always elicit a full history of over the counter (OTC) and herbal medicines use by their patients, such problems may go unnoticed for some time. There is an increased recognition that herbal medicines will benefit from being more closely regulated. Partly because they may have been freely available for the treatment of minor or self-limiting conditions for many years, many do not have robust clinical trial data confirming their efficacy. New European legislation was therefore enacted to ensure that these products, which are not eligible for a marketing authorisation, should nevertheless be regulated so that the public could have the necessary guarantees of quality, safety and efficacy. A Traditional Herbal Medicines Directive (20002004/24/EEC) was therefore passed on the 31st of March 2004 by the European Parliament and Council (2). Each member state is required to establish a simplified registration scheme for traditional herbal medicines suitable for use without medical supervision. The Directive does not cover homeopathic remedies, nutriceuticals, nutrients or food supplements; although herbal combinations with vitamins or minerals are included, providing the action of the latter is only "ancillary". The requirement to demonstrate efficacy is replaced by the requirement to demonstrate 30 years' traditional use, at least 15 years of which should normally have been within the European Union. However data on traditional use is not sufficient in itself if the efficacy is not plausible on the basis of longstanding use and experience. The safety of the product is based upon a full scientific review of the literature, but regulators can ask for more data if their safety concerns remain. Data on genotoxicity, mutagenicity, carcinogenicity and reproductive toxicity of herbal medicines are often limited. Discussions are underway to determine when such evidence is required and what tests (e.g. *in vitro* and *in vivo* tests) might be most appropriate. Other areas where safety information is limited concern safety of use in children, perioperative use and drug-herb interactions. Quality must also be assured in the same way as with conventional medicines, and manufacturers must have adequate pharmacovigilance systems in place to monitor safety, including a Qualified Person resident in the EU and the submission of Periodic Safety Update Reports (PSURs). Patient information is similar to that for any over the counter (OTC) medicine, but there is an additional requirement for a statement on labels and in advertisements that the indication is based on traditional usage. The Directive allowed the establishment of a European Committee on Herbal Medicinal Products (CHMP) to assist harmonisation of procedures across Europe and to further integrate herbal Medicinal Products into the European regulatory framework. As well as giving advice to member states, CHMP is establishing community herbal monographs. A European positive list of herbal substances will also be developed and if a product complies with the positive list or a published monograph, it can benefit from a mutual recognition procedure, although traditional herbal medicine registrations will continue to be granted on a national basis. Member states in Europe were required to comply with the provisions of the Directive by 30th October 2005, although products already on the market when the Directive became law need not comply with these provisions for a further seven years. In some member states, national advisory committees have also been established. In the UK, for example, a Herbal Medicines Advisory Committee (HMAC) was established in 2005 to advise on issues related to the registration scheme and the safety of herbal medicines. Health professionals are often unaware of the possible toxicity and interactions of herbal medicines with other co-prescribed medicines. Undergraduate curricula and continuous professional development (CPD) programmes are often deficient in information on these forms of treatment, and users of herbal medicines do not always share all relevant information with their health professional. In addition, some members of the public and the media believe that "natural always means safe." it is important that health professionals, users of herbal medicines and the wider general public are aware of potential herbal safety issues and that they are encouraged to report suspected adverse reactions via national spontaneous reporting schemes. Consideration should also be given, where necessary, to the regulation and registration of herbal medicine practitioners so that appropriate standards of training and professional practice can be ensured. Improved intelligence on potential public health concerns, coupled with effective enforcement is also a vital part of the risk management process, since those who choose to take herbal medicines expect to be able to do so with acceptable safety, in an environment where their decisions are informed by clear and up-to-date advice on possible benefits and risks. *References:* 1. http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=96 2. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2004_24/dir_2004_24_en.pdf

130. Traditional Chinese Medicine-Related Poisonings in Hong Kong

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Objective: To review the dominant clinical features, herbs involved and the underlying reasons for common traditional Chinese medicine (TCM) related poisonings referred to a tertiary clinical toxicology laboratory serving a 7-million, principally Chinese, population since its establishment in 2004. *Case series:* Among 1300 cases referred to the laboratory during this period, 27% were related to TCM. The four most common classes of poisonings were reviewed. 1) Sixteen cases (5 males and 11 females, age range 20–83 years) of aconite poisoning were confirmed. Aconite herbs are commonly used in TCM for the treatment of musculoskeletal disorders. Aconitum-alkaloids are the active ingredients and the toxic compounds of these herbs. The principal clinical features in this series included numbness (81%), weakness (56%), hypotension (63%), dizziness (44%), bradycardia (38%), ventricular ectopics (25%), sinus tachycardia (13%) and ventricular tachycardia (13%). In seven cases, poisoning was the result of either single herb over-dosage or the administration of multiple aconitum-alkaloid containing herbs, leading to additive over-dosage. Failure to provide clear instructions on the correct method of preparation of the decoction (by prolonged boiling, which is essential in converting the toxic compounds into much less toxic ingredients) is another cause of toxicity. In another seven cases, aconite herbs were not prescribed but were accidentally included in the decocted herbs. The source of error could not be determined in any of the seven cases. The other herbs used did not overlap, making systematic substitution or contamination of one particular herb unlikely. Inadvertent, random contamination of herbs is the most likely explanation. This form of aconite poisoning is potentially very dangerous as the patient ingests the toxins unwittingly. One of the patients developed a pulseless ventricular tachycardia in the emergency room. Fortunately, he was resuscitated promptly and made a full recovery. Laboratory analysis revealed an important clue to the source of contamination. Yunaconitine, an aconitum-alkaloid present in aconite herbs of Yunnan origin, was detected in 6 out of 7 such cases. In contrast, aconitine, mesaconitine and hypaconitine are the principal aconitum alkaloids detected in the other cases (1). 2) Diagnosis of anticholinergic poisoning was made in seventeen cases (4 males and 13 females, age range 9–83 years) following ingestion of various TCM herbs. Clinical signs include delirium (82%), tachycardia (82%), dilated pupils (65%), dry skin (53%), flushing (29%), urinary retention (18%) and fever (6%). Nine cases were associated with *Rhizoma Atractylodis*, which does not, when grown and stored in isolation, contain any anticholinergic substance. Contamination of this herb by other anticholinergic plants is the most likely explanation for the problem. This herb should be considered a potential source of anticholinergic poisoning. In four independent patients, *Flos Campsis*, a non-toxic herb, was replaced by *Flos Daturae*, an anticholinergic herb used for treatment of asthma. These two herbs are both dry flowers and similar in appearance. 3) Prolonged usage of Aristolochic acid (AA)-containing herbs, which are numerous, induces a nephropathy characterised by rapidly progressive interstitial fibrosis. Development of urothelial carcinoma is another possible complication (2). These herbs have been banned in many parts of the world but were still allowed in Hong Kong in 2004 when the laboratory opened. Five such cases (2 males and 3 females, age range 41–75 years) were diagnosed within 6 months in 2004. Three cases had end stage renal failure and one had urothelial carcinoma. The specific herb involved in three of these cases was *Herba Aristolochia Mollissemae,* which had been mistakenly used as *Herba Solani Lyrati*, a non-toxic herb, by the local TCM industry. The substitution stemmed from a common alternative name, "white furry ivy," which describes the appearance of both herbs. After these incidents all AA-containing herbs were banned in Hong Kong. 4) Herbs with hepatotoxic potential are numerous. However, the causal relationship is often poorly characterised. Clinically relevant liver enzyme elevation occurs in 1% of TCM herb users (3). Twenty-three cases (9 males and 14 females, age range 19–85 years) with suspected TCM herbs related hepatotoxicity were referred to the laboratory. The majority (83%) was associated with prolonged intake of the same herb. The most frequently incriminated herbs are *Radix Polygoni Multiflori* (seven cases) and *Rhizoma Dioscoreae Bulbiferae* (six cases). *Radix Polygoni Multiflori* is used as a tonic for prevention or reversal of premature graying of the hair. *Rhizoma Dioscoreae Bulbiferae* is used for thyroid and skin disorders. Hence, both herbs tend to be used on a prolonged basis. These liver insults were discovered incidentally while investigating other problems. In all cases, the elevated serum alanine aminotransferase activities returned to normal after discontinuation of the herbal remedy. Other incriminated hepatotoxic herbs referred to the laboratory included *Fructus Xanthii, Fructus Toosendan, Scolopendra, Herba Polygalae Chinensis, Semen Cassiae* and *Radix Tripterygii* (4). As in other similar series, the causal relationship could not be confirmed with certainty. *Conclusion:* TCM is a common alternative mode of healthcare in Hong Kong. There are many factors involved in poisonings associated with such remedies. Over-dosage as a result of prescribing error should be reduced by better training and education. Substitution of a non-harmful herb by a toxic herb is a serious, on-going concern, as illustrated in this series. The quality of herbs in general requires stricter control. The standard of dispensing also needs to be enhanced. *References:* 1. Poon WT, Lai CK, Ching CK, *et al*. Aconite poisoning in camouflage. *Hong Kong Med J* 2006; **12**: 456–9. 2. Nortier JL, Martinez MC, Schmeiser HH, *et al*. Urothelial carcinoma associated with the use of a Chinese herb (*Aristolochia fangchi*). *N Engl J Med* 2000; **342**: 1686–92. 3. Melchart D, Linde K, Weidenhammer W, *et al*. Liver enzyme elevations in patients treated with traditional Chinese medicine. *JAMA* 1999; **282**: 28–9. 4. Yuen MF, Tam S, Fung J, *et al*. 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131. Clinical Toxicology of Ayurvedic Medicines

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Ayurveda (meaning science of life in Sanskrit) is a comprehensive holistic medical system which evolved in India more than 5000 years ago. This medical system subsequently evolved into 2 schools of learning: the School of Physicians and the School of Surgeons, similar to allopathic medicine. Ayurvedic physicians are encouraged to prepare their own Ayurvedic medicines which are remedies based on natural sources such as herbs, metals and minerals and prepared using traditional methods. They are classified in the Ayurvedic pharmacopoeia according to the constituents, taste, potency, postdigestive effect and any special action. Apart from being used by 80% of India's population as a traditional system of healthcare, ayurvedic medicine has gained widespread acceptance in the Western world over the last few decades. As Ayurvedic medicines are marketed as dietary supplements, they are not subject to the same stringent regulations as pharmaceutical drugs with regards to efficacy and safety. The large increase in immigrant populations from the Indian subcontinent has led to increased availability and utilisation of traditional Ayurvedic medicines which may be purchased from retail stores and over the internet without medical consultation. This has been associated with a concomitant rise in reports of toxicity associated with these traditional remedies. Toxicity may arise from use of herbs and plants containing recognised pharmacologically active ingredients e.g. *Papaver somniferum* (Ahipheman used for anxiety and diarrhoea) and *Rauwolfia serpentina* (Sarpaghanda

for hypertension). Pharmacodynamic drug interactions may arise from concomitant use of such preparations and conventional pharmaceutical drugs. Some preparations such as Ashagandha contain withanolides which are structurally similar to digoxin and interfere with some digoxin assays, giving a falsely lowered digoxin concentration, potentially leading to unwarranted increase in the digoxin dose. Inherently toxic plant extracts e.g. from *Aconitum* and *Ricinus communis* are included in some Ayurvedic formulations, although the traditional preparation process includes an elaborate detoxification technique (known as samskaras) specific to the ingredient. The usefulness of this process is unclear but has been shown to be effective in completely eliminating the toxicity of aconite in mice (1). Commercially available Ayurvedic preparations may not adhere rigidly to this complex procedure, therefore exposing patients to toxic unprocessed herbal ingredients. Ayurvedic practitioners believe in the healing properties of heavy metals which form part of an estimated 40% of these preparations. Bhasmas, Ayurvedic metallic preparations with herbal juices or fruits are used for treating a variety of chronic ailments and contain metals such as mercury chelated with organic ligands derived from medicinal herbs. A study in Boston showed that 20% of Ayurvedic preparations imported from South Asia contained toxic concentrations of heavy metals such as lead, mercury and arsenic (2). Studies conducted in India have shown that 64% contained lead and mercury, 41% arsenic and 9% cadmium (3). Such studies raise concern that chronic use of Ayurvedic medicines may cause heavy metal poisoning. 9 of 12 cases of lead, arsenic or mercury poisoning reported to a toxicology unit in London over a 5-year period were due to ayurvedic medicines (4). Numerous cases of lead toxicity arising from use of Ayurvedic formulations have been reported in Western countries, with features ranging from anaemia and abdominal pain to status epilepticus and fatal encephalopathy (5). Furthermore, in a retrospective analysis of 47 adult lead intoxications due to Ayurvedic medicines and 19 due to lead paint, patients using ayurvedic medicines had significantly higher blood lead concentrations, more basophilic stippling and lower haemoglobin (6). There are anecdotal reports of mercury and arsenic poisoning in 2 patients treated for eczema with a remedy containing inorganic mercury sulphide and arsenic trioxide respectively (7). Combined lead, mercury and arsenic poisoning has also been reported. In view of the herbal nature of these medicines, contamination with pesticides is also a matter of concern. Organochlorine pesticide residues have been found in the stems and roots of herbs used in Dashmoola, a widely used Ayurvedic formulation (8). The widening market for ayurvedic medicines has resulted in the manufacture of fake preparations adulterated with synthetic drugs such as steroids. Finally, little is known about the potential genototoxic and teratogenic effects of Ayurvedic formulations. Extracts of Asparagus racemosus roots, used as a reproductive tonic, have been shown to be teratogenic in rats (9). *In vitro* genototoxicity testing showed that extracts of *Salacia oblonga* roots used for diabetes may be weakly genotoxic (10). Exposure to lead-containing preparations in utero has caused congenital paralysis and sensorineural deafness. Although there are no reported cases of malignancy attributable to use of ayurvedic medicines, preparations containing arsenic may predispose to skin and haematological cancers. It is not possible to make accurate estimates of the risk of heavy metal poisoning associated with ayurvedic medicines but they have now surpassed environmental factors as the major cause of lead poisoning in Western countries. A history of ayurvedic medicine use should be actively sought in patients presenting with symptoms and signs of lead poisoning. Education of users about the potential risks and more effective regulation of these traditional remedies are required. *References:* 1. Thorat S, Dahanukar S. Can we dispense with Ayurvedic samskaras? *J Postgrad Med* 1991; **37**: 157–9. 2. Saper RB, Kales SN, Paquin J, *et al.* Heavy metal content of ayurvedic herbal medicine products. *JAMA* 2004; **292**: 2868–73. 3. McElvaine M, Harder E, Johnson L, *et al*. Lead poisoning from the use of Indian folk medicines. *JAMA* 1991; **264**: 2212–2213. 4. Shaw D, Leon C, Kolev S, *et al*. Traditional remedies and food supplements. 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132. Herbal Medicines and Problems with Contamination

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Objective: To provide an overview of the most common contaminants that cause problems in herbal medicines, with specific examples of the problems encountered in the United Kingdom. Additionally, some of the measures taken to help address these problems are discussed. *Methods:* The flourishing herbal market in the UK currently comprises of several different types of herbal medicines. These originate from different parts of the world for example Europe, China, India, America and Africa. Herbal medicines or herbal medicinal products as they are frequently referred to, are medicinal products containing single or several herbal substances or herbal preparations. In order to guarantee the quality of herbal preparations and herbal medicines, the herbal substance/s must be of high quality and free of impurities. This unfortunately is not always the case and the most common forms of contamination arise from foreign organic matter such as small amounts of related parts of plant or other plants, insects or other animal matter, microbial contamination, pesticides, fumigants, fungicides, mycotoxins, inorganic and toxic metals (1). Contamination by adulteration/substitution or with toxic compounds also contributes to numerous problems. The safety implications of the problems experienced due to contamination of herbal medicines varies enormously, largely depending on the type and level of contaminant, the patient population taking the product and the dose taken. In the worse case scenario contaminated products have led to irreversible organ damage and even death. Over the past years, the UK has had to increasingly deal with cases resulting from contaminated herbal medicines with toxic metals (arsenic, mercury, lead), microbial sources, adulteration/substitution with other plant species for example *Aristolochia* or with prescription medicines such as corticosteroids. *Results:* The quality of herbal medicines is a major concern with regard to the safety of herbal products, especially in a notably unregulated market. A significant step aimed at reducing the problems encountered with contamination is the EU Directive on Traditional Herbal Medicinal Products 2004/24/EC that came into force in 2004. Under this Directive, a simplified registration procedure is provided for traditional herbal medicinal products known as the Traditional Herbal Registration Scheme. The quality aspects of the product and manufacture are fully controlled as they have to take place in compliance with Good Manufacturing Practice (GMP). All products currently on the UK market when the Directive came into force will need to comply by 30 April 2011. No new herbal medicines can be introduced onto the UK market after 30 April 2004 unless through the Traditional Herbal Registration Scheme. This essentially means that by April 2011, herbal medicines on the UK market should be controlled for quality and safety as the European guidelines on the quality of herbal medicines apply. Companies are required to submit a registration dossier taking account of existing guidelines including Good Agricultural Practice (GACP), European Pharmacopoeia tests for pesticide residues, limits for aflatoxins, microbial limits and stability requirements. *Conclusion:* With the introduction of the Traditional Herbal Medicinal Products Directive and the registration scheme where the quality aspects of the product and manufacture have to take place in compliance with GMP, some of the main problems with contamination will be addressed, leading to safer herbal medicines. *Reference:* Barnes J, Anderson LA, Phillipson JD. Herbal Medicines, 3rd edition. London: Pharmaceutical Press 2007.

133. CAM Scams: Poisons as Cancer Cures

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Objective: To review briefly the history of several complementary or alternative therapies for cancer still in use today despite lack of efficacy and widely publicized toxicity. The mechanism of toxicity and clinical findings are discussed. *Methods:* A literature review was performed using the PubMed database with permutations of the keywords alternative medicine and cancer and toxicity with a focus on fraudulent or unproved claims. A search using an online search engine was similarly performed. *Results:* Laetrile is a trade name of an extract of fruit pits that contains l-mandelonitrile-beta-glucuronoside, or amygdalin, a cyanogenic glycoside. This CAM has been proffered for more than a century as an active anticancer regimen, generally administered by intravenous injection. Proponents claim that cancer cells, unlike normal cells, are rich in an enzyme that causes amygdalin to release cyanide which destroys the cancer cells. Laetrile has shown little anticancer effect in laboratory studies, animal studies, or human studies. Not surprisingly, the adverse effects of Laetrile are similar to those of cyanide. A clinical trial of 178 cancer patients who received Laetrile found no benefit, and several patients experienced clinical cyanide toxicity or had significantly elevated blood concentrations of cyanide (1). Claims for Laetrile's effectiveness shifted from a cancer cure, to a cancer control agent, to a "vitamin" (called B17) purported to prevent cancer. The Internet search found several websites still selling Laetrile or offering related clinical services. Hydrazine sulfate (HS) was studied as a treatment for cancer and certain side effects caused by cancer. Randomized clinical trials have failed to prove a benefit of HS though some report a reduction in the anorexia and cachexia caused by cancer. A 1990 randomized, double blinded, placebo controlled trial of 65 patients found no difference between HS and placebo groups on cancer progression or survival rate in patients with non-small cell lung cancer (2). The HS treated group had increased appetite and some weight gain. The beneficial effects of hydrazine sulfate are based on its purported ability to inhibit gluconeogenesis thus allowing normal anabolic pathways to function more efficiently. Neurotoxicity, as with other hydrazine derivatives, remains an undefined, but evident, risk. HS is still sold on the Internet as an alternative therapy for cancer patients, both to reduce tumor burden and improve cancer-related clinical syndromes. Elements and simple molecules are widely touted as cancer cures, and a few are discussed here. Intravenous ozone was administered to cancer patients as "hyperoxygenation therapy". It is claimed by proponents that ozone can dissolve malignant tissues due to their deficiency of the protective enzyme catalase. A 20 year old woman collapsed during the "autohemotransfusion" of ozone, in which blood was removed from the body and mixed with ozone and retransfused. Clinical and postmortem studies revealed gas embolism and patent *foramen ovale* (3). A 75-year-old man with prostate cancer ingested 10 g of sodium selenite after reading misleading information on an Internet website. He developed a series of concerning ventricular dysrhythmias terminating in asystole (4). Another patient with colon cancer using cesium chloride developed a QTc of 645 msec and torsade de pointes (5). Cesium blocks the outward potassium current, an effect which is associated with torsade. *Conclusion:* Despite being long debunked as ineffective and uncovered as having significant toxicity, some alternative therapies are still being offered by CAM providers and frequently discussed as effective by Internet sites. *References:* 1. Moertel CG, Fleming TR, Rubin J, *et al.* A clinical trial of amygdalin (Laetrile) in the treatment of human cancer. *N Engl J Med* 1982; **306**: 201–206. 2. Chlebowski RT, Bulcavage L, Grosvenor M, *et al*. Hydrazine sulfate influence on nutritional status and survival in non-small-cell lung cancer. *J Clin Oncol* 1990; **8**: 9–15. 3. Marchetti D, La Monaca G. An unexpected death during oxygen-ozone therapy. *Am J Forensic Med Pathol* 2000; **21**: 144–147. 4. See KA, Lavercombe PS, Dillon J, *et al*. Accidental death from acute selenium poisoning. *Med J Aust* 2006; **185**: 388–9. 5. Lyon AW, Mayhew WJ. Cesium toxicity: a case of self-treatment by alternate therapy gone awry. *Ther Drug Monit* 2003; **25**: 114–116.

134. Teaching Health Professionals about Complementary and Alternative Medicines (CAM)

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Objectives: To review CAM teaching to health professional students including evaluating the effectiveness of an integrative approach to teaching evidence-based CAM to pharmacy students. *Methods:* The effectiveness of an integrative approach to teaching CAM to pharmacy students was evaluated using surveys and interviews to examine CAM use, attitudes, perceptions and knowledge in 2nd, 3rd and 4th year pharmacy students. *Results:* More than 50% of the world's population uses CAM, mostly combined with conventional medication. CAMs can be beneficial for health and wellbeing, but can also cause adverse effects. Medical and pharmacy students support including CAM education in their curricula (1,2). In an Australian survey 69% of 1067 respondents had used CAM in the last 12 months; less than half had informed their doctor (3). Many Australian pharmacists view CAM positively, supplying both CAM product and information (4). However, pharmacists lack sufficient CAM knowledge and access to CAM information (4–6). Most studies indicate that students and health professionals have insufficient knowledge to recommend or counsel about CAM (7,8). During interviews, 57% of Australian community pharmacists reported that their training had not met their needs regarding CAM

knowledge (5). At the Gold Coast Hospital (Queensland, Australia) a pilot study of documenting patients' CAM use found that of the 215 in-patients interviewed, 46 used CAM and this use was recorded by pharmacists in 44 cases (96%), but for only for 2 patients (4%) by doctors. The use of the medication history checklist by pharmacists, accessible CAM resources, education for all health professionals and patients on CAM, and a CAM Hospital Policy may be valuable in improving the documentation of CAM use by patients. Studies of pharmacy schools in the US concluded that while approximately 80% of schools offer some form of CAM training in the curriculum, CAM education was primarily offered as electives and generally focused on natural products rather than the full range of CAM practices (7). The extent to which CAM is taught and integrated varies widely among Australian and NZ pharmacy and medical schools (5,10). In 2003 the Expert Committee on Complementary Medicines in the Australian Health System recommended an improvement in CAM education for healthcare professionals and consumers, (9) a recommendation that was endorsed by the Australian government (10). Both the Australian Medical Association and Pharmaceutical Society of Australia acknowledge the need for CAM to be integrated into health professional education and at the University of Sydney steps are being taken to introduce CAM into the medical curriculum. The Pharmacy School at Griffith University integrates CAM education into its core pharmacy programme. In an evaluation of the overall effectiveness of this programme, 95% of pharmacy students believed that pharmacists should be able to advise patients about CAM and most (94%) used CAM prior to course enrolment. The majority of pharmacy students (89%) preferred CAM education to be delivered as an integral part of their professional degree instead of an additional postgraduate degree. They identified a greater need for education in complementary medicines (herbals, vitamins, minerals) than complementary therapies (e.g. acupuncture, meditation, bio-magnetism). A significant increase in knowledge scores from second to fourth year coincided with an increase in CAM curriculum content, yet only 30% of the fourth year students stated that they had received sufficient CAM education. The students' attitudes to CAM were influenced not only by the use of CAM by family, friends and self, but also to a large extent by CAM education and to a lesser degree by clinical placement preceptors. The integrated curriculum approach to CAM education rationalised rather than marginalised students' attitudes towards CAM, developing a balanced and more pluralistic student view on systems of healthcare beyond the medical mainstream. Students who began their degree with a more positive attitude to CAM adopted a more careful assessment of CAM therapy, whereas students with a more negative attitude realised that some CAM therapies were based on significant evidence and were possibly beneficial in patient care. *Conclusion:* The evaluation of integrated CAM teaching to pharmacy students illustrates that this approach was effective in generating knowledge of general CAM philosophies and specific CAM modalities. In addition, the demand for instruction in CAM is strong but is still not satisfied. Further developments will focus on the integration of CAM education into the pharmacy curriculum from the first year of study and the introduction of multidisciplinary teaching of CAM in the undergraduate curricula for health professionals. Firm recommendations and required competencies from professional and educational bodies to assist CAM curriculum development are urgently needed. *References:* 1. 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135. Seromucosal Transport of Intravenously Administered Carbamazepine is not Enhanced by Oral Doses of Activated Charcoal in Rats

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Objective: To evaluate the effectiveness of orally administered activated charcoal (AC) in enhancing the clearance of 14C-carbamazepine and metabolites (CBZ/M) after IV injection (15 mg/kg b.w.). The quantities of CBZ/M excreted into bile, urine and intestines were determined. *Methods:* Rats were randomized into four treatment groups of 6 animals each: all underwent single-pass perfusion of the small intestine; two groups received AC (3 g/kg^{-1} b.w.; in Ringer's solution (RS) with (AC+BD+) or without cannulation of the common bile duct (AC+BD–). The remaining two groups received solely RS with (AC-BD+) or without (AC-BD) cannulation of the common bile duct. The right and left internal jugular vein and the left internal carotid artery were cannulated for blood sampling and delivering anaesthesia agents or CBZ. The proximal duodenum and the distal ileum were cannulated for intestinal perfusion. In the (BD+)-group, bile was collected continuously from the cannulated common bile duct. Urine was collected continuously. Animals were observed for 210 min after IV injection and euthanized finally. CBZ in plasma was determined using a FPIA-based method. Radioactivity of 14C-CBZ (and metabolites) in perfusate, bile, and urine was determined by liquid scintillation counting after combustion. *Results:* The cumulative amount of CBZ/M exsorbed into the small intestine within 3.5 h after intravenous injection was about 15% in (BD)-animals and about 3% in (BD+)-animals. About 20% of the dose was detected in the externalized bile. AC did not influence the amount exsorbed into the small intestine. Terminal half-life in plasma ranged from 159 to 194 min within the four treatment groups without statistical significant difference ($p = 0.751$). Correspondingly, the AUC did not vary significantly and ranged between 1.13 and 1.41 $g \bullet min \bullet L^{-1}$ ($p = 0.378$). Excretion of CBZ/M into urine varied between 3% and 6% of dose within all groups. A twofold intestinal perfusion rate (50 mL/h; n=8) rendered no fundamental results compared to the main experiment. *Conclusion:* The lack of effect of AC on the elimination of CBZ/M must be contributed to the small amount of the drug being exsorbed into the intestine and may be further influenced by reduced intestinal permeability of CBZ/M or inadequate luminal stirring.

136. Are Pets More Vulnerable Cannabis Intoxications than Humans?

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Objective: In recent years, the Δ9-tetrahydrocannabinol (THC) concentration in cannabis sold on the Dutch drug market has increased (1). Besides humans, pets are also at risk of exposure to cannabis (2). For pets, exposure mainly takes place via ingestion. Our aim was to investigate whether or not the frequency and clinical symptoms of cannabis intoxications in pets has increased, and if pets are more vulnerable to cannabis exposure than humans. *Case series:* The mean THC concentrations in Dutch weed have increased from 8.6% in January 2000 to 16.0% in January 2007 (1). Hashish contains on average 13.3% THC. In this period, 126 cases of cannabis intoxications in pets were recorded at the National Poisons Information Centre (NVIC), after oral intake of weed (48%), hashish (21%), space cake (30%) or a cannabis cigarette (2%). In 2000 the NVIC was consulted about 5 pets exposed to cannabis, in 2001 11, in 2002 16, in 2003 21, in 2004 22, in 2005 29 and in 2006 23. In 87% of the reported intoxications it concerned dogs, 10% were cats and 2% were ferrets. The amount of cannabis ingested ranged from 0.02 to 10 g of weed or hashish and up to 400 g space cake (containing 2% weed). The lowest THC dose at which symptoms occurred was 0.14 mg/kg, the highest reported dose was 221 mg/kg. No fatal intoxications were recorded in this period. In dogs, 85% of the recorded symptoms were neurological (as incoordination, drowsiness and behavior disorders such as headshaking, anxiousness, restlessness), 8% were gastrointestinal (nausea, vomiting) and 7% were cardiovascular (bradycardia, tachycardia). Acute treatment performed by the veterinarian was inducing vomiting and active charcoal administration. Observation period was a minimum of 3 hours with symptomatic treatment if necessary. *Conclusion:* We observed an increase in cannabis intoxications in pets in recent years, especially in dogs. This increase could be attributed to higher THC concentrations in cannabis, or to an increase in reporting to our centre. The symptoms in dogs are comparable to those observed in humans and are mainly neurological. Nevertheless, it seems that dogs are not more vulnerable than humans. *References:* 1. Niesink RJM, Rigter S, Hoek J. THC-concentraties in wiet, nederwiet en hasj in Nederlandse coffeeshops (2006–2007). 2007. Trimbos Institute, Utrecht, the Netherlands. 2. Janczyk PDVM, *et al*. Clinical Reports: Two hundred and thirteen cases of marijuana toxicoses in dogs. *Vet Human Toxicol* 2004; **46**: 19–21.

137. Treatment of 1080 Poisonings in Canines - A Survey of New Zealand Veterinarians

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Objective: Compound 1080 (sodium monofluoroacetate) is used in New Zealand for the management of possums. 1080 is applied aerially as cereal pellets or mixed with carrots (coloured green or blue, to reduce visual attractiveness to birds). In bait stations it takes the form of cereal bait, paste or gel. Domestic animals are at risk of exposure either by ingesting toxic baits or ingesting a poisoned carcass. Dogs are particularly sensitive to 1080 and each year dogs are poisoned following 1080 poisoning operations. A survey of veterinary practitioners across New Zealand was undertaken to determine both the extent of 1080 poisonings in dogs and how these poisonings were managed in New Zealand veterinary practice. *Method:* A mail survey was sent to 125 randomly selected registered veterinarians. *Results:* Fifty two replies were received; 33 servicing urban areas, 30 practising in rural New Zealand (30 veterinarians covering a combination of both regions). The veterinarians' years of experience in treating cases of poisoning ranged from two to forty years (mean 16.5, standard deviation 8.9). Sixty–five cases of 1080 poisoned dogs in a one year period were reported by 17 veterinarians. The largest number of cases seen was 10 (by each of three veterinarians). The mainstay in treatment was to remove the ingested 1080, either by giving an emetic or, once sedated, intubating and performing gastric lavage. Washing soda was the emetic of choice if treated by the owner; while most veterinarians used apomorphine. Dogs were sedated with barbiturates or diazepam. Other supportive measures included intravenous (iv) fluids, oxygen, cardiac management, keeping the dog warm and rolling it over frequently to reduce lung congestion. Only a few veterinarians used "antidotes" (glycerol monoacetate or acetamide). The reported survival rate was low (25.4%). Once the dog was showing clinical signs of toxicity, respondents considered there was little chance of survival; one veterinarian advocated euthanasia in most cases. *Conclusion:* Poisoning of dogs by 1080 is widespread with no defined effective management in place. The survival rate of a poisoned dog was influenced by factors including recognition by the owner and prompt management (emesis, lavage, sedation, iv fluids).

138. When the Remedy is Worse than the Poisoning: The Use of Table Salt as a Household Emetic

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Objective: The use of 1–3 teaspoons of table salt (sodium chloride) as a household emetic for pets after ingestion of a toxic substance is no longer recommended in recent veterinary toxicology handbooks. If the administration does not result in vomiting or when an excessive amount is given, this can result in serious hypernatraemia. Salt intoxications are reported to the Dutch National Poisons Information Centre occasionally as some veterinarians still advise this treatment to pet owners to achieve quick gastric decontamination and it is widespread on the internet as a first aid measure. A fatal case is presented here in which the remedy was certainly worse than the poisoning. *Case report:* After ingestion of 1 tablet of 0.125 milligram digoxin by a 4.5 kilogram 'Schipperke' dog, the veterinarian advised the owner to give the dog table salt to

induce vomiting. The actual amount is unknown, as 'a large amount' of salt was directly poured from the salt container in the mouth of the dog. The animal was transferred to the Emergency Clinic for Animals with signs of salt intoxication and the NVIC was contacted. Laboratory analysis indeed showed hypernatraemia >180 mmol/L (reference: 141–150) and hyperchloraemia >160 mmol/L (reference: 111–120). Neurologic symptoms of restlessness, nystagmus and convulsions were initially treated successfully with diazepam. Lacrimation, hyperthermia (40.7 degrees Celsius) and tachycardia (180 beats/minute) were noted. Despite administration of parenteral fluids the dog's neurological condition deteriorated and it died the night following the intoxication. *Conclusion:* The use of table salt as emetic can have dangerous complications and should be considered obsolete. Poison Centres should be aware that this treatment is occasionally still advised by veterinarians and is recommended as household emetic on the Internet.

139. Intoxications in Zoo Animals in the Netherlands

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Objective: Each year the National Poisons Information Centre (NVIC) receives between 3000 and 3500 questions about intoxications in animals. A small number of these questions concern zoo animals. Our aim was to evaluate if there is a particular pattern and if a specific strategy can be developed in order to handle intoxications in zoo animals. *Case series:* Since 1994, 28 intoxications in zoo animals were reported to the NVIC. These intoxications concerned a great variety of animal species, such as kangaroos, lions, monkeys, and dolphins. In several cases more than one animal was involved. The circumstances of the intoxications were very different and the following intoxicants were suspected to be involved: plants or plant material (18%), pesticides especially herbicides and rodenticides (18%), therapeutics such as anthelmintics (21%), contaminated water or soil (21%), others (18%), unknown (4%). However, in several cases it did not become clear whether the symptoms were the result of an intoxication or may be ascribed to other causes such as infection or stress. *Case report:* It was suspected that some dolphins had ingested lead from a damaged diving belt because lead particles were found in the drainage system. Furthermore the dolphins suffered from anorexia, leukocytose, liver- and kidney failure, symptoms compatible with a lead intoxication. Therefore it was advised to determine blood lead concentrations. The maximal lead concentration in blood was 95 microgram/dL. Chelation therapy was initiated and after 2 weeks the blood concentration dropped to 16 microgram/dL. Unfortunately this dolphin died 7 days after terminating chelation therapy. It is uncertain whether the concentration has increased again after cessation of chelation therapy, or that 16 microgram/dL is toxic to dolphins, because at autopsy 6 gram lead was found in the stomach and duodenum. *Conclusion:* Intoxications in zoo animals are rarely reported to the NVIC. The circumstances are very diverse and no particular strategy other then normal clinical toxicological approach can be developed to handle these kinds of intoxications. Most practical is a close interaction between the Poisons Information Centre and the Zoo's veterinarian. Furthermore, the dolphin case illustrates toxic reference values for animals are regularly not available.

140. The Role of a Poison Control Centre in Animal Poisonings

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Objective: The Spanish Poison Control Centre (SPCC) data represent the only national statistics of the occurrence of poisoning cases in animals in our country. The aim of this study was to determine the main characteristics of acute poisoning in animals according to the experience of the SPCC. *Methods:* A retrospective review of calls to our centre during 2006 was compiled and analysed. The following parameters were recorded: type of caller, type of animal, product, route of exposure and setting of the poisoning. *Results:* The SPCC received a total of 4,122 enquiries concerning animals during the study period. A percentage of 39.1% were made from veterinary hospitals, and 60.9% from the general public. 80.6% of them involved exposures or potential exposures in dogs and 12.3% in cats. The remaining enquiries concerned exposures in birds, horses, livestock, rabbits, and miscellaneous and exotic species. The environments were domestic (42.7%), farms (1.3%), the zoological gardens (0.1%), in the country (0.3%) and the rest unknown. Route of exposure was oral in 92.0% of cases, dermal 3.8% and respiratory 1.2%. The most common consults were about pesticides (47.8%) followed by therapeutic drugs (19.3%) and cleaning products (10.9%). Pesticides included: anticoagulant rodenticides (19.7%), cholinesterase inhibitor insecticides (9.7%), pyrethroids (6.4%), herbicides (2.7%), fertilizers (1.3%) and fungicides (1.3%). Drugs involved were essentially analgesic and antianxiety agents (4.2%), followed by dermatological drugs (2.4%), vitamins and minerals (2.1%), oral contraceptives (1.6%), anti-inflammatory drugs (1.7%), antibiotics (1.5%), and others. Consults related to cleaning products concerned mainly bleaches (2%), soaps and detergents (1.3%), floor cleaners (0.8%), and other. Twenty-six deaths by toxic exposures have been detected (0.7%) and were due to: pesticides (4 cases), cleaning products (2), batteries (1), food (1), sting/bites (1), and unknown (17). *Conclusion:* The vast majority of poisoned animals were domestic so preventive measures should be implemented among the pet owners. Since animal poisoning consults received in the poison control centres are frequent, a better preparation in animal toxicology for PCC personnel is considered relevant as well as a network of collaboration with other veterinary services.

141. Dopey Dogs – A Review of Cannabis Exposures in Canines

Sturgeon K, Campbell A. *Veterinary Poisons Information Service (London), Guy's & St Thomas' Poisons Unit, London, UK.*

Objective: Dogs are renowned scavengers and cases of cannabis ingestion have been reported to the Veterinary Poisons Information Service (VPIS) both as an "occupational" hazard in sniffer dogs, as well as in the domestic setting. A retrospective analysis of cases was performed to determine occurrence and severity of cannabis exposure in canines. *Method:* Case details from 1985 to October 2007 were extracted from the VPIS database for all exposures of cannabis in dogs. This database stores the essential case information recorded at the time of the telephone enquiry, with postal follow-up questionnaires providing more in-depth details and case outcome where known. *Results:* A total of 431 cases of cannabis exposure in dogs were reported, 219 (51%) with further follow-up information. Only 14 (6%) out of the 219 cases remained asymptomatic, with 3 of these receiving no treatment. The remainder underwent emesis and/or adsorbent therapy. In the symptomatic the most common clinical effects reported were ataxia, dilated pupils, drowsiness and hyperaesthesia. Both bradycardia (21 cases, 10%) and tachycardia (19 cases, 9%) were documented, and hyperthermia and hypothermia in 11 (5%) and 21 (10%) cases respectively. Just over a quarter of dogs (26%) exhibited some convulsant activity (tremors, twitching, muscle fasciculations or convulsions). Clinical effects usually commenced within 4 hours of ingestion, with total recovery occurring in the majority of cases within 24–72 hours. One dog died and 1 was euthanased. Ingestion was the only route of exposure reported. *Conclusions:* Our findings highlight that canine cannabis ingestion is a common occurrence, and that the majority of cases become symptomatic. Although clinical signs are rarely severe, time to full recovery can be prolonged and therefore potentially costly to the owner. For cases involving police or customs dogs these data are likely to be detailed and accurate. However, whilst cannabis remains an illegal drug, owners may be reluctant to provide accurate histories, so these case data may be flawed. In animals presented to surgery with unexplained neurological signs cannabis ingestion should be considered as a differential diagnosis.

142. Theobromine Toxicity in Dogs – is it Exaggerated?

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

Objective: Theobromine has featured within the 5 most common canine enquiries to the Veterinary Poisons Information Service (VPIS) for the past 5 years. Its toxicity is well documented and the clinical course is often considered challenging for the treating veterinary surgeon. This study aims to re-evaluate the morbidity and mortality of canine theobromine exposure. *Method:* Retrospective analysis of cases of canine exposures to theobromine from the VPIS database. Case data concerning dogs that died or were euthanased were assessed individually, specifically noting the quantity and type of chocolate ingested, clinical effects and their time course. *Results:* From April 1992 up to October 2007, 3014 cases of canine exposure to chocolate were reported; 1025 (34%) had follow up data collected by postal questionnaire. In these cases 436 (43%) of the dogs remained asymptomatic. Hyperactivity, tachycardia and collapse were the most commonly reported clinical effects, although not reported in every case. Convulsions were present in 12 (2%) of symptomatic cases and were reported in 2 (9%) of those that resulted in death or euthanasia. There were 23 fatalities (13 deaths and 10 were euthanased); death was reported as sudden in 2 cases. Three deaths were attributed to renal failure. Quantity and type of chocolate ingested causing fatalities was variable (range 100–2000 g). Enquiries were notably seasonal, with a higher frequency around the Christmas and Easter holidays. *Conclusions:* These data indicate that although the number of enquires are high, fatalities are fewer than anticipated. Correlation between amount ingested and clinical effects appears unclear. In the VPIS cases the clinical effects in fatal cases differ from those usually associated with severe theobromine toxicity (1). Animals euthanased did not appear to have received adequate treatment. Multiple dose activated charcoal was seldom used although theobromine undergoes enterohepatic recirculation. This and meticulous supportive care should be the mainstay of treatment. Although mortality is low, morbidity is high and therefore pet owners and veterinary surgeons should be particularly vigilant around the festive periods. *Reference:* 1: Owens JG, Dorman DC. Drug poisoning in small animals. *Vet Med* 1997; **92**: 149–156.

143. Plastic Explosive Poisoning in Dogs

Sturgeon K, Campbell A. *Veterinary Poisons Information Service (London), Guy's & St Thomas' Poisons Unit, London, UK.*

Objective: A retrospective evaluation of cases of plastic explosive ingestion by dogs, reported to the Veterinary Poisons Information Service (VPIS) London. *Method:* Case data from the VPIS database from 1991 to date for all canine exposures to plastic explosives were reviewed. The database stores the both case information taken at the time of enquiry, and additional data on case progression and outcome captured by means of postal follow-up questionnaires. *Results:* 16 cases were reported to the VPIS (London) in the study period, 9 with additional follow-up data. In 4 instances the dogs remained asymptomatic, although 3 of those received gut decontamination, and 1 was sedated. Those that became symptomatic developed convulsions, with 1 report of recurring seizures alternating with periods of relative calm. A similar presentation is described in a literature report (1). Vomiting was present in 4 cases, 2 dogs were hyperaesthetic, 2 developed ataxia and 2 had hypersalivation. Quantity of explosive ingested, when known, varied from 1–30 g. The onset of clinical effects ranged from 20 minutes to 5 hours, with duration up to 48 hours. All the dogs involved were or were training to be police or service sniffer dogs, and all made full recovery. *Conclusions:* The findings show ingestion of any quantity of any plastic explosive can cause toxicity and precipitate to convulsions. These case data indicate that although this is a rare enquiry and that no fatalities occurred, cases are often serious and may require prolonged and costly treatment. Management should be supportive, although early use of benzodiazepines and/or barbiturates as sedatives/anticonvulsants, or anaesthesia should be considered in any symptomatic animal. Emesis is contra-indicated owing to the potential for convulsions, however adsorbents or gastric lavage could be considered with airway protection. Cases in humans are fewer still, however they follow a similar course to those in dogs (2). *References:* 1. De Cramer KGM, Short RP. Plastic explosive poisoning in dogs. *J South African Vet Assoc* 1992; **63**: 30–31. 2: Davies JOJ, Roberts DM, Hittarage A, Buckley NA. Oral C-4 plastic explosive in humans - a case series. *Clin Toxicol* 2007; **45**: 454–457.

144. *Vipera Berus* (Adder) Bites in Animals – Does Antivenom Availability Affect Case Outcome?

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Objective: To determine whether the outcome of cases of *Vipera berus* envenomation in animals is affected by difficulties in sourcing antivenom. *Method:* Retrospective analysis of case reports on the Veterinary Poisons Information Service (VPIS) database for the years 2006–2007.

These reports frequently document additional commentary on the cases made by veterinarians on VPIS postal follow-up questionnaires. *Results:* 268 enquiries about adder bites in animals were received in the study period (254 dogs, 13 cats and 1 horse). Follow-up data was available in 94 (37.1%) cases (92 dogs, 2 cats), and in these cases only 2 animals, both dogs, remained asymptomatic. Two cases, both dogs, were fatal despite heroic intervention, though in neither was antivenom used. European Viper Venom Antiserum was administered in 52 canine cases, 2 feline cases and the equine case. 19 veterinarians made comments about antivenom on their questionnaires. All were treating dogs. Three were comments about efficacy or indications for usage. 16 reported great difficulties in locating supplies although their patients were *in extremis*. Explanations were that local hospitals had limited supplies (2) and/or were reluctant (6) or refused (2) to provide it, owing to concerns about stocks for human cases. Despite these difficulties, the antivenom was sourced and used for 11 of these cases. For 4 of these the VPIS provided the drug direct. Five veterinarians found antivenom impossible to obtain. For all these cases with commentary there was a favourable outcome, although at the time of follow-up one case where no antivenom had been sourced, was ongoing. In one additional case one dog developed severe coagulopathy and anaemia and following blood transfusions and intensive care was referred to the Royal Veterinary College in London and thus lost to further follow-up, though it did recover. *Conclusions:* These data confirm that many veterinarians experience difficulties obtaining antivenom for *Vipera berus*, although most succeed eventually. This difficulty was not associated with poor outcomes. However, fatalities may occur if antivenom is not used in severe cases. Veterinarians in "Adder-rich" areas should be encouraged to obtain and hold their own stocks.

145. Patterns of Ibuprofen and Paracetamol Ingestion in Cats and Dogs

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Objective: Some veterinary analgesics (e.g. carprofen) are specifically formulated to make them palatable for dogs and cats, and this occasionally leads to animals actively seeking them out. Comparing patterns of ingestion of paracetamol and ibuprofen preparations intended for human use may demonstrate if palatability influences frequency and severity of poisoning in cats and dogs. *Methods:* A retrospective search of the Veterinary Poisons Information Service (VPIS) database was undertaken. Data was taken from case data regarding canine and feline exposures to ibuprofen or paracetamol from 1992 to 2007. *Results:* 4376 cases of canine exposure to analgesics were examined. Of these, 69% concerned ingestion of ibuprofen, while only 31% concerned exposure to paracetamol. 249 feline cases of exposure to analgesics were identified. 68% of these calls were regarding paracetamol and 32% concerned ibuprofen. In dogs, multiple tablet ingestion is common, 81% of cases concerning ibuprofen and 76% concerning paracetamol regarded exposures of more than one tablet. In only 9.3% of feline cases, cats had ingested large amounts (defined as over 400 mg). *Conclusion:* Greater awareness of ibuprofen poisoning to dogs and paracetamol poisoning in cats may affect the number of cases reported to the VPIS. Dogs do not appear to find ibuprofen preparations significantly more palatable. Multiple tablet ingestions are common in both exposures to ibuprofen and paracetamol. Similarly, cases of feline ingestion do not imply a preference for either tablet. However, large ingestions of both paracetamol and ibuprofen are not frequently reported in cats.

146. How Veterinary Practices Made Use of the Veterinary Poisons Information Service, London in 2006

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

Objective: The study examined frequency of veterinary practice use, circumstances behind enquiries and the distribution of calls over 2006. *Method:* Enquiry data from 2006 were reviewed retrospectively and prospective data was also gathered from 571 user satisfaction questionnaires sent out in early 2007. *Results:* In 2006 the Veterinary Poisons Information Service, London (VPIS) took 14,346 enquires, 83% of the VPIS call load that year. Follow-up questionnaires were returned for 3,385 cases. In 2006 1057 businesses registered with the service operating from 2388 outlets. Practice usage was variable; one outlet used the service over 100 times, 18 called over 50 times and 121 called 20 to 50 times. One large out-of-hours group called over 600 times. 91.6% (13,158/14,346) of the VPIS enquiries concerned cats or dogs. 76.7% (11,003/14,346) of enquiries were taken with the animal present at the surgery, whilst 16.4% (2,350/14,346) of enquiries were to determine whether attendance was necessary. 53% (7,515/14,170) of calls were "in-hours" (between 9am and 6pm Monday to Friday). More enquiries were received during autumn and winter months, with the volume peaking in December (1,381 calls). The user satisfaction survey revealed that 19.5% (109/559) of respondents called for every case of poisoning, 63.15% (353/559) for most cases, 15.03% (84/559) only in serious cases and 2.33% (13/559) rarely. 93.23% (496/559) of responses indicated that they would call for advice on animals other than dogs and cats. 95.1% (3,049/3,206) of the respondents of the follow-up questionnaires stated that the only source of information they used to guide the management of their cases was the VPIS. Other users gained additional information from text books (39/152), product manufacturers (33/152), and other vets (19/152). *Conclusions:* the VPIS meets the high demand of the veterinary community, even outside "normal" working hours, and is used both as a triaging service and for advice with the animal in surgery. Although the majority of enquiries concern domestic pets, the VPIS is considered able to provide useful information about other animals.

147. A Comparison of *Allium Species* Poisoning in Cats and Dogs

Sturgeon K, Campbell A. *Veterinary Poisons Information Service (London), Guy's & St Thomas' Poisons Unit, London, UK*

Objective: The *Allium species* is known to cause oxidative damage to erythrocytes in dogs. Feline haemoglobin is potentially more susceptible to oxidative damage owing to its different structure and morphology. This retrospective study reviewed cases reported to the Veterinary Poisons Information Service (VPIS) to determine if *Allium spp* poisoning is a problem in cats. *Method:* Details of every VPIS enquiry are recorded at the time of enquiry, and in most cases a follow-up questionnaire is posted requesting further data on the course and outcome from the treating veterinarian. These data are then collated and entered into the VPIS database. Case information for all *Allium spp* ingestions for cats and dogs were extracted from 1994 to date; only those that had follow-up information were included in this study. *Results:* 69 cases of canine *Allium spp* poisoning were reported. In 14 (20.3%) the dog remained asymptomatic; 3 received no treatment. Vomiting, diarrhoea and abdominal tenderness were the most commonly observed clinical effects, with over half (56%) of dogs suffering at least one of these. 11 dogs (20%) were reportedly anaemic, with a further 3 found with a low packed cell volume. Haematuria was reported in 6 cases (11%) and convulsions in 4 (7%). 2 dogs died and 2 were euthanased. Only 4 feline cases were reported. One cat remained asymptomatic without treatment. Gastrointestinal signs, lethargy and polydipsia occurred in 1 case with full recovery. Anaemia and jaundice were ongoing problems at the time of follow-up from a second case, and 1 cat died from haemorrhage into the pleural and abdominal cavities. *Conclusions:* These data show that the incidence of *Allium spp* cases reported in cats are comparatively low, possibly owing to cats being more selective about what they eat. However, these limited data indicate that feline cases are likely to be serious and to follow a similar clinical course as those in dogs (1). Treatment in all domestic animals should seek to limit absorption and focus on treating any effects of haemolytic anaemia. *Reference:* 1: Cope RB. Allium species poisoning in dogs and cats. *Vet Med* 2005; **100**: 562–566.

148. Hydroxycarbamide (Hydroxyurea) Overdose Causes Methaemoglobinaemia in Dogs

Bates NS, Campbell A. *Veterinary Poisons Information Service, Guy's & St Thomas' Poisons Unit, London, UK.*

Objective: Hydroxycarbamide (hydroxyurea) is an antineoplastic drug used in dogs for the management of polycythaemia vera, mastocytomas and leukaemias. It is currently only available in the UK as 500 mg capsules and the therapeutic dose in dogs is 50–80 mg/kg orally every 3 days or 50 mg/day for 1–2 weeks. Hydroxycarbamide acts by inhibiting ribonucleoside diphosphate reductase and thereby interferes with DNA synthesis without affecting RNA or protein synthesis. Toxicity in humans is characterised by mild bone marrow suppression. *Case series:* A retrospective analysis of the VPIS case database located 11 cases, 8 with follow up. Of these 8 cases only two dogs remained asymptomatic; one had reportedly ingested only 33 mg/kg (less than the therapeutic dose) and the other, a 12 month old cross breed of unknown weight, had taken 3.5 g. All the remaining 6 dogs developed cyanosis and 3 developed methaemoglobinaemia. Collapse, tachycardia, tachypnoea or dyspnoea, congested mucous membranes, dullness or lethargy, tachycardia and thrombocytopenia were all reported twice. The reported dose of hydroxycarbamide taken in symptomatic cases ranged from 80 to 400 mg/kg. The onset of clinical signs was rapid; where reported it was within 1–2 hours of ingestion. Three dogs were treated with methylthioninium chloride (methylene blue) and 4 received oxygen. Acetylcysteine was also given in one case; this case has been reported in detail (1). Five dogs recovered but the sixth case was ongoing at the time of follow up and the final outcome was not determined. *Conclusion:* Methaemoglobinaemia is the major concern following ingestion of hydroxycarbamide in dogs. Any dog that has ingested an overdose of hydroxycarbamide should be urgently assessed for methaemoglobinaemia and hypoxia. Methaemoglobin concentrations will not be readily available in most cases and methaemoglobinaemia should be suspected if the blood is chocolate brown and does not change on exposure to air, dyspnoea is unresponsive to oxygen and the animal has a normal oxygen saturation. Methylthioninium chloride is an antidote for methaemoglobinaemia. *Reference:* 1. Wray JD. Methaemoglobinaemia caused by hydroxycarbamide (hydroxyurea) ingestion in a dog. *J Sm Anim Pract* 2007 Sep 7 [Epub ahead of print].

149. The Effect of Publicity on the Frequency of Feline Permethrin Exposures Reported to the Veterinary Poisons Information Service, London

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

Objective: Permethrin is a pyrethroid insecticide commonly found in "over-the-counter" canine flea treatments. Although permethrin is of low toxicity to most mammals, it is highly toxic to cats. The Veterinary Poisons Information Service (VPIS) frequently receives reports of severe and fatal feline exposures. On the 1st August 2007 the VPIS published data stating that of 286 cases, 87.8% (251/286) of cats developed muscle fasciculations, twitchings, tremors or convulsions, and that 10.5% (30/286) of cats died (1). The article gained significant coverage within the UK veterinary media, with two consecutive front page headlines (30/07/07 and 06/08/07) in the weekly "Veterinary Times". This study reports how increased awareness of feline permethrin toxicity affected the number of cases reported to the VPIS. *Method:* Case information is gathered at the time of enquiries, and by means of postal follow-up questionnaires. These data are entered on to the VPIS database, and were retrospectively analysed. *Results:* In the two months prior to publication the VPIS were referred 15 and 25 cases of feline permethrin exposure (June and July, respectively). Within one month of publishing, 37 cases had been reported. Prior to this the largest number of related calls in one calendar month was 25 (both October 2006 and July 2007). Follow up data collected within one month of publication revealed that fatalities accounted for 21.4% (6/28) of cases. Prior to this the largest number of deaths reported in one month was 3. *Conclusions:* The number of reported feline exposures to permethrin increased with publicity and veterinary awareness, confirming our suspicion that cases are underreported. Fatalities were recorded more frequently post publication, suggesting an increased reporting of severe cases. A large number of deaths were also reported in the month prior to publication. This could be due to follow-up questionnaires being sent out in late July, and thus being completed once awareness had been raised. *Reference:* 1. Sutton NM, Bates N, Campbell A. Clinical effects and outcome of feline permethrin spot-on poisonings reported to the Veterinary Poisons Information Service (VPIS), London. *J Feline Med Surg* 2007; **9**: 335–9.

150. User Perception of the Veterinary Poisons Information Service

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

Objective: The Veterinary Poisons Information Service (VPIS) is a 24-hour emergency telephone service for veterinary professionals and staff of animal welfare organisations. The VPIS

operates from two centres, London and Leeds, giving advice on poisoning in animals. In 2006 the VPIS received 17,292 enquiries (London 14,346, Leeds 2,946). The study aimed to examine how users rated the service provided by the VPIS. *Method:* Data was prospectively gathered from user satisfaction questionnaires sent out to all users in early 2007, and also retrospectively from 3,230 returned follow-up questionnaire sent out after enquiries received by the London centre in 2006. *Results:* Prospective data from user satisfaction questionnaires showed that 63% (359/571) of respondents exclusively called VPIS London, 13% (72/571) exclusively called VPIS Leeds and 18% (102/571) called both centres. Both centres were rated highly for; call waiting time, providing answers and friendliness of staff. Users rated London and Leeds positively in >90% and >85% of questionnaires respectively. When asked to comment on how the service could be improved 50% (82/186) of users said that the service was already good, or that no improvement was required. The majority of suggested improvements were concerned with providing courses, leaflets, newsletters etc. Retrospective data gathered from the London centre's follow-up questionnaires showed that 99.69% (3,220/3,230) of respondents found the information given by the VPIS to be useful. Respondents were invited to comment on the service given by the VPIS, 95.43% (1,106/1,159) of users gave a positive review, suggesting that the VPIS; was "helpful" (381), "provided a good service" (273), was "prompt" (150) and "reassuring" (61). 25 Negative comments were received and mostly concerned lack of information (11) and call waiting time (4). *Conclusions:* Users are satisfied with the service provided by both London and Leeds centres. Improvements to the service could be made by increasing telephone capacity, as well as providing additional training, such as courses, and literature e.g. regular newsletters and leaflets.

151. 5-Hydroxytryptophan (5-HTP) Ingestion and Serotonin Toxicity in Dogs

Bates N, Campbell A. *Veterinary Poisons Information Service (London), Guy's & St Thomas' Poisons Unit, London, UK.*

Objectives: 5-Hydroxytryptophan is a serotonin precursor available without prescription usually in doses of 50 or 100 mg. Rapidly absorbed and converted to serotonin (5-hydroxytryptamine) it is used in humans for depression, as a mood enhancer, for insomnia and headaches. Serotonin toxicity (or syndrome) is caused by drug-induced excess of serotonin in the central nervous system (CNS). This results in overstimulation of serotonin receptors and produces CNS, gastrointestinal and neuromuscular effects. Dogs are reportedly at particular risk of rapid-onset toxicity following ingestion of 5-hydroxytryptophan (1). *Case series:* Retrospective analysis of the VPIS case database located 10 cases, 5 with follow up. One 35 kg dog was asymptomatic after ingestion of 20 tablets (dose not stated). A 4.5 month old whippet developed lethargy after 1 g, and a dose of 28.6 mg/kg caused lethargy and abdominal pain in a Dalmatian. Both dogs recovered. Another Dalmatian was found convulsing after ingestion of 55 tablets (so either 115 or 229 mg/kg) and was euthanased at the owner's request owing to financial constraints. The final case involved ingestion of 15 tablets by a 7 month old Labrador. Within 1–2 hours it was depressed with abdominal bloating. By 3 hours it was hyperaesthetic, rigid, inco-ordinated, hypersalivating, tremulous, vocalising and hyperthermic with flatulence and severe diarrhoea. It also had blindness and exposure keratitis due to ventrally rotated eyes. Management involved cooling measures, diazepam and cyproheptadine tablets (crushed and given rectally for 10 hours). By 12 hours the hyperaesthesia was resolving and vision returned. Although the dog could walk at 24 hours it was still trembling, and fully recovered by 48 hours. *Conclusion:* Dogs develop life-threatening signs within hours of 5-hydroxytryptophan ingestion including behavioural changes and neuromuscular activity; in severe cases developing coma, rigidity, hyperpyrexia and convulsions. Treatment is supportive with cooling measures and sedation as required. Cyproheptadine, a non-specific serotonin antagonist, has been used successfully to manage dogs with serotonin toxicity. Most animals recover with aggressive and prompt supportive care. Humans do not appear to develop such severe signs and so poisons centre staff advising veterinarians should be aware of this different canine response. *Reference:*
1. Gwaltney-Brant SM, Albretsen JC, Khan SA. 5-Hydroxytryptophan toxicosis in dogs: 21 cases (1989–1999). *J Am Vet Med Assoc* 2000; **216**: 1937–40.

152. Low Toxicity Associated with Low Levels of Embutramide in a Survivor after Tanax (T-61)-attempted Suicide

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Tanax is widely used in veterinary euthanasia: constituents are the general anaesthetic embutramide, the local anaesthetic tetracaine, the neuromuscular blocking agent mebezonium, and the solvent N,N-dimethyl-formamide. Several human cases of attempted suicides and death are reported, principally attributed to the anaesthetic and neuromuscular blocking properties, whereas delayed hepatotoxicity observed in nonfatal cases has been attributed to N,N-dimethyl-formamide. Elevated post-mortem blood concentrations of embutramide are reported in fatal cases (1–3), but no data in survivors are available. *Objective:* To report a case of attempted suicide by intramuscular injection of Tanax that manifested only mild symptoms and in which embutramide blood levels were detected. *Case report:* A 78-year-old man was found unresponsive after self administration by intramuscular injection of an unknown amount of Tanax. At admission he was unresponsive with effective spontaneous breathing, no signs of neuromuscular block nor hypertonia or myoclonus: four hours later the patient regained a normal level of consciousness, with normal ECG and biochemical parameters. Serum embutramide concentrations (HPLC-UV) at 4, 12 and 22 hours were 1.4, 0.53 and 0.37 micrograms/ml respectively, showing first order kinetics of elimination with an half life of 9.6 hours. Embutramide was detected in a drop found in the syringe (GC-MS). The patient was discharged on day 3. *Conclusions:* Toxic and lethal concentrations of embutramide in humans are unknown: blood levels in three post-mortem examinations resulted 31, 43 and 90 micrograms/ml respectively (1–3). Even if initially an entire vial of 50 ml of Tanax was suspected, the dose of Tanax really injected in this case remains unknown. According to kinetics parameters (3), the low levels of embutramide detected may signify, *a posteriori*, an injection of only 5 ml of Tanax. This is in agreement with the mild symptomatology observed for a short time, followed by complete recovery: no renal or hepatic alterations were recorded in the follow-up. Embutramide can be easily detected in suspected liquids and in the biological samples confirming the kind of poisoning. *References:*
1. Smith, L. *Vet Hum Toxicol* 1989; **31**: 319–320; 2. Kintz, *et al. J Anal Toxicol* 2002; **26**: 529–531. 3. Abe, *et al. J Anal Toxicol* 2004; **28**: 118–121.

153. Detection of Medication Errors: Role of a Poison Control Center

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Objective: The aim of this study is to evaluate the importance of spontaneous detection of medication errors (ME) among calls received by physician responders in the Moroccan PCC and to assess those ME according to type, cause and reason for occurrence. *Method:* It is a retrospective study of the ME cases collected by telephone in the Moroccan PCC during the year 2006. All ME cases notified to the Moroccan PCC during the period under study were eligible for the study. *Results:* During the study period the Moroccan PCC received 1992 calls for poisoning amongst which 919 cases were due to drugs (46.1%). 98 cases of drug poisoning were related to ME. The mean age of the victims of ME was 19.18 ± 19.89 years (1 day to 70 years). Children under 15 years were involved in 46.9 %. The overall sex ratio was 1.04. Benzodiazepines (anxiolytic and hypnotic) were the most common therapeutic classes involved in ME (14.2%), followed by analgesics/antipyretics (13.3%), anti-inflammatory and antirheumatic products (11.2%). The most frequent active ingredient was acetaminophen (12.2%). The most common formulation subject to error remains tablets (50%), oral solutions (21.4%) and suppositories (13.3%). 49% of the patients were symptomatic (child: 32.6%, adult: 63.4%). Symptomatology was dominated by neuromuscular symptoms (47.4%). The reason for the ME was dominated by self medication (54.3%), followed by problems of dispensing (16.2%), of observance of treatment (12.4%), of administration (9.5%), and prescription (7.6%). The responsibility for the error was due to the patient himself (46.8%) or to his family (23.4%), to pharmacists (15.9%), physicians (6.5%), or nurses (7.4%). 8 types of error were found. ME were due to some error of dose (42.6%), of product (28%), route of administration (7.5%), wrong patient (7.5%), drug expiry date (4.6%), disregard of contraindication (1.8%), or lack of monitoring (1.8%). *Conclusion:* PCC is able to participate in this data collection of high quality. The ME happens more often with drugs, even with an analysis of the critical points being at the interface of each person's role.

154. Unintentional Adult Medication Poisoning: A Significant Challenge to Poison Centres

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Objective: Poison Centres often pay limited attention to poison prevention messages directed to adults since unintentional poisonings in adults are often considered to be an uncommon occurrence. We undertook to characterize the nature and frequency of adult unintentional medication exposures with a view to identify poison prevention messages targeted to the adult population in Saskatchewan. *Methods:* All adult unintentional poisonings due to medications reported to the Saskatchewan Poison Centre from April 1, 2006 to March 31, 2007 were retrospectively reviewed. Inclusion criteria were age ≥ 20, accidental exposure, including administration error, and sufficient narrative to determine activity, practices, products, and routes of exposure. *Results:* Of the 421 unintentional adult medication exposures, 352 (84%) cases met the inclusion criteria. Exposures were equally distributed among all ages 20–39 (36%), 40–59(31%), 60+ (33%) with 63% occurring in females. Oral dosing errors accounted for 50% of all medication errors due to double dosing (72%), larger than double dose taken (15%) and super-dosing for therapeutic effect (13%). The main reasons for double dosing were forgetfulness (20%), usually occurring in the elderly, timing error (14%) and dosage amount error (8%). Over half the patients who took a larger than double dose were in the 60+ age group (54%) and predominantly female (81%). Super-dosing for therapeutic effect predominated in the 20–39 age group with pain relief as the main reason. Unintentional alternate route errors accounted for 25% of all medication exposures with 58% of these due to an agricultural needle-stick occurring most often while vaccinating livestock. Inadvertent errors accounted for 23% (81) of all medication errors with an adult ingesting one medication instead of another being the main cause (55%), taking a medication by an other than prescribed route (15%), cognitive dysfunction(15%) or caregiver errors (14%) route. *Conclusion:* Adult unintentional medication exposures can occur across all age ranges due to a variety of circumstances. Developing prevention schemes to reach a diverse adult population who normally do not consider themselves at risk for poisoning is the next essential challenge.

155. Iatrogenic Poisoning with Atropine Containing Eye Drops

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Objective: German ophthalmologists use atropine containing eye drops, mainly for diagnostic purposes. One drop of a 0.5% solution contains 0.25 mg atropine, which corresponds to an intravenous therapeutic dose for children. Atropine is easily absorbed from the mucous membranes of the eye and the gastrointestinal tract. Therefore, as recognized already 100 years ago, regular ocular application may lead to systemic poisoning (1). Today, poisons centres are still involved in such cases and may be able assess the frequency and risk of poisoning. *Methods:* The GIZ-Nord Poisons Centre Göttingen (GIZ-Nord) is serving 13 million inhabitants in Northern Germany; the Poisons Centre Erfurt (PC EF) is serving 11 million people in the Eastern part of the country. A retrospective analysis of all cases of ocular exposure to atropine eye drops reported to these poisons centres between January 1996 and August 2007 was performed. *Results:* In total, 69 cases were identified in the databases of GIZ-Nord (21 cases) and of PC EF (48 cases) that fulfilled the inclusion criteria, corresponding to 1.3 and 3.8 cases per year for 10 million inhabitants, respectively. Age of patients varied between 0.5 to 8.0 years. Besides intended mydriasis the most frequently reported symptoms were flushing (28 cases), tachycardia (26), agitation (16) and hyperthermia (14). Three cases were evaluated to be severe because of severe tachycardia (>190/min) and 12

cases were evaluated moderate according to Poisoning Severity Score (2). In 9 cases only mydriasis was reported. *Conclusion:* Children suffer from systemic intoxications caused by atropine eye drops which can be life threatening. The frequency varies by a factor of 3 between North and East Germany. Data from poison centres are a solid basis to initiate surveillance measures for pharmaceuticals. *References:* 1. Gray LG. Avoiding adverse effects of cycloplegics in infants and children. *J Am Optom Assoc* 1979; **50**: 465–470. 2. Persson HE, Sjöberg GK, Haines JA*, et al*. Poisoning Severity Score. Grading of acute poisoning. *J Tox Clin Toxicol* 1998, 36: 205–213.

156. Iatrogenic Intravenous Medication Errors Reported to the PICs Erfurt and Göttingen

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Objective: Referring to a previous study (1) we investigated the incidence of iatrogenic intravenous medication errors (IIME) reported to the Poisons Information Centres (PICs) Erfurt and Göttingen (responsible for 24.1 million inhabitants in 8 federal states). *Methods:* Calls regarding IIME received by the two PICs from 1997 to 2006 were analysed retrospectively. Data were categorised into error types, age groups, drugs involved, and estimated risk of toxicity. *Results:* 396 cases of IIME were consulted by the PICs. Patients affected were children (25%; 75% of them babies and toddlers) and 75% adults. Among adults 43% were in the mean age group 18 to 65 years; 21% were seniors, but in 36% the age remained unknown. Cases of IIME increased from 18 in 1997 to 75 in 2006. Most frequent drug classes (ATC classification) involved were antipsychotics (8.3%), antithrombotics (5%), antihistamines for systemic use (5%), other systemic drugs for obstructive airway diseases (4.5%), and antimetabolites (3.8%) The main types of errors were overdosage (58.6%) and wrong route of administration (27.8%). The estimated risk of toxicity was: 14.1% none, 80% risk, and 5.9% unpredictable risk. In 34 cases (8.6%) poisoning was estimated to be severe. Medical treatment was recommended in 94.1% of cases. 71 patients (17.9%) were followed to a known outcome. 34 (47.9%) of these patients were asymptomatic and 37 (52.1%) symptomatic with minor (14 cases), moderate (1 case), and severe features (8 cases) but most recovered completely. In 8 patients with severe symptoms consequential damage could not be excluded and in 6 patients IIME resulted in death. *Conclusion:* Although the proportion of IIME (0.1% of all calls) was low the incidence of severe symptoms in IIME followed to a known outcome was high (21%). Therefore, especial care should be taken in intravenous medication. *References:* 1. Deters M, Prasa D, Schaper A, *et al*. Iatrogenic Intravenous Medication Errors Reported to the PIC Erfurt. Clin Toxicol 2007; *In press*.

157. Frequency of Medication Errors with 21-hour IV Acetylcysteine Administration for Acetaminophen Overdose

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Objective: Acetadote®, an intravenous preparation of acetylcysteine, became commercially available in the United States in June 2004 for the treatment of acetaminophen poisoning. The dosing regimen is complex, consisting of a loading dose followed by two maintenance doses, each with different infusion rates. The purpose of this study is to analyze the frequency of medication errors related to the complex dosing regimen for intravenous acetylcysteine. *Methods:* A retrospective chart review of poison center records of all patients treated with intravenous acetylcysteine from August 1, 2006 to August 31, 2007 was performed. Data collected included acetylcysteine dose, infusion rate, interruptions in therapy, and unnecessary administration. *Results:* There were 221 acetaminophen overdose cases treated with intravenous acetylcysteine that met inclusion criteria. Of these, 83 medication errors occurred in 73 patients (33%). The frequency and types of medication errors were 1.4% incorrect dose, 4.5% incorrect infusion rate, 18.6% more than 1 hour interruption in therapy and 13.1% unnecessary administration. *Conclusion:* Medication administration errors occur frequently with intravenous acetylcysteine. A simpler dosage regimen and/or better communication between the ED, the units to which these patients are admitted, and the pharmacy would help decrease the frequency with which intravenous acetylcysteine dosage regimen related errors occur.

Table: Type of errors involved in IV acetylcysteine administration

Type of error	# of cases
Incorrect dose	3
Loading dose administered at 140 mg/kg	1
Loading dose administered at 70 mg/kg	1
4-hr maintenance infusion skipped	1
Incorrect rate	10
Loading dose administered over 15 minutes	5
4-hr maintenance infusion error	3
16-hr maintenance infusion error	1
Unknown which infusion	1
Interruption in therapy > 1 hour	41
Needless Administration	29
Started prior to 4-hr level, which was subtoxic	22
Started despite subtoxic level and normal LFT's	4
Continued beyond 21 hours when not needed	3

158. A Thousand Fold Clonidine Dosing Error

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Objective: To present the details of a 1000 fold overdose of clonidine. *Case report:* A 10 yo boy prescribed clonidine for aggressive behavior presented to hospital several days after his daily dose was increased from 50 to 100 micrograms. At presentation he was lethargic, with a heart rate of 44, and blood pressure163/105. CT scan, lumbar puncture and screen for abuse drugs were negative. Atropine given for the bradycardia resulted in a heart rate of 127 and blood pressure of 190/130. Naloxone 2 mg was given without response. The patient's blood pressure normalized within 24 hours, but he remained bradycardic, lethargic and disoriented for three days. On day four the patient was awake and alert, but developed tremor, tachycardia, and hypertension attributed to clonidine withdrawal. Intravenous lorazepam 2 mg was given for symptomatic care. Subsequently, the patient became combative, with HR 190 and BP 162/95. The patient was discharged after 8 days and restarted on a tapering dose of clonidine. Initially, the patient's condition was attributed to doubling his daily dose. However, symptoms did not occur until after the forth daily dose at the higher level and were inconsistent with a small clonidine overdose. Investigation revealed the patient had been taking an extemporaneous liquid preparation of clonidine. When the dose increase caused his normal supply to run out early, the pharmacist prepared an additional six teaspoonfuls. Unfortunately the preparation contained 110 miligrams/5 mililiters rather than 110 micrograms as written – a 1000 fold error. The patient developed toxicity after taking the first dose of this preparation. *Conclusions:* In large overdoses, the central blood pressure lowering action of clonidine is overwhelmed by its stimulation of peripheral alpha receptors with resultant hypertension. Bradycardia in this setting is secondary to hypertension. Though not commonly described in children, clonidine withdrawal syndrome may occur when it is stopped abruptly after chronic use. In the United States, clonidine use in children with behavioral problems is becoming more common. A commercially prepared liquid dosage form is not available. Pharmacist prepared dosage forms may be an attractive alternative. Pharmacists in modern practice may be poorly prepared to make these dosage forms.

159. Unintentional Intravenous Injection of Barium Sulfate in a Child

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Objective: Barium sulfate is relatively insoluble and intravasation into the portal system during barium enema may be tolerated, although barium deposits in the liver can be inflammatory and persist for years. Intravasation into the systemic circulation carries a worse prognosis because of a high rate of mortality from massive pulmonary embolism (1). We report a case of barium sulfate injection directly into the superior *vena cava* during an upper gastrointestinal series (UGIS) in which the patient's central venous catheter (CVC) port was mistaken for her gastrostomy tube. *Case report:* A 17 month old girl was brought to the fluoroscopy suite for an UGIS with barium sulfate contrast. Her past medical history was significant for a premature birth at 34 weeks gestation, short gut syndrome after bowel resection for necrotizing enterocolitis and gastroschesis, and multiple bouts of sepsis. She was admitted to hospital for replacement of her CVC but developed a diarrheal illness with multiple bouts of projectile vomiting, and was therefore was scheduled for the UGIS. While in the fluoroscopy suite approximately 3 mL of barium sulfate was injected into her CVC instead of her gastrostomy tube. The error was recognized when radiography demonstrated barium in the right atrium, and 10 mL of blood containing a chalky white suspension was immediately aspirated from the catheter. The patient vomited three times, but then appeared well until 30 minutes later when she developed rigors. That evening she developed fever which was treated with broad-spectrum antibiotics. Subsequent radiographs failed to show residual barium, no signs of respiratory distress developed, and she was discharged in stable condition four days later. *Conclusion:* Previous reports of barium intravasation into the systemic circulation have described a high mortality rate from massive pulmonary embolus. To our knowledge this is the first report of direct injection of barium sulfate into the systemic venous circulation. We believe the patient survived because the error was immediately recognized, and the barium removed prior to embolism. *Reference:* Takahashi M, Fukuda K, Oshkubo Y, *et al*. Nonfatal barium intravasation into the portal venous system during barium enema examination. *Int Med* 2004; **43**: 1145–1150.

160. Therapeutic Errors; Enquiries to a Scottish Centre 2004–2007

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Objective: Retrospective review of telephone enquiries to a poisons centre relating to therapeutic errors. Analysis included: types of products involved in these enquiries, reason(s) for the error (if known), demographic details (age, gender) of patients involved, and severity of symptoms. *Results:* 579 enquiries were identified in the three years from 1st April 2004 to 31st March 2007, representing 10% of our total enquiries over this period. Median patient age (where known) was 45 years (range 2 days - 103 years). 60% of patients were female, 36% male. 11% of patients were aged under 5 years; 24% over 70 years. Therapeutic errors fell broadly into three categories; patients receiving an excess dose, patients receiving the wrong medication, and taking medication the wrong way. The most common agent was paracetamol. 105/579 (18%) of the enquiries involved one or more paracetamol-containing product. There was a bimodal distribution in patient age; adult patients tended to take multiple paracetamol-containing products, e.g. for dental pain, whereas paediatric enquiries often related to 'double dosing', e.g. both parents giving the same cold remedy to a child. 26 enquiries (4.5%) involved tiotropium bromide (Spiriva®). Median patient age was 72 (range 50–84 years). The apparent elderly bias of these patients likely reflects the nature of this drug. 100% of these patients were exposed by ingestion, e.g. they inadvertently swallowed the inhaler capsule. Elderly patients were also predominant in cases of accidental ingestion of calamine lotion, where it was mistaken for an oral medication (often Gavsicon®). Only one patient was said to have severe toxicity at the time of the initial enquiry. This was a patient who had taken a large quantity of digoxin. The patient recovered, but did require treatment with digoxin specific FAB fragments (Digibind®). *Conclusion:* Therapeutic errors continue to represent a significant proportion of NPIS telephone enquiries following the major shift to TOXBASE in the UK. While fortunately mainly of low toxicity, data on these enquiries give us the opportunity to target harm-reduction messages. Review of our enquiries enables identification of areas which may benefit from further outreach or educational work.

161. Low Molecular Weight Heparin Overdose

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Objective: Low molecular weight heparin (LMWH) is used for the treatment and prevention of coagulative disorders. Major hemorrhage has been reported in 0.5–4% of patients receiving therapeutic doses of LMWH (1). However, there have been no reports in the literature on acute overdose in adults. We report a case series of patients with acute overdose of LMWH. *Methods:* A retrospective chart review of California Poison Control System (CPCS) database between 1997–2007. Inclusion criteria included all patients with a reported parenteral overdose of LMWH including ardeparin (Normiflo®), dalteparin (Fragmin®), anaparoid (Orgaran®), enoxaparin (Lovenox®), fondaparinus (Arixtra®), nadroparin and tinzaparin (Innohep®). Cases were excluded if therapeutic doses of LMWH were administered. *Results:* There were 21 patients, all whom were exposed to enoxaparin. These included 7 females, 13 males and 1 patient whose gender was not documented. The ages ranged from 25 days to 92 years old (mean 42.4 years). The reasons for overdose included medical miscalculation (3 cases, all infants), intentional misuse (2 patients), accidental overdose (7 cases), self-harm attempt (7 cases) and unknown in 2 patients. The magnitude of the overdose ranged from 50 mg to 1300 mg (representing 0.1–80 times the recommended therapeutic dose). Seven cases were documented to have overdosed on more than 2 times the therapeutic dose. No patients were reported to have clinical evidence of bleeding. Two patients were treated with protamine because they had received more than 2.5 times the therapeutic dose of LMWH. *Conclusion:* Given the rarity of LMWH overdose, there is no clear consensus on its management. No patients in this series had bleeding complications and only two were treated with protamine. *Reference:* 1. Ellis MH, Hadari R, Tchuvrero N, *et al*. Haemorrhagic complications in patients treated with anticoagulant doses of a low molecular weight heparin (Enoxaparin) in routine hospital practice. *Clin Appl Thrombosis/Hemostasis* 2006; **12**: 199–204.

162. Lethal Dose of Opiates Contained in an Elastomeric Capsule Labeled as Vancomycin

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Objective: This is a case of a 67 year-old male who received a lethal dose of opiates instead of his prescribed antimicrobial agent via an elastomeric capsule. *Case report:* A 67 year-old male presented with alteration in mental status. On arrival he had vital signs: pulse 110, BP 173/83, oxygen saturation 57% and temperature 36.1 degrees Celsius. His past medical history included hypertension, hyperlipidemia, and recurrent cellulitis treated with vancomycin. Except for coma, pinpoint pupils, and agonal respirations, the patient's exam was unremarkable. He was intubated after 2.2 mg IV naloxone failed to reverse respiratory depression. The patient had no access to or history of opioid use. Thirty minutes before presentation, however, he had received an intravenous infusion of vancomycin administered by his wife at home. The vancomycin, obtained from a home infusion medication supply company, was contained in one of five sealed elastomeric capsules delivered earlier that day. The patient was admitted to the ICU and managed with supportive care. He was discharged with intact neurologic status 25 days later after multiple complications including pneumonia, atrial fibrillation, pneumothorax requiring a tube thoracostomy, and bacterial tracheitis requiring a tracheostomy. A qualitative comprehensive toxicology screen of urine for 1043 substances identified morphine, codeine, naloxone, lidocaine and caffeine. The original elastomeric container was not available for testing, but another container from the same delivery was submitted for testing to the state forensic laboratory. This intact container was labeled as Vancomycin 1 g in 240 mL of normal saline. The forensic laboratory confirmed that the alkaloidal contents of the elastomeric capsule were 10% codeine, 4.4% 6-monoacetyl morphine, and 84% morphine. No vancomycin was identified in the infusion bottles. The case was referred to the local police department and the state department of health drug control board. The home infusion company was also immediately notified to prevent similar occurrence. Unfortunately, the source of the narcotics within the elastomeric container was never identified. *Conclusion:* We are reporting the first known case of opioid overdose from an adulterated elastomeric capsule that was labeled as containing an antimicrobial agent.

163. Self Harm Repetitions in One Year Follow up of Adolescents Deliberate Self Poisoning

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Objective: Acute poisoning is a significant health problem all over the world. Poisonings are a well-known cause of morbidity and mortality in adolescents in Iran (1, 2). The main aim of this study is to determine the incidence of self-harm repetition in adolescents poisoning who were admitted to Loghman-Hakim Poison Hospital (LHPH) which is the only referral teaching hospital in Tehran. *Methods:* 400 randomly selected adolescents (12–18 years) who were hospitalized for deliberate self-poisoning from 5/15/2005–3/15/2006 and who agreed to participate in a one year follow-up study were selected and demographic factors focused on repetition of act and circumstances. The study factors were: age, gender, history of repetition, physical and mental disorder and family history of attempted suicide. *Results:* F/M ratio was 3.1/1. The median and modal age was 16 ± 1.3 and 17 year respectively. 29.9% and 31.4% had chronic physical disease and/or mental disease. History of mental disease in family was claimed in 42.5%. Nearly 76% of parents were living together. Repetition was confirmed in 29.9% of adolescents (F/M = 2.8/1) and 19.7% of family units while 17.9%, 4.5%, 4.9% had one, two and remained in the study during the follow-up period of whom 12.9% repeated self harm once (43.6%), twice (33.3%) and (23.1%) up to 5 occasions and in 94.7% by self poisoning (F/M = 2.3/1). Self-mutilation happened in 13.8% on one (37%), two (17%) and up to 12 occasions (46%). Considering 20 patients who used both methods, there was significant correlation between self-harm and self-mutilation ($p<0.001$). In total 63% of all patients did not make an appointment with health care for their act or its complications after discharge. The remainder were visited by psychiatrists (11.9%), psychologists (11.5%), neurologists (3.5%) or others. Hospitalization occurred in 34 patients (11%), of whom 26.5% were due to a suicidal act, 20.6% mental illness and 14.7% different accidents. No mortality was found. *Conclusion:* Efforts need to be targeted toward suicide prevention in the young population, especially among female adolescents. *References:* 1. Afshari R, Majdzade R, Balali-Mood M. Pattern of acute poisonings in Mashhad, Iran 1993–2000. *J Toxicol Clin Toxicol* 2004; **42**: 965–75. 2. Hassanian-Moghaddam H, Pajoumand A. Epidemiology of adolescents poisoning in Tehran. 6th Annual Congress of Asia Pacific Association of Medical Toxicology; 2007; 12–14 December, Bangkok, Thailand.

164. Findings from the Italian Program for Surveillance of Acute Pesticide-related Illness, 2005

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Objective: To report on an Italian program for surveillance of acute pesticide related illness. *Results:* In 2005, the Italian Program for Surveillance of Acute Pesticide-Related Illness identified 1,028 cases, 90% of which were notified by the poison control centers. Among these cases 864 (84%) were unintentionally exposed and included 520 (60%) subjects exposed to agricultural pesticides and 344 (40%) subjects exposed to non agricultural pesticides. The majority of the agricultural pesticide-related illnesses were men (75%). About 63% of all exposures occurred at work, especially in agricultural settings (76% of occupational exposures). The mean age was 45 years. 5% of individuals were aged less than 5 years. Some 70% of all the reported exposures occurred between May and September. Most of the illnesses were of low severity (94%). Severity was moderate in 5% of the cases, and high in four cases (1%). No fatalities were identified. Insecticides were responsible for 45% of all illnesses. The active ingredients responsible for the largest number of cases were: glyphosate (n = 56), copper sulphate (n = 55), methomyl (n = 52), metam-sodium (n = 24). Three episodes of collective environmental exposure to soil fumigants involving 23 cases were also detected. Cases unintentionally exposed to non agricultural pesticides were evenly split between males and females. The majority of these individuals (80%) were exposed at home. The mean age was 35 years. 17% of these individuals were aged less than 5 years. About 68% of the exposures occurred between May and August. Severity was low in 93% of the cases, and moderate in 7%. No cases of high severity nor fatalities were reported. Insecticides were responsible for 87% of all illnesses. The active ingredients responsible for the largest number of cases were: propoxur, cyfluthrin and tetramethrin in combination (n = 23), propoxur alone or in combination with other compounds (n = 22), cyfluthrin alone or in combination with other compounds (n = 21), and N,N-diethyl-m-toluamide (n = 20). *Conclusions:* Surveillance provides an important tool to identify emerging pesticide problems and associated risk factors. The observations available in Italy suggest that greater efforts are needed to prevent acute pesticide-related illness.

165. Withdrawn

166. Fatal Hospital Cases Diagnosed as Acute Poisonings from 1999 to 2005

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Objective: Official statistics on mortality are partly based on hospital activity records. The coding of diagnoses is difficult, and this process may be biased partly because it contributes to the hospital income. To assess the reliability of these records, we performed a study of all fatal cases recorded as acute poisonings in three different hospitals in Norway in the period 1999–2005. *Methods:* Inclusion criteria were fatal hospital cases with an ICD-10 primary or additional diagnosis of acute poisoning. The patient records were retrospectively evaluated independently by two physicians experienced in clinical toxicology. Consensuses were subsequently made for each record by the physicians in collaboration with a pharmacist. *Results:* 142 patients met the inclusion criteria, three records were missing, and 139 (98%) were studied. 29 (21%) cases were not poisonings: 11 (38%) were coded as acute poisonings by pure mistakes, 10 (34%) were chronic effects of alcohol or drug abuse, while 8 (28%) were side effects of pharmaceuticals given in conventional doses. The latter group was older (mean 78 years) than the other excluded (mean 63 years), t-test p-value 0.03. The remaining 110 cases were considered as real acute poisonings, and were analyzed further. Among the patients with a primary hospital diagnosis of acute poisoning (n = 32), poisoning was considered to be the single most important cause of death in 28 (88%). Among the patients with acute poisonings as additional hospital diagnoses (n = 78), poisoning was considered to be the single most important cause of death in 41 (53%). In patients younger than 70 years of age (n = 79), acute poisonings was considered to be a major cause of death (alone or in combination with other major causes) in 69 (87%), while only in 10 (32%) patients older than 70 years (n = 31). *Conclusion:* Hospital activity records provide inaccurate statistics regarding deaths from acute poisonings. 1/5 of the lethal cases with a diagnosis of acute poisoning were not poisoned. Acute poisoning as a major cause of death was commonly not reflected by the primary diagnosis. The border between acute poisonings and side effects of medications was especially vague among older patients.

167. What Evidence is there that the Methamphetamine is a Significant Issue in the UK Compared to Established Recreational Drugs such as MDMA ('Ecstasy')?

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Objective: Methamphetamine use is common in Eastern Europe and there is increasing interest in whether it is an emerging recreational drug in the UK, with increased expenditure on campaigns to highlight the potential risks of methamphetamine (1). *Methods:* We undertook a retrospective study collating data on the number of enquiries to our poisons

information service relating to methamphetamine and MDMA; presentations to our ED with acute methamphetamine or MDMA toxicity; and the frequency of positive urine tests for methamphetamine and MDMA in workplace drug screening programmes. *Results:* There was a small increase in the number of methamphetamine related calls to the poisons service, but it remained uncommon (0.1% of all recreational drugs cases in 2000 to 1.23% in 2006) compared to MDMA (17.3 – 42.7% of all recreational drugs cases). There were 5 presentations to our ED relating to methamphetamine over a 15 month period compared to 171 for MDMA. Of the 254,440 urine samples screened for the presence of drugs in the workplace (2000–2006), 3 were positive for methamphetamine and 147 for MDMA. *Conclusions:* We could find no evidence of increasing use of methamphetamine from the occupational screening or that acute methamphetamine poisoning is a significant clinical problem compared to established recreational drugs, such as MDMA. The limited resources available for recreational drug issues should be proportionally directed towards drugs causing an immediate and continuing healthcare risk such as MDMA, rather than specifically to emerging drug issues such as methamphetamine. *Reference:* 1. The Times on line. Crystal meth: coming to a town near you. http://www.timesonline.co.uk/tol/life_and_style/health/article1755178.ece

168. Impact of Licence Change on Co-Proxamol Mortality in Scotland

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Objective: Co-proxamol (paracetamol 325 mg and dextropropoxyphene 32.5 mg) causes death after overdose (1). Many deaths occur out of hospital, due to cardiac effects of dextropropoxyphene (2). The Committee on Safety of Medicines withdrew co-proxamol in January 2005 (3). The effect of this legislative change on the mortality from co-proxamol poisoning in Scotland is reported. *Methods:* Mortality data related to poisoning in Scotland were obtained from the General Register Office. Proportional co-proxamol mortality before the change in legislation (2000–2004) was compared to that afterwards. Quarterly primary care prescribing data for 2000–2006 were obtained from the Information and Statistics Division of the Scottish Executive Health Department. *Results:* While no significant fall in the number of deaths secondary to co-proxamol poisoning was noted in 2005 (20.6%) compared to the previous 5 years (21.8%; Fishers Exact Test p=0.82), the number of deaths fell significantly in 2006 (7.8% vs 21.8% (2000–4); p<0.0001). The total number of deaths due to poisoning also fell significantly following the withdrawal of co-proxamol (mean 2000–4 vs 2005–6; 171.2 vs 129.5; p=0.005). Amongst co-proxamol deaths, a significant decline was observed in males in 2006 (3.6% vs 19.4% (2000–4); p=0.0001) with the greatest effect on out of hospital deaths (2000–4 vs 2006; 21.8% vs 2.9%; p < 0.0001). A sharp decline in co-proxamol prescriptions occurred following legislation (mean of 6 quarters pre-legislation change (07/03–12/04) 300,555 items/quarter; first quarter 2006/07 67,997 items. *Conclusions:* A significant fall in the number of deaths due to co-proxamol poisoning, particularly in males, was observed. Whether this fall accounts for the decline in total poisoning deaths in Scotland is unclear. Total mortality figures began to fall from 2005, mortality rates from co-proxamol poisoning alone did not fall significantly until 2006. The data demonstrate the benefits of the legislation in reducing death caused by co-proxamol poisoning. *References:* 1. Afshari R, *et al*. *Br J Clin Pharm* 2005; **60**: 444–447. 2. Afshari R, *et al*. *J Toxicol Clin Toxicol* 2004; **42**: 476–477. 3. Medicines and Healthcare products Regulatory Agency. http://www.mhra.gov.uk

169. Outcome of Parenteral Epinephrine Autoinjector Exposures - A 12 Year Review

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Objective: To describe the outcome and treatment of parenteral exposures to epinephrine autoinjectors. *Methods:* A 12 year retrospective review of autoinjector cases were analyzed from a national database (AAPCC TESS) and included the years 1994–2005. Charts were reviewed where specific treatments were noted. *Results:* A total of 9,981 potential exposures were reported with a median age of 14 years (range 1–89). Four exposure sites were identified: own/other residence (89%), workplace (5%), school (3%), and healthcare facility (HCF) (< 1%). 41% of exposures were managed on-site (not referred to a HCF), while 57% were managed in a HCF. General treatments reported: some treatment 59% (n=5899), observation only/ no therapy 28% (n=2737), unknown 12% (n=1177). Medical outcomes for these patients included: not followed/ minimal effect expected 19%, no effect 7%, minor 49%, moderate 15%, severe < 1%. In a nested sample of 157 patients whose specific treatments were noted and charts were available for review: 33% (n=51) received warm water, 44% (n=68) received nitropaste, 31% (n=48) received phentolamine, and 1% (n=2) received terbutaline. All 157 pts had a good outcome. *Conclusions:* In this study sample of 9,981 cases, parenteral exposures to epinephrine autoinjectors resulting in moderate to severe outcomes were less than 16%. However, in the nested sample (n=157), pharmacologic treatment was provided in 76% of cases where specific treatment was noted. Specific prospective studies are needed to provide more concise estimates of morbidity and to provide a controlled comparison of supportive versus specific pharmacologic treatment. *Reference:* Mrvos R, Anderson BD, Krenzelok EP. Accidental injection of epinephrine from an autoinjector: invasive treatment not always required. *South Med J* 2002; **95**: 318–320.

170. Declining Frequency of Hospital Admission Following Overdose with Some Antiepileptic Drugs

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Objective: Overdose with antiepileptic drugs is common. One reason has been the use of some of these agents (e.g. sodium valproate, carbamazepine and lamotrigine) as mood stabilising agents for mania. Others may be involved because of their use for conditions associated with an increased risk of self harm, including chronic pain (e.g. gabapentin) or anxiety (e.g. clonazepam). This study investigated the changing patterns of primary care prescribing and overdose admissions involving antiepileptic drugs in the north of England. *Methods:* Prescribing data for antiepileptic drugs was obtained from prescription analysis and cost (PACT) data for Newcastle Primary Care Trust (available for October 2002 to March 2007). Overdose admission data were obtained from the two Newcastle hospitals admitting patients with acute drug overdose and was available for the period 2000 to 2006. *Results:* There were small increases in primary care prescribing of gabapentin, lamotrigine and sodium valproate and reductions in prescribing of phenobarbital and phenytoin over the period for which data were available, but no important changes in prescribing of carbamazepine. There were 346 overdose admissions between 2000 and 2006. The mean annual numbers of presentations over the periods 2000–2002, 2003–2004 and 2005–2006 were 25, 10 and 14 for sodium valproate, 22, 12 and 8 for carbamazepine, 6, 0.5 and 0 for phenytoin, and 3, 3.5 and 0.5 lamotrigine. For carbamazepine, phenytoin and lamotrigine, reductions were out of proportion or opposite in direction to changes in prescribing. Over the same time periods there was a small increase in gabapentin overdoses (2, 3 and 5.5 presentations annually). Overall, 10 (2.9%) patients required ITU or HDU admission. These were associated with overdose of phenobarbital (2/10, 20%), lamotrigine (1/19, 5%), valproate (4/138, 2.9%) and carbamazepine (3/112, 2.7%); 25 (7.2%) patients required a hospital stay of more than 2 days, associated with overdoses of phenobarbital (5/10, 50%) carbamazepine (14/112, 12.5%) gabapentin (2/23, 8.7%), phenytoin (1/18, 5.6%), clonazepam (1/12, 8.3%) and valproate (2/138, 1.4%). There were no deaths. *Conclusions:* Presentations with overdose involving some older antiepileptic drugs have fallen sharply in recent years. These changes are not explained by changes in primary care prescribing volume and may reflect reduced prescribing of these drugs to patients with psychiatric disorders associated with a higher risk of drug overdose.

171. Severe Acute Poisonings in Childhood

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Objective: The aim of the study is to define the incidence of severe acute poisonings in childhood presenting to the emergency room in Italian hospitals that contacted the Milan Poison Control Centre (MPCC) for toxicological advice in 2006 in order to estimate incidence, agents involved, course, treatment and outcomes. *Methods:* Using "CAVOL", the MPCC's database, we have analyzed all the clinical cases for which toxicological advice was requested due to severe acute exposure to toxic substances in childhood with "High Risk of admission to Intensive Care Unit". *Results:* We considered 101 clinical cases (n=101 equivalent to 0.45%) consistent with the criteria for inclusion in the study, from a total of 22,092 paediatric consults. During the study we have observed the involvement of agents pertaining to different categories such as drugs, household products, industrial and agricultural products, finding a peak of incidence connected with children aged from 1 to 4, due to accidental ingestion of single toxic agents, and from 15 to 17, due to intentional self-injury ingestion. In every age group, the exposure has been mostly accidental (n=69) and it has taken place above all due to ingestion (n=86) of single substances (n=87), drugs (n=84) and in a domestic environment (n=88). Decontamination has been carried out by gastric lavage and activated charcoal (n=58) or forced diuresis (n=14). Endotracheal intubation has been necessary in 22 patients and the use of vasoactive drugs in 5 patients. The outcome has been unknown in 4 cases; we have recorded complete recovery (n=89), gastric sequelae (n=5) in cases of caustic ingestions, death in 3 cases due to corticosteroids, amphetamines and hypoglycemic agent ingestions. *Conclusion:* Analyzing the literature (1,2) and the several cases collected, makes it imperative to act on prevention, information and optimization of treatment and on timely toxicological advice to improve the patients' outcome. *Reference:* 1. Lai MW, Rodgers GC, *et al*. Annual report of the American Association of Poison Control Centers' national poisoning and exposure database. *Clin Toxicol* 2006; **44**: 803–932. 2. Liebelt E, DeAngelis C. Evolving trends and treatment advances in pediatric poisoning. *JAMA* 1999; **282**: 1113–1115.

172. Suicide Attempts by Self-Poisoning Among the Elderly in Noor Hospital, Isfahan, Iran

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Objective: The investigation assessed patients treated for self-intoxication in the Department of Clinical Toxicology of Noor Hospital, Isfahan, Iran. The aim of this study was to present suicidological problems in the elderly. *Methods:* Medical documentation of the entire population of subjects aged over 65 and hospitalized in the years 2006–2007 was examined from the point of view of demographic and clinical factors. *Results:* The examined population consisted of 43 subjects including 30 males and 13 females ranging in age from 65 to 83 years (mean age=72.5 in male and 73.5 in female). The majority of subjects were retired (35, 81.4%) and, in many cases, lived with her or his family (39, 90.6%). A significant number of subjects had been undergoing psychiatric treatment (12, 27.9%). depressive disorders (reactive) and endogenic depression (affective) were recognized in 30 subjects (69.7%). A significant percentage (22, 51%) had suffered from chronic diseases; the most frequently determined somatic diseases were hypertension (33.3%) and coronary artery decease (30.4%), COPD (15.9%) and diabetes (10.1%). For 41 of the subjects (95.3%), it was the first suicide attempt and in 2 cases there was a history of previous suicidal attempt. The substances most frequently used in the attempts were drugs (25, 58%) including (psychotropic, antidepressant, cardiological and mixed-type drugs), opioids (10, 23.2%), pesticide (5, 11.6%) methanol (2, 4.6 %), hair remover (1, 2.3%). The mean duration of hospitalization was 1.3 days. *Conclusion:* The description of the data indicates that there is a close relation between depression and chronic diseases and suicidal attempts in the case of the elderly. Therefore, an adequate treatment of depression and chronic diseases should be give priority in programs for preventing suicide among the elderly (1,2,3,4). *References:* 1. Shah R, Uren Z, Baker A, *et al*. Trends in suicide from drug overdose in the elderly in England and Wales, 1993–1999. *Int J Geriatr Psychiatr* 2002; **17**: 416–421. 2. Hoxey K, Shah A. Recent trends in elderly suicide rates in England and Wales. *Int J Geriatr Psychiatr* 2000; **15**: 274–279. 3. Suominen K, Isometsa E, Lonnqvist J. Elderly suicide attempters with depression are often diagnosed only after the attempt. *Int J Geriatr Psychiatr* 2004; **19**: 35–40. 4. Juurlink DN, Herrmann N, Szalai JP, *et al.* Medical illness and the risk of suicide in the elderly. *Arch Int Med* 2004; **164**: 1171–72.

173. A One Year Survey of Toxic Exposures in Children Under Eighteen Years of Age

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Objective: To assess the incidence and nature of toxic exposure in children and adolescents seventeen years and younger in Iceland over one year as well as to compare its prevalence in this age group to that of the rest of the population. *Methods:* The research period was from 1st April, 2001, to 31st March, 2002. A prospective study was carried out in every hospital and health centre in the country and data from the Icelandic Poison Information Centre was collected for the same period. *Results:* Eight hundred and seventy one exposures were recorded. This corresponds to 1.11% of all Icelandic children and adolescents, whereas the prevalence is 0.44% in the rest of the population. Fifty nine percent of the exposures occurred in children under 3 years of age. Three hundred and ninety nine (45.8%) of the exposures involved pharmaceuticals and 472 (54.2%) non-pharmaceuticals. Ingestion was the most common route of exposure (87.5%). The majority of the exposures (82.7%) were accidental, 7.5% were suicide attempts and 4.1% abuse of drugs. One hundred and twenty six (14.5%) children received some kind of treatment in a health-care facility and 67 (7.7%) required hospitalization. *Conclusions:* The prevalence of toxic exposures was observed to be higher in children and adolescents compared with the rest of the population. Toxic exposures in children under 3 years old accounted for almost sixty percent of all toxic exposures in children and adolescents. The majority of the exposures were accidental and minor and did not require hospitalization.

174. Drug Poisoning in Slovenia

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Objective: The Slovenian Register of Intoxications managed by the Poison Control Centre at Ljubljana University Medical Centre was established in 2001. It offers a continuous review of poisoning in Slovenia. Our aim was to study the epidemiology of acute drug poisoning in adult patients admitted to hospitals in Slovenia. *Methods:* We analyzed the data reported for acutely poisoned patients older than 16 years who were treated in hospitals in Slovenia between 2001 and 2005. *Results:* A total of 1,838 adult acutely poisoned patients were reported in the Register of Intoxications between 2001 and 2005, of whom 1,234 (67%) were poisoned by drugs. 67% of patients poisoned by drugs were women and 76% of patients ingested drugs at home. 85% of patients ingested drugs in suicide attempts. Anxiolytics, hypnotics, sedatives, antipsychotics and antidepressants represented 68% of all ingested drugs due to self-poisoning. Drugs for the musculo-skeletal system and drugs for the cardiovascular system followed poisoning by these drugs. There were 6 benzodiazepines and related drugs among the 10 most commonly ingested drugs due to self-poisoning. The most common signs of acute drug poisoning were somnolence and coma (75%). Gastric lavage was performed in 64% of patients, activated charcoal was given to 73% of patients and 35% of patients were treated with an antidote. *Conclusions:* Poisoning by drugs for the nervous system, particularly benzodiazepines, is the most common form of poisoning by drugs in Slovenia. It is necessary to report all acutely poisoned patients to the Register of Intoxications, since we need data about all poisoning in Slovenia to improve their prophylaxis and treatment.

175. Mercury Exposure According to the Czech Toxicological Information Centre (TIC) from 1995 to 2007

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Objective: Thermometers filled with mercury are commonly used in the Czech Republic. The objective is to describe the development and course of mercury exposure, and the frequency, based on calls to the TIC with a country-wide population of approximately 10 million. *Methods:* Data on mercury exposure in years 1995 to 2007 (till 12.11.2007) was taken from the Czech Toxicological Information Centre (TIC) database. *Results:* Between 1995 and 2007 TIC responded to 1201 inquiries following mercury exposure resulting in 1.18 % of total calls to TIC. The average number of calls per year did not fall below 1% (median 1.13%). Most cases dealt with oral intake. In 63.1% of total cases metallic mercury was involved: 97% ingested e.g. in tea which was stirred by a mercury thermometer, 2% per rectum (broken mercury thermometer) and 1% intravenous, paravenous or intramuscular (self-administration). 7.2% of total cases were people endangered by mercury vapours. In 1.6% soluble mercury salt was identified and in 28.1% only suspicion of ingestion by children occurred. In 81 cases (from 4 to 13 cases per year) a suicidal attempt was registered. From 132 calls obtained during the last 12 months the most severe case concerned an 83 year old man with pre-existing cardiovascular disease who ingested 1 g of mercury chloride in a suicide attempt. He was admitted to the ICU due to a sudden loss of consciousness and convulsions however he recovered en-route. On admission he was awake with vital signs: BP 118/70 mmHg, HR 70/min. Gastric lavage was performed, one dose of the antidote DMPS was given intravenously and hemodialysis due to acute renal failure was performed 3 times. Mercury plasma level of 4.96 mg/L confirmed the high dose ingested. Moreover he experienced haemorrhagic enterocolitis and as a complication bronchopneumonia. He was discharged on the 15th day with borderline renal parameters. *Conclusions:* In the overwhelming majority of calls the prognosis was good, due to low oral absorption and negligible inhalational exposure of metallic mercury. However, the vast majority of accidents could be prevented and healthcare service saved by replacing mercury in thermometers by a less toxic filling. *Acknowledgement:* MSM 0021620807, GAČR grant No. 203/07/1195.

176. Acute Chemical Poisonings in Children in Russia

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Objective: A study of morbidity of acute poisonings in children in Russia. *Methods:* Analysis of statistical data from the Ministry of Health and Social Development of Russia, and toxicological monitoring and reports from the Moscow Paediatric Toxicological Centre for the years 2004–2006. *Results:* Every year about 105,000 children aged 1 month-15 years present to Russian hospitals with different poisonings with 42,000 being admitted. Boys were 1.7 times more likely to be admitted than girls. 3.4% of the children were younger than 1 year. Hospital lethality from poisonings averaged 0.27%. According to toxicological monitoring data from Moscow for 2004 to 2006 the number of poisonings in children younger than 3 years increased from 55.8% to 71.5%, while at the age of 10 to 14 years it decreased by half. Teenagers in 15% of cases were intoxicated with alcohol increasing the numbers of registered cases, in 3.4% they were also doped with drugs and narcotics. Suicidal poisonings decreased from 9.1 % to 4.1%, but cases of medicine misuse and intoxications from other agents rose from 16.5 % to 20.6 %. Self-treatment was registered in 2% of cases. In children 66% of cases involved medications. The number of poisonings by caustic substances increased 1.2 times. Every year about 2000–2,500 patients were admitted to Moscow Paediatric C Toxicological Centre, 41 % of them aged under 3 years, 36% between 10–15 years. 35% demonstrated severe poisonings. 65% were admitted with drug poisonings, the number of alcohol intoxications reached 23% in 2006. Among pharmaceutical poisonings psychotropic agents predominated; 72.8% involving benzodiazepines and neuroleptics. Agents affecting cardiovascular system reached an average of 30%. A notable growth in the number of poisonings by drugs for rhinitis (naphazolin) was seen, with 183 cases in 2004 rising to 314 in 2006, especially in young children. For 2004–2005 there were no lethal outcomes, but in 2006 lethality was 1.3 %. *Conclusion:* Poisonings in children happen most frequently at the age of 1–3 years. Psychopharmacological agents and alcohol predominate in older children, whilst poisonings by agents for rhinitis and neuroleptics occurred in younger age groups.

177. Epidemiological Profile of Acute Poisoning Cases Admitted to the ICU II Toxicology - Emergency Clinical Hospital Bucharest in 2006

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Objective: Patients with acute poisoning, from Bucharest and the surroundings, are hospitalized in the ICU II Toxicology of the Emergency Clinical Hospital Bucharest. The number of poisoned patients presenting to the Emergency Department is large, approximate 3000–4000 per year, but only the serious cases are admitted to ICU II Toxicology. After clinical recovery all suicidal patients are examined psychiatrically and approximately 85% of these suicidal patients are referred to a specialist psychiatric clinic. We present an epidemiological profile of acute poisoning cases admitted in 2006. *Method:* The medical records of the cases were reviewed retrospectively. Demographic (age and sex) characteristics, seasonal distribution, type of poisoning, toxic agent involved and outcome were recorded. *Results:* During the year 2006, 1191 cases with acute poisoning were collected. The study data showed that from 3501 patients presenting at hospital with acute poisoning, only 34% (1191 cases) were hospitalized. There was a predominance of female patients (n=671, 56%) compared to males (n=520, 44%). The mean age was 26+/–10 years (age range 13–99) with 60% of patients below 40 years. Seasonal distribution peaked in winter (carbon monoxide poisonings) and summer months. Area of habitation: 72 % urban and 23% rural. Mechanism of intoxication: 72.3% were intentional (suicide attempts) and 27.7% were accidental (overdose, errors). The aetiological factors were pharmaceuticals 57% (675), non-pharmaceuticals 26% (316), miscellaneous 17% (200). Pharmaceutical poisonings were with a single type of drug 34% (410) and combinations of drugs 22% (265). Illicit drugs (overdose, withdrawal) accounted for 5% (57). The most common drugs ingested in the single pharmaceutical poisonings were barbiturates (5.63%), followed by benzodiazepines (4.37%) and anticonvulsants (3.78%). Non-pharmaceutical poisoning was dominated by carbon monoxide poisoning (10.41%), followed by ethanol intoxication (4.28%) and pesticide poisoning (3.78%). Combination of ethanol with other drugs was encountered in 6.30%. A total of 64% were discharged home without complications, 6% with minor complications and 30% were transferred to other departments. The overall mortality was 3.2% (39). *Conclusion:* In 2006 there was a decrease in the number of poisonings admitted because of legal measures which do not allow the delivery of medications without medical prescription.

178. The Change in the Structure of Suicidal Poisonings in a Large Industrial Region (Sverdlovsk Oblast) in the Last 5 Years

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Objective: The mean level of suicidal poisonings in the region is 53.2 per 100,000 population, which is several times higher then in most European countries. Such a situation triggers great concern and makes the toxicologists improve their work with the patients who survived suicidal poisonings. *Methods:* According to the hospitals and the office of forensic medical examination, acute poisonings were analyzed in the periods between 1997–2001 and 2002–2006 in a region of 4,350,000 population. *Results:* In the period between 1997–2001 the level of suicidal poisonings increased from 2170 cases (25.5%, 46.1 per 100,000) to 2593 cases (30.5%, 55.8 per 100,000); 43.3% of patients were poisoned by medicaments, 36.5% by acetic acid and 9.1% by insecticides and household chemicals. Mortality was 3%. In the period between 2002–2006 11,962 cases of self-poisoning were registered (31.8% of all poisonings), however the number of self-poisonings decreased from 2724 (34.7% of all poisonings, 58.6 per 100,000) in 2002 to 2138 (30.7% of all poisonings, 50.3 per 100,000) in 2006. For suicidal poisonings the patients used pharmaceuticals (80%), acetic acid (8%), and insecticides (7%). 383 people died of suicide attempts in the last 5 years (3.2%), 37.7% of whom took acetic acid, 30.4% took pharmaceuticals, 31.9% took insecticides. As compared to the 1990s the number of suicidal poisonings increased, but their structure changed: the number of poisonings by acetic acid decreased, but the number of poisonings by pharmaceuticals increased. About 55% of patients were admitted to poison centers, others were treated in local hospitals. The distinguishing feature of the acute poisonings treatment management in Sverdlovsk Oblast is that 2 of 3 poison centers are based in the major mental hospitals. There is a possibility to engage a psychiatrist 24-hours in the examination of the patients who have attempted suicide, which makes it possible to start the treatment of psychiatric pathology earlier or to discharge a patient from the hospital, if the

psychiatric pathology was not identified. Thus, in Sverdlovsk regional poison center for the last 5 years 400 (16.2%) of 2468 patients, admitted to hospital after suicidal attempts, were moved to psychiatric and rehabilitation units, which deal with the treatment of depression; 28 (1.1%) were moved to narcological units. *Conclusion:* A great number of patients being moved from poison to psychiatric units (17.3%), and vice versa from psychiatric to poison units (2.4%) prove that it is reasonable to locate poison centers in mental hospitals.

179. Epidemiology of Poisoning in Tehran, Iran

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Objective: The aim of this study was to characterize the poisoning cases admitted to the Loghman-Hakim Hospital Poison Center (a teaching hospital of Shaheed Beheshti University of Medical Sciences) Tehran, Iran. *Methods:* All cases admitted to the Loghman-Hakim Hospital Poison Center from January 2003 to December 2003 were evaluated retrospectively. Data were obtained from the hospital medical records and included the following factors: sociodemographic characteristics, agents and cause of poisoning, and the mortality rate of the acutely poisoned patients. *Results:* During this period, 24,179 patients with acute poisoning were referred to the emergency department, from whom 10,206 patients were admitted. Of these 51% were males and 49% females. The majority (38%) of the cases were from the age group 21–30 years. Most (79%) poisonings were intentional and only 21% were unintentional. The most important agents of acute poisoning were drugs (69.13%) especially sedative-hypnotic drugs followed by opioids (12.34%), and pesticides especially organophosphates (6.21%). 318 (1.3%) patients died. The poisons responsible for most of the mortality were opioids (41.54%), drugs (28%) and pesticides especially organophosphates (12%). *Conclusion:* The prevention and treatment of poisoning due to opioids, pesticides (primarily organophosphates) and drugs especially sedative-hypnotics drugs should merit high priority in the health care of the indigenous population of Tehran.

180. The Poisons Triangle: Where do our Patients Go?

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Objectives: To describe cases of acute self-poisoning presenting to an adult general hospital, the agents taken and where patients were treated. *Methods:* The notes of 20,000 consecutive attendances at the hospital Emergency Department (ED) (between 07 January and 12 June 2004 inclusive) were retrospectively reviewed and cases of acute self-poisoning with drugs/pharmaceuticals were identified (1). Patients admitted to the hospital with a diagnosis of poisoning during the same period were identified from the Hospital In-Patient Enquiry system, and their medical charts reviewed. Data on patients admitted to the Intensive Care Unit (ITU) was also collected prospectively as part of another study. Patients intoxicated with alcohol alone, cases of chronic toxicity or non-drug/pharmaceutical poisoning, and those whose medical charts could not be located, were excluded from further analysis. Data collected included patient gender and age, agents ingested and treatment location. *Results:* Drug overdoses accounted for 287 (1.4%) ED attendances during the study period. The majority of these patients were treated in the ED and discharged home, with further care provided by psychiatric services or their general practitioner. 34 patients admitted with a diagnosis of poisoning met the study criteria, including 7 patients admitted to ITU. There was a slight predominance of females in all groups (52.9% of ED cases, 58.8% of admitted cases and 57.1% of ITU admissions). The average age of those attending the ED or admitted to hospital was 34 years. Alcohol was co-ingested by 134 (46.7%) of the patients who attended the ED and 13 (38.2%) of those admitted to hospital. Ingestion of multiple drugs was common. The drugs most frequently ingested by patients attending the ED were benzodiazepines, antidepressants and paracetamol. Benzodiazepines, antipsychotics and paracetamol were most commonly taken by those admitted to hospital, and benzodiazepines and antidepressants by patients admitted to ITU. *Conclusions:* The majority of patients who attended the ED following a drug overdose were treated within the department. 11.8% were admitted to hospital and 2.4% required admission to ITU. *Reference:* 1. Marchant V, Gleeson A, Casey PB, *et al*. Retrospective study of drug overdoses in a suburban emergency department. *Clin Toxicol* 2007: **45**; 379.

181. Pesticide Poisoning: Experience of the Poison Control Centre of Morocco

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According to the WHO report, the annual number of intoxications by pesticides is estimated at between 1 and 5 million, of whom several thousands die (1). In Morocco, only a small number of studies has concerned pesticide poisoning, but some of them show that pesticides constitute a significant cause of intoxication (2,3,4). *Objective:* The purpose of our study is to describe the epidemiological characteristics, clinical features and outcome of pesticide poisoning. *Patients and Methods:* This is a retrospective study. We collected all cases related to pesticide poisoning received by telephone enquiry to the poison control centre of Morocco from January 1992 to December 2006. We analyzed demographic features, circumstances, symptomatology, and outcome. A classification of the patient's clinical state was made according to the Poisoning Severity Score "PSS" (5). To detect the possible relationship between two variables chi 2 or Fisher test and Student tests were used. *Results:* 2319 cases were collected, representing 11.6% of all of poisonings. The mean age was 19.7 ± 14.0 years; range 1 day to 82 years. The female sex is more prevalent; sex ratio was 0.92. Oral route was involved in 81.72% of cases and inhalation in 9.27%. 49.24% of cases were accidental exposures and 41.78% were suicide attempts. Insecticides were implicated in 55.67% and included organophosphates (30%), pyrethrins (8.67%), carbamates (8.58%) and organochlorines (1.16%). 33.1% of patients were classified in grade 2d (PSS). The mortality was 3.49%. Mortality was significantly influenced by pesticide chemical class ($p<0.05$). *Conclusion:* Authorities should carry out plans to prevent pesticide poisoning and the mortality engendered. *References:* 1. Joint note for the media WHO/FAO/UNEP 2004. Children are facing high risks from pesticide poisoning. Site - Web: www.who.int/mediacentre/news/notes/2004. Last consultation on November 12, 2007. 2. Madani N, Abidi K, Moussaoui A, *et al*. Les intoxications aigues admises en réanimation (à propos de 500 cas). *Maghreb Médical* 2000; **20**: 264–268. 3. Chara B, Louardi H. Prise en charge des intoxications aigues aux urgences. *Journal du Praticien* 2002; **XII**: 10–14. 4. Zahidi N. Etude des intoxications aigues (à propos de 1172 cas enregistrés en réanimation médicale et en pédiatrie de l'hôpital Ibn Zohr à Marrakech de 2000 à 2002). [Thèse] Pharmacie- Rabat- 2004 (42). 5. Persson HE, Sjöberg GK, Haines JA, *et al*. Poisoning Severity Score. Grading of Acute Poisoning. *J Toxicol Clin Toxicol* 1998; **36**:205–213.

182. Requirement for Initiative in the Field of Acute Poisoning Situations in Romania Using Data from an Emergency Children's Hospital

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Objective: To demonstrate the need for Poison Centers in the main cities of an Emerging EU Country. We present acute poisonings admitted to an Emergency Department (Louis Turcanu Emergency Children Hospital Timisoara) during a period of 2.5 years. We focus on the problematic features from diagnosis to treatment and the need for guidelines. *Methods:* We studied all cases of acute poisoning admitted to our Emergency Department between Jan 2005 - Aug 2007. The following criteria were used: patient age, sex, substance, region (urban/rural). Children were divided according to age into four groups: 0-<1, 1–5, 6–12, 13–18 years. *Results:* 232 children with acute accidental poisoning were admitted to our department in this retrospective study period. The groupings by age were: 0-<1 years: 14 cases (6.03%); 1–5 years: 106 cases (45.68%); 6–12 years 33 cases (14.22%); 13–18 years: 79 cases (34.07%). There were 139 girls (59.91%) and 93 boys (40.09%). 132 (56.9%) were from cities, 100 (43.1%) cases were from rural areas. The substances involved were: drugs 117 cases (50.43%); alcohols 26 (11.2%); chemical substances 17 (7.32%); volatile agents 15 (6.46%); caustics 12 (5.17%); carbon monoxide 11 (4.74%); nitrites 11 (4.74%); mushrooms 6 (2.58%); phytosanitary/pesticides 5 (2.51%); heavy metals 4 (1.72%). None of the cases were investigated to confirm the substance involved. From analysis of the patient records we identified the time interval to admission and to appropriate access to antidotal therapy. *Conclusion:* Prescription drugs still remain the most common agents involved; therefore acute poisoning in children must be given special attention by toxicologists, the general public and the authorities. Access to antidotes is significantly low. There is a deficiency of publications, research and well-trained personnel. Our Ministry of Health is approving, for 2008, 8 Poison Centers with 24 hour phonelines, with access to antidotes and toxicological tests. There is a need for protocols and the provision of appropriate equipment for centers. *Reference:* Flanagan RJ, *et al*. Fatal poisoning in childhood. *Forensic Sci Int* 2005; **148**: 121–9.

183. Severe and Fatal Intoxications Registered in the Slovak Toxicological Information Centre During the Years 2002–2006

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Objective: To examine the incidence of serious and fatal intoxications in the Slovak Republic. *Methods:* Severe (graded according Poison Severity Score) and fatal poisonings were analysed by age, sex of patient, involved agent and type of intoxication. *Results:* During this 5 year period NTIC recorded 202 cases of severe intoxications. These were more frequent in male (47%), than in female (40%). Most of them were suicidal (81%), only 11% were accidental. 67% of intoxications were caused by drugs, 18% by chemicals, 6% by alcohol and 1% by mushrooms, drugs of abuse and plants. 27 children had signs of severe intoxication. The majority of these were teenagers with personal problems. The other large group were children from 0–3 years old. Most of the childhood intoxications were caused by neuroleptic, antiepileptic, antidepressant and anxiolytic drugs. NTIC registered 66 fatal intoxications during the years 2002–2006, 59 cases in adults, 7 cases in children. 28 cases of death were caused by drugs - calcium channel blockers, antiarhythmics- propafenone, prajmalin and other combination of drugs. From the group of chemicals, deaths were mostly caused by strong acids, ethylene glycol and organophosphorus pesticides. 13 people died after eating *Amanita phalloides* (5 children). *Conclusions:* Obligatory reporting of every poisoning to NTIC (similar to the reporting of adverse drug reactions), including the poisonings not resulting from a consultation with NTIC came into force in October 2006. Before that we received only 30% of feedback information on poisonings about which we were consulted, which does not enable us to carry out the full analysis of the efficacy of treatment.

184. Effects of Restrictive Prescribing Guidance on Venlafaxine Prescribing and Overdose

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Objective: Venlafaxine, a serotonin noradrenaline reuptake inhibitor antidepressant was launched in the UK in 1995 and subsequent uptake was rapid. Following reports of cardiovascular toxicity and a high fatal toxicity index (FTI, deaths/million prescriptions) (1) advice restricting venlafaxine prescribing was published in the UK in December 2004. We investigated the effects of this advice on venlafaxine prescribing in primary care and the frequency of overdose presentations. The hypothesis that the high FTI may result from use of the drug in patients at higher initial risk of drug overdose was investigated by measuring the ratio of overdose admissions to prescription numbers. *Methods:* Prescribing data for antidepressants was obtained from prescription analysis and cost (PACT) data for Newcastle Primary Care Trust. Overdose admission data were obtained from the two Newcastle hospitals admitting patients with acute drug overdose over the period of study from October 2002 to December 2006. *Results:* Prescribing volume for venlafaxine increased progressively until the first quarter of 2005 when this trend was reversed. Overdose presentations were 58 in 2003, 47 in 2004, 28 in

2005 and 28 in 2006. The ratio of overdose admissions to prescriptions (in thousands) was higher for venlafaxine (1.92) than for fluoxetine (1.74), sertraline (1.56), lofepramine (1.49), mirtazepine (1.39), paroxetine (1.29), citalopram (1.23), and amitriptyline (0.96), consistent with selective prescribing of venlafaxine for patients at higher risk of overdose, as shown previously in Scotland (2). Between 2003 and 2005 the ration of venlafaxine overdose admissions to prescriptions fell (2003–2.68, 2004– .91, 2005 1.34, 2006 1.53) suggesting reduced venlafaxine prescribing to patients at higher overdose risk. *Conclusion:* These data suggest that venlafaxine was prescribed to patients at higher initial risk of drug overdose and this will have the effect of increasing the fatal toxicity index. Such selective prescribing declined following publication of prescribing guidance restricting use. *References:* 1. Morgan O, Griffiths C, Baker A, *et al*. Fatal toxicity of antidepressants in England and Wales, 1993–2002. *Health Stat Q* 2004; **23**: 18–24. 2. Bateman DN, Chick J, Good AM, *et al*. Are selective serotonin re-uptake inhibitors associated with an increased risk of self-harm by antidepressant overdose? *Eur J Clin Pharmacol* 2004; **60**: 221–4.

185. Epidemiological Study of Scorpion Envenomation in the Hospital Beni Mellal Province

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In Morocco, Beni Mellal province is one of the regions most affected by scorpion envenomation. *Objective:* The aim of this research is to reduce cases of morbidity and mortality subsequent to scorpion envenomation through the analysis and interpretation of data recorded in hospital admission forms. *Methods:* Our study covered 63 retrospective cases of scorpion poisoning during the year 2005, which were reported by the hospital's intensive care service in Beni Mellal province. *Results:* Results indicate that scorpion envenomation occurs mainly during summer, in particular during June and July. Moreover, stings happen at night between 6PM and 6AM (60.3%). Youngsters with age ≤ 15 years are those most exposed to envenomation, with a male age of 10.2 ± 1.72 years. In addition, 72.6% of the envenomed patients arrived at the hospital with general symptoms and 27.4% exhibited signs of severe distress. The therapy given was variable, and the rate of lethality at the hospital was 28.57%. There were three admission classes: 1. local signs only, 2. envenomed patients with general signs, 3. patients with respiratory, neurological and cardiovascular effects. Variance analysis of various factors studied in relation to survival prediction (recovery and mortality) showed a highly significant difference for each admission class ($F=96.94$ and $p<0.0001$). Fatal cases had a mean class of 2.83 ± 0.09 compared with the recovery group. Age of less than 15 years and signs of vital distress be it neurological, respiratory or cardiovascular are factors of risk for envenomed patients. *Conclusion:* Scorpion envenomation remains a public health problem in Morocco. *Acknowledgement:* This work is within PROTARS III D63/15 program and National Campaign for the control of scorpion stings and envenomation.

186. Enquiries to the National Poisons Information Centre from Members of the Public

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Objective: To investigate the incidence and reasons for telephone enquiries to the National Poisons Information Centre, Ireland, from members of the public. *Methods:* A 1 year prospective study of telephone enquiries to the National Poisons Information Centre (NPIC) was conducted from May 2005 to April 2006 inclusive. A single investigator reviewed daily paper records of telephone enquiries from members of the public. Epidemiological data on patient demographics, poisoning circumstances, type of agent(s) involved, clinical features, enquiry time, and treatment advice was collated. *Results:* During the study period, the NPIC received a total of 9,475 enquiries between the hours of 8am-10pm. 1,776 (18.7%) of these enquiries were from members of the public and related to 1,806 cases of human poisoning (926 male, 867 female, 13 gender unknown). In addition, a further 154 enquiries were received from members of the public requesting information only, but these enquiries were excluded from data analyses. The majority of patients (n=1,449) were under the age of 14 years and there were 357 individuals aged over 14 years. 1,547 patients (1,338 children, 209 adults) were poisoned accidentally, 177 patients received excessive doses of medication as a result of a therapeutic error (107 children, 70 adults), 64 adults took a deliberate overdose and the circumstances were unknown/not applicable in 18 poisoning cases. The principal agents included pharmaceuticals (44.4%), household products (21.6%), industrial chemicals (11.4%), cosmetic or personal hygiene products (9.1%), plants (4.2%), agricultural agents (3.8%) and other agents (5.5%). The pharmaceuticals involved in poisoning (n=801) comprised prescription only medications (39.1%) and over-the-counter products (60.9%). 13.9% (n=251) of callers were immediately referred to a hospital emergency department and 6.1% (n=111) were immediately referred to their general practitioner. 1,444 patients did either not require urgent medical treatment or could be managed at home. Of these, 369 patients were advised to seek medical advice if symptoms developed. *Conclusion:* The majority of enquiries from members of the public concerned children. Medical treatment in a healthcare facility was recommended in 20% of cases.

187. No Evidence for a Decrease in Admission for Severe Cardiotropic Drug Intoxications, A Study in Critical Care Department

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Since the mid nineties, regional poison control centers in France have claimed a decrease in severe poisonings. However, this is not our experience at the Medical and Toxicological Critical Care Department in the Paris area. *Methods:* We compared 1000 consecutive acute poisonings involving potentially cardiotoxic drugs studied over two periods of time separated by a 20-year delay. Data over 1984–85 were collected at F Widal hospital using the local database. Data over 2004–05 were collected at Lariboisière hospital using the Fusion F format database used by all French Critical Care Departments. *Results:* Table. *Conclusion:* Calcium channel blockers were not studied. Meprobamate, Quinidine, Ajmaline, Disopyramide, Trichloroethylene, and colchicine poisonings, and CO/smoke inhalation decreased. However, within the same period of time polycyclic antidepressants, SSRI, digitalis, chloroquine, and beta-blockers increased. As a whole, there was approximately a two-fold increase in the number of poisonings involving potentially cardiotropic drugs. Mortality rate decreased only for digitalis poisonings.

188. Are Clubbers Who Develop Recreational Drug Toxicity Novice or Recurrent Drug Users?

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Objective: The use of recreational drugs amongst clubbers is common, particularly those who frequent men who have sex with men (MSM) venues. Many large club venues in the UK have 'club first aiders' and first aid rooms where unwell individuals are initially assessed and managed. There is no published data as to whether individuals who develop recreational drug toxicity are first-time drug users or whether individuals attend these first aid rooms on a recurrent basis. *Methods:* Data on clubbers who attended the first aid room at one large MSM nightclub venue was collected over a 3 month period. Information on the individual's sex and age, who brought them to the room and the reason for attendance was collected. Where recreational drugs were the reason for attendance, the drug(s) used, previous club first aid room attendance and individual's previous use of the drug(s) were also recorded. *Results:* Of the 48 presentations to a 'club first aid' room, 45 (93.8%) were male and the mean (SD) age was 26 ± 5.3 years. Individuals were predominately brought in by club staff (n=35, 72.9%) or 'friends' (n=9, 18.8%); only 3 (6.3%) self-presented. The majority of presentations involved recreational drug use (n=41, 85.4%). The drugs ingested prior to attendance were GHB and/or GBL (n=31, 75.6%), ketamine (n=11, 26.8%) and cocaine (n=3, 7.3%). A significant minority had previously required 'club first aider' assistance following use of recreational drugs (n=20, 41.7%), although most had previously used the drugs that had cause this attendance (n=30, 62.5%). *Conclusions:* This pilot study demonstrates that the majority of individuals who become unwell following use of recreational drugs whilst out clubbing in an MSM environment are not first-time users and that individuals commonly develop recurrent recreational drug toxicity. There is the potential role for using brief interventions in recurrent drug users who become unwell in club environments, and clinical toxicologists should help to develop these interventions.

Table: Comparison of cardiotropic admissions and deaths for 1984–5 and 2004–5

	1984–1985		2004–2005	
Toxicants	**Frequency (%)**	**Death ratio (%)**	**Frequency (%)**	**Death ratio (%)**
Polycyclic antidepressant	10	1	15.5	3.8
SSRI			23.3	3
Meprobamate	7	1.2	1.2	0
Digitalis	1.6	13	2.2	4.5
Quinidine	1.6	0	0.1	0
Chloroquine	1.1	10	5.1	13.7
Ajmaline	1	10	0	0
Beta-blockers	0.8	0	8	7.5
Disopyramide	0.4	0	0	0
Colchicine	2	5	0.8	12.5
Trichloroethylene	1.7	9	0.2	0
Cyanides	0.2	0	0.1	0
Organophosphates	0.2	50	0.2	0
Carbon monoxide / Smoke inhalation	2	5	1.2	8
Total	296		579	

189. Coagulation Status of Severely Poisoned Patients Treated with Extracorporeal Life Support in Relation to Refractory Cardiac Failure or Arrest

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Objective: Extracorporeal life support (ECLS) represents an ultimate rescue technique in poisonings. The optimal anticoagulation protocol remains unclear. We aimed to investigate the coagulation status at ECLS decision in order to validate the best heparin protocol to administer. *Methods:* Prospective study including all poisoned patients treated with ECLS in 2003–2007; interpretation of clotting tests measured at cannulation by 2 blinded biologists; heparin infusion to obtain an activated partial thromboplastin time (APTT) at 2–3N; transfusions to maintain hemoglobin >8 g/dl, platelets >30 G/l and prothrombin index (PI) >20%; descriptive study [percentiles 10–90%]; comparisons using Chi-2 and Mann-Whitney tests. *Results:* Fifty-seven poisoned patients (19M/38F, 41 years [21–59]) were included, in relation to refractory cardiac failure (26/57) or arrest (31/57). Patients had ingested elevated doses of cardio-toxicants in 49/57 cases. Sixteen patients (28%) survived. When deciding to perform ECLS, the clotting tests were as follows : platelets 177 G/l [104–219], PI 31% [13–53], APTT 2.8 N [1.3–7.0], V-factor 23% [10–55], II-factor 46% [21–67], fibrinogen 1.2 g/l [0–2.8], C-protein 34% [20–77], and antithrombin III 42% [16–68]. The presence of disseminated intravascular coagulation (DIC, soluble complexes >2+) and/or marked hepatocellular failure (PI <20%) did not significantly differ between patients cannulated for cardiac failure or arrest. However, there was a significantly prolonged APTT ($p=0.04$) and a trend towards a more significant defibrination (euglobulin lysis time <2h00, $p=0.06$) in case of cardiac arrest, thus justifying the absence of heparin requirement. Comparison of clotting tests in regard to survival showed a significant difference in platelets (148 G/l [97–197] versus 107 G/l [54–204], $p=0.03$), fibrin (1.4 g/l [0.9–2.8] versus 1.1 g/l [0–2.6], $p=0.03$) and antithrombin III (55% [27–77] versus 34% [14–66], $p=0.04$).

Blood (5 packs [2–12]) and fresh plasma (4 packs [2–12]) transfusions were required within the first 24 hours. Hemorrhages (9/57), thrombosis (3/57) or lower limb ischemia (4/57) seemed equivalent to previous series using more complicated anticoagulation protocols. *Conclusions:* Poisoned patients present at ECLS time with important alteration in their clotting tests, associated with various degrees of hepatocellular failure, DIC, defibrination, as well as dilution. A simple heparin protocol appears optimal to reduce complications in these critical situations.

190. 1-Benzylpiperazine (BZP) and 3-trifluoromethylphenylpiperazine (TFMPP) Detection in Recreational Drug Users Presenting to the Emergency Department

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Background: Recreational drug use is common throughout Europe and is increasing. Legally available synthetic compounds with actions similar to controlled recreational drugs have previously been sold as 'recreational drugs' within nightclubs (1). *Case series:* Three male patients (aged 18, 18 and 19) presented to the Emergency Department (ED) following use of supposed 'MDMA' purchased within a nightclub. All had ingested 4 of the purchased tablets over the course of an evening. Following ingestion, they developed symptoms of anxiety, nausea, vomiting, non-specific abdominal pain and dizziness. On presentation they had features of sympathomimetic toxicity (tachycardia, bruxism and dilated pupils); none were pyrexial; one had inducible clonus, hypertonia and hyperreflexia. They were treated with IV fluids and oral diazepam and admitted for observation. All were asymptomatic after 6 hours observation and were discharged home with no long-term sequelae. *Results:* Serum samples obtained from them on admission were subsequently analysed by gas chromatography-mass spectrometry (GC-MS). BZP (260–270 ng/mL) and TFMPP (30 – 60 ng/mL) were detected in all of the samples obtained; no other recreational drugs or other compounds, apart from diazepam given in the ED, were detected with extended toxicological screening. *Conclusion:* We report here a case series of 3 patients who presented following ingestion of a combination of BZP and TFMPP, purchased as supposed 'MDMA', who developed features of sympathomimetic toxicity with associated anxiety. Clinical Toxicologists should be aware of the possibility that patients presenting following use of recreational drugs, may have unknowingly ingested 'novel' or legally available drugs. Increased surveillance using toxicological screening is necessary to monitor trends in recreational drug use and the emergence of novel recreational drugs. *Reference:* 1. Wood DM, Dargan PI, Button J, *et al*. Collapse, reported seizure-and an unexpected pill. *Lancet* 2007; **369**: 1490.

191. Development of the P-CAP (Poisoned Clubbers Avoidance Project) Ambulance Referral Guidelines

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Objective: Recreational drug use and acute toxicity associated with recreational drugs is common amongst clubbers. Therefore many large clubs have 'club first-aiders', who undertake the initial assessment of individuals with acute toxicity. We became aware of a number of instances in which patients with significant poisoning were not identified by 'club first-aiders' resulting in delayed transfer to and initiation of appropriate management in hospital. The "Safer Clubbing" initiative provided guidance to promote the safety of clubbers (1), but did not include recommendations on when individuals with acute recreational drug toxicity should be referred to hospital. *Methods:* A working party of Clinical Toxicologists, Emergency Physicians, the Metropolitan Police and Club owners/'first-aiders' was established. Guidelines for when an ambulance should be called for those with recreational drug toxicity were developed to try and identify those with significant toxicity requiring immediate hospital assessment. These guidelines were audited six months after introduction. *Results:* The audit identified training needs for 'club first-aiders' in assessing recreational drug toxicity. A training module was developed and delivered to them and the guidelines were edited to clarify areas of uncertainty identified. After the training, 12/13 (92.3%) and 13/13 (100%) of 'club first-aiders' were confident in the assessment of poisoned clubbers and use of the P-CAP guidelines respectively. *Conclusions:* This initiative has demonstrated the benefits of a multi-disciplinary, multi-agency approach to the management of clubbers with recreational drug toxicity. Wider dissemination of these guidelines through an update of "Safer Clubbing" is planned which should lead to improved pre-hospital management of poisoned clubbers. *Reference:* 1. Safer clubbing: Guidance for licensing authorities, club managers and promoters http://www.cityoflondon.gov.uk/Corporation/our_services/law_order/community_safety/drugs_action_team/dat_clubbing.htm

192. Withdrawn

193. Detection of the Novel Recreational Drug Diphenyl-2-pyrrolidinemethanol (D2PM) Sold 'legally' in Combination with Glaucine

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Background: There is increasing use of synthetic 'herbal highs' sold legally within Europe, either through self-purchase from high-street shops/the internet, or sold as 'recreational drugs' by illegal dealers (1). The European Monitoring Centre for Drugs and Drugs Abuse (EMCDDA) review the legal status of novel recreational drugs, but can only do so when more information on their use and clinical effects becomes available. *Case report:* A 20 year old male presented to the ED with ischaemic sounding chest pain and palpitations lasting 1 hour following ingestion of 3 legally purchased 'BZP-free herbal highs' and one 'sniff' of amyl nitrate. He had features of sympathomimetic toxicity with hypertension (213/109), tachycardia (125) and dilated pupils; neurological examination and temperature were normal. A 12-lead ECG and methaemoglobin concentration (0.5%) were normal on presentation; Troponin T at 12 hours was not elevated (<0.01microgram/L). He was treated with oral diazepam 10 mg and his tachycardia and hypertension settled. Following 12 hours observation he was asymptomatic and he was discharged with no long-term sequelae. *Results:* A serum sample obtained on admission to the ED was analysed by gas chromatography-mass spectrometry (GC-MS). Glaucine and D2PM were detected; no other recreational drugs or other compounds, apart from diazepam given in the ED, were detected with extended toxicological screening. *Conclusion:* We report a case of ingestion of a 'BZP-free herbal high', which contained a combination of Glaucine and D2PM. This is the first report of recreational use of D2PM. Involvement of clinical toxicologists and increased toxicological screening will improve the detection of novel recreational drugs and assist legislative authorities. *Reference:* 1. Wood DM, Dargan PI, Button J, *et al*. Collapse, reported seizure - and an unexpected pill. *Lancet* 2007; **369**: 1490.

194. Chronic Volatile Nitrite Neurotoxicity

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Objective: Nitrous oxide abuse has been associated with a disabling polyneuropathy that resembles subacute combined degeneration of the cord coupled with pernicious anemia. To date, no other nitrites have been reported to cause a similar syndrome. We report a case of chronic amyl and butyl nitrite abuse that resulted in the development of profound ataxia and pernicious anemia. *Case report:* A 65 year old man with a history of migraine headaches and chronic renal insufficiency presented to our ED complaining of sudden onset of bilateral lower extremity weakness that resulted in a fall. The patient described a two year history of increasing balance problems especially when he was walking in the dark or climbing stairs. This progressive ataxia was accompanied by a cognitive decline which the patient characterized as memory loss. Of note, the patient had been diagnosed with pernicious anemia by his primary care physician around the same time as these symptoms began, and was started on B-12. Upon questioning, the patient admitted to using "poppers" for sexual excitation 2–3 times per week since 1980. On exam the patient had normal vital signs, paratonia, a wide based gait, intention tremor, a slight decrease in vibration sense and dysdiadokinesis. Brain and brainstem MRI revealed frontal and cerebellar atrophy. The patient's symptoms improved during his admission and he was discharged with close neurologic follow-up. Several months later, he presented to the ED with a mild recurrence of his symptoms which improved with observation. However, he did exhibit a persistent residual effect upon discharge. *Discussion:* Nitrous oxide oxidizes cyanocobalamin and irreversibly inhibits the enzyme methionine synthase. This prevents the synthesis of methionine and tetrahydrofolate, which can lead to diminished myelin production and decreased DNA synthesis producing neuropathy and a pernicious anemia-like syndrome. We propose that chronic abuse of volatile nitrites may have caused this patient's symptoms. *Conclusion:* Chronic volatile nitrite abuse may lead to a syndrome similar to subacute combined degeneration of the cord.

195. Amphetamine-Induced Cardiomyopathy

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Objective: To describe three cases of acute amphetamine-induced cardiomyopathy, with a discussion of pathophysiology and literature review. *Case series:* Case one presented 10 hours after IV amphetamine with cardiogenic shock and pulmonary oedema, and died in the Emergency Department. Two further cases with similar presentations subsequent to amphetamine use required ICU admission and multiple inotropic agents, with an intra-aortic balloon pump used in one case. Both surviving cases had markedly decreased ejection fractions on initial echocardiography, with resolution to normal by the time of discharge. Pathophysiological changes may be similar to the catecholamine-induced cardiomyopathy seen in phaeochromocytoma. *Conclusion:* Amphetamine-induced cardiomyopathy can present in extremis with cardiogenic shock. Extraordinary measures such as mechanical circulatory support are justified as complete resolution of the toxicity is possible. *References:* 1. Watts DJ, McCollester L. Methamphetamine-induced myocardial infarction with elevated troponin I. *Am J Emerg Med* 2006; **24**: 132–4. 2. Turnipseed SD, *et al*. Frequency of acute coronary syndrome in patients presenting to the emergency department with chest pain after methamphetamine use. *J Emerg Med* 2003; **24**: 369–73. 3. Wijetunga M, *et al*. Crystal methamphetamine-associated cardiomyopathy: tip of the iceberg? *J Tox Clin Tox* 2003; **41**: 981–6.

196. Neurological Complications Related to Cocaine Use

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Objective: To evaluate the impact that the extensive use of cocaine is producing on the nervous system. *Methods:* Retrospective study in patients hospitalized in the Neurology Department of our hospital between September 2004 and May 2007. Patients with stated use of cocaine and having positive levels at admission. Patients without objective data on its use were excluded. *Results:* 20 cases with an average age of 34.5 years (range16–48 years). 12 men and 8 women. Toxicological history: tobacco use 85%, alcohol abuse 65%, cannabis 30%, designer drugs 15% and opiates 10%. Intranasal administration 95%. Main diagnosis: ischemic stroke in 7 cases (35%) and haemorrhagic stroke in 3 cases (15%), headache in 2 cases (10%), psychiatric disorder in 5 cases (25%), seizure crisis in 2 cases (10%), and other diagnoses (CCT) in 1 case (5%). Secondary diagnoses: cephalgia in 3 cases (15%), seizure crisis in 1 case (5%), discopathy in 2 (10%), leukoencephalopathy in 1 case (5%) and others in 3 cases (15%). The average number of hospitalization days: 8.8 days (range 3–15 days). Neurological history: 6 cephalgia cases (30%), 1 case of polyradiculoneuritis (5%). Psychiatric history: 3 cases of mood disorders (15%) and 1 case of personality disorder (5%). Cardiovascular risk factor: 3 cases of dyslipidemia (15%), 1 case of diabetes mellitus (5%) and 1 case of high BP (5%). Laboratory data revealed dyslipidemia in 6 cases (30%) and acute rhabdomyolysis in 1 case (5%). Neurological sequelae in 5 cases (25%): 2 cases with motor deficit, 1 case with sensory deficit, 1 case with sensory - motor, language and visual deficit and 1 case of vigilant coma. Fatal cases: 2 cases (10%): 1 by massive ischemic stroke and posterior hernia and 1 by brain stem - encephalic

and cerebellar haemorrhage. *Conclusions:* It is important to observe the increase in neurological events at an early age produced by the use of cocaine and its social-health implications, through prospective studies. Target organs are especially the cardiovascular system and the nervous system and among the mechanisms involved are vasospasm, increase in blood pressure and neurotransmitter alterations.

197. Increasing Drug and Alcohol Abuse Detection Rates in Pediatric Emergency Departments: A Prospective Cohort Study

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Objective: To improve the detection rates of drugs and alcohol use among adolescents presenting to pediatric emergency departments (ED) by introducing structured guidelines for toxicological laboratory workup. *Methods:* The study was conducted in two pediatric ED's [Assaf Harofeh Medical Center" (AHMC) and "Meir Medical Center" (MMC)] between September 1st 2006 and August 31st 2007. These hospitals are affiliated to the Sackler School of Medicine, Tel-Aviv University, Israel. The annual census is nearly 20,000 patients in both hospitals and the demographics are similar. Physicians in the AHMC were instructed to send blood for ethanol levels and urine for toxicological screening in any adolescent (age 12–18) presenting to the ED with a new psychiatric disorder, any change in the level of consciousness, suicidal attempt or past history of alcohol or drug abuse. Physicians in the MMC did not receive any special instructions. *Results:* During the study period, 3200 adolescents (51% males) were seen in AHMC and 3493 (47% males) in MMC. The mean age was 15.2 ± 1.7 years and 14.9 ± 1.7 respectively. Urine drug screen was ordered for 138 patients from AHMC and 48 patients from MMC (P<0.001). Illicit drugs were detected in 13 patients from AHMC and in 4 patients from MMC (P=0.034). Ethanol levels were measured in 75 patients from AHMC and 31 patients from MMC (P<0.001) and were higher than 10 mg/dl in 49 and 30 patients respectively (P<0.001). *Conclusion:* Introducing structured guidelines for ordering toxicological screening increases the detection of alcohol and drug of abuse among adolescents presenting to pediatric emergency departments. Further studies are needed to determine whether or not the increased detection rate also improve medical treatment and the cost effectiveness of this approach. *Acknowledgement:* Supported by a grant from the Israel Anti-Drug Authority.

198. Detection of Phencyclidine in Urine: Real Poisoning or Pharmacological Interaction

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Objective: Phencyclidine (PCP) or angel dust is a drug of abuse that is uncommon in Spain. It is normally detected by using a technique that may cause cross-reactions with the metabolites of some drugs, especially venlafaxine. The objective of this study was to analyze the characteristics of patients who tested positive for the detection of PCP in urine in an emergency department. *Methods:* We made a retrospective analysis of the clinical histories of patients testing positive for PCP in urine during 1999–2006. Epidemiological data, drug consumption, psychiatric disease and treatment, reason for consultation and analytical results (detection of drugs of abuse in urine) were collected. Patients were divided into two groups according to whether they were treated with venlafaxine (A) or not (B). *Results:* Forty patients were included, with a mean age of 29.8 years; 21 were male. A total of 70% of patients were receiving drug treatment for a psychiatric disease and 50% were habitual consumers of drugs of abuse. The most common reasons for consultation were psychiatric alterations in 30%, attempted suicide in 27.5% and neurological manifestations in 17.5% of the cases. Group A included 21 patients, of whom 13 tested positive for PCP alone in urine, while the remaining 8 also tested positive for other drugs of abuse: cocaine (4), cannabis (2), methamphetamine (2) and amphetamine (1). Group B included 19 patients, of whom nine tested positive for PCP alone in urine; five were receiving treatment for antidepressants or neuroleptic drugs. The remaining eight patients also tested positive for other drugs of abuse: cocaine (5), cannabis (4), opiates (3), amphetamines and methamphetamine (2); three were receiving treatment with antidepressants or neuroleptic drugs. *Conclusions:* The routine detection of PCP in urine can give rise to diagnostic errors when possible interactions with other drugs are not known. In case of doubt, more specific techniques should be performed to confirm the consumption of PCP.

199. Use of Physostigmine in the Treatment of the Anticholinergic Syndrome Related to Abuse of Cocaine Adulterated with Atropine

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In recent years anticholinergic syndrome (AS) caused by adulterated cocaine is more frequent (1) and has been described in various European countries (2,3). *Objective:* We describe symptoms, toxicological analysis and treatment in two patients presenting to the emergency department (ED) after sniffing cocaine adulterated with atropine. *Case series:* Case 1 - A 24 year old man presented to the ED for persisting AS after sniffing 2 grams of cocaine 4–6 hours before. Clinical investigation revealed excitability, auditory and visual hallucinations, delirium, mydriasis, flushing and dry mouth. Body temperature (BT) was normal and heart rate (HR) was 93 bpm. The patient was initially treated with benzodiazepines and physostigmine 0.2 milligrams infusion. Physostigmine 0.2 milligrams was repeated 30 minutes later for persistent hallucinations. Complete neurological recovery resulted and the patient was discharged the following day. Toxicological laboratory data revealed cocaine and atropine in the urine sample. Case 2 - A 42 year old man was admitted to the ED 3 hours after abuse of cocaine. The patient presented with unreactive wide pupils and hallucinations. HR and BT were 130 bpm and 39.6^{o} centigrade respectively. Benzodiazepines and physostigmine 0.5 milligram were immediately administered. A complete clinical recovery was observed within 30 minutes. Atropine urine level was 500 ng/ml. Atropine blood levels were below the laboratory detection limit (2 ng/ml) in both cases. *Conclusion:* Clinical evaluation and toxicological analysis are very important for diagnosis and specific treatment of poisoned cocaine patients with unexpected AS at ED admission; nowadays atropine and other anticholinergic adulterants have to be considered in cocaine abusers in Italy. Physostigmine seems to be effective in the treatment of AS related to cocaine-atropine mixture abuse, without adverse effects. *References:* 1. Weiner AL, Bayer MJ, McKay CA Jr, *et al*. Anticholinergic poisoning with adulterated intranasal cocaine. *Am J Emerg Med* 1998; **16**: 517–520. 2. Bacis G, Papa P, Rocchi L, *et al*. Cocaine adulterated with atropine: an epidemic poisoning in northern Italy in 2004. *Clin Toxicol* 2005; **43**: 664. 3. Intoxications with cocaine adulterated with atropine in four EU Member States (Nov/Dec 2004-Feb 2005). www.emcdda.eu.int

200. Severe Acute Neurotoxicity after Yohimbine Ingestion in a Body Builder

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Yohimbine is an alkaloid obtained from *Corynanthe yohimbe* and other biological sources (1). Yohimbine is used clinically in the treatment of certain types of erectile impotence (2) and has undergone a resurgence in street use as an aphrodisiac and mild hallucinogen (3). In recent years yohimbine has been very common in body-building communities for its hypothesized lipolytic and sympathomimetic effect. *Objective:* We describe a case of a bodybuilder in whom severe acute neurotoxic effects presented 1–2 hours after yohimbine ingestion. *Case report:* After ingestion of 5 grams of yohimbine mixed with niacin for a body-building competition a 37 year-old man presented early with generalized malaise, vomiting, loss of consciousness and seizures spontaneously resolving in a few minutes. At first evaluation the GCS was 3 so orotracheal intubation and fluids infusion were immediately started. At admission to the ICU the patient presented with hypertension (acme 259/107 mmHg) and tachycardia (acme 140 pulse/minutes) and was treated with furosemide and labetalol; chest radiographs and cranial CT scan were normal. The patient's history was negative for neurological diseases. An extensive gastric lavage was immediately performed, followed by oral administration of activated charcoal and cathartics. Twelve hours later the patient was extubated with normal hemodynamic parameters and neurological examination; he was discharged the following day. The yohimbine blood levels at 3, 6, 14 and 22 hours after ingestion were 5240, 2250, 1530, 865 ng/ml respectively. *Conclusion:* Yohimbine utilization in body-building communities is a known problem but few data are available about its toxicity and the related blood levels. The most common adverse effects due to yohimbine administration include antidiuresis, tachycardia, hypertension, vasodilation, nausea, tremor, irritability, dizziness, headache and hallucinations. This patient showed severe hemodynamic and neurological manifestations; to our knowledge it is the first case of intoxication with such high blood levels of yohimbine. *References:* 1. Shannon M, Neuman MI. Yohimbine. *Pediatr Emerg Care* 2000; **16**: 49–50. 2. Tam SW, Worcel M, Wyllie M. Yohimbine: a clinical review. *Pharmacol Ther* 2001; **91**: 215–243. 3. Linden CH, Vellman WP, Rumack B, *et al*. Yohimbine: a new street drug. *Ann Emerg Med* 1985; **14**: 1002–1004.

201. Cyclical Hyperemesis Associated with Frequent Marijuana Use: A Case Report

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Objective: Cyclical hyperemesis associated with frequent marijuana use has been recently described, though few reports exist. This is a case of cyclical hyperemesis with daily marijuana use in an adolescent female. *Case report:* A 19 year old female presented to the emergency department complaining of multiple episodes of nonbloody, nonbilious vomiting. She had experienced similar episodes occurring in every few months over the previous two years, as confirmed by chart review. Review of systems was negative for fever, abdominal pain, diarrhea, vertigo, headache, or other symptoms commonly associated with vomiting. She denied any history of pregnancy. She reported no medication use but did report use of marijuana multiple times daily for the six preceding years. Physical examination revealed a well-appearing female with normal vital signs, and normal abdominal, neurologic, cardiac, pulmonary, abdominal, musculoskeletal, and dermatologic examination. Urine toxicology testing was positive for THC/cannabinoids and urine pregnancy test was negative. Laboratory values of blood count, comprehensive metabolic panel including liver function tests, amylase, lipase, were all within normal limits. Abdominal ultrasound and CT were also normal. The symptoms were deemed to be consistent with cyclic hyperemesis associated with chronic marijuana use (1,2) and the patient was advised to discontinue marijuana use. She disbelieved the diagnosis and refused to cease smoking marijuana instead choosing to follow up with a gastroenterologist. *Conclusion:* The pattern of symptoms in this case is consistent with previous descriptions of cyclical hyperemesis due to frequent marijuana use. Since this syndrome develops after years of marijuana use and is cyclical in nature, patients commonly dispute the association or causality of marijuana and vomiting and are unwilling or unable to discontinue use. Patients who cease marijuana use have resolution of symptoms that recurs after resumption of marijuana use. This phenomenon remains an esoteric, possibly under recognized entity that should be considered in patients with hyperemesis. *References:* 1. Allen JH, GM de Moore, R Heddle, *et al*. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. *Gut* 2004; **53**: 1566–70. 2. Roche E, Foster PN. Cannabinoid hyperemesis: not just a problem in Adelaide Hills. *Gut* 2005; **54**: 731.

202. Cocaine Intoxication: Analysis of 327 Cases

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Objective: To describe the characteristics of subjects with acute cocaine intoxication (CI) attended by the emergency department. *Methods:* Retrospective study of all cases of acute CI

treated during 2003 and 2004. *Results:* A total of 327 cases of acute CI were collected, which accounted for 21.4% of all acute intoxications. The mean age was 31 (± 8) years. A total of 76.5% were men, and 69.1% came to the emergency room by ambulance. Most subjects attended during the weekend (46.8%), and 54.1% between 21:45 p.m. to 7:30 a.m. (night shift). A total of 25.4% of subjects were sporadic consumers, 53.2% regular consumers, 4.6% ex-consumers, and 1.5% had consumed cocaine for the first time. More than two drugs were used by 55.7% of subjects, alcohol in 53.5%, benzodiazepines in 17.4%, opioids in 31.2%, cannabis in 17.1%, MDMA pills in 5.5%, amphetamines in 2.4%, GHB in 11.3%, ketamine in 2.1%, and LSD in 0.3%. Cocaine was consumed in a public place in 77.1% of cases. Previous cocaine intoxication was recorded in 59.3% of cases. Symptoms were present in 93% of cases (gastrointestinal 8.3%, cardiovascular 28.4%, respiratory 19%, neurologic 52.6%, behavior disturbances 48%). Mydriasis was observed in 47.3% of cases. Non-specific treatment was indicated in 31.5% of cases. Antidotes were given to 20.5% (physostigmine 0.9%, naloxone 14.4%, flumazenil 5.2%). In 58.4% of cases urine drug screening was performed, with positive results for cannabis (23.2%), cocaine (50.2%), phencyclidine (0.6%), opiates (16.8%), amphetamines (2.1%), meta-amphetamines (3.7%), and benzodiazepines (18.7%). Of 31.4% of subjects in which plasma ethanol levels were measured, positive results were obtained in 18.3%. A total of 60.9% of subjects were discharged from the emergency department within the first 12 h, 18.7% remained in the emergency room for more than 12 h, 14.6% requested voluntary discharge, and 5.7% were admitted to the hospital. 2.1% of subjects were visited by a psychiatrist. *Conclusions:* The profile of the subject attending the emergency department because of acute CI corresponds to a 26-year-old man, transferred to the emergency room by ambulance, at weekends, during the night shift, who is a regular consumer, presenting with cardiologic and neurologic symptoms, and being discharged within the first 12 h. In most of the cases, acute cocaine intoxication was associated with concomitant use of other drugs, particularly alcohol, opioids, benzodiazepines, cannabis, and GHB. Less than one fourth of subjects underwent psychiatric assessment.

203. Liquid Ecstasy (GHB) Intoxications Attended by Hospital Emergency Departments of the City of Barcelona (Spain)

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Objective: To analyze cases of poisoning by liquid ecstasy (GHB) attended by the Emergency Departments (ED) of two urban hospitals of the city of Barcelona. To describe the epidemiological profile, reasons for attending the ED, clinical manifestations, the associated consumption of other poisons, the treatment administered and the evolution. *Methods:* During two years (2003–2004) all cases of poisoning or overdose due to GHB attending the ED of the Hospital del Mar and the Hospital Clinic of Barcelona were collected. The diagnosis was clinical and/or by toxicological analysis. Epidemiological, clinical, analytical and therapeutic variables and the history were collected. *Results:* A total of 339 patients (mean age 23.5 years, 62% male) were identified. Most (89%) patients were admitted during the early morning and during the weekend (89%). Symptoms began in a public place in 97%. The symptoms were heterogeneous, particularly reduced consciousness, since 72% of patients had a Glasgow Coma Score of 12 or less. Seventy per cent stated having consumed GHB with other substances, mainly ethyl alcohol (53%) and cocaine (16%). Some form of treatment (serum therapy, oxygen therapy) was required in 32% of cases and 20 cases were administered an antidote: naloxone (12 cases), flumazenil (8 cases) and physostigmine (6 cases). Five cases needed orotracheal intubation and one patient required advanced ventilatory support. There were no deaths. *Conclusion:* GHB intoxication leading to reduced consciousness is a frequent reason for admission to the ED, mainly in young people and in the early morning during the weekend. GHB intoxication should be considered in all cases of coma of unknown origin.

204. Recurrent Heroin Toxicity in an Unrecognized Body-packer Presenting Trapped Packets in the Pylorus

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Objective: We describe an unusual case of recurrent heroin toxicity in a body-packer presenting mechanical pylorus obstruction. *Case report:* A 39-year-old foreign male presented at the emergency department with ventricular fibrillation. Cardiopulmonary resuscitation was performed and naloxone 1.6 mg was administered for miosis. Then he was extubated, conscious and without cardiorespiratory failure. Urine qualitative analysis revealed the presence of morphine, and the absence of ethanol, cocaine and benzodiazepines. Admission to the emergency medicine department with diagnosis of heroin overdose followed. The day after, the patient refused further care and exited the ward. Thirty minutes later he came back and after three hours progressively sunk into coma. Six hour later, he was admitted to the intensive care unit (ICU), for respiratory failure, intubated and ventilated. A cerebral computed tomography (CT) revealed brain edema and morphine was found in urine. The tentative diagnosis was a second heroin overdose. Two days later, he was extubated. On day 5, he was transferred to a medical ward, without signs of opioid toxicity. He refused to provide a history. The next day bradypnea and coma required intubation and ventilation in ICU. Miosis was observed. Cerebral CT was normal. Abdominal CT revealed two opacities in the stomach and two in the colon, and the detection of a significant morphine serum level (1.9 mg/L; therapeutic lower than 0.05 mg/L) confirmed the suspect of body-packing. The patient vomited polyethylene glycol solution given by nasogastric tube. A gastroscopy showed mechanical obstruction of the pylorus due to two trapped packets presenting signs of initial rupture. Owing to the risk of complete rupture, surgical removal was performed: intact packets were found in the colon, whereas torn packets, approximately 2.5 X 2.5 cm in size, in the pylorus. Morphine serum levels immediately before and after surgery were 1.1 and 0.6 mg/L, respectively. Packets analysis revealed the transport of heroin 33 g. The patient had a good recovery. *Conclusion:* Leaking packets trapped in the pylorus resulted in recurrent release of heroin with subsequent intoxication, because heroin abuse on three occasions seems implausible as an explanation. Body-packers may present opioid toxicity recurrence due to trapped packets.

205. A Case Study of a Bodypacker and Review of Imaging Techniques Used in Such Cases

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Objective: To describe a case of cocaine body packing and review imaging methods used to detect packages within the body as described in the literature. *Case report:* A forty year old female was detained at Heathrow airport suspected of concealing drugs, a plain abdominal x-ray was negative for packets, she was released. Several hours later she presented at the accident and emergency department in Cardiff and although unwell did not admit any drug involvement. The police contacted the hospital to inform them that she was a possible "body packer". Plain abdominal and chest x-rays were negative for packages, however, the patient continued to deteriorate and started to have seizures. Computer tomography (CT) was performed which clearly showed the presence of multiple packages in the abdomen. The patient was immediately transferred for surgical removal of the packages but died during the procedure. Fifty packages of cocaine were retrieved from her body. *Conclusion:* This case highlights the need for caution when interpreting results of x-rays in cases of suspected body-packing. Even on review with CT images present it was not possible to identify any packages on the radiograph. Cases in the literature may show false negative x-ray (1), false negative CT scan (2), positive x-ray (3) and false positive CT scan (4). In conclusion, a negative image regardless of method cannot exclude the presence of packages and all patients should be observed carefully. *References:* 1. Gherardi R, Marc B, Alberti X, *et al*. A cocaine body packer with normal abdominal plain radiograms. *Am J Forensic Med Pathol* 1990; **11**: 154–7. 2. Hahn I, Hoffman RS, Nelson LS. Contrast CT scan fails to detect the last heroin packet. *J Emerg Med* 2004; **27**: 279–283. 3. Krishnan A, Brown R. Plain abdominal radiography in the diagnosis of the "body packer". *J Acc Emerg Med* 1999; **16**: 381. 4. Traub SJ, Hoffman RS, Nelson LS. False-positive abdominal radiography in a body packer resulting from intraabdominal calcifications. *Am J Emerg Med* 2003; **21**: 607–608.

206. Self-Treatment of Chronic Pain and Opioid Withdrawal with Kratom

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Objective: Kratom (*Mitragynia speciosa korth*) is a medicinal herb endogenous to southeast Asia traditionally used as a treatment for opium withdrawal (1). Patients with chronic pain are increasingly aware of kratom as opioid replacement therapy. We examine the pharmacologic basis for the putative efficacy of kratom and report an adverse herb-drug interaction between kratom and modafinil. *Case report:* A 43-year old male with chronic pain abruptly ceased illicit injection of hydromorphone; to attenuate withdrawal, he ingested kratom and experienced only mild sleep disturbances. He used kratom for $3^1/_2$ years without identifying specific adverse effects; after co-administering the herb with modafinil, he seized. After this event, he stopped taking kratom; he experienced minimal abstinence symptoms. Using HPLC we confirmed the identity of the plant matter obtained from the patient as kratom and identified no contaminants or adulterants. Using high throughput molecular screening, we found that mitragynine, the predominant alkaloid of kratom, binds with high affinity at human adrenergic, serotinergic, and adenosine CNS receptors. We also determined the binding affinity of mitragynine at mu (KD=204 ± 26 nM), delta (KD=2250 ± 47 nM) and kappa (KD=455 ± 47 nM) receptors. *Conclusion:* These data suggest that the mu-opioid agonism of mitragynine may minimize opioid withdrawal symptoms; as a kappa agonist, the molecule may oppose mu-opioid effects to modulate reinforcement and produce aversion (2). Furthermore, adrenergic agonist activity at alpha-2 receptors may permit kratom to mimic adjunctive therapies for opioid withdrawal such as clonidine. Although contributions from non-opioid receptor systems to the modulation of opioid withdrawal by kratom in humans are speculative, they are supported by murine studies that have identified agonist activity of mitragynine at CNS adrenergic and serotinergic receptor systems (3). Adverse effects of kratom are poorly described; mitragynine is a mu agonist but respiratory depression, pulmonary edema, and death have not been reported in humans. The exact mechanisms that contributed to seizure are unknown but could be related to CNS adenosine binding. Mitragynine or other kratom components could exhibit proconvulsant properties similar to tramadol, normeperidine, and propoxyphene (4). *References:* 1. Boyer E, Babu K, Macalino G, *et al*. Self-treatment of opiod withdrawal with a dietary supplement, Kratom. *Am J Addiction* 2007; **16**: 352–56. 2. Shellard EJ. Ethnopharmacology of kratom and the Mitragyna alkaloids. *J Ethnopharmacol* 1989; **25**: 123–4. 3. Matsumoto K, Mizowaki M, Suchitra T, *et al*. Central antinoceptive effects of mitragynine in mice: contributions from noradrenergic and serotoninergic systems. *Eur J Pharmacol* 1996; **317**: 75–81. 4. Wills B, Erickson T. Drug- and toxin-associated seizures. *Med Clin North Am* 2005; **89**: 1297–321.

207. Complementary and Alternative Medicine Remedies: Toxicological Evaluation and Reports from the Poison Control Centre of Milan, Italy

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Objective: The widespread belief that herbal and homeopathic medicines are harmless induces people to use them without any care or medical supervision. We report the toxicological aspects of Complementary and Alternative Medicine (CAM) products by analyzing the calls handled by the Poison Control Centre of Milan, the leading toxicological Centre in Italy. We also highlight the essential role of Poison Control Centres in monitoring toxic effects due to contaminated or dangerous products. *Methods:* A review of 2036 calls concerned with CAM remedies collected from January 2001 to December 2006 was analysed. *Results:* Among the calls collected, 1330 calls were related to herbal supplements and 706 calls to homeopathic medicines. The toxicological evaluation of CAM products (especially herbal supplements) was difficult because of inadequate information about composition and poor documentation about the pharmacological action of ingredients. The most serious cases were due to ingestion of contaminated products (heavy metals in ayurvedic products, tropane alkaloids in a batch of *Coleus forskolii*) and to possible adverse effects of active principles (a life-threatening gastric haemorrhage in a child treated with a salicylate containing herbal syrup, a case of rhabdomyolysis from Guggul, several cases of hepatitis,

others). The use of psychoactive herbs sold in health food stores or over the internet, such as *Salvia divinorum* or *Argyreia nervosa*, led to acute poisonings in the young. *Conclusions:* The surveillance of CAM medicines appears to be more difficult than pharmacovigilance of conventional drugs. Quality control of these products is difficult and they could be adulterated or contaminated, or the ingredients quite different from that declared. Moreover, information about pharmacological action, kinetics and therapeutic/toxic dose of medicinal plants is not currently available, especially if they do not belong to the European Pharmacopoeia. The identification of dangerous products allows effective interventions of the Authorities to protect public health, such as the withdrawal from the market and the issuing of countrywide alerts.

208. A Comparative Study of the Ventilatory Effects of Four Opioids Administered at Toxic Doses in the Rat

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Objective: Opioid analgesics (morphine and fentanyl) and maintenance treatments used in heroin addicts (methadone and buprenorphine) are known to induce respiratory depression. Here, we wished to characterize the ventilatory effects in response to each opioid administered at toxic dose, in order to identify molecule-specific patterns. *Methods:* We performed an experimental study in Sprague-Dawley rats, to compare the respiratory effects of these 4 opioids. We measured the arterial blood gases as well as the respiratory times and volumes using plethysmography (N=8 rats/group). Body temperatures were measured using telemetry devices, intraperitoneallly (IP) implanted 72 h before the day of experimentation. Drugs were IP administered at equivalent doses to 80% of LD_{50} (15 mg/kg methadone, 160 mg/kg buprenorphine, 80 mg/kg morphine, and 2.5 mg/kg fentanyl). Animals were pre-treated when required with subcutaneous injections of specific antagonists of opioid receptors, including 30 mg/kg-naloxonazine [a mu-1-receptor antagonist] and 5 mg/kg-Nor-BNI [a delta-receptor antagonist], at 24 and 6 hours before drug injections, respectively. We performed comparisons using ANOVA for repeated measurements followed by Bonferroni post-tests. *Results:* All 4 opioids except buprenorphine induced significant respiratory depression (decrease in PaO_2 and elevation in $PaCO_2$, $p<0.001$) characterized by a significant increase ($p<0.001$) of inspiratory time (TI) and thus a significant decrease in respiratory rate, without any significant modification of tidal volume. Regarding methadone and fentanyl, there was a significant increase ($p<0.01$) in expiratory time (TE) and thus a significant decrease in minute ventilation. Rat pre-treatment with naloxonazine (which we proved to be devoid of significant effects on arterial gases) significantly diminished the effects of methadone and fentanyl on $PaCO_2$ and PaO_2. This effect corresponded to a reduction in TI increase ($p<0.05$) and to 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. *Conclusions:* Mechanisms of respiratory depression in relation with opioid toxic doses is not uniform, depending on the molecule. Our results clearly suggest a different control pattern of inspiratory and expiratory times by opioid receptors. To our knowledge, this is the first experimental study showing that opioid-related TE increase is mediated by mu-1 receptors.

209. A Comparative Study in Mice of Tolerance to Methadone Analgesic and Respiratory Effects

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Objective: Methadone may be responsible for severe and even fatal poisonings during maintenance treatments. Methadone toxicity may be related 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 treated with intraperitoneal methadone and comparison of both analgesic (using hot plate, N=10 /group) and respiratory effects (using plethysmography without and under 4%-$FiCO_2$, N=6–8/group); determination of an experimental protocol inducing tolerance to methadone; calculation of the 50%-effective dose (ED50); and comparisons using ANOVA for repeated measurements followed by Bonferroni post-tests. *Results:* Methadone analgesic effects were dose-dependent. Analgesia peaked 20 min after methadone injection, with a linear dose-effect relationship (ED50=4 mg/kg). Tolerance was reached with 10 mg/kgx3/day-repeated administration during 10 days, with a 1.5-time increase in ED50. Kinetics of methadone respiratory effects were parallel to the analgesic effects with a significant increase in the inspiratory time (TI), 15 min after injection ($p<0.05$). Respiratory effects were dose-dependent: response to 4%-$FiCO_2$ resulted, in the 10 mg/kg methadone-treated animals in comparison to controls, in a significant increase of TI ($p<0.001$) and of expiratory time (TE) ($p<0.001$) as well as a significant decrease in t tidal volume (VT) ($p<0.01$). In mice treated with 10 versus 2.7 mg/kg methadone, there was a significant increase in TI ($p<0.001$) and TE ($p<0.001$), without any significant reduction in VT. Using the same protocol, we obtained comparable tolerance for respiratory and analgesic effects: there was for analgesia, a 1.5-times increase (5.8 mg/kg to 3.8 mg/kg) in the methadone-treated animals in comparison to controls; similarly, regarding the respiratory effects, we reported a variation under 4%-$FiCO_2$ of 1.5-times for TI, 1.2-times for TE, and 1.9-times for VT at day 10 when comparing to day 1 of methadone administration. *Conclusions:* Tolerance to the methadone analgesic and respiratory effects is similar at day 10. Consequently, using our model, we were unable to support the hypothesis that attributes methadone toxicity to the development of a weaker tolerance to its respiratory effects. Thus, other mechanisms of toxicity should be considered, to explain the occurrence of respiratory depression in drug-addicts.

210. Intravenous Silibinin for the Management Amatoxin Poisoning: First Usage in an American Cohort

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Objective: Intravenous silibinin, derived from common milk thistle, is approved for the management of amatoxin poisoning in 14 European Countries but remains unavailable in the USA. We describe the first American use of silibinin for amatoxin poisoning. *Case report:* An immigrant Mexican family of six ate tacos containing *Amanita phalloides* foraged at a state park in California. Symptoms began 8 hours later with hospital presentation ~15 hours post ingestion. All initial lab results were unremarkable. All received aggressive intravenous hydration, MDAC, intravenous penicillin, NAC, and (later) thioctic acid. By 72 hours post ingestion four had developed laboratory evidence of profound hepatotoxicity with ALTs of 8553 to 19972, PT/INRs of 26.4/3.6 to >100/14.9, and Factor Vs of 20% to 9%. The family was transferred to a liver transplant program in San Francisco. An Emergency Investigational New Drug petition for silibinin (Madaus Pharm, Germany) was granted by the FDA, and the drug was couriered to California. Infusions of 5 mg/kg every 4 hours began at ~ 78 hours post ingestion. 72 hours later two patients were discharged with INRs of 1.4/1.5, Factor Vs of 52%/63%, and ALTs of ~3500. An 83 year old woman recovered Factor V to 49%, INR 1.9, and ALT 4456 48 hours after silibinin infusions began, but later succumbed to anuric renal failure. One patient required continuous infusion FFP and developed hepatic encephalopathy (serum ammonia 129) before silibinin. He was later discharged with an ALT of 791, PT/INR of 21.5/1.9 and Factor V of 47%. All survivors had completely normal lab values two months later. *Conclusions:* Intravenous silibinin has been used for amatoxin poisoning in much of Europe for over 20 years. It has been shown to effectively inhibit OATP1B3 mediated transport of amatoxin into hepatocytes at relatively low concentrations. It is safe and well tolerated. While there have been no randomized prospective trials of this or any other treatment modality in the management of amatoxin poisoning, silibinin use was associated with the lowest mortality in 20 year retrospective analysis published in 2002. The FDA should consider fast track orphan drug approval for silibinin.

211. Red Blood Cell Acetylcholinesterase (RBC-ACHE) Inhibition and Intermediate Syndrome

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Background and objectives: We previously described that the intermediate syndrome (IMS) is a spectrum disorder, with one group developing classical IMS who are at high risk of late respiratory failure and sequential electrophysiological abnormalities: another group developing *forme fruste* intermediate syndrome (1). Persistent accumulation of acetylcholine at the neuromuscular junction is believed to cause IMS but the evidence is weak. The objective of this study was to assess the relationship between RBC-AChE inhibition and the development of IMS. *Method:* A prospective case series of 78 consenting symptomatic patients with acute organophosphate poisoning were assessed. Repeated physical examinations with neurological assessments were done. Repetitive Nerve Stimulation (RNS) studies were done on R/L Median and Ulnar nerves at 1, 3, 10, 15, 20 & 30Hz. RBC-AChE level was assessed on admission, 1, 4, 12 and 24 hours after admission and daily thereafter. Summary statistics for serial RBC-AChE level were calculated using area under the curve (AUC). The Mann Whitney test was used to compare groups. *Results:* Forty of 78 developed IMS spectrum disorder with characteristic weakness and typical RNS abnormalities (severe decrements, combined decrement increment decrement and decrement increment patterns) and 38/78 did not. Ten of 40 developed classical IMS and 30/40 developed *forme fruste* IMS. There was a significant difference in serial RBC-AChE level within the first 48 hours, between those who developed IMS spectrum (n=18 median AUC 3347: IQR 2075–4970 mU/µmol Hb(Fe)*h) and those who did not (n=17 median AUC 12410: IQR 3150–18700) with a p value of 0.02. On the day they demonstrated most severe RNS abnormalities, there was no significant difference in the RBC-AChE level between the patients who developed classical IMS (n=6 median 23.5: IQR 12.5–54 mU/µmol Hb(Fe)) and those who developed *forme fruste* IMS (n=17 median 36: IQR 21–66) with a p value of 0.31. *Conclusions:* Persistent RBC-AChE inhibition is associated with the development of IMS spectrum disorder. However, RBC-AChE may not be of value in predicting the severity or risk of late respiratory failure. *Reference:* 1. Jayawardane P, *et al*. Progression of electrophysiological abnormalities in acute organophosphate poisoning and the intermediate syndrome. *Clin Toxicol* 2007; **45**: 370–371.

212. Histamine Release is the Associated Mechanism Following Acetylcysteine Adverse Reaction in Man

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Introduction: The acetylcysteine (NAC) protocol for paracetamol poisoning in the UK is that of Prescott (1). Many patients developed adverse reactions and the mechanisms are not fully understood. A non-allergic release of histamine as a direct effect of NAC with inter-individual susceptibility has been proposed (2). Anti-histamines reduce the severity of reaction, supporting histamine-associated pathogenesis. *Objective:* To investigate the mechanisms of adverse reactions to IV NAC *Method:* An ethically approved prospective study was conducted on patients with significant paracetamol overdose admitted to our unit who required NAC between July 2006-May 2007. Consent was obtained from all patients. Blood was taken for serum paracetamol, serum histamine, tryptase, NAC and clotting factors at baseline and frequent time points after infusion commencement (+ 15, 30, 60 min, 2, 4, 20 h). All patients were monitored for adverse reactions: skin: respiratory; gastrointestinal; cardiovascular and others. Patients were categorized by ADR severity, minimal (nil and GI effects), moderate (mild flush, PFR reduction 25–50%, need for anti-emetic), severe (generalised flushing, respiratory distress PFR <50%, hypotension, chest pain). The relationships between ADR severity, serum histamine, tryptase and NAC were examined. *Results*: 22 subjects (mean ± sem) (11 M, 11 F; age 35.0 ± 3.3 y) completed the study. 10 subjects had minimal reaction; 5 developed moderate and 7 severe adverse reactions. Serum NAC concentration reached maximum at 30 minutes after initiation. Histamine AUC change from baseline 0-2 h was significantly higher in the groups with reactions [median (IQR)] (Minimal: n = 10, −6.5 (−58.0 to 11.0); moderate: n = 5, 26.0 (4.0 to 114.8); severe: n = 7 49.0 (27.8 to 64.5) ng/ml.min. Kruskals Wallis for severity p = 0.014). Maximum change in serum histamine occurred between 30 min to 1 h and returned to baseline after 2 h. There was no significant difference in serum tryptase. Serum NAC concentration in the groups with and without reactions were similar. *Conclusions*: Adverse reactions after NAC IV are common. Serum histamine release seems the mechanism of adverse reaction, and appears unrelated to NAC level.

213. A Controlled Study of Pesticide Regulation to Reduce Deaths from Pesticide Self-Poisoning

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Objective: Pesticide self-poisoning causes more than 300,000 deaths every year in rural Asia. As a result, the WHO now considers it to be the most important global suicide issue. Sri Lanka has successfully reduced its suicide rate from 47/100,000 in 1995 to 23/100,000 in 2005 by banning the most toxic organophosphorus pesticides and the organochlorine endosulfan. However, poisoning with WHO Class II toxicity organophosphorus pesticides, particularly dimethoate and fenthion, remains a problem. We aimed to determine whether local bans of these two pesticides would result in an overall decrease in case fatality from pesticide poisoning. *Methods:* We set up a controlled study in the North Central Province of Sri Lanka. The sale of dimethoate and fenthion was banned by the Sri Lankan Government in June 2003 in most of the Polonnaruwa district but not Anuradhapura district. All cases of pesticide poisoning admitted to the two district hospitals were prospectively followed from July 2002. We aimed to compare the case fatality of pesticide poisoning in Polonnaruwa with Anuradhapura, for one year before the ban (Jul02-Jun03) and for two years after the ban became effective (Jul04–Jun06). *Results:* Hospital admissions for dimethoate and fenthion poisoning fell by 43% after the ban in Polonnaruwa, while increasing by 23% in Anuradhapura. The overall case fatality for pesticide poisoning fell from 14.4% to 9.0% in Polonnaruwa (OR 0.59, 95%CI 0.41–0.84) and from 11.3% to 10.6% in Anuradhapura (OR 0.93, 95%CI 0.70–1.25; Mantel-Haenszel test of heterogeneity P<0.051). Unfortunately, this fall was not sustained in Polonnaruwa, with the case fatality rising back up to 12.1% in 2006–7, apparently due to an increased number of deaths from carbamate insecticides and to a lesser extent paraquat. *Conclusion:* Banning just two organophosphorus insecticides in a Sri Lankan district resulted in their reduced use and a marked initial fall in case fatality. However, this reduction was not sustained as farmers started using carbamates on their crops, and possibly switched to using paraquat for self-harm. Pesticide regulation will have to reduce the use of all moderate to highly toxic pesticides to make an impact on global suicide deaths.

214. Prognostic Factors of Poisonings Treated with Extracorporeal Life Support in the Intensive Care Unit

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Objective: Massive drug ingestions may be associated with refractory cardiac failure, the reversal of which despite prolonged arrest makes extracorporeal life support (ECLS) look promising (grade C recommendation, based on case reports). Once implemented, the purpose of ECLS is to take over heart function until recovery can occur, thus minimizing myocardial work and improving organ perfusion. ECLS is feasible in the intensive care unit (ICU) (1). Our objective was to determine the prognostic factors of ECLS-treated patients. *Methods:* Prospective study including all poisoned patients treated with ECLS in 2003–2007; surgical cannulation of femoral vessels in ICU to perform ECLS (Rotaflow®, Jostra-Maquet SA) in collaboration with a cardio-surgical team of a neighboring hospital; descriptive analysis (median, [percentiles 10–90%]); univariate comparisons using Chi-2 and Mann-Whitney tests. *Results:* Fifty-seven poisoned patients (19M/38F, 41 years [21–59], SAPS II: 75 [49–94]) were treated with ECLS over a 4-year period in relation to cardiac failure (26/57) and arrest (31/57). Patients had ingested high doses of cardio-toxicants in 49/57 cases (chloroquine 19%, Class I-anti-arrhythmic drugs 19%, beta-blockers 14%, calcium channel blockers 11%). Sixteen patients (28%) survived, including five after prolonged cardiac arrest (maximal duration: 180 min). Death was consequent to multiorgan failure, anoxic encephalopathy or capillary leak syndrome if ECLS was performed under cardiac massage. Four patients presented with documented brain death, allowing organ donation in 2 cases. Among these patients, the heart of one flecainide-poisoned patient was successfully transplanted, after normalization of ECG and myocardial function as well as toxicant elimination under ECLS. Prognostic factors in ECLS-treated poisoned patients were as follows: QRS enlargement on admission (p=0.009), SAPS II score on admission (p=0.005), ECLS performance under massage (p=0.008), arterial pH (p<0.001), lactate concentration (10.7 [6.6–19.6] versus 15.0 mmol/l [6.2–29.5], p=0.003), as well as red cell (p=0.008), fresh plasma (p=0,003), and platelet (p=0.03) transfusions within the first 24 h. *Conclusions:* To our knowledge, this is the larger series of ECLS-treated poisoned patients ever reported. ECLS appears to be an efficient salvage technique in case of refractory toxic cardiac failure or arrest, with a 28% survival rate. Our series clearly demonstrate that toxic refractory cardiac failure remains the best indication with a 46% survival rate.

215. *In Vitro* Oxime Protection of Red Blood Cell Acetylcholinesterase Inhibited by Diisopropyl-Fluorophosphate

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Objective: Oximes are enzyme reactivators used in poisoning with organophosphorus cholinesterase inhibitors. The oxime dose which can be safely administered is limited by the intrinsic toxicity of the substances such as their own cholinesterase inhibiting tendency. Clinical experience with the available oximes is disappointing. To meet this need, over the years new reactivators of cholinesterase of potential clinical utility have been developed. The purpose of the study was to estimate "*in vitro*" both the intrinsic toxicity of and the extent of possible protection conferred by established (pralidoxime, obidoxime, HI-6, methoxime, trimedoxime) and experimental (various K-type) oximes, using diisopropyl-fluoro-phosphate (DFP) as an esterase inhibitor. *Methods:* The IC_{50} of DFP was determined. Measurements were then repeated in the presence of increasing oxime concentrations, leading to an apparent increase in DFP IC_{50}. Calculated apparent IC_{50} values were plotted against oxime concentrations to obtain an IC_{50} shift curve. The slope of this shift curve (tan alpha) was used to quantify the magnitude of the protective effect (nM IC_{50} increase per µM oxime). *Results:* The IC_{50} of DFP was 120 nM and increased with increasing concentration of most oximes used in a linear manner. Tan alpha and binding constant values are presented in the table. *Conclusion:* Based on our tan alpha determinations, some of the new K-oxime reactivators are far superior to pralidoxime, obidoxime, HI-6, trimedoxime and methoxime, with K-107, K-108, and K-113 being the outstanding compounds. *In vivo* testing of the new oximes as DFP-protective agents is therefore indispensable.

Table: Oximes, IC_{50}, tan alpha and binding constants

Oxime	IC_{50} [µM[of oxime for human RBC AChE	tan α [nM/µM]	Binding constant K [µM]
Pralidoxime 2-PAM	592 ± 26 (535–650)	0.8 ± 0.05 (0.7–0.9)	158
Obidoxime Lue H-6	702 ± 39 (606–798)	1.5 ± 0.07 (1.3–1.7)	79
Trimedoxime TMB-4	652 ± 93 (413–891)	5.2 ± 0.4 (3.5–6.9)	36
Methoxime MMC-4	1.514 ± 157 (1.111–1.917)	5.9 ± 0.3 (5.1–6.8)	25
HI-6	310 ± 28 (239–381)	0.8 ± 0.06 (0.6–1.0)	158
BI-6	83 ± 5 (72–95)	0.7 ± 0.1 (0.5–0.8)	141
K-27	414 ± 28 (346–483)	0.9 ± 0.1 (0.8–1.0)	112
K-33	21 ± 0.7 (20–23)	6.8 ± 0.2 (6.1–7.4)	20
K-48	461 ± 18 (417–505)	1.3 ± 0.1 (1–1.6)	100
K-53	115 ± 10 (88–141)	8 ± 0.5 (6.6–9.3)	13
K-74	103 ± 3 (94–111)	1.4 ± 0.3 (0.7–2.0)	47
K-75	63 ± 6 (46–80)	7.3 ± 1 (4.5–10)	21
K-107	6 ± 0.7 (4.4–7.9)	17 ± 1 (14–19)	7
K-108	8 ± 0.3 (7.5–9.0)	20 ± 1 (17–23)	5
K-113	9 ± 0.6 (6.0–11)	16 ± 2 (11–21)	7
K-114	13 ± 0.9 (11–15)	14 ± 1 (12–15)	9

216. Pralidoxime Induces a Sustained Cholinesterase Reactivation but Only Transient Normalization of Paraoxon-Induced Respiratory Distress

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Objective: The efficiency of oximes in organophosphate poisoning is a matter of debate. In rats poisoned with paraoxon (PO), we studied the effects of pralidoxime (PX) methylsulfate on respiratory distress and blood cholinesterase (ChE) activities. *Methods:* We tested in whole blood *in vitro* the efficiency of various PX concentrations to reactivate PO-induced ChE inhibition. Sprague-Dawley male rats were treated with PX (base: 10, 25, 50 $mg.Kg^{-1}$) using IV and IM routes to assess the dosage regimen providing plasma PX > 4 mg/l during the longest period of time. PO (0.215 $mg.Kg^{-1}$ e.g. 50% LD_{50}) was administered subcutaneously. Rats were treated with PX 30 min post injection of PO. Respiratory function was assessed using whole body plethysmography. ChE activities were measured in whole blood. Results are expressed as mean +/– SEM. Statistical analysis used Student's t test and ANOVA tests with p< 0.05. *Results:* The 50 $mg.Kg^{-1}$ IM dose resulted in plasma PX concentrations > 4 $mg.L^{-1}$ during 35 min post infusion. PO induced an increase in total time, expiratory time and tidal volume, and a decrease in respiratory rate. In the same time, whole blood ChE activities were decreased to 40% of the basal value. Thirty minutes after PO administration, PX (50 $mg.Kg^{-1}$, IM) infusion induced: 1-) a fast, total and prolonged ChE reactivation (> 180 min), 2-) a rapid (< 5 min), complete but only transient (< 30 min) reversal of PO-induced respiratory effects. *Discussion:* A 50% LD_{50} of PO induced respiratory distress and decrease in ChE activity. A single dose of PX rapidly corrected both effects which were dependent on PX concentrations. Thereafter, normalization was sustained for ChE activity but only transient for respiratory distress. *Conclusion:* Our data suggest that ChE reactivation is a necessary but not sufficient condition for the antidotal effect of PX. ChE reactivation cannot be used alone to assess the antidotal efficiency of oximes.

217. Efficacy of Two New Asymmetric Bispyridinium Oximes (K-27 And K-48) in Rats Exposed to Diisopropylfluorophosphate (DFP): Comparison with the Established Oximes Pralidoxime, Obidoxime, Trimedoxime, Methoxime and Hi-6

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Objectives: Oximes are enzyme reactivators used in poisoning with organophosphorus cholinesterase inhibitors. Clinical experience with the available oximes is disappointing. To meet this need, over the years new reactivators of cholinesterase of potential clinical utility have been developed. The new K-oximes, K-27 and K-48, show good *in vitro* and *in vivo* (rodents) efficacy in protecting acetylcholinesterase (AChE) from inhibition by different organophosphorus compounds (OPC), including nerve agents. To assess their efficacy *in vivo*, the extent of oxime-conferred protection from mortality induced by diisopropylfluorophosphate (DFP) was quantified and compared with that of the established oximes. *Methods:* Rats received DFP in a dosage of 6, 8 or 10 µMol, and immediately thereafter intraperitoneal injections of K-27, K-48, pralidoxime, obidoxime, trimedoxime, methoxime or HI-6. The relative risk of death over time was estimated by Cox survival analysis, comparing results with the no-treatment group. *Results:* Best protection was observed when K-27 was used, reducing the relative risk of death (RR) to 19% of control RR ($p \leq 0.005$). The efficacy of obidoxime (RR=31%, $p \leq 0.005$), K-48 (RR=31%, 27%, $p \leq 0.005$) was comparable, whereas RR of≈$p \leq 0.005$) and methoxime (RR death was only reduced to about 37% by HI-6, to 48% by trimedoxime and to 63% by 2-PAM ($p \leq 0.005$). Whereas the differences between the best oximes (K-27, obidoxime, methoxime, K-48) were not significant, these four oximes were significantly more effective than pralidoxime ($p \leq 0.05$). The efficacy of K-27 was also significantly higher than that of HI-6, trimedoxime and pralidoxime ($p \leq 0.05$). Similar results have been previously reported with paraoxon and methyl paraoxon (1,2). *Conclusion:* Pralidoxime's role as a reactivator should be reassessed. *References:* 1. Petroianu GA, Nurulain SM, Nagelkerke N, *et al.*

Five oximes (K-27, K-33, K-48, BI-6 and methoxime) in comparison with pralidoxime: survival in rats exposed to the organophosphate paraoxon. *J Appl Toxicol* 2006; **26**: 262–268. 2. Petroianu GA, Nurulain SM, Nagelkerke N, *et al*. Five oximes (K-27, K-48, obidoxime, HI-6 and trimedoxime) in comparison with pralidoxime: survival in rats exposed to methylparaoxon. *J Appl Toxicol* 2007; **27**: 453–457.

218. Acute Toxicity of Tramadol – Analysis of 287 Cases

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Objective: To establish the acute toxicity of tramadol and the relation between toxic dose and pertinent clinical features. *Methods:* Case records submitted by Swedish hospitals concerning tramadol overdose during a nine year period (1997–2005) were studied. Poisoning accidents in children less than 10 years and mixed poisonings, apart from those involving ethanol, were excluded. The circumstances were documented and the cases were graded according to the Poisoning Severity Score (1). *Results:* In total 287 patients were studied. The majority of poisonings (90%) were intentional or of unclear origin, 5% related to abuse and 5% were accidental. The most common symptoms were CNS depression (56%), stomach upset (29%), convulsions (20%) and tachycardia (20%). Convulsions occurred after ingestion of >1.5 g - at lower doses only exceptionally and when predisposing factors were at hand, e.g. spasticity, a history of convulsive disorder, repeated high doses, ethanol abuse and recent general anaesthesia. Less common symptoms were hypotension, bradypnoea (only at high doses, mostly in combination with ethanol and with doubtful response to naloxone), miosis, urinary retention, agitation and diaphoresis. Severity grading was done in 261 patients (26 were excluded from the clinical grading because of insufficient data). 15% of the patients were asymptomatic, 50% developed mild, 26% moderate and 8% severe poisoning. In two cases outcome was fatal (0.7%). In a previous study of dextropropoxyphene poisoning (2) 18% of the patients were asymptomatic, 44% had mild, 22% moderate and 16% severe symptoms. *Conclusion:* CNS depression was the most common symptom (56%) whereas convulsions proved to be the most serious expression of toxicity, observed in 20% of the cases. With a few exceptions convulsions occurred only when the toxic dose exceeded 1.5 g. Respiratory depression was observed only at high doses and mostly in combination with ethanol. The response to naloxone was difficult to assess. A comparison with an earlier study on dextropropoxyphene poisoning highlights the comparatively lower toxicity of tramadol. *References:* 1. Persson H, Sjöberg G, Haines J, *et al*. Poisoning Severity Score. Grading of acute poisoning. *J Toxicol Clin Toxicol* 1998; **36**: 205–213. 2. Torell E, Irestedt B, Persson H, *et al*. [Poisonings with analgesics. Paracetamol and dextropropoxyphene dominate and cause the most severe symptoms in a 3-year material] *Analgetikaförgiftningar Lakartidningen* 1996; **93**: 1955–1960.

219. Is Venlafaxine Cardiotoxic in Overdose? Evaluation of a Case Series Using a QT Nomogram

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Objective: Previous studies of venlafaxine overdose have suggested that it is cardiotoxic in overdose based on assessment of the QTc using Bazett's correction and case reports of massive ingestions. The aim of this study was to investigate serial electrocardiogram (ECG) parameters following venlafaxine overdose. *Methods:* The study included a cohort of 62 patients presenting on 79 occasions with venlafaxine overdose to a tertiary toxicology unit. Median age was 36 years (Interquartile range [IQR]: 27–41 yr) and 80% were female. ECG parameters (HR, QT, QRS) were manually measured on all ECGs. QT intervals were plotted on a QT nomogram (1) to investigate the presence of abnormal QT prolongation and compared to a control dataset of non-cardiotoxic poisonings. QRS intervals were measured and compared to controls. *Results:* A total of 254 ECGs were available for the 79 admissions for venlafaxine overdose. Abnormal QT, HR pairs occurred in 30 of the 254 ECGs and in 13 out of 79 cases (16%). For admissions with an abnormal QT the median dose ingested was 3750 mg (IQR: 2400 – 4500 mg) compared to a median dose of 2250 mg (IQR 1500–4000 mg) in patients with a normal QT interval. The median QRS width was 90 msec (IQR: 80 to 100msec) and 7% of were 120 msec or more. There was a linear relationship between dose and QRS width (r^2=0.16; p=0.0003). There were no cases of arrhythmias. *Conclusion:* Venlafaxine causes a modest effect on the QT interval in overdose which was not associated with any cases of arrhythmias in this dataset and this appears to be a dose dependent effect. Venlafaxine toxicity also causes moderate QRS widening which is related to dose. Cardiotoxicity in venlafaxine overdose is uncommon but patients with large ingestions should have cardiac monitoring. *Reference:* 1. Chan A, Isbister GK, Kirkpatrick C, *et al*. Drug-induced QT prolongation and Torsades de Pointes: evaluation of a QT nomogram. *QJM* 2007; **100**: 609–15.

220. Relationship of Systemic Inflammatory Response Syndrome to Digestive Tract Injury and Mortality in Corrosive Substance Ingestion

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Objective: Systemic inflammatory response syndrome (SIRS) may develop as a clinical response to nonspecific insults, including infection, trauma and burns. Clinical criteria of SIRS include: fever or hypothermia (temperature >38 or < 36ºC), tachycardia (> 90 beats/minute), tachypnea (> 20 breaths/minute) and abnormal white blood cells (WBC) count (>12,000 or < 4,000/mm^3). SIRS score of 2 points or more (one point for each criterion) indicate the presence of an inflammatory response. We examined the relationship between SIRS score and severity of corrosive injury. *Methods:* Prospective data were collected in a 3-year period on all admissions due to corrosive substance ingestion (n=126). SIRS criteria were evaluated on admission, and day 2, 3 and 7 post-ingestion. According the grade of esophagus and/or stomach injuries and the outcome, poisonings were classified as mild (36 patients), moderate (32 patients), severe (21 patients) and lethal (37 patients). *Results:* In case of mild and moderate injuries maximal SIRS score was 2, with leukocytosis and tachycardia as individual components. Its incidence on admission was 8.3% in case of mild injuries and 31.2% in case of moderate injuries. Derangements resolved within one or two days. In case of severe poisoning the incidence of SIRS was 71.4% on admission, and it declined to 66.7%, 33.3% and 14.3 % on day 2, 3 and 7 respectively. Lethal poisonings were characterized by high incidence of SIRS on admission (91.9%) and its persistence during the whole observational period (94.4%, 100% and 88.9% on day 2, 3 and 7, respectively). The most frequent value of SIRS score was 3 due to leukocytosis, tachycardia and tachypnea. Analysis of individual SIRS components showed that leukocytosis was the most sensitive parameter of digestive tract injury. *Conclusion:* This study demonstrated that persistence of SIRS for more than two days post-ingestion may be significant predictor of mortality in severe corrosive digestive tract trauma. However, clinical criteria of SIRS are nonspecific, and may be present in case of less severe injuries, but with lesser incidence and duration.

221. The Strategic Approach to International Chemicals Management (SAICM) and Funding Opportunities for Strengthening Chemicals Management

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Objective: To review recent intergovernmental initiatives to streamline and integrate efforts to safety manage hazardous chemicals and wastes. *Methods:* To analyze progress with the establishment of the Strategic Approach to International Chemicals Management (SAICM), adopted by governments in February 2006 (Dubai) at the International Conference on Chemicals Management (ICCM) and the role of poisons centres in supporting the sound chemicals management. SAICM a key initiative supporting the achievement of the goal agreed at the 2002 Johannesburg World Summit on Sustainable Development (WSSD) "ensuring that, by the end of the year 2020, chemicals are produced and used in ways that minimize significant adverse impacts on the environment and humans". *Results*: As of October 2006, 136 governments had nominated a SAICM focal point in their country responsible for ensuring communication between relevant ministries about SAICM activities. Regional Focal Points, Intergovernmental organization focal points and focal points of designated non-governmental institutions have also been put in place to sustain the integrated approach. A SAICM Quick Start Programme (QSP) has been established to support initial enabling capacity building and implementation activities in developing countries, least developed countries and small island developing States and countries with economies in transition. Over 6 million USD of project funding has been approved in the three rounds of operation of the SAICM QSP under a voluntary Trust Fund. The SAICM QSP Trust Fund receives applications for project funding every six months and the next two rounds will have application cut-offs of March and September 2008 respectively. Knowledge, and articulation of the role of poisons centres with respect to the broader chemicals management agenda, such as SAICM remains an outstanding need. Institutional support; even in developed economies is at best patchy. In some countries the expertise found in poisons centres is the sole source of expertise in how to detect, respond and advise on cases of environmental exposures to chemicals. *Discussion:* The presentation will discuss the ground rules of the SAICM QSP and what potential opportunities exist therein for poisons centres. The potential role of professional bodies such as EAPCCT and networking activities among professionals are crucial aspects of the Strategic Approach. Links to other related activities such as the GHS will be emphasized.

222. Documentation of Poisonings and Preparations According to German Chemicals Law

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Background: Unlike pharmaceutical products, chemical substances are not systematically tested in humans. Knowledge of substances gained by systematic documentation and analysis of adverse effects of chemicals in humans due to poisonings is therefore a valuable tool for a realistic assessment. Due to the regulations of the German Chemicals Act Para 16 e, amended in 1990, physicians who are consulted for treatment or evaluation of sequelae of diseases are requested to report health effects from real or suspected exposures to chemical substances to the BfR. Additionally, in different regulations, manufacturers or distributors of products are obliged to notify formulations of chemical products (1990), cosmetics (1997), biocidal preparations (2002) and surfactants (2007) to the BfR Documentation Centre for Poisonings and Products (DCPP) for risk assessment and to provide the German Poison Centres (PC) with formulations for emergency advice. The PCs assist the BfR by submission of data on health hazards resulting from their work. So in cooperation with the BfR Committee: "Evaluation of Poisonings" which has members of the German PCs, Industry, Consumer Councils and Ministries and based on two joint research projects with the German PCs, the BfR has implemented an effective toxicological network. *Results:* Since 1990 the DCPP received more than 52,000 reports. Additionally, the German PCs were provided with more than 260,000 product records. The "classic" distribution of cases in PCs is different to the BfR reports: The greatest part (90%) was due to accidents, 6% were hazards during normal use and only 2% of the cases were related to attempted suicides. 93% of the cases happened in adults, most of them in the workplace. Only 7% concerned children. Since 1990 the following fields had been developed under the Chemicals Law: 1. The development of instruments for documentation and evaluation of cases of poisoning according to the recommendations of the EAPCCT. This includes particularly the assessment of the causal relationship between exposure to a chemical substance or product and manifestation of a disease. Increasingly, the respective cases are documented in a database. 2. As a consequence of documentation and evaluation of health hazards, a "Toxicovigilance" procedure for the provision of rapid information to industry, ministries and industrial associations on the health risks of products on the basis of immediate and summarised reports has been inaugurated. For severe cases of toxic effects in humans, producers - as well as responsible authorities and ministries - are directly informed and asked to take risk reducing measures. From 1998 -2006 we had 25 immediate reports [(impregnating agents, solvents, lamp oils, garden torch, bubble bath, drugs, industrial/lavatory/drain cleaner, tea (bio drug), depilatatory cream, disinfectants, food supplements, fumigant, detergents and poppy seed bread]. Every year more than 120 manufactures/distributors were provided with periodically summarised reports. These reports led to additional warnings, classification, and labelling and promoted the development of lamp oil substitutes. 3) BgVV-ESPED Lamp oil Study: Since lamp oils involve the highest risk of severe health effects in infants and small children in household chemicals in Germany, the BfR initiated different measures for risk minimisation: child-resistant closures, warnings, a new R 65-Phrase and a new EC-standardisation of oil-lamps in accordance with the competent Ministries, which at least led to sale restrictions from July 1st, 2000 onwards in all EU countries. This has consequently led to the introduction of lamp oil substitutes into the German and EU market. To follow the consequences, a BfR monitoring study "Dangerous Lamp oils" was initiated together with 450 German Children's Hospitals. The results have shown that the replacement of paraffins by fatty acid esters obviously leads to a marked reduction of risk. 4) BfR Exposure study: To evaluate the circumstances of exposures during accidents, a study was initiated to collect data describing the circumstances of exposures to a number of selected chemical substances (paints, solvents, glues and pesticides). Cases to be studied are selected from the reports sent to the BfR, and questionnaires are to be filled out by the exposed persons to collect data that can

give a better description of the accident and to allow quantitative exposure evaluations. 5) Product labelling: A general BfR analysis of the product labels especially in the fast-growing and fluctuating international markets of household and cosmetic products has shown that there must be better orientation on the labels and packages to identify the real trade name in emergencies. To improve the product identification on the basis of the true trade name, the BfR has initiated investigations to preserve an "Easy-to-Identify Area" on the labels of consumer products in close proximity to the barcode via an EC-standardisation procedure. The standardisation came into force in October 2007. 6) Human case data base: Cases of particular scientific interest (e.g. rare poisonings, high-/ low-dose exposures, cases with unexpected clinical course, substances of special interest etc.) were documented as case records and collected in a special BfR case database. The case reports were written down in uniform documents, provided with keywords and additional information. The bilingual (German/English) case database is still implemented in the BfR intranet structure, but it will be opened for specialists in future. 7) Annual reports: Since 1995 the DCPP publishes regular annual reports with statistics, case reports and fields of special toxicological interest for physicians, industry, government, tertiary education and the public. Due to the increasing interest we publish annual reports also in English since 2004. *Conclusions:* For initiating preventative measures by governmental regulations, Germany implemented a monitoring system for documentation of human health hazards and to characterise the typical scenarios of accidents and exposures related to the respective hazardous products/compounds. This instrument can also serve as a basis for classification and labelling of hazardous products and substances, provide arguments for educational advertising and create the basis for co-operation with manufacturers/distributors and Ministries. These instruments might effectively support consumer's safety in addition to the new REACH regulation.

223. Improving the Notification of Dangerous Products at the EU-level

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Background: In 2008, the new EU-GHS legislation will replace both the Dangerous Substances Directive (67/548/EC) and the Dangerous Preparations Directive (1999/45/EC). Likewise, the Directive for Safety Data Sheets (91/155/EC) has already been incorporated in the new legislation for REACH (1907/2006). Both EU-GHS and REACH legislation will have a serious impact on all Poisons Information Centres (PICs) and governmental competent authorities involved with receiving product information. The EU-GHS legislation is currently under development and creates the opportunity for the (start of) harmonisation of the process of product notification. For the first step to harmonisation it is essential to reach consensus on the requirements of the notified product information. A survey by the Dutch PIC (conducted in 2006, published in 2007) showed a wide variety in requirements on product composition and ingredient concentrations (1). Comparing the 1989 EAPCCT proposal on product notification (2) with the various requirements of the EU member states shows that this document is still a reasonable compromise. Nevertheless, as the EU-GHS legislation will completely change the classification and labelling of substances and preparations, as will be pointed out below, it is necessary to rewrite the EAPCCT proposal now. *Problem identification:* EU-GHS legislation introduces, amongst others, new (criteria for) hazard classes (e.g. four toxicity levels replacing T and T+) and categories, new hazard pictograms and changes in hazard ('R') and precautionary ('S') statements. From 2008 until 2015 companies have to newly classify all their substances and preparations and to produce new Material Safety Data Sheets (MSDS) and product labels accordingly. A changed hazard class for a product requires renewed notification by manufacturers resulting in an increased workload for the receiving authorities such as PICs that need to process the information. This is complicated by the fact that both old and new regulations of classification will exist simultaneously until 2015. EU-GHS will also incorporate Article 17 of the Dangerous Preparations Directive (1999/45/EC) in which the legal obligation to notify product information of dangerous products to competent authorities is laid down. Our survey concluded that at this moment article 17 is differently implemented in EU member states as it does not define which information should be notified and how. Therefore, a considerable variation in methods of notification, formats used and country specific requirements on product composition, and ingredient concentrations are introduced. All parties involved, the competent authorities as well as the industry, would benefit from European harmonisation of notification of product information to the competent authorities. The latest draft proposal of EU-GHS (at end June 2007) contains an article 45 that is almost a copy of article 17 and thus will not solve the problem. *Problem solving:* To establish harmonisation of product notification at an EU-level, a delegation of the Dutch government suggested that article 45 or an Annex should provide a specification of the required product information. Alternatively, a provision could be incorporated stating that such a specification should be provided by the European commission before a certain date. This provision option is supported by the Dutch PIC and the Dutch industry. If included in the new EU-GHS legislation, it provides the time necessary to go through some essential steps to establish harmonisation of product notification. All parties involved will benefit when a uniform format for the notification of product information is developed. The present MSDS might be a suitable starting point for the (development of an electronic) format. The MSDS is a widely accepted, legally implemented EU standard to inform professional and industrial users on the risks of a product. Our survey shows that for most EU member states the MSDS does not provide all the required information to perform a good risk assessment in case of acute intoxications (1). Therefore, before PICs and competent authorities can accept the MSDS as a standard, it requires an upgrade with additional information to meet these requirements. Both EU-GHS and REACH legislation will not change the quality of the MSDS with respect to product composition and ingredient concentrations. REACH, however, might improve the quality of the available toxicological information on the MSDS, as producers and downstream users need to exchange more information on substances and products in the specific context of (the risks of) their use. This information either becomes an integral part of the MSDS or has to be supplemented to the MSDS as Chemical Safety Reports. *Conclusion:* The EU-GHS legislation will have considerable effect on daily practice in the PICs, based on the changes in classification of products. There is now an unique opportunity to include harmonisation in the new EU-GHS legislation, as suggested by the Dutch government. If so, PICs and competent authorities need to define which information should be notified and how as soon as possible. *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.

224. Are Poisons Centres Recognized by EU Legislation?

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Objective: The ongoing work of European poisons centres, EAPCCT, WHO-IPCS and UK HPA on the EU Public Health Project 'Development of an Alerting System and Criteria for Development of a Health Surveillance System, for the Deliberate Release of Chemicals by Terrorists (ASHT)' has stimulated strong interest regarding the official role of poisons centres in recognition of chemical threats. A view on all legal duties for poisons centres defined in EU regulations would be helpful in presenting poison centre functions at a national or regional level. A compilation of legal sources is provided. *Method:* A database search of European Commission's official website (section 'European Law') was performed using appropriate keywords. Results were discussed and compiled at ASHT project meetings. *Results:* Seven official EU documents were identified as relevant. Poisons centres are specified in three documents: the resolution on prevention and treatment of human poisonings, the 28th adaptation of the dangerous substances directive, and the biocides directive. Indirectly, poisons centre functions are described in four documents, i.e. the cosmetics directive, the directive on dangerous preparations, its annex and the new detergents regulation. A complete overview is presented in Table 1. EU directives have to be transformed to national law before they are in force in member states. Member states' parliaments have modified EU regulations to a substantial degree. *Conclusion:* Poisons centres are recognized by European law. They have legally founded rights and duties. Knowledge of these may help to promote recognition of poisons centres' work and to ensure continuous financial resources.

225. Impact of Reach Regulation (1907/2006/EC) on Poison Centers Activities: Experiences from a Pilot Framework

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Background: The REACH Regulation, entered into force in European countries on 1st June 2007, represents a great innovation in the assessment and management of risks posed by chemicals to the health and the environment. Based on the principle "no data, no market", it shifted to industries the responsibility to provide data and to demonstrate the safety of chemicals. It is well known that up to now toxicological information on new and existing chemicals is often incomplete or lacking; even when some data exist, they may not be easily available, therefore limiting the possibility of professionals and authorities to properly handle risks. This experience is familiar to Poison Centers (PC) when they are faced with human acute or chronic exposures to chemicals with a not well defined toxicological profile. *Case study:* A pilot framework was established in our country among the main chemical industries associations, selected companies and a PC in order to identify synergies and collaboration areas for REACH operations. Three starting items were identified. (i) Update of safety data sheets (SDS). PC should act as referral service for emergency calls, providing highly specialized assistance in case of acute events involving chemicals; this task could be further improved by a close collaboration between PC and industries in identifying first aid measures to be reported on SDS, including the list of

Table 1. Poisons Centres in European Legislation

Short title	Document ID	Content
Cosmetics directive, article 7	76/768/EEC	National allowance for definition of bodies responsible of receiving cosmetic product information to meet medical demands
Resolution on prevention and treatment of human poisonings	90/C 329/03	Poisons centres' annual report; definition of report format.
Directive on specific information relating to dangerous preparations, annex	91/155/EEC	Emergency telephone number of 'official advisory body' on safety data sheets
Biocides directive, article 23 (labelled 'Poison Control'); article 24	98/8/EC	(I) Definition of bodies responsible of receiving biocide products information to meet medical demands; (II) member states' report on any poisonings involving biocidal products every three years
Directive on dangerous preparations, article 17	1999/45/EC	Definition of bodies responsible of receiving product information to meet medical demands
Directive on dangerous substances, annex VI, chapter 3.1.1	2001/59/EC (L225/271) based on 67/548/EEC	Role of 'poison information units' experience with human poisonings more valuable than animal toxicity data
Detergents regulation, article 9	648/2004	National allowance for definition of bodies responsible of receiving detergent product information to meet medical demands

special treatment means (e.g. antidotes) that shall be immediately available at the workplace. (ii) Toxicovigilance programmes. In the risk assessment procedure, information from cases of human exposure are expected to have great value: PC toxicovigilance programmes can offer unique human data to better characterize the risks of chemicals and can provide a clinical basis to address substance substitutions. For these reasons, the participation of PC in REACH SIEF (Substance Information Exchange Fora) was advised. (iii) Education. Since 2004, a university post-doctoral master degree in risk assessment and management was jointly implemented, in order to provide industries with trained professionals. *Conclusion:* REACH Regulation gives PCs a great opportunity to become industry partners in the regulatory process, where a high degree of broad spectrum toxicological competence is required.

226. The New Norwegian NBC Centre – An Uplift for Clinical Toxicology?

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Objective: Due to several recent terrorist attacks worldwide, the Norwegian medical community and government agencies have focused on the non-military preparedness in response to a possible terrorist attack. On request from the Norwegian Directorate for Health and Social Affairs, a National Competence Centre for medical treatment of NBC (Nuclear, Biological & Chemical) events was provisionally established in our department in 2003, and given permanent status in 2007. The goals were to educate medical personnel, establish national standard procedures for decontamination and medical response to NBC incidents, and establish a 24-hours-a-day consultation service in case of such events, also those caused by industrial accidents and pandemics. *Methods:* We describe the structure, organization, and running of the Norwegian NBC centre. *Results:* The centre was established in a preexisting clinical setting in the largest emergency hospital in Norway, being also a level 1 trauma center. Our medical intensive care unit (MICU) is experienced in acute toxicology and closely cooperates with our National Poisons Information Centre. Patients exposed to NBC incidents in the Oslo area will primarily be admitted to our hospital. The senior on-call physicians in the MICU are specially trained in the C-part of NBC medicine, and these doctors are responsible for handling all calls regarding NBC incidents in Norway. All physicians connected with the centre (MUCU doctors, infectious disease (B-part) and hematology specialists (A-part)) also do regular patient work to retain their clinical skills. The centre cooperates closely with the Norwegian defence research establishment and other institutions with special NBC competence, and a major task is to convert mostly military strategies into civil medical use. All strategies, recommendations and treatment protocols will be published in a handbook, available to health care facilities. *Conclusion:* Implementation of the NBC center in the preexisting hospital structure enables expert consultancy immediately when needed. A competence centre deeply rooted in clinical everyday hospital practice hopefully ensures that routines and algorithms mostly derived from military and foreign sources are transformed to suit civil medical health care. Clinical toxicology units abroad may consider following our strategy because our common discipline benefits in many ways, especially financially.

227. Harmonisation of Collection of Data and Statistical Information by Poisons Centres

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Data collection for documentation and toxicovigilance has always been part of poison information centre (PIC) operations. Powerful computers have made it possible to gather more data, do it more easily and to process data more efficiently. The number of entries in the PIC databases is often impressive, in a single PIC in tens or hundreds of thousands. The PIC data is frequently used, and misused, nationally or locally by the authorities, manufacturers and the media when looking for an answer to the question how common human exposures are. The public health need for effective early warning systems to detect mass poisonings has become more obvious with terrorism threats. Legislative measures like REACH also create new needs for data on human poisonings. The PICs routinely accumulating significant amounts of data are an obvious interesting source to be utilized for those purposes. However, there are some inherent basic limitations to the use of PIC data, the first being the uncertainty of the details of the exposure. The most interesting data is not in the big numbers that change relatively little over time but in the small numbers that are often difficult to find. In our world of today, where big is beautiful and more is better the idea of combining data from several PICs is attractive. This has been done successfully in the US in the Toxic Exposure Surveillance System (TESS). As TESS shows, pooling data from many PICs of one country is feasible and can be used to produce extensive reports with impressive numbers. The idea of pooling PIC data has been discussed in Europe too. Some projects indicate that pooling of European PIC data is not only interesting but also feasible. However, there are some prerequisites, some obvious and others less so. Technically the challenge is to combine data from various database systems. It requires that the structure and form of the data of different PICs are compatible. This may need a certain amount of work, but is doable. So far most of the efforts have been focused on these mostly technical issues. Less attention has received the much more critical question, whether it is acceptable to pool the data at all. The answer depends partly on how the data is generated and partly what it is to be used for. From a public health point of view the most interesting questions to be answered are either related to epidemiology or to finding a signal of toxicity. To allow pooling of data from different sources, the data has to be comparable. Generally PICs take good care of the quality of the process to collect and enter data into their database, but possibilities to verify course and outcome of a poisoning may vary. Technically it may be possible to automate conversion of entries and classifications to some extent, but more difficult to harmonize criteria for classifications. The real barrier for pooling data from PICs, and one that is not possible to harmonize, is the population the calls represent. Although all PICs provide advice to enquiries on acute poisonings, the population the callers represent and how representative the calls are is inherently variable. Many PICs take calls from both the public and health professionals while others only answer calls from physicians. This difference profoundly affects the population the calls represent. It also biases the data collected, for instance, in relation to the age distribution of the exposed, delay from exposure to contact, substances involved, and distribution of severity of poisonings and treatments. Other basic differences in operation of the PICs cause additional bias. Different professional background of the persons answering the calls may cause filtering bias. This is likely to be most evident in cases where diagnostic skills are required, like identifying toxic syndromes or alternative explanations for the symptoms described as possible poisoning. The previously mentioned biases may be enhanced if data is pooled unless the size of the population the PIC covers is accounted for. Generally the biases caused by differences in the operations of the PICs are such that pooled data cannot be considered valid for epidemiological analyses, unless all these confounding factors can be accounted for. The inherent differences between PICs may be less of a concern, if their data is used to find toxicity signals. In this approach, detected cases of poisoning are used to formulate well-defined studies to either verify or reject the original findings. However, it is not clear that pooling of the data is the optimal way to detect signals, as it may cause a delay compared with the analyses for signal detection being done at the PIC level. Nevertheless, efforts to harmonise PIC data collection and statistical information are worth pursuing at the level of comparable geographical areas and markets like the EU. The first effort should be put into developing harmonised descriptors of PIC operations and agreement on comparability of the data produced. The Nordic Association of Poison Centres (NAPC) has agreed on first common indicators of PIC operations to be tested. These descriptors should then be used for standard reporting of PIC activities and could be valuable for benchmarking. Efforts for harmonisation of data collection would then become meaningful between comparable PICs. Subsequent pooling of harmonized, and comparable data remains only a technical challenge. The major challenges for harmonisation of collection of data and statistical information by PICs are not technical but avoiding 'data-laundering', making the data look comparable although it is not, and willingness of the PICs to change their current routines for the sake of harmonisation.

228. Failure of Antivenom for Venom Induced Consumption Coagulopathy in Australian Snakebite

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Objective: There has been significant controversy about the dose, timing and recovery of venom induced consumption coagulopathy (VICC) in Australian elapid envenoming. Simulations from a semi-mechanistic turnover model of the coagulation pathway found the half-life of the prothrombin activator in the blood to be 10 to 15 minutes and predicted that neutralization by antivenom must occur immediately after venom enters the circulation to reduce the recovery time of VICC. We aimed to investigate the effectiveness of antivenom in treating VICC from patient data. *Methods:* Patient data was extracted from the Australian Snakebite Project (ASP) for cases with VICC including age, sex, snake type, antivenom dose, time to antivenom, time to recovery of VICC defined as time to INR≤2 and fresh frozen plasma (FFP) administration. The effect of antivenom on recovery of VICC was investigated by visual inspection and a fully Bayesian time to event analysis in WinBUGS 1.4 including effect of age, sex, snake type, timing and dose of antivenom, and use of FFP. *Results:* There were 112 cases of VICC from ASP; median age 43 years (Interquartile range[IQR]: 26–53yr) and 89 were male (79%). Sixty six were brown snake bites, 41 bites by tiger snake or related genera and 5 taipan bites. Antivenom was administered a median of 3.5 hours (IQR:2.3–5.5hr) after the bite and the median dose was 4 vials (IQR:3–6vials). Recovery of VICC occurred after a median of 13.6 hours (IQR:10.5–17.3hr). There was no relationship between time to antivenom and time to recovery from VICC. FFP appeared to shorten the time to recovery of VICC with 54% and 78% recovered at 6 and 12 hours respectively versus 34% and 56% when FFP was not given. *Conclusion:* Antivenom did not appear to improve the recovery of VICC in patients with severe coagulopathic snake envenoming supporting the previously developed semi-mechanistic model of the coagulation pathway. The administration of FFP appeared to shorten the time to recovery of VICC.

229. 1,4-Butanediol Pharmacokinetics after Inhibition of Alcohol Dehydrogenase with 4-Methylpyrazole – Pilot Data

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Introduction: Since regulatory restriction of gamma-hydroxybutyrate (GHB) was enacted in the US in 2000, illicit use of precursors (which are rapidly and extensively converted to GHB) such as 1, 4 butanediol (BD) has increased. Few studies exist examining the clinical pharmacology of BD after oral administration. Metabolism of BD is thought to be similar to ethanol, with 2-step conversion to GHB via alcohol dehydrogenase (ADH) and aldehyde dehydrogenase. This is blocked when ethanol is co-ingested – frequently the case in recreational use. We utilize 4-methylpyrazole (4MP) (fomepizole/Antizol®), a highly effective antagonist of ADH, to isolate the pharmacokinetic, pharmacodynamic and clinical effects of BD. *Methods:* Prior to full study, and to address safety concerns, we performed a low-dose pilot study in two patients who were administered 10 mg/kg of BD orally, after intravenous administration of 15 mg/kg of 4-MP. *Results:* For patient one peak measured [BD] of 13.3 mcg/mL occurred at 90 minutes and [GHB] ranged from non-detectable to 3.07 mcg/mL. In patient two peak [BD] of 16.2 mcg/mL occurred at 30 minutes and [GHB] ranged from non-detectable to 5.82 mcg/mL. In a previous study involving 8 subjects administered 25 mg/kg of BD the mean Cmax of BD and GHB respectively was 3.84 mcg/mL (SD 4.57) and 45.6 mcg/mL (SD 19.7). Although [GHB] measurements were above endogenous production levels (<1 mcg/mL - blood) [GHB] measured substantiates significant blockade. Clinical findings and subjective reports included mild euphoria with sedation and light sleep 1.5 hours after BD dose. Subjects (both had participated in prior GHB studies) suggested that the effects were "like the GHB . . . " No significant hemodynamic changes, or other adverse events, occurred. *Conclusion:* This pilot data suggests 4-MP given prior to BD significantly blocks its conversion to GHB and findings suggest BD may have activity similar to GHB, is metabolized via alternative pathways to metabolites with these effects, or, as previously suggested, is converted in the CNS to GHB via non-ADH-mediated pathways.

230. Colchicine Antibodies – Principles of Treatment and Future

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Objectives: The alkaloid colchicine is responsible for rare poisonings with potential high-rate morbidities and fatalities. It is widely used as an anti-inflammatory agent in gouty arthritis and familial Mediterranean fever as well as the ultimate treatment in systemic diseases. In 2005, the American Association of Poison Control Centers (AAPCC) reported 312 exposures resulting in 10 cases of major toxicity and 4 deaths (1). In the same year, a 5-year European Poisons Centers

survey reported 355 cases of poisonings with a 4.2% fatality-rate (2). An incidence of 220 colchicine poisonings per year was estimated for Europe. Toxicity is dose-dependent with delayed onset and multiorgan involvement, including GI, respiratory, hematological, cardiovascular, renal, and neurological. Mortality rate is strongly dependent on the dose (up to 90% if dose ^{3}0.8 mg/kg of body weight). Prognostic factors include dose, prothrombin index ≤20% and white blood cell count ≥15x109/l in the 24th hours, as well as onset of acute respiratory distress or cardiogenic shock in the 72nd hours. Mechanisms of colchicine-induced circulatory failure are multiple, including hypovolemia, alterations in systemic vascular resistance, and myocardial depression. Cardiac failure is usually associated with a very poor prognosis. Management is mainly supportive, based on aggressive fluid replacement and vasopressors, guided by a closed monitoring of hemodynamic parameters (3). Although anti-colchicine specific Fab fragments were shown efficient in several animal studies and even in one human case report (4), they are still not commercially available. The objectives of this presentation were to describe the mechanisms of action as well as the hopes and disappointments of anti-colchicine Fab fragments development for the future years. *Methods:* Review of the international literature, including experimental and clinical studies. *Results:* Colchicine is a good candidate for the development of a successful antibody-based therapy (5). Colchicine neutralization with antibodies was shown effective in several experimental studies (6–12). Toxicity is in the milligram range with severe or fatal consequences. Antibodies are easily obtained in animals using colchicine/protein conjugates. Anti-colchicine Fab fragments are able to simultaneously extract, redistribute, sequester, and eliminate colchicine. Colchicine distribution volume is much greater than its corresponding antibodies, with a rapid redistribution from tissue to blood. Moreover, although colchicine is a low-molecular weight acting intra-cellular poison, redistribution is possible to the vascular compartment. Finally, due to colchicine direct extensive cellular injuries, it is necessary to hypothesize that neutralizing the residual unbound colchicine may avert a lethal outcome, even if some part of the toxin has already damaged the organism. The unique use in a human case of anti-colchicine specific Fab fragments was reported in 1995 (4). A 25-year-old severely poisoned woman who ingested 0.96 mg/kg colchicine was treated with anti-colchicine Fab fragments 36 h after ingestion. Treatment immediately resulted in a spectacular reversal of cardiovascular failure, but did not prevent the delayed occurrence of bone marrow aplasia, complete hair loss, and transient peripheral neuropathy. Anti-colchicine Fab fragments increased the total plasma colchicine concentration (12 to 122 ng/ml), as soon as 10 minutes after the start of infusion, whereas the free colchicine concentration became undetectable. A 6-fold increase in colchicine urinary excretion was reported, initially bound to Fab fragments. To date, no commercial preparation of anti-colchicine Fab fragments is yet available. However, at least one manufactured preparation is theoretically ready for clinical studies. Polyclonal antibodies have been preferred to enlarge specificity to more epitopes, in comparison to monoclonal antibodies. Consistently, antibodies with high affinity (^{3}109 M-1, a critical minimal value for efficient antibodies) have been obtained. Ovine appeared preferable to equine antibodies, in order to reduce serum sickness and to increase productivity, as sheep tend to produce a higher proportion of specific IgGs per total IgGs in response to immunization. Regarding its therapeutic interest in humans, many concerns are still not addressed regarding the time to treat, the minimal efficient dose to administer, and the symptoms to be reversed (cardiac failure versus bone marrow aplasia). Both animal and human reports showed that the rapid administration of inframolar neutralizing Fab fragments was efficient enough to dramatically improve outcome. Removal of even a modest portion of colchicine appeared thus sufficient to challenge the classical theory of molar neutralization. The time has come to develop an European multicentric controlled clinical trial. EAPCCT is ideally positioned to encourage a large cooperation between its members. Such a trial is now the ultimate step to allow the marketing of this orphan but potentially efficient antidote. *Conclusions:* Fab fragment-based treatment seems to represent the only potentially efficient antidote for severe colchicine poisoning. However, it is still not commercially available. A European multicentric trial is thus urgently required to assess its interests and conditions of administration, in order to reduce morbidity and lethality of colchicine poisoning. *References:* 1. Lai MW. *Clin Tox* 2007; **44**: 803–932. 2. Kupeferschmidt H. *Clin Tox* 2005; **43**: 399 (abstract). 3. Mery P. *Intensive Care Med* 1994; **20**: 119–23. 4. Baud FJ. *N Engl J Med* 1995; **332**: 642–5. 5. Bismuth C. *Hum Exp Toxicol* 1997; **16**: 602–8. 6. Rouan SE. *Am J Pathol* 1990; **137**: 779–87. 7. Chappey ON. *J* Pharmacol Exp Ther 1995; **274**: 1072–6. 8. Terrien N. *Toxicol Appl Pharmacol* 1990; **104**: 504–10. 9. Sabouraud AE. *Toxicology* 1991; **68**: 121–32. 10. Sabouraud AE. *J Pharm Pharmacol* 1992; **44**: 1015–9. 11. Sabouraud AE. *J Pharmacol Exp Ther* 1992; **260**: 1214–9. 12. Sabouraud AE. *Drug Metab Dispos* 1993; **2**: 997–1002.

231. Antidotes for European Viper Envenomation

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There are seven main types of venomous viper in Europe. The adder (*Vipera berus*) has the widest distribution and is even found above the Arctic Circle. The asp viper (*V. aspis*) replaces the adder in much of Italy and France. The Nose-horned viper (*V. ammodytes*) is restricted to south-eastern Europe and its bite is probably the most serious. The similar Lataste's viper (*V. latastei*) occurs in Spain and Portugal. One subspecies of the blunt-nosed viper (*Macrovipera lebetina lebetina*) is found in Cyprus and another (*M.l.obtusa*) in Turkey. The Rock viper (*V. xanthina*) occurs in extreme north-eastern Greece and some Greek islands, as well as parts of Turkey. Finally, Orsini's viper (*V. ursinii*) is smaller than the others and is found only in a few places in southern Europe. It rarely bites humans. Immediate (up to 2 hours) clinical effects include pain and tingling at the site. Local swelling can occur within minutes but may be delayed for up to 30 minutes or more. Absence of local swelling within two hours generally excludes envenomation. Anaphylactoid symptoms associated with envenomation itself may occur within five minutes, but may also be delayed, and hypotension developing within the first two hours is an important prognostic sign of severe poisoning (1). Between 2 and 24 hours, reddish lymphatic lymphangitis lines and bruising may develop. Other signs include abdominal pain, vomiting, diarrhoea, sweating, pallor, fever, tachycardia, urticaria, and oedema of the lips, guns, tongue, throat and epiglottis. Urticaria and bronchospasm may also occur. Swelling may spread to involve the whole limb, but generally resolves without necrosis. Severe effects include hypotension, cardiac tachyarrhythmias, and in very rare circumstances, myocardial infarction, or cardiac arrest. Although consumption coagulopathy is rare, spontaneous bleeding from the gums or nose or into the lungs, the gastrointestinal and genitourinary tracts, and even retroperitoneal bleeding has been reported. The risk of bleeding is greatly increased by treatment with heparin, which has little or no place in therapy. Other features include a peripheral neutrophil leucocytosis, raised creatine phosphokinase (CPK). ARDS and acute renal failure brackets have been reported, especially in children. Treatment involves immobilisation of the limb (the usual site of a bite) with a splint or sling, (avoiding local incision or suction, the use of potassium permanganate, ice packs, or tourniquets or ligatures or compression bandages). All cases of suspected envenomation require observation for at least two hours, even if puncture sites are not visible. Supportive management should be provided as required. Polyspecific (polyvalent) antivenoms are those raised against two or more venoms (2). They have the advantage that specific identification of the snake is less important. However, they have less neutralising activity per dose of IgG/ fraction than monospecific antivenoms and so a larger dose is necessary. This may, theoretically at least, increase the risk of adverse reaction to the antivenom. The most widely used polyspecific antivenom is Viper Venom Antiserum, European (equine) produced by the Institute of Immunology, (Zagreb antivenom). This neutralises venom of 6 of the 7 European vipers, (neutralising activity against *V latastei* venom is not reported in the product information). A purified preparation of equine F(ab')2 (VIPERFAVTM, Aventis Pasteur, France) against *V. aspis*, *V. berus*, and *V. ammodytes* venom is also available, as is an ovine polyclonal antibody fragment (Fab) (VIPERATABTM, Protherics USA) antivenom raised against the venom of *V berus*. All appear to be effective for their specific indication, and relatively well tolerated (3–5). In the UK there are 8 recommended indications for considering antivenom administration after envenomation by *V. berus*, the only species occurring there (6). These are 1. persistent (>2 hours) fall in blood pressure (systolic to < 80 mm Hg or a decrease of more than 50 mm Hg from normal or admission value) with or without signs of shock, 2. hypotension unresponsive to fluid therapy, 3. definite leucocytosis (especially if over 20 x 109/L), 4. electrocardiographic (ecg) abnormalities, 5. acidosis, 6. elevated creatine phosphokinase levels, 7. severe local envenomation within 2 hours of the bite (even in the absence of systemic signs) e.g. swelling beyond the next major joint from bite site. Any cases involving significant swelling of forearm or leg should also receive antivenom. 8. any other evidence of systemic envenomation e.g. pulmonary oedema, spontaneous bleeding etc. Early administration of antivenom may reduce the risk of severe local or systemic features. However late administration (up to 30 h) has been associated with marked benefit in some cases. Adverse reactions to antivenoms are rare. However, because allergic reactions can occasionally occur, and sometimes progress to systemic anaphylaxis with hypotension, bronchospasm and angioneurotic oedema, antivenom is only administered if there are symptoms of severe local envenomation or evidence of systemic envenomation. Rarely, serum sickness may develop one to two weeks after antivenom administration, with fever, urticaria, arthralgia and albuminuria. In a retrospective study of 540 individuals in Croatia who had been bitten predominantly by *V. ammodytes*, there was only one reported case of anaphylaxis (0.2%) and three cases of serum sickness (0.6%) after early administration of Zagreb antivenom. Most of the patients in the study had been pre-treated with antihistamines (73%) or corticosteroids (78%), although the benefits of these pre-treatments are unknown (3). In 46 patients (17 <16 years old) given 79 infusions of ViperFAV^{TM}, six mild reactions, and no severe reactions were reported (4). No severe immediate reactions or serum sickness occurred in 30 patients given specific, ovine Fab fragments (5). The bites of European vipers are associated with significant morbidity and occasional fatalities (3–5). Effective and well-tolerated antivenoms are available, and may be underused in some parts of Europe (1). Early administration of antivenom may be associated with reduced morbidity (7). *References:* 1. Warrell DA. *BMJ* 2005; **331**: 1244–1247. 2. Theakston RDG, *et al. Toxicon* 2003; *41*: 541–557. 3. Luksic B, *et al. S Coll Antropol* 2006; **1**: 191–197. 4. de Haro L, *et al. Ann Fran Anesth Reanim* 1998; **17**: 681–687. 5. Karlson-Stiber C, *et al. J Intern Med* 1997; **241**: 53–58. 6. TOXBASE http://www.toxbase.org (accessed 8/11/07). 7. Karlson-Stiber C, *et al. Clin Toxicol* 2006; **44**: 25–30.

232. The Effect of Amiodarone and Calcium Resuscitation on a Rodent Model of Systemic Fluoride Toxicity

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Objective: Systemic fluoride toxicity causes cardiac dysrhythmias and death from hypocalcemia and hyperkalemia. Prior work demonstrated that amiodarone improved survival in a mouse model of systemic fluoride toxicity and decreased the incidence of fluoride-induced ventricular tachycardia (VT) in rats. We hypothesized that IV amiodarone and calcium supplementation will improve survival in a rat model of systemic sodium fluoride (NaF) toxicity. *Methods:* We performed a randomized, blinded, placebo-controlled trial using 45 rats. The rats were anesthetized with 1.5% isoflurane via a tracheostomy and instrumented to continuously measure mean arterial pressure (MAP) and to monitor the electrocardiogram. All rats were infused with NaF (40 mg /kg) and observed for 3 hours. After 15 minutes, the rats were randomized to three groups: 1) IV 5% dextrose bolus with infusion and calcium boluses; 2) IV amiodarone bolus with infusion and normal saline boluses; 3) IV amiodarone bolus with infusion and calcium boluses. Arterial blood gases were drawn every 30 minutes to measure base excess, potassium and calcium. Survival time, incidence of VT, and change in MAP, HR and base excess were analyzed. *Results:* Median survival time was higher in amiodarone plus calcium (117 min) compared to amiodarone alone (80 min) but not calcium alone (95 min) (log rank 0.025). Incidence of VT was higher in calcium alone (8/15, 53%) compared to amiodarone alone (0/15, 0%) and amiodarone plus calcium (0/15, 0%) (p=0.00). Base excess was significantly lower in amiodarone plus calcium compared to calcium and amiodarone alone at 30 (p=0.031) and 60 minutes (p=0.007). Heart rate was significantly higher in calcium alone compared to amiodarone alone and amiodarone plus calcium at 45 (p=0.009), 60 (p=0.000), 75 (p=0.000), 90 (p=0.008), and 120 minutes (p=0.001). MAP was not significantly different between the groups at any time. *Conclusion:* Amiodarone with calcium improved survival compared to amiodarone alone and had better perfusion as measured by base excesses compared to amiodarone or calcium alone. Amiodarone with and without calcium decreased the incidence of VT compared to calcium alone but was associated with slower heart rates.

233. Inaccuracies in Acetylcysteine Dose Calculation or Infusion Rates in Patients with and without Anaphylactoid Reactions

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Objective: The standard intravenous acetylcysteine regimen for paracetamol (acetaminophen) overdose consists of 3 sequential infusions (150 mg/kg over 15 min, 50 mg/kg over 4 h and

100 mg/kg over 16 h). Anaphylactoid reactions (AR) to this regimen are frequent and dose-related and usually appear early. Since inaccuracy of dose calculation is apparently common (1), prescribing error and/or inappropriate initial infusion rates might account for a significant proportion of AR. *Methods:* To examine this, data were collected prospectively from all patients treated with intravenous acetylcysteine for paracetamol poisoning in Newcastle over 1 year from December 2005, including doses prescribed and speed of infusion (available for the first 2 infusions). *Results:* 128 patients received acetylcysteine and 23 (18%) had AR. Comparing those with and without AR, no significant differences were noted for mean age (39.6 vs 37.3 y), proportion of males (48% vs. 42%), reported paracetamol dose (20.2 vs. 20.9 g), body weight (71.8 vs 68.1 kg) or interval to acetylcysteine (10.8 vs 11.2 h). Paracetamol concentrations were lower in those with than without AR (104 ± 86 vs. 75 ± 62 mg/L, $P < 0.05$). For the 353 infusions administered where adequate information was available, 5 (1.4%) dose calculation errors of >10% were identified, but only 2 (0.6%) were clinically significant. These were >3-fold excess doses involving the second infusion, both in patients who developed AR. There were no significant differences in mean acetylcysteine doses infused between patients with and without AR for any of the 3 infusions. The durations of infusions 1 and 2 were longer than recommended but there were no differences between patients with and without AR for infusion duration (infusion 1: 45 vs. 31; infusion 2: 298 vs. 296 min) or infusion rates (infusion 1: 5.6 vs. 6.8 [recommended 10]; bag 2: 0.27 vs. 0.17 [infusion 0.21] mg/kg/min). *Conclusions:* AR to acetylcysteine are common, but errors in dose calculation or infusion rates appear to account for very few of these. *Reference:* 1. Ferner RE, Langford NJ, Anton C, *et al*. Random and systematic medication errors in routine clinical practice: a multicentre study of infusions, using acetylcysteine as an example. *Br J Clin Pharmacol* 2001; **52**: 573–7.

234. Carnitine in the Treatment of Valproic Acid-Induced Toxicity

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Valproic acid (VPA) is a broad-spectrum antiepileptic drug, now commonly used in many other neurological or psychiatric indications. VPA is usually well tolerated, but rare serious complications may occur in some patients receiving VPA chronically, including haemorrhagic pancreatitis, bone marrow suppression, VPA-induced hepatotoxicity (VHT) and VPA-induced hyperammonaemic encephalopathy (VHE). Acute VPA intoxication also occurs as a consequence of intentional or accidental overdose and its incidence is increasing, because of use of VPA in psychiatric disorders. Although it usually results in mild central nervous system depression, serious toxicity and even fatal cases have been reported. VPA is a branched chain carboxylic acid, with a chemical structure very similar to that of short chain fatty acids. VPA is extensively metabolized by the liver via glucuronic acid conjugation, mitochondrial β- and cytosolic ω-oxidation to produce multiple metabolites, some of which may be involved in toxic effects of VPA, either in patients on chronic dosing or after an acute overdose. For example, 2-propyl-2-pentenoic acid (2-en-VPA), a byproduct of β-oxidation, and 2-propyl-4-pentenoic acid (4-en-VPA), a byproduct of ω-oxidation, have been incriminated in the development of cerebral oedema and in the hepatotoxicity of VPA, respectively. 4-en-VPA and propionic acid metabolites resulting from ω-oxidation could also promote hyperammonaemia. Mitochondrial β-oxidation of VPA involves its transport within the mitochondrial matrix, using the same pathway as do long chain fatty acids. This pathway is sometimes called the 'carnitine shuttle': VPA needs to be transformed into valproyl-CoA, then into valproylcarnitine and valproyl-CoA to cross the mitochondrial membranes. The ω-oxidation is normally responsible for only a small component of VPA metabolism. However, during long-term or high-dose VPA therapy, or after acute VPA overdose, a greater degree of ω-oxidation occurs, potentially increasing the risk for toxicity. Carnitine is an amino acid derivative that thus appears as an essential nutrient to ensure proper metabolism of VPA. It mainly comes from the diet, particularly in red meat and dairy products but is not a true vitamin because it is also biosynthesized endogenously from dietary amino acids. The two main metabolic functions of carnitine are to facilitate fatty acyl group transport into mitochondria and to maintain the ratio of acyl-CoA to free CoA in the mitochondria. Some data suggest that VHT and VHE may be promoted either by a pre-existing carnitine deficiency or by deficiency induced by VPA per se. Several studies or isolated clinical observations have also suggested the potential value of L-carnitine supplementation in reversing carnitine deficiency or preventing its development, as well as some adverse effects due to VPA. VPA-induced hepatotoxicity (VHT: In up to 44% of patients, chronic dosing with VPA may be associated with elevation in transaminases during the first months of therapy. It commonly resolves completely when the drug is discontinued. Severe VHT in association with hepatic failure is rare, but it may develop as an idiosyncratic reaction that is often fatal. It usually occurs during the first 6 months of VPA therapy and is often but not always preceded by minor elevations in transaminases. Reports of severe VHT following acute VPA overdose are rare. The common mild elevation in aminotransferases is usually reversible when VPA therapy is discontinued or the dose reduced. Even in severe VHT, the prognosis seems to be improved if VPA therapy is promptly stopped. Some experimental and clinical evidence also suggests that the early administration of intravenous L-carnitine could further improve survival in severe VHT. VPA-induced hyperammonaemic encephalopathy (VHE: In chronic VPA dosing hyperammonaemia occurs in nearly 50% of patients). Very high ammonia levels have been reported, even with normal liver function tests, but hyperammonaemia remains asymptomatic in almost half of cases. VHE is a rare phenomenon in adults, especially when VPA is used as monotherapy. It is typically characterized by impaired consciousness, focal neurologic symptoms and increased seizure frequency. Carnitine supplementation (commonly 50–100 mg/kg per day) has been shown to speed the decrease of ammonia levels in patients with VHE, likely by enhancing the β-oxidation process and production of acetyl-CoA, and relieving the inhibition of urea synthesis. However, a correlation between ammonia levels and clinical condition is not always observed. *VPA overdose:* In VPA overdose, carnitine appears to normalize the metabolic pathways of VPA. A few isolated observations have suggested that L-carnitine may be useful in patients with coma or in preventing hepatic dysfunction after acute VPA overdose. Because hepatotoxicity is rare after acute overdose, the lack of transaminase elevation following prophylactic carnitine administration does not demonstrate its hepatoprotective properties. As far as CNS depression is concerned, the clinical data available do not suggest that carnitine is able to hasten the recovery of consciousness. Nevertheless, carnitine supplementation is commonly recommended for children with VPA overdoses, especially above 400 mg/kg. *Carnitine supplements:* Carnitine supplementation during VPA therapy in high-risk patients is now recommended by some scientific committees and textbooks, especially paediatricians. It does not appear to be harmful. *Conclusion:* Although interesting results have been produced, a better delineation of the therapeutic and prophylactic roles of L-carnitine in each of these conditions deserves further investigation in controlled, randomized and probably multicentre trials, especially to evaluate the clinical benefit and the appropriate regimen.

235. Predicting Intubation, Duration of Ventilation and Cardiac Monitoring in Quetiapine Overdose and the Effect of Activated Charcoal

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Objective: A population pharmacokinetic analysis of quetiapine overdose demonstrated that charcoal reduced the absorption of quetiapine by 35% (1). However, it is unclear if charcoal is beneficial in quetiapine overdose and what predicts clinical effects and requirement for intervention. *Methods:* The study included a cohort of 163 patients presenting on 252 occasions with quetiapine overdose to a tertiary toxicology unit. Median age was 32 years (Interquartile range: 23–38 yr) and 67% were female. The following data were extracted: dose ingested, therapeutic use of quetiapine, charcoal administration, requirement for intubation, duration of mechanical ventilation and ECG parameters (HR, QT, QRS). A fully Bayesian approach using logistic regression and time to event analysis was undertaken to investigate the relationship between predictor variables and the requirement for intubation and the duration of ventilation respectively. QT intervals were plotted on a QT nomogram (2) to investigate the presence of abnormal QT prolongation. *Results:* Logistic regression demonstrated that only dose predicted whether patients required intubation and the administration of charcoal either at any time or prior to intubation did not influence the requirement for intubation. A nomogram for the probability that a patient requires intubation based on dose was developed which showed the probability of intubations was 5% for 5 g, 25% for 10 g, 50% for 13.5 g, 75% for 17 g and 95% for 24.5 g. Time to extubation was independent of all predictor variables, including administration of charcoal and dose ingested. Abnormal QT intervals occurred in 6.5% of cases with HR <105 bpm and there were no cases of arrhythmia. *Conclusion:* The requirement for intubation in quetiapine overdose can be predicted from dose. The administration of charcoal is unlikely to be beneficial in quetiapine overdose, not affecting major clinical outcomes. ECG monitoring is not required in quetiapine overdose. *References:* 1. Isbister GK, Friberg LE, Hackett LP, *et al*. Pharmacokinetics of quetiapine in overdose and the effect of activated charcoal. *Clin Pharmacol Ther* 2007; **81**: 821–7. 2. Chan A, Isbister GK, Kirkpatrick C, *et al*. Drug-induced QT prolongation and Torsades de Pointes: evaluation of a QT nomogram. *QJM* 2007; **100**: 609–15.

236. Does Aluminum Citrate Block the Renal Toxicity of Ethylene Glycol *In Vivo*?

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Objective: Ethylene glycol (EG) is responsible for ~5000 poisonings a year. EG metabolites, especially calcium oxalate monohydrate (COM), produce the observed renal toxicity. Therapy from accumulated COM is needed for patients who are not diagnosed rapidly. Aluminum citrate (AC) decreases and reverses COM induced cytotoxicity in human proximal tubule (HPT) cells. The current study was designed to show that AC can decrease EG-induced renal toxicity *in vivo*. *Methods:* Male Wistar rats were treated with EG (2 g/kg) or an equal volume of water by oral gavage. At 6 h post EG treatment, animals received either 1 mmol/kg AC by oral gavage or 0.1 mmol/kg AC by IV infusion. Urine was collected for 24 h, at which time, the right kidney was perfused with ethidium homodimer, the animal was sacrificed and the kidneys were harvested for analysis. Urine oxalate was decreased in rats treated with EG and AC compared to EG. N-acetyl-b-D-glucosaminidase (NAG) and g-glutamyltransferase (GGT) were measured as markers of nephrotoxicity. *Results:* While GGT appeared unchanged, NAG appeared to be decreased in AC treated rats. H and E staining indicated the presence of COM crystals in all EG treated animals, but ethidium homodimer histology suggested a decrease in kidney cell necrosis of AC-treated rats compared to EG controls. *Conclusion:* The results of this study indicate that AC may be a useful in treating the renal toxicity associated with EG poisoning.

237. Albumin Dialysis (MARS) vs. Standard Therapy in Management of *Amanita phalloides* Poisoning

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Objective: Albumin dialysis with Molecular Adsorbent Recirculating System (MARS) is currently the most widespread extracorporeal liver support system. The data supporting the use of albumin dialysis in the treatment of mushroom poisoning is limited to case reports and case series. The aim of the study was to compare the efficacy of MARS vs. standard medical therapy in management of acute *Amanita phalloides* poisoning. *Methods:* Records of patients treated in two Poison Units in Gdansk and in Poznan in the 2005–2006 period due to acute *Amanita phalloides* poisoning were compared retrospectively. Patients younger than 65 years who had significant decrease in prothrombin activity defined as international normalized ratio (INR) value higher than 2 in the course of poisoning were included into the study. Both units used high-dose penicillin, hydrocortisone, N-acetylcysteine and oral silibinin as standard therapy. One unit employed MARS in management of acute hepatic failure while the other did not. Statistical comparisons were performed using the Student's t and Pearsons's chi-square tests. *Results:* The demographic data, significant biochemical parameters, and treatment outcome are presented in Table 1. *Conclusion:* Albumin dialysis using MARS seems beneficial in management of acute *Amanita phalloides* poisoning. Liver regeneration rate was higher in the albumin dialysis group than in the group of patients receiving medical therapy, but the trend did not reach statistical significance due to small sample size. More experience with use of albumin dialysis is necessary to determine its benefits and qualification criteria.

Table 1. Demographic data, biochemical parameters and outcomes of patients treated due to *Amanita phalloides* poisoning

	MARS+standard therapy (N = 7)	Standard therapy (N = 14)	p
Age (mean +/– SD)	43.3+/–12.3	35.9+/–13.9	0.24 (2)
Sex (M/F)	5/2	10/4	1.0 (3)
INR (mean +/– SD) (1)	5.22+/–3.4	5.35+/–3.2	0.93 (2)
AST (IU/L) (mean +/– SD) (1)	6313+/–4183	5033+/–4706	0.55 (2)
ALT(IU/L) (mean +/– SD) (1)	5715+/–1379	4154+/–2442	0.13 (2)
Total bilirubin (mg/dL) (mean +/– SD) (1)	5.3+/–2.9	5.8+/–6.6	0.86 (2)
Outcome (regeneration/transplantation/death)	6/1/0	8/3/3	0.33 (3)
Regeneration rate (%)	85.7	57.1	0.19 (3)

SD-standard deviation AST-aspartate transaminase, ALT-alanine trasaminase (1)-highest value observed during hospitalization, (2)-t Student's test, (3)-Pearson's chi-square test.

238. Intravenous Lipid Emulsion Therapy for Poisonings

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Objective: To review the pertinent literature regarding intralipid emulsion (ILE) therapy for poisoning. *Methods:* MEDLARS search using the terms 'lipid emulsion' and 'poisoning', together with reference review from pertinent articles. *Background:* Recent publications have demonstrated dramatic improvement in survival from local anesthetic poisonings treated with ILE. The use of ILE to enhance elimination of lipophilic drugs from the plasma is not a new concept. In 1962, ILE was reported to enhance plasma elimination of thiopental in rats and reduce thiopental-inhibition of oxygen consumption in brain slices (1). Lipid dialysis was reported to enhance elimination of lipophilic drugs in poisoned patients based upon plasma extraction by lipid dialysate (2). Amberlite XAD resin hemoperfusion was utilized for patients poisoned by lipophilic drugs that could be extracted by the resin (3). *In Vivo Studies: In vivo* studies of ILE in poisonings are summarized in Table 1. In bupivacaine toxic rats, ILE pretreatment with 30% ILE increased the LD50 by 48%. As the amount of lipid increased in the treatment groups (saline, 10%, 20% and 30% ILE), the mean lethal dose increased (17.7, 28, 50, and 82 mg/kg respectively) as did the mean bupivacaine level at death (93, 115, 177, and 212 mcg/ml respectively). Mean lipid:aqueous ratio of bupivacaine in a plasma-ILE mixture was 11.9 (4). In dogs, bupivacaine-induced cardiac arrest was treated with internal cardiac massage for 10 min, all dogs subsequently treated with ILE survived compared with none treated with saline. EKG signs, BP and myocardial pH and pO_2 were improved with ILE compared with saline (5). In isolated rat hearts with bupivacaine-induced asystole, ILE resulted in more rapid recovery of cardiac function, more rapid drop in heart bupivacaine levels and increased bupivacaine levels extracted from the heart (6). In paced isolated rat hearts, ILE had a beneficial effect on +dP/dt, BP and myocardial VO2. Neither levobupivacaine nor ILE had an effect on measured energy charge. A lipid concentration of 500 uL/mL plasma was necessary to lower aqueous phase plasma bupivacaine levels (7). In rats with verapamil toxicity, the fatty acid oxidation inhibitor oxfenicine did not block the beneficial effects of ILE (8). ILE Therapy in *Human Poisoning*: Four cases have been published and three listed on LipidRescue.com of ILE resuscitation from drug-induced cardiac arrest, five involving local anesthetics and one each involving haloperidol and bupropion (9). LipidRescue.com was established to disseminate information about ILE and to post cases and comments. Other cases with early signs of severe local anesthetic toxicity such as marked alterations in consciousness, seizures or shock (typically seen before cardiac arrest), successfully treated with ILE, have also been published and posted. *Mechanisms of Action*: The primary proposed mechanisms for ILE include: lipid phase extraction ('lipid sink'), improved myocardial fatty acid oxidation, and/or shunting of toxin to the liver and away from target organs (such as the heart and brain). The evidence that ILE reduces myocardial tissue and aqueous plasma drug levels (6), does not affect myocardial energy charge (7) and that the beneficial effects are not blocked by oxfenicine (8) favor the "lipid sink" mechanism. *Conclusions:* ILE is a promising rescue therapy for local anesthetic and lipophilic toxin poisonings. Waiting until the case has proven to be refractory to conventional resuscitation before utilizing ILE may result in preventable complications of prolonged cardiac arrest. *References:* 1. Russell RI, Westfall BA. Alleviation of barbiturate depression by fat emulsion. *Anesth Analg* 1962; **41**: 582–585. 2. Shinaberger JH, Shear L, Clayton LE, *et al*. Dialysis for intoxication with lipid soluble drugs: Enhancement of glutethimide extraction with lipid dialysate. *Trans Amer Soc Artif Int Organs* 1965; **11**: 173–177. 3. Rosenbaum JL, Kramer MS, Raja R, *et al*. Resin hemoperfusion: a new treatment for acute drug intoxication. *N Engl J Med* 1971; **284**: 874–877. 4. Weinberg GL, VadeBoncouer T, Ramaraju GA, *et al*. Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. *Anesthesiology* 1998; **88**: 1071–1075. 5. Weinberg G, Ripper R, Feinstein DL, *et al*. 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239. Relative Toxicity of Pesticides in the Developing World

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Objective: Pesticide poisoning is a public health problem in the developing world. The extent of clinical toxicity is a function of both the intrinsic toxicity of the pesticide and treatment resources. Targeted pesticide restrictions in Sri Lanka have reduced pesticide deaths without decreased agricultural production. Our aim is to provide information about the relative toxicity of pesticides that could inform regulatory policy and clinicians. *Methods:* We examined the case fatality for patients presenting with a variety of pesticides. This data was prospectively collected from a cohort of patients presenting to clinical trial centers from April 2002 to April 2007. Identification of pesticides was based on history or positive identification of the container and plasma assays in 60% of cases. *Results:* Identified pesticides were ingested by 6449 patients, a further 1558 had ingested an unknown pesticide. Plasma assays revealed that history of ingestion at admission correctly identified the pesticide ingested in over 90% patients. The case fatality for commonly ingested pesticides is presented in Table 1. Data analysis suggests paraquat removal could lead to a 30% reduction in deaths after adjusting for increased ingestion of other herbicides. Similarly removal of dimethoate would reduce overall mortality by 12%. *Discussion:* The national effects of organophosphate restriction may be underestimated as clinical research units reduce mortality. Mortality from paraquat is likely to be a robust estimate as there is no treatment which clearly alters outcome. More aggressive substitution to select compounds from within a class or indication could produce greater potential benefits. It is clear that within a class of pesticides there is a significant range of fatal toxicity. The usefulness of point estimates of zero fatalities which have wide confidence intervals can be enhanced by including other more sensitive clinical markers of toxicity based on animal toxicity data and known mechanisms of action. This may strengthen the evidence for clinical safety of some newer agents. This data can inform a restricted pesticide policy that operates within the constraints of local health systems. Implementation of such restrictions requires political leadership to be initiated and education of farmers to be most effective. A cost-minimization approach should be explored, using models similar to those developed for drug regulation and subsidy. *Conclusion:* We have sufficient information to iteratively develop a minimum pesticide list. This iterative implementation of the list will continue to require continuous sentinel monitoring of usage and clinical presentations. *References:* Gunnell D, Fernando R, Hewagama M, *et al*. The impact of pesticide regulations on suicide in Sri Lanka. *Int J Epidemiol* 2007; 36: 1233–1242. Eddleston M, Karalliedde L, Buckley N, *et al*. Pesticide poisoning in the developing world - a minimum pesticides list. *Lancet* 2002; **360**: 1163–1167.

Table 1. In-vivo IV lipid emulsion studies

Lead Author	Year	Animal	Toxin	Outcomes	ILE Load Dose	ILE Infusion
Krieglstein	1983	Rabbit	Chlorpromazine	Death	1 ml/min x 50 min	
Weinberg	1998	Rat	Bupivacaine	LD/LD50	15 ml/kg/5 min	
				LD50	7.5 ml/kg Bolus	6 ml/kg/2 min
Shaltiel	2002	Rat	Clomipramine	Death	6.25 ml/kg Bolus	
Weinberg	2003	Dog	Bupivacaine	Death/CV Tox	4 ml/kg/2 min	5 ml/kg/10min
Morey	2004	Rat	Bupivacaine	CV Tox	0.4 mg/kg	
Cave	2005	Rat	Thiopentone	Respiratory Rate	8 ml/kg Bolus	8 ml/kg/4 min
Bania	2005	Mice	Paroxon*	LD/LD50/Tremor	15 ml/kg IP	
Cave	2006	Rat	Verapamil	LD/CV Tox	12.4 ml/kg/5 min	
Cave	2006	Rat	Propranolol*	LD/CV Tox	16 ml/kg/4 min	
Bania	2006	Rat	Propranolol	CV Tox	15 ml/kg/15 min	
Bania	2007	Dog	Verapamil	Death/CV Tox	7 ml/kg/30 min	
Cave	2007	Rabbit	Clomipramine	CV Tox	12 ml/kg/4 min	
				CV Tox	8 ml/kg/2 min	
Bania	2007	Dog	Verapamil*	Death/CV Tox	15 ml/kg/60 min	
Bania	2007	Rat	Verapamil	LD/CV Tox	15 ml/kg/5 min	
Chassard	2007	Piglet	L-bupivacaine	Survival	4 ml/kg/1 min	0.25 ml/kg/min

*No benefit.
Published reports of *in-vivo* ILE studies. ILE - IV Lipid Emulsion, LD - lethal dose, LD50 - dose that kills 50% of test group, CV - cardiovascular, Tox – toxicity.

Table 1. Pesticides, deaths and case fatality percentages

PESTICIDE		No. of Patients	Deaths	% Case Fatality	95% confidence interval
Insecticides	chlorpyrifos	1272	96	7.5	6.1–9.1
Organophosphates	coumaphos	5	0	0	0–52.2
	diazinon	73	2	2.7	0.3–9.5
	dimethoate	693	143	20.6	17.6–23.8
	fenitrothion	2	0	0	0–84.2
	fenthion	237	31	13.1	9.1–18.1
	malathion	173	5	2.9	0.9–6.6
	oxydemeton-methyl	8	1	12.5	0.3–52.6
	phenthoate	155	11	7.1	3.6–12.3
	phoxim	7	0	0	0–40.9
	pirimiphos-methyl	9	0	0	0–33.6
	profenofos	106	11	10.3	5.3–17.8
	prothiofos	12	1	8.3	0.4–34.7
	quinalphos	101	13	12.9	7.03–21
Carbamates	carbaryl	16	1	6.25	0.2–30.2
	carbofuran	403	8	2	0.8–3.9
	carbosulfan	272	29	10.6	7.2–15
	fenobucarb	98	7	7.1	2.9–14.1
	methomyl	5	0	0	0–52.2
	propoxur	19	0	0	0–17.6
	thiodicarb	5	0	0	0–52.2
Pyrethroids	beta-cyfluthrin	5	0	0	0–52.2
	cyhalothrin	3	0	0	0–70.8
	cypermethrin	8	0	0	0–36.9
	d-trans allethrin	1	0	0	0–97.5
	deltamethrin	9	0	0	0–33.6
	etofenprox	84	1	1.2	0.02–6.4
	fenvalerate	10	1	10	0.2–44.5
	permethrin	16	0	0	0–20.6
Other insecticides	acephate	8	0	0	0–36.9
	acetamiprid	8	0	0	0–36.9
	azadirachtin	2	0	0	0–84.2
	chlorfluazuron	35	1	2.8	0.07–14.9
	fipronil	23	0	0	0–14.8
	imidacloprid	66	0	0	0–5.4
	tebufenozide	4	0	0	0–60.2
Herbicides	alachlor	6	0	0	0–45.9
	bispyribac	94	3	3.2	0.6–9
	fenoxaprop-ethyl	63	0	0	0–5.7
	glyphosate	627	21	3.3	2.1–5.1
	MCPA	576	28	4.8	3.2–6.9
	oxyfluorfen	10	0	0	0–30.8
	paraquat	532	251	47.1	42.9–51.5
	pretilachlor	6	0	0	0–45.9
	propachlor	1	0	0	0–97.5
	propanil	420	49	11.6	8.7–15.1
	quinclorac	3	0	0	0–70.8
Fungicides	carbendazim	5	0	0	0–52.2
	chlorothalonil	7	0	0	0–41
	edifenphos	17	2	11.8	1.4–36.4
	hexaconazole	4	0	0	0–60.2
	mancozeb	6	0	0	0–45.9
	propiconazole	1	0	0	0–97.5
	propineb	5	0	0	0–52.2
	tebuconazole	3	0	0	0–70.8
	thiophanate	1	0	0	0–97.5
	thiram	1	0	0	0–97.5
Rodenticides	zinc phosphide	95	2	2.1	0.2–7.4

240. Avermectin Poisoning

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Introduction: Avermectins are a family of macrocyclic lactones which have a novel mode of action against a broad spectrum of nematodes and arthropods in doses as low as 10 ug/kg (1). Avermectins were first isolated from a soil-dwelling microorganism, *Streptomyces avermitilis*, at the Kitasato Institute in Japan. After conducting numerous bioassays in Merck laboratories, 8 natural avermectin components, namely A1a, A1b, A2a, A2b, B1a, B1b, B2a, and B2b, were discovered. Compounds of the B series of avermectins were found to be extremely effective against helminthes and arthropods, and ivermectin (22, 23-dihydro-avermectin B1) was released for veterinary and human use in 1981. Because of its high tolerability, prolonged post-treatment effect, and broad spectrum of anti-parasitic activity, ivermectin has become the drug of choice in the treatment of many animal and human parasite infestations, such as onchocerciasis. Other avermectins, such as abamectin, doramectin, and emamectin were subsequently commercialized and have been used as agricultural insecticides and miticides in animal health and crop protection. *Pharmacology/toxicology:* Various avermectin components differ in their potency and safety. Nevertheless, all avermectins are believed to share common pharmacologic/toxicologic mechanisms (1). Avermectins exert their anti-parasitic activity via the activation of a glutamate-gated chloride channel present in the invertebrate nerve and muscle cells, and/or through the effect on gamma-aminobutyric acid (GABA) receptors (1–4), leading to paralysis and death of target organisms. In vertebrates, avermectins produce GABA-mimetic effects by acting as an agonist at GABAA receptor, stimulating the release of GABA, or through other mechanisms. Mammals, however, are less susceptible to the toxic effects of avermectins because GABA-mediated nerves occur only in the central nervous system (CNS) and avermectins do not readily cross the blood-brain barrier (BBB) (1). In addition to GABA-mimetic effects, avermectins may induce hypotension in vertebrates through an increase in serum nitric oxide levels. *Pharmacokinetics/toxicokinetics:* Avermectins can be absorbed orally, parenterally and dermally. Following their absorption, maximum serum concentrations of ivermectin appeared some 4 hours after oral dosing, and elimination half-life was 28±10 hours among healthy volunteers and treated subjects (4, 5). Avermectins are largely excreted into the feces, and urinary excretion accounts for only 0.5% to 2.0% of the administered doses (1). Information on the distribution and elimination of avermectins in poisoned subjects is not yet available. *Animal toxicity:* Although avermectins have a wide margin of safety, high doses of avermectins or mutations in p-glycoprotein can allow avermectins to pass through the BBB to cause neurotoxicity in animals (3), manifesting mydriasis, emesis, diarrhea, drooling, depression, ataxia, stupor, coma, tremors, and death (1–4). For example, cattle injected subcutaneously with 20 to 40 times the recommended dose of ivermectin (e.g. 4 to 8 mg/kg) developed toxicity and death. Dogs (beagles) given a single dose of 5 mg/kg of ivermectin manifested mydriasis, and tremors, and more pronounced toxicity occurred at 10 mg/kg (1). Dose-related toxicity was also found in chickens. Young animals are generally more sensitive to the toxicity of avermectins. A kitten was reported to exhibit toxicosis after receiving subcutaneous administration of 0.3 mg/kg of ivermectin (2). Certain breeds of dogs (e.g. collies) allow more avermectins into the CNS and are thus vulnerable to avermectin poisoning. Animals deficient in p-glycoprotein, a component of the BBB, are also more sensitive to avermectin toxicity than animals without p-glycoprotein deficiency. Solvents and additives of commercial avermectins (e.g. hexanol, butylated hydroxytoluene) may enhance the toxicity as well. *Human toxicity:* Adverse effects of ivermectin therapy are not uncommon and most of them appear within 48 hours of initiating therapy, presenting with myalgia, pruritus, painful skin edema, hypotension, and dyspnea (Mazzotti-type reaction) (3, 4). On the contrary, there is little data concerning human avermectin poisoning. Two children manifested vomiting, somnolence, tachycardia, hypotension, and mydriasis after ivermectin overdose (3). A 46-year-old man developed marked drowsiness, unconsciousness, weakness, ataxia, and visual changes after iatrogenic overdose by 200 mg of ivermectin. Chung *et al* reported 19 patients with abamectin poisoning (3). Among them, most patients had certain CNS and gastrointestinal effects, such as diarrhea, vomiting, drowsiness, dizziness, and weakness, while hypotension and coma were the major manifestations of severe poisoning. Sriapha *et al* in Thailand further reported 49 cases with abamectin poisoning. Most of the patients were asymptomatic or developed only mild symptoms. However, 16 cases had serious symptoms, including coma, hypotension, and metabolic acidosis, and 5 of them died. Emamectin poisoning in a 67-year-old man resulted in mild CNS depression and gastrointestinal toxicity. *Management:* The therapy for avermectin poisoning is mainly symptomatic and supportive. Because absorbed avermectins are largely excreted through feces, prompt gastrointestinal decontamination may be helpful, given that the airway is properly secured. Picrotoxin, a GABA antagonist, has been proposed as an antidote in treating ivermectin toxicosis in animals (2). However, its use is not recommended because of its seizure activity and narrow margin of safety. Physostigmine and neostigmine were shown to have some effects in the management of comatose animals (2), possibly due to increased concentrations of acetylcholine in affected neurons. Avermectins nevertheless do not regulate cholinergic nerve transmissions (1) and both medications are unlikely to be effective. *Conclusion:* Avermectins are newer pesticides that have a wide margin of safety. Although avermectin poisonings are uncommon, avermectins can produce toxicity primarily through their effects on GABA receptors. Severely poisoned patients may manifest coma, hypotension, metabolic acidosis, and even death due to the toxicity of avermectins and/or the additives in the pesticides. Despite the lack of specific therapy, the prognosis of patients with avermectin poisoning is likely to be favorable unless they are complicated by severe hypotension or aspiration. *References:* 1. Campbell WC, Fisher MH, Stapley EO, *et al*. Ivermectin: a potent antiparasitic agent. *Science* 1983; **221**: 823–8. 2. Roder JD, Stair EL. An overview of ivermectin toxicosis. *Vet Hum Toxicol* 1998; **40**: 369–70. 3. Chung K, Yang CC, Wu ML, *et al*. Agricultural avermectins: an uncommon but potentially fatal cause of pesticide poisoning. Ann Emerg Med 1999; **34**: 51–7. 4. Agarwal AK. Avermectin. In: Wexler P eds. Encyclopedia of Toxicology, 1st ed. San Diego: Academic Press, 1998: 89–90. 5. Edwards G, Breckenridge AM. Clinical pharmacokinetics of anthelmintic drugs. *Clin Pharmacokinet* 1985; **15**: 67–93.

241. Poisoning Due to Neonicotinoid Insecticides

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Introduction: The neonicotinoid insecticides are the only major new class of insecticides developed in the past three decades. Seven neonicotinoids are marketed currently: acetamiprid, clothianidin, dinotefuran, imidacloprid, nitempyram, thiacloprid and thiamethoxam. In commercial terms imidacloprid is the most important. *Uses:* Neonicotinoids are now employed widely against sucking and soil insects, as seed dressings and as soil and foliar treatments. Increasingly, neonicotinoids are replacing organophosphorus and carbamate insecticides in the control of piercing-sucking insect pests. Imidacloprid and nitempyram are also highly effective in controlling fleas in cats and dogs. *Mechanisms of toxicity:* Neonicotinoids block the postsynaptic nicotinergic acetylcholine receptor (nAChR), particularly the $\alpha 4\beta 2$ nAChR subtype (1), thereby causing acetylcholine excess (the cholinergic syndrome). The specificity of neonicotinoids for insect nicotinic receptors has been demonstrated. For example, the selectivity ratio of imidacloprid for insect nAChR compared with vertebrate nAChR is 565 (1). In addition, humans are thought to be partially protected from neonicotinoid toxicity because of the poor permeability of the blood-brain barrier to these compounds. *Toxicokinetics:* There are few data on the toxicokinetics of neonicotinoids in humans. However, it is known that imidacloprid is rapidly and very extensively absorbed (>92%) from the gastrointestinal tract of rats (2), with peak plasma concentrations of radio-labelled compound being reached within 2–3 hours of dosing. On average, 75% of an administered dose is eliminated in the urine; the remainder is excreted in the faeces. *Epidemiology:* Despite their widespread use, only 77 cases of human exposure to neonicotinoids have been reported. Two cases have been documented from

Portugal (3), four from Taiwan (4–7), one from Japan (8), two from India (9, 10) and 68 from Sri Lanka (Mohamed *et al*. on behalf of the South Asian Clinical Toxicology Research Collaboration - Personal communication). Overall, six of these 77 patients died, though at least two had co-ingested an organophosphorus insecticide. Most had consumed commercial pesticide products so the toxic features they exhibited were not necessarily attributable to neonicotinoid alone; the co-formulants may have contributed. *Features:* Mohamed *et al.* (Personal communication) have collected data prospectively in 68 patients poisoned with imidacloprid who were admitted to three hospitals in Sri Lanka. Sixty-one of the 68 cases followed ingestion and seven were due to occupational exposure. Ingestion was confirmed in 38 patients by HPLC/MSMS. All seven cases of occupational exposure were discharged within 24 hours of admission without any specific treatment. In 26 of the 61 non-occupational cases, the amount ingested was unknown; the median amount ingested in the remaining 35 patients was 15 mL (IQR 10–50) and the median time of presenting to hospital following ingestion was 240 minutes (IQR 135–360). The median GCS on presentation was 15 (IQR 10–15). Fifty-six of 61 patients had only one of the following mild symptoms: nausea, vomiting, headache, dizziness, abdominal pain and diarrhoea. Five patients became symptomatic with nicotinergic features. Four patients developed respiratory arrest and were mechanically ventilated, but three of these had co-ingested another pesticide, namely quinalphos (2 patients) and fenthion (1 patient). In patients ingesting only imidacloprid the mortality was 0%, whereas two patients co-ingesting quinalphos died. The clinical course in nine additional patients has been reported (2–10). The features observed in some of these nine patients, including sweating, hypersalivation, breathlessness, bronchorrhoea, hyperactive bowel sounds, miosis and bradycardia, are strongly suggestive of the development of the cholinergic syndrome. It is somewhat surprising, however, that so few patients treated in Sri Lanka were symptomatic. *Management:* Gastric lavage or activated charcoal, which is known to adsorb neonicotinoids, may be considered if a patient presents within one hour of ingesting a significant quantity of pesticide, but it is not known whether lavage and charcoal alter outcome. In patients who are unconscious, a clear airway should be established and, if ventilation is impaired, assisted ventilation should be commenced. Hypotension and cardiac dysrhythmias should be managed conventionally and acid-base and electrolyte balance should be corrected. Since the major features of neonicotinoid poisoning are due to cholinergic overactivity, atropine 2 mg should be given intravenously and the dose repeated until the signs of atropinization are present (dry skin and sinus tachycardia) and cholinergic features are controlled. *References:* 1. Tomizawa M, Casida J E. Neonicotinoid insecticide toxicology: mechanisms of selective action. *Annu Rev Pharmacol Toxicol* 2005; **45**: 247–68. 2. Solecki R. Imidacloprid. In: Pesticide residues in food – evaluations 2001. Part II – Toxicological. Geneva: WHO/IPCS, Joint FAO/WHO meeting on pesticide residues. 2002: 79–100. 3. Proença P, Teixeira H, Castanheira F, *et al*. Two fatal intoxication cases with imidacloprid: LC/MS analysis. *Forensic Sci Int* 2005; **153**: 75–80. 4. Wu I-W, Lin J-L, Cheng E-T. Acute poisoning with the neonicotinoid insecticide imidacloprid in N- methyl pyrrolidone. *J Toxicol Clin Toxicol* 2001; **39**: 617–21. 5. Hung Y-M, Meier K H. Acute ®Confidor (imidacloprid-N-methyl pyrrolidone) insecticides intoxication with mimicking cholinergic syndrome. *Toxicol Ind Health* 2005; **21**: 137–40. 6. Hung Y M, Lin S L, Chou K J, Chung H M. Imidacloprid-N-methyl pyrrolidone insecticides poisoning mimicking cholinergic syndrome. *Clin Toxicol* 2006; **44**: 771–72. 7. Huang N-C, Lin S-L, Chou C-H, *et al*. Fatal ventricular fibrillation in a patient with acute imidacloprid poisoning. *Am J Emerg Med* 2006; **24**: 883–85. 8. Tamura M, Endo Y, Kuroki Y *et al*. [Investigation and case study of imidacloprid insecticide caused poisoning]. *Chudoku Kenkyu* 2002; **15**: 309–12. 9. David D, George I A, Peter J V. Toxicology of the newer neonicotinoid insecticides: imidacloprid poisoning in a human. *Clin Toxicol* 2007; **45**: 485–86. 10. Agarwal R, Srinivas R. Severe neuropsychiatric manifestations and rhabdomyolysis in a patient with imidacloprid poisoning. *Am J Emerg Med* 2007; **25**: 844–45.

242. Phenylpyrazole Insecticides

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Insecticides are responsible for the majority of pesticide poisoning cases and deaths globally – in particular, organophosphorus, carbamate, and organochlorine pesticides cause many deaths. However, less toxic insecticide classes have recently been developed, including neonicotinoids (e.g. imidacloprid), chitin synthesis inhibitors (e.g. diflubenzuron), and phenylpyrazoles (e.g. fipronil). Their widespread introduction into agricultural practice will markedly reduce the number of deaths from pesticide self-poisoning worldwide. Despite the use of organochlorines since the 1940s, the mechanism of action of the two main classes (cyclodienes and cycloalkanes) was only elucidated in the early 1980s. These pesticides work by inhibiting the passage of Cl^- ions through GABAA-gated chloride channels, producing neuronal hyperexcitability. Following this discovery, interest was renewed in the development of insecticides acting at GABAA-gated chloride channels. Work with trioxabicyclooctanes resulted in a number of new compounds, of which the first to come to market was fipronil in 1993. Fipronil (CAS 120068–37–3) is the best characterized phenylpyrazole; others include ethiprole, pyraclofos, pyrafluprole, pyriprole, and vaniliprole. It has a broad spectrum of activity, being used for control of insect pests of rice and cotton, locusts and grasshoppers, and fleas and ticks on domestic animals. It is available for agricultural use as a 4.95% solution; in Western countries it is commonly used for treating ants and termites in construction sites. Phenylpyrazoles bind the GABAA receptor, but at a different site than the picrotoxin site used by organochlorine insecticides. The mammalian GABAA receptor is a transmembrane hetero-oligomeric glycoprotein made up of five subunits. At least one α, one β, and one γ subunit are required for fully functional receptors. *In vitro*, fipronil binds to native insect receptors or mammalian β3 homo-oligomeric receptors with high affinity. However, binding to the native mammalian hetero-oligomeric receptor is relatively weak. Non-β3 subunits modulate the ability of fipronil to bind to native β3-containing receptors and this appears to explain the selectivity for insects over mammals. Of all GABAA receptor-binding pesticides in use, fipronil has the highest specificity for native insect receptors over native mammalian receptors with 150–2,000 fold selectivity. Fipronil is highly neurotoxic to insects; however, due to its lower affinity for mammalian GABAA receptors, its human toxicity is less than that of organochlorines. Among the first seven fipronil poisoned patients seen in our Sri Lankan cohort, two had significant CNS toxicity with seizures. However, unlike significant organochlorine poisoning, the seizures were self-terminating or responsive to diazepam, and both patients made a full recovery. Symptomatic patients had sweating, nausea, vomiting and agitation; all were well within 12 h of ingestion and discharged within four days. Nonetheless, our clinical experience of phenylpyrazole poisoning is still limited - no other symptomatic cases of fipronil poisoning or any cases of poisoning with other phenylpyrazole insecticide have yet been published. It is possible that more severe seizures will be noted one day; however, the low concentration of agricultural fipronil (4.95% compared to 36% for the organochlorine endosulfan) will probably continue to limit human toxicity.

243. On the Horizon – New Pesticides, New Applications, Predicting Future Risks From Today's Experiments

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Objective: A fundamental principle of pesticide regulations is to protect the health of those who apply pesticides, those who are exposed as bystanders, and those who are exposed to residues in food and water. This presentation describes how risk assessment can be used in decision making early in the development of new products and new applications of existing products. *Methods:* Risk assessment is a step-wise process which typically consists of hazard identification, dose-response relationships, exposure assessment and risk characterisation (1). It is carried out using toxicology data from laboratory studies and estimates, model predictions and measurement of human exposure. Early in the development process of new products much of this information is not readily available, yet decisions have to be made e.g. which lead compound to choose from a series of analogues, or whether the predicted safety profile is likely to be acceptable. For new molecules, the emphasis is on hazard identification through appropriate studies (see example 'A'), while for new applications of existing compounds the assessment or modeling of human exposure, combined with use experience, is particularly important (example 'B'). *Results:* A) Anthranilic diamides (AD), such as DuPont™ Rynaxypyr™, are a new class of insecticides which act on a novel target for insect control, the ryanodine receptor (RyR) channels which regulate release of internal calcium stores (2). As RyR channels remain open, internal Ca^{2+} stores become depleted. The most potent analogues provide target insect control at significantly lower use rates than current commercial insecticides. Insecticidal effects are flaccid paralysis in skeletal muscle and contractile failure in cardiac muscle without affecting nerve conduction (3). Early *in vivo* studies showed very low mammalian toxicity in acute and subchronic studies (4). This is most likely due to differential activation of RyRs with mammalian receptors being activated at several orders of magnitude higher concentrations. Thus, risk assessment at the early stage of development was dominated by receptor-based studies and by low acute hazard of representative molecules. Subsequently, this process proved highly predictive for DuPont™ Rynaxypyr™, as this product exhibits an exceptionally favourable mammalian profile with regard to mutagenicity, carcinogenicity, neurotoxicity, immunotoxicity and developmental and reproductive toxicity. B) The comparatively low mammalian toxicity and high insecticidal efficacy of pyrethroid insecticides have made them attractive for vector control in public health applications. In recent years, the use of pyrethroid-treated bed nets has been shown to significantly reduce mortality and morbidity from malaria (5). Because of the development of insect resistance to the commonly used pyrethroids, there is a need to consider the use of alternative insecticide classes both for the treatment of nets and the residual treatment of dwellings to prevent malaria transmission. This requires safety assessment of such treatments before they are used in the field. There is also a need to assess the risks from the various methods of bednet treatment that may be used, including the types of insecticide formulation used and the newer, more persistent insecticide treatments that can be generated through incorporating insecticide in the plastic fibres or via more durable coating technology, both of which have different implications for the assessment of risk. This is particularly important since the application of insecticide treatments can be carried out by non-professionals, and the users of bed-nets of all types include vulnerable groups such as small children and pregnant women. A generic risk assessment model has therefore been developed based on typical scenarios for the preparation and use of insecticide-treated bednets and on average or 'worst case' values for environmental and human parameters, and applicable to any insecticide (6). Since the hazard profile of the products considered for this application is well understood, the most important feature of the model is a realistic exposure assessment. *Conclusion:* Risk assessment is an important activity in the development of new pesticides and new applications of existing products and is integral to every stage of the process. The challenge is to design products which provide maximum efficacy in their chosen applications while minimising human health and environmental risks. *References:* 1. Cohrssen JJ, Covello, VT. 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A generic risk assessment model for insecticide treatment of mosquito nets and their subsequent use. WHO/CDS/WHOPES/GCDPP/2004.6; WHO/PCS/04.1. Geneva, Switzerland: World Health Organization, 2004.

244. Poisonings Associated with Illegal Use of Aldicarb as a Rodenticide – Campinas Poison Control Center, Brazil, 2000–2007

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Objectives: Aldicarb (2-methyl-2 (methylthio) propanal o (methylamino)-carbonyl I oxime), a carbamate pesticide sold under the tradename Temik, used as an insecticide and nematicide, is illegally used as a household rodenticide in Brazil as Chumbinho, and in the Caribbean islands as Tres Pasitos. We present here a retrospective study concerning 177 cases of aldicarb poisoning referred to the UPC, from Jan 2000- Mar 2007. *Methods*: We analysed data from 443 confirmed or suspected carbamate poisoning from the UPC. We excluded 91 with non compatible clinical manifestations, non identified product or chronic cases, and 59 without clinical manifestations and considered only exposures. Among the 293 cases, 177 were due to aldicarb and 116 to other carbamates. *Results:* Among the 177 aldicarb poisoned patients, 63 were treated at the University Hospital (57 Chumbinho with one death and 6 Temik with no deaths), and 114

were treated in other health services (86 Chumbinho with 2 deaths and 28 Temik with 2 deaths). Among the 177 aldicarb patients the most frequent muscarinic manifestations were myosis 115 (65.0%), salivation 101 (57.0%), pulmonary secretion 95 (56.7%), diaphoresis (41.8%), vomiting 43 (24.3%), bradycardia 32 (10,1%), dyspnea 22 (12.4%), diarrhea 19 (10,7%), nausea 14 (9,9%), tachypnea 11 (6.2%), urinary and/or fecal incontinence 10 (5.6%), abdominal cramps 8 (4.5%), cyanosis 8 (4.5%), epigastralgia 7 (4.0%), pulmonary edema 5 (2.8%), visual disturbances 5 (2.8%), shock 3 (1.7%); nicotinic manifestations included tachycardia 29 (165.4%), muscle fasciculation 22 (12.4%), hypertension 21 (11.9%), tremor 17 (9.6%), muscle weakness 3 (1.75%); CNS and other manifestations were CNS depression 87 (49.2%), seizures 19 (10.7%), confusion 18 (10.2%), agitation 16 (9.0%), hypotension 15 (8.5%), hypothermia 11 (6.2%), hyperthermia 5 (2.8%), bradypnea 3 (1.7%), and paresthesia 2 (1.1%). Of the 177 cases, 172 (97.1%) involved ingestion; 147 (83.1%) were suicide attempts; 142 (80.2%) received atropine and 63 (35.6%) were intubated. 2 (1.1%) had cerebral vascular accidents. Mortality at other health services was 3.5% (4/114) and 1.59% (1/63) at our hospital, a patient who arrived at ED after a cardio respiratory arrest, presenting with hypertensive pneumothorax, and severe pulmonary aspiration. *Conclusion:* Despite the severity of aldicarb poisoning adequate and prompt treatment can be highly efficient.

245. The Time Dependant Protective Effect of Hyperbaric Oxygen on Neuronal Cell Apoptosis in Carbon Monoxide Poisoning

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Objective: The progressive clinical course with delayed encephalopathy in carbon monoxide (CO) poisoning may be due to neuronal apoptosis. One of the key events in the process of apoptosis is the activation of caspase-3. The time dependant hyperbaric 100% oxygen (HBO) efficiency in preventing neuronal cell apoptosis after CO-poisoning is not known. The aim of our study was to evaluate HBO efficacy in preventing neuronal cell apoptosis in different time periods after CO exposure in an animal model. *Methods:* Wistar rats were exposed to 3,000 ppm of CO for 60 minutes. The control group was left afterwards on ambient air. The rest of the rats were grouped and exposed to HBO immediately (Group 1), 1 hour (Group 2) and 3 hours (Group 3) after CO exposure. 24 hours after CO exposure the rats were sacrificed and immunohystological analysis with antibodies against activated caspase-3 was performed to evaluate apoptosis of hippocampal ganglionic cells. A percentage of apoptotic ganglionic cells in the hippocampus was reported. *Results:* Analyses of differences in percentage of apoptotic cells between different kinds of therapy showed that the percentage of apoptotic cells of the first group (20.6 ± 2.1%,) immediately treated with HBO and the second group (21.9 ± 5.1%) treated with HBO 1 hour after CO exposure were similar, and both of them were significantly different, with a much lower percentage of apoptotic cells, from the control group left on ambient air (31 ± 3.0%) and with a much higher percentage of apoptotic cells than the third group treated with HBO 3 hours after CO exposure (8.6 ± 1.7%). *Conclusions:* CO-poisoning results in brain ganglionic cell apoptosis. HBO has a protective effect on CO-induced ganglionic cell apoptosis, but it seems that HBO 3 hours after CO exposure is more effective in preventing apoptosis than HBO within 1 hour after CO exposure. These results suggest the modification of currently used indications for HBO according to the time elapsed after CO exposure since immediate or premature HBO might not be so effective in preventing apoptosis. The evaluation of HBO in preventing neuronal cell apoptosis and necrosis more than 3 hours after CO poisoning is in progress.

246. Button Battery Induced Cell Damage, a Pathophysiological Study

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Objective: Button batteries are frequently swallowed by children and must be removed immediately if they remain in the oesophagus. Indeed batteries lodged in the oesophagus can cause severe damage, like fistula and cataclysmic bleeding with fatal prognosis. The purpose of this work is to better understand the mechanism of oesophageal damage. *Methods:* Therefore we performed (i) a calorimetric study of heat transfer during discharge of a button battery with a diameter of 20 mm delivering 170 mAh, (ii) a pH study of physiological media during the discharge timecourse, (iii) an electrochemical study, (iv) a measure of leaked metals by damaged battery and (v) a cellular study with emphasis on cytotoxicity and apoptosis on human U937 monocytes. *Results:* Calculated transferred heat varied from 241 to 247 J, with similar values whatever the battery capacity or the medium used. The maximal increase of temperature varied from 4.64 to 7.26 °C per gram of medium. Typical lithium 3 V battery discharge range was 11.6 ± 3.8 mV/min and followed a 2-slope kinetic. Typical overall increase range of medium temperature was 0.0144 ± 0.0040 °C/min. Cell viability decreased, as only 63.2 ± 2.1 % of U937 monocytes remained viable after 90 min of incubation in medium retrieved after a 1-h contact period with a discharging battery. An electrochemical study that mimics a button battery discharge showed that, in absence of stirring, the pH reached in the bottom of the tube was from 7.03 to 9.05 units, reflecting culture medium electrolysis. Metal dosing reflected metal leakage in medium as chrome, iron, manganese and nickel levels following a 1-h contact period with DMEM medium were respectively: 193.6 ± 4.3, 504.8 ± 6.1, 20.8 ± 0.4 and 282.3 ± 9.5 mg/L. Similarly, a small amount of lithium was also found in the culture medium: 1.40 ± 0.03 mg/L. *Conclusion:* Altogether, those results suggested that cytotoxicity and tissue injury induced by button battery discharge is due to multiple causes combining at least thermic, caustic and toxic - due to metal leakage - effects. Maximal effects occur in less than one hour which prompts fast removal of the battery if lodged in the oesophagus.

247. Thallium Challenge Test Using Prussian Blue in Two Patients Exposed to Thallium – Comparison with Controls

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Objective: Thallium is excreted into faeces and urine, in a proportion of about 2:1. The biological half-life of thallium in the poisonings described in the literature is in the range of 1–30 days. Diagnosis several months after intentional and homicidal attempts is usually difficult. A challenge test with an antidote with negligible toxicity might help to solve this problem. However, there are no data on the excretion of thallium after the antidote challenge test in the "unexposed" population, where it originates from environmental sources, especially emissions from processing fossil fuels. *Methods:* 6 g of Prussian blue, $Fe_4[Fe(CN)_6]^3$, ferric hexacyanoferrate were given and urine was collected for 12 hours in 7 volunteers. Thallium in urine and faeces was measured before the treatment, in the 12 hour urine collection sample and in the first blue coloured faeces by voltammetry (1). Results are shown in Table 1 compared with the findings in two women - 5 weeks and 4 months after severe intoxication (2). *Conclusion:* Challenge test with Prussian blue appears useful, as it increased thallium excretion in urine after 4 months latency after intoxication by more than one order and in faeces by about two orders, compared with the controls. Low-cost voltammetric analysis can be used. *References:* 1. Pribil R, Zabransky Z. Polarographic determination of thallium. *Chem Listy* 1951; **45**: 427–428. 2. Pelclova D, Senholdova Z, Lukas E, *et al*. Diagnosis and elimination of thallium after an intentional intoxication. *Chem Listy*, in print. *Acknowledgement:* MSM 0021620807.

Table 1. Thallium in urine and faeces before and after Prussian blue in 2 severely exposed and 7 control subjects

		Latency after thallium intoxication		Controls N = 7	
Material	**Units**	**5 weeks N = 1**	**4 months N = 1**	**mean**	**range**
Urine before treatment	mcg/l	580	*	*	*
Urine collection 0–12 h	mcg/l	1170	21	1.3	0–4
Urine collection 0–12 h (abs.)	mcg	1750	31	1.4	0–5
Faeces before treatment	mcg/g	Not measured	Not measured	*	*
Faeces after treatment	mcg/g	55	5.5	0.044	0–0.116

*under detection limit.

248. Evaluation of a Poison Prevention & Education Website Traffic

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Objective: The New Zealand National Poisons Centre Poison Prevention and Education Website (www.poisons.co.nz) was launched in October 2006. Subsequent to this there was no direct campaign to promote the website. This gave a valuable opportunity to access the effect of "word of mouth" promotion of the website without the impact of any specific interventions on website accessibility or operational process to increase search engine ranking. *Method:* Traffic to this website was evaluated for six months from the beginning of 2007 to determine the number of visitors, the location of these visitors, and how they accessed the site, including software and search terms. *Results:* Over this six month period, the number of visitors increased substantially, from 428 in January to 1292 in June (a 201% increase). This overall increase reflected a considerable increase between April and May (a 35% increase), and another between May and June (a 63% increase). On average approximately 31% of visitors added the site to their favorites, indicating that they intend to visit the site again, or value it highly enough to want to find it again quickly. This correlates well with the percentage of return visits within the month (22%). New Zealand consistently ranked as the top country utilising the site. The other main users were the United States, Australia, Great Britain, Canada and India. Others included Malaysia, Netherlands, Mexico, Spain, Trinidad & Tobago, Ireland, Pakistan, Macau, Philippines, Germany, Sri Lanka, Kenya & Latvia. Windows based operating systems were by far the major operating system used; on average 94% of hits are from a Windows operating system. *Conclusion:* The evaluation of the National Poisons Centre Poison Prevention and Education Website (www.poisons. co.nz) revealed some interesting trends in visitors, the location of these visitors, and how they access the site. The increase in number of visitors by "word of mouth" is very promising, given the lack of a direct campaign to promote the website, and even more promising is the obvious worth of the information to these visitors given the number of page views per visit and time spent on the website.

249. A Needs Assessment for a New Zealand National Poison Centre Poisoning Prevention Internet Site

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Objective: Poisoning prevention activities are an important part of the spectrum of services provided by Poison Information Centres. Some countries have developed Internet sites relating to poison prevention education but prior to 2006 this media had not been utilized in New Zealand by the National Poison Centre. The principal aim of this project was to evaluate the need for up-to-date and readily accessible information via the Internet on poison prevention. *Method:* 300 child education services (covering pre-schools, primary schools, intermediate schools, secondary schools, along with child and parent agencies) were randomly selected from the New Zealand Telecom directory and mailed a survey. *Results:* Of the 300 surveys sent, 156 (52%) replies were received. Of these, 149 (95%) were recognised as valid responses with 5% classed as invalid. Of the valid responses, all stated that it would be beneficial for the National Poisons Centre to provide a freely accessible web-based New Zealand poison prevention education site. Of the valid responses 131 (89%) indicated that inclusion of a teaching tool for caregivers/teachers into the web site would be effective, with only 16 (11%) not favouring the idea. There were many and varied responses for suggestions on how the site could possibly be used as an educational aid. The survey indicated that such a web site be directed at those aged 9 to 50 years, e.g. the site should be designed for year five school education and beyond, while also including education for adults such as parents. The

responses also suggest that the site be made freely available through Primary Schools, Intermediate Schools, Secondary Schools and, most importantly households. *Conclusion:* The results of the study suggested that it would be beneficial for the National Poisons Centre to provide a freely accessible poison prevention education web site. This site should be directed at both households and educational organisations and contain a varied collation of information on poison prevention directed at and customised for the various sectors of the target population. The study provided a basis for the development of an interactive Poisons Prevention Internet site for the Poison Centre.

250. Acute Ethanol Poisonings in Adolescence in Bulgaria – Psychosocial Aspects and Prevention of Alcohol Abuse (Preliminary Results)

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Objective: Alcohol is one of the most common contributors to injury and criminal behaviour among young people. Early onset of alcohol use increases the risk of chronic alcohol addiction. One of the major challenges nowadays is prevention of underage alcohol access. The aim of the study is to develop effective preventative strategies for reducing underage alcohol consumption. *Methods:* We have studied prospectively acute alcohol poisoning in adolescents, hospitalized in the Children Toxicology Department, EMI "Pirogov" for the period 2006–2007. The patients were followed-up with regard to severity of poisoning, level of consciousness, blood ethanol level (measured on admission by thin-layer chromatography), and various psychosocial aspects. Psychiatric interview and inquiry with special questionnaire card was used. The received data were analyzed and preliminary results presented. *Results:* We have studied 64 adolescents, aged 12 to 18 with acute alcohol poisoning. 33 are boys and 31 girls. On admission most of them had different levels of depressed consciousness: 35.9% were somnolent, 40.6% were soporous and 12.5% comatose. Blood ethanol concentration was over 2 mg/ml in 43.8%. Combination alcohol-illicit drug was observed in 4 children (6.29%). First alcohol consumption was at the age of 13.4. The students have approximately 1.20 euro daily. 64% of the children come from complete families. Both parents have higher education in 34.4% and in 48% both parents are employed. 22% of children were the second child in the family. Hereditary predisposition was found in 21.9%. The most frequent reason for alcohol consumption was meeting and communicating with friends (60%). All patients underwent brief intervention prior to discharge. No repeated hospitalization for acute alcohol poisoning in the study group for that period has been registered. *Conclusion:* 1) Influence of "the group" is the main cause of alcohol consumption in adolescence. 2) Family background does not play an important role in prevention of alcohol poisonings. 3) We registered high blood ethanol levels on admission. 4) There is no increasing tendency for combining alcohol with other psychoactive drugs. 5) We consider the brief intervention prior to hospital discharge as a preventive factor for repeated poisonings.

251. Low Dose Toxicity of *Veratrum Album* in Children – A Case Series

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Objective: White or false hellebore (*Veratrum album*) is an alpine herb which can be easily mistaken for *Gentiana lutea* ignoring the different leaf position. The veratrum alkaloids (e.g. veratridine, cevadine) can cause cardiovascular, neurological and severe gastrointestinal symptoms after ingestion. Symptoms are probably caused by interaction at the sodium channel (1). On this background we present a case series of pediatric poisoning with small amounts of *Veratrum album* roots. Data were retrieved from written follow-ups by the treating physicians and from a parental questionnaire. *Case series:* 11 children (8–12 years) ingested the root of *Veratrum album* accidentally at a youth camp where they had collected herbs to prepare fresh herb tea. The roots were taken in form of slices (4 children ingested an amount from a quarter of one slice up to two slices) or as tea made of cubes (7 children took from one gulp up to 2 cups). Two children who took only a mouthful of tea did not develop symptoms. Nine children showed at least gastrointestinal symptoms (nausea, vomiting, dysgeusia). Six developed neurological symptoms (vertigo, impaired vision, somnolence, dysarthria). Remarkably two children presented with bradycardia which responded to atropine and resolved without further treatment, respectively. None of the children received primary gastrointestinal decontamination as charcoal was not available at the camp, and at hospital admission it was too late. All children recovered completely within 10 hours. The plant was identified at the ED, but detection by HPLC in the blood sample of the child with the most severe symptoms was negative (cut-off 0.01 ng/mL). The detection of veratridine is an uncommon and complex procedure. Blood concentrations of 0.17 and 0.4 ng/mL are reported in two fatal courses in the literature (2). *Conclusion: Veratrum album* can cause relevant symptoms in children even after ingestion of small amounts. *References:* 1. Nanasi PP, Effects of veratrine on ion currents in single rabbit cardiomyocytes. *Gen Pharmacol* 1994; **25**: 1667–72. 2. Gaillard Y, LC-EI-MS determination of veratridine and cevadine in two fatal cases. *J Anal Toxicol* 2001; **25**: 481–5.

252. Ciguatera Poisoning in Early Pregnancy and Severe Visual Impairment in the Child: A Case Report

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Background: Few case reports have suggested that ciguatoxins cross the placenta and may affect the fetus. *Case report:* A 33 year-old pregnant woman ate barracuda in Cuba. At that time she was at the 3rd gestational week. She developed mild gastrointestinal and neurological symptoms which resolved within 6 weeks. The course of the pregnancy was normal. Prenatal screenings for congenital and genetic diseases were negative. At 39 weeks she delivered a healthy male infant. Visual impairment was suspected at the age of 3–4 months, because of difficulties in following moving objects. Clinical examination performed at the age of 6 months showed pendular nystagmus and normal pupils response to light; visual acuity was markedly reduced (0.6 cycles/degree, corresponding to 0.2/10); fundus examination showed mild aspecific pigment deposits; visual evoked potentials (VEP) were normal for age. The child was followed until the age of 4.5 years. Nystagmus disappeared while visual acuity remained low (1/10 at 2 m, 1.5/10 at 40 cm) with moderate photophobia. Brain magnetic resonance imaging was negative, VEP demonstrated bilateral delay; electroretinography showed photopic abnormalities. No cognitive impairment was present. *Conclusion:* In published experiences of ciguatera poisoning during pregnancy no congenital abnormalities have been reported, but the value of these reports is limited by the fact that outcome was assessed at delivery with no prolonged follow-up. No experimental studies have been conducted in order to assess neurodevelopmental toxicity of prenatal ciguatoxin exposure in mammals. In the patient described here, the clinical course is similar to that of congenital retinal dystrophies, except for the normal pupils' response to light and the disappearance of nystagmus with age. Therefore, a role of the *in utero* ciguatoxin exposure should be considered, since (i) nervous system is the main target organ of ciguatoxin toxicity, (ii) ciguatoxins can persist in the body for a long period, and (iii) their ability to cross placental barrier has been clinically suggested, therefore making plausible a prolonged *in utero* exposure. If future observations will document other cases of visual impairment after *n* exposure to ciguatoxins, the teratogenic potential of this poisoning should be reconsidered.

253. Rare Envenomation with *Crotalus oreganus* in Slovak Republic

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Case report: A 30 year old snake keeper was bitten on the left ring finger while feeding the snake *Crotalus oreganus* (Great basin rattlesnake). Immediately after the bite, he had a burning sensation in his hand, nausea, weakness and diarrhoea. He was admitted to the hospital 40 minutes after the bite. On arrival he was in shock, he had negligible blood pressure, pulse rate 130/min, shallow breathing, tremor and fasciculations of the whole body. He had two puncture wounds in the distal phalange of the ring finger. His hand was pale and swollen, the finger became cyanotic. NTIC was consulted about treatment and antivenom. In the Slovak Republic, the only available antivenom is the one for *Vipera berus*. We searched for crotalidae antivenom in the neighbouring states. According to the web site www.toxinfo.org/antivenoms we found that the antivenom was available in Munich. Antivenom was donated and transported from Munich to Bratislava by aeroplane. First dose was given to the patient 7 hours after the bite. The state of the patient improved rapidly. The antivenom stopped the development of disseminated intravascular coagulation, also diuresis improved and there was no need of further oxygen support. After the third dose of antivenom all laboratory results returned to normal state and the local symptoms improved. However, the edema of the finger phalange still remained, also local necrosis 2 × 3 mm, which was present in the middle of the phalange and also local necrosis 2 × 2 mm was present at the lateral side. All 12 vials of antivenom were given to the patient. On the eighth day after envenomation the patient was discharged home, with the possibility of further treatment with hyperbaric oxygen therapy (HBO) in Trencin´s Hospital. After 13 cycles of HBO the patient recovered completely. There is no visual sign of snake bite on his hand now. According to the patient, partial loss of sensibility of the distal phalange still persists. *Conclusions:* International cooperation of poison information centres, hospitals, pharmaceutical firm and airline together with very good supportive treatment helped to save life of this seriously envenomed patient.

254. Three Cases of *Amanita muscaria* Ingestion in Children – Two Severe Courses

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Objective: Amanita muscaria (Fly Agaric mushroom) is a psychoactive agaric species containing muscimol and ibotenic acid. Ibotenic acid shows potent activity at both NMDA and certain metabotrobic receptor subtypes, and it is a weak agonist at non-NMDA receptors. Muscimol is an agonist on both the GABA-A and GABA-B receptors (1). Symptom onset is usually within 30–90 min, peaking at approximately 2 hrs. The initial symptom of drowsiness is quickly followed by confusion, ataxia, dizziness, euphoria, and may proceed to increased activity, illusions, or even manic excitement (2). Deep sleep or coma is found in the later stages, usually lasting 4–8 hrs. Severe vomiting is rare (3). *Case series:* All three children (4–5 yrs), from a nature kindergarten, were brought to the ER following ingestion of *Amanita muscaria*. FEMALE-1 had allegedly consumed some bites of an *Amanita muscaria*. She arrived somnolent, increasing to coma with respiratory arrest. Other vital parameters were within normal range, however, the pupils were miotic. The patient was intubated, and transferred to ICU. Gastric lavage was performed followed by instillation of activated charcoal. Eight hours after admission, the patient awakened, responding but confused. Following extubation, the respiration was normo-frequent and steady. FEMALE-2 vomited after consuming some bites of an *Amanita muscaria*. Vital signs were within normal range. The actual dose of activated charcoal ingested was uncertain as the patient vomited following both the first and the repeated dose. MALE-1 had allegedly consumed one *Amanita muscaria*. Shortly after admission he became confused, drowsy and hallucinating, progressing into coma. Respiratory instability, bradycardia and cholinergic symptoms with miosis developed, followed by intubation and transfer to the ICU. Next morning spontaneous awakening, presenting dizziness and photophobia with pain. Extubated, and improved within 1–2 hrs. *Conclusion:* All children were discharged approximately 20 hrs following admission without sequelae. Although *Amanita muscaria* normally presents relatively a low degree of toxicity among the Amanitas, occasional severe courses are observed and each incident

needs appropriate attention as the course might become severe, even if initial symptoms are absent. *References:* 1. Krogsgaard-Larsen, *et al*. A textbook of drug design and development. 2nd ed. Amsterdam, The Netherlands: Harwood Academic Publishers, 1996:243,259. 2. www.intox.org 3. www.micromedex.com

255. Four Cases of Poisoning by *Entoloma vernum*

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Objective: Poisoning after ingestion of *Entoloma vernum* (=*Rhodophyllus vernus*, =*Nolanea verna*) has been mentioned in some books and described in only a few mycological publications to date (1–3). We report four cases of illness after ingestion of *E.vernum* on two different occasions. *Case series:* In 1999, a couple ate mushrooms mistaken for *Marasmius oreades*. Ten hours after the meal, the 58-year-old woman with a history of breast cancer presented with bilious vomiting, diarrhoea and some signs of dehydration (serum protein: 90 g/L). The 51-year-old man with no medical history presented 12 hours after the meal with nausea, uncontrollable vomiting and watery diarrhoea. They were both rehydrated with intravenous fluids and treated with antiemetic and antispasmodic agents. The mushroom leftovers were identified as *E.vernum* by a mycologist. In 2006, a mother and her daughter ate three spoonfuls each of mushrooms mistaken for *Entoloma aprile*. Ten hours after ingestion, the 66-year-old mother treated for arterial hypertension presented with nausea, frequent vomiting, diarrhoea and a nosebleed. Her daughter, a 48-year-old woman, presented 8.5 hours after the meal initially with severe vomiting, followed by headache, abdominal pain, diarrhoea and signs of dehydration (hematocrit: 0.53); total serum bilirubin level was 28.7 µmol/L. They were both rehydrated with intravenous fluids for 24 hours. The next day, a mushroom species found at the place of mushroom gathering was identified as *E. vernum* by a mycologist. *Conclusion:* A severe gastrointestinal syndrome occurred in four patients within 8–12 hours of ingestion of *E.vernum*. These characteristics (severity, late onset) also are also typical of *Entoloma lividum* poisoning. Differential diagnosis with cyclopeptide poisonings can thus be problematic, especially in the initial phase of such a poisoning. A headache is sometimes present in the case of *E.lividum* poisoning; the hyperbilirubinaemia was not explained; the nosebleed may have been related to the physical stress of vomiting in a hypertensive woman. *References:* 1. Ayer F. Rhodophyllus vernus. Note critique, toxicité. *Schweiz Zeit Pilzk* 1974; **52**: 17–9. 2. Veselsky J. Vergiftungen mit dem Frülings-Giftrötling - Nolanea verna Drastisches Purgativ-Syndrom. *Ceska Mykol* 1979; **33**: 247–9. 3. Pouchet A. Un cas d'intoxication par Rhodophyllus vernus. *Bull Mens Soc Linn Lyon* 1964; **33**: 281–2.

256. Scorpion Stings in Campinas, São Paulo State, Southeastern Brazil (1994–2005)

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Objective: To report the epidemiological and clinical features of 922 patients stung by scorpions admitted to our Emergency Unit from January 1994 to December 2005. *Case series:* Nine hundred and twenty-two patients (ages 3 mo to 84 yr, median 28 yr; 62.7% male) were admitted from 10 min to 22 h (median=99 min) after being stung by *Tityus bahiensis* (N=266, 28.9%), *Tityus serrulatus* (N=127, 13.7%) or unidentified scorpions (N=529, 57.4%). Most of the stings occurred in the extremities (hands 39.8%, feet 23.3%) during daylight hours (56.8%), from October to January (47.2%). Based on the severity scale defined by the Brazilian Ministry of Health Guidelines (1998), the cases were classified as asymptomatic (2.9%), mild (83%), moderate (11%) or severe (3.1%; N=29; 28 children under 12 yr, median=3 yr, third quartile=8.5 yr). Local complaints were frequent and included pain (93.6%; irradiating in 28.1%), erythema (30%), paresthesia (16.2%) and sudoresis (5%). Vomiting was significantly more frequent in severe cases (28/29) compared with moderate (17/101) and mild (1/765) cases, respectively ($p<0.001$). Envenoming by *T. serrulatus* (13/127) was significantly more severe than that caused by *T. bahiensis* (2/266) ($p < 0.001$). Procedures to relieve pain were frequently used, including analgesics (51.1% p.o. and 10.4% i.v.) and local anesthesia (23.4%). Scorpion antivenom [Fab'2, Instituto Butantan, Brazil; 1–6 vials (5–30 ml); median=4 vials, infused i.v. over 5–20 min] was administered in 35 cases [3.8%; 21 severe, 14 moderate (eleven <10 yr old)]; seven severe cases received antivenom at other health services. Mechanical ventilation (8/29) and dobutamine infusion (9/29) were also used in ten children classified as severe cases to control cardiac failure, shock and/or pulmonary edema. There were no deaths. *Conclusions:* Scorpion stings are common in the region of Campinas. Children stung by *T. serrulatus* and who develop emesis, especially those <9 yr old, should be considered at risk of severe envenoming.

257. Outcome Predictors in Patients Treated with Albumin Dialysis Due to *Amanita phalloides* Poisoning

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Objective: Molecular Adsorbent Recirculating System (MARS) is the most widespread extracorporeal liver support system in Poland. Use of albumin dialysis in *Amanita phalloides* poisoning is not a part of standard treatment regimens due to lack of sufficient randomized studies. We attempted to identify the predictors of outcome in patients treated with albumin dialysis due to acute liver failure in the course of *Amanita phalloides* poisoning. *Methods:* The demographic, clinical and biochemical parameters of twenty five patients treated with MARS due to amatoxin induced liver failure in two Poison Units in Poland in 2005–2006 were analyzed. Statistical comparisons were performed using the Student's t and Pearsons's chi-square tests, C&RT method was used to identify the threshold values for liver regeneration. *Results:* The patients were divided into two groups: A – the patients with liver regeneration and B – those who died or underwent liver transplantation. The demographic, clinical and biochemical data of both groups are presented in Table 1. The threshold value of the highest INR value observed during treatment was 5.82. The probability of liver regeneration was 91.6% below this value and 23.1% in patients whose INR exceeded it. *Conclusion:* The maximum INR values are the only predictor of outcome identified in this study. There was no relationship of other parameters especially the AST and ALT with the outcome of amatoxin induced acute liver failure.

Table 1. Demographic and biochemical data in the studied groups

	Group A (liver regeneration) N = 14	Group B (transplantation/death) N = 11 (4/7)	p
Age (mean +/– SD)	53.8+/–17.2	50.9+/–20.2	0.56 (2)
Sex (M/F)	7/7	5/6	0.82 (3)
INR (mean +/– SD) (1)	4.8+/–2.6	9.1+/–1.9	<0.01 (2)
AST (IU/L) (mean +/– SD) (1)	6679+/–4030	8745+/–5329	0.28 (2)
ALT(IU/L) (mean +/– SD) (1)	6458+/–2746	6927+/–2474	0.66 (2)
Total bilirubin (mg/dL) (mean +/– SD) (1)	6.34+/–4.4	8.7+/–6.0	0,26 (2)

SD- standard deviation, (1)-highest value observed during hospitalization, (2)-t Student's test, (3)-Pearson's chi-square test.

258. Spectrum of Snake Bite in the Southern Regions of South Africa: A Retrospective Analysis

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Objective: To establish the spectrum of snake bite in the southern regions of South Africa. *Methods:* 1544 snake bite consultations processed by the Tygerberg Poison Information Centre over a period of 14 years were analyzed. *Results:* Of the 1544 consultations, 495 were actual bites. Contrary to popular belief, the incidence of Cape cobra (*Naja nivea*) bite, was found to be higher (17%) than that of puff adder (*Bitis arietans*) bite (15.5%). 68% of Cape cobra bites resulted in neurotoxic effects. The shortest latent period for flaccid paralysis to develop was 11/2 hours. 53% of patients received antivenom. Although the antivenom reduced the time of paralysis, it did not prevent respiratory failure from developing. The mortality rate was 7% and all died outside a medical facility. 90% of puff adder bites presented with prominent cytotoxic effects, and in 74% antivenom was administered. Although morbidity was high, no deaths were recorded. The snake could not be identified in 21% of the 495 bites. In the category identified as "other" (10%), a wide spectrum of venomous snakes was involved which included the mamba as well as exotic snakes from other countries kept as pets. 15.5% of bites were inflicted by dwarf adders. Of these, 40% were berg adder (*Bitis atropos*) bites: 93% presented with cytotoxic and neurotoxic effects and hyponatraemia was noted in half of the cases. Other dwarf adders included *Bitis caudalis, cornuta, xeropaga* and *peringueyi*. Although previously believed to be exclusively cytotoxic, 12% of these envenomings surprisingly showed signs of neurotoxicity. Spitting cobras, including the rinkhals, comprised 12% of cases, of which the majority (65%) caused envenoming of the eyes. Boomslang bite occurred in 3.5% of cases. *Conclusion:* Puff adder has always been considered to be responsible for the majority of serious snake envenomings in South Africa. However, this study showed that the incidence of Cape cobra bite is slightly higher than that of puff adder bite. Due to the rapid action of Cape cobra venom, early respiratory support is mandatory. Antivenom cannot prevent full paralysis from developing and should therefore not be seen as an emergency drug.

259. Spider Bite Induced Clinical, Paraclinical and Electocardiographic Changes

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Introduction: Envenomations including spider (*L. Treducimgutatus*) bite are relatively common in North East Iran (1). This particular envenomation induces local and generalized pain, malaise, chilling, sweating, nausea, abdominal pain, confusion and palpitation (2). We previously reported that total CPK may increase in this envenomation (3). We aimed to evaluate a potential relationship between electrocardiologic indices and laboratory findings. *Methods:* All cases admitted with suspected spider bites between 20th September 2006 and 20th September 2007 was studied prospectively. The patients with known previous cardiac problems were excluded. None of them received specific antitoxin, which is not available in this country. *Results:* Spider bites accounted for 31 cases. No deaths were recorded. Mean (SD) age was 33.3 (± 14.8) years. A male predominance (70%) was found. One case was referred to ICU. Most common bitten parts were leg (32%), foot (28%), hand (16%), forearm (8%) and head and neck (16%). On admission, mean systolic and diastolic blood pressures were 123 (± 17) and 73 (± 10) mmHg respectively, heart rate was 78 (± 17) bpm, respiratory rate was 19 (± 11) bpm and temperature was 37 (± 0.4) C. Pain, sweating, chill, head pain, dyspnea, vomiting, nausea were the most common clinical findings. CPK was 519.1 (± 425.5) U/L, CPK-MB was 40.6 U/L and creatinine was 10.3 ± (2.0) mg/L. Troponin was also positive in 2 cases. ECG findings included PR 148 (± 39) mSec, QRS duration 61 (± 15) mSec, and QTc 412 (± 35) mSec. ST segments were elevated in 39% and depressed in 19% of cases in at least two of the leads. CPK, however, was significantly higher in patients with ST depression (P=0.017, n=29) or ST elevation (P=0.05, n=29) in at least one lead. Also almost all high CPK MB cases showed ST depression or ST elevation, but not vice versa. *Conclusion:* CPK, CPK MB and Troponin can be used to predict potential cardiologic complications in spider bite. *References:* 1. Afshari R *et al. J Toxicol Clin Toxicol* 2004; **42**: 965–75. 2. Afshari R, 3352, 1995, Mashhad University of Medical Sciences (M.D Thesis). 3. Afshari R *et al*. *J Toxicol Clin Toxicol*, 2007; **45**: 371.

260. Envenomation by Stonefish (*Synancea sps.*) in French Polynesia: A Case Series from the Surgery Unit of the Papeete Hospital

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Objective: Stonefish (*Synancea sp.)* is considered as the most venomous fish in the world. Authors describe the experience of the surgery unit of the Papeete Hospital of Synancea stings. *Case series:* Between 2000 and 2006, 46 patients with *Synancea* stings were managed (26 men and 20 women, average age 17.38 years). 40 patients were stung on the foot, 6 on the hand. The average delay between the sting and medical management was 4.6 days (from 1 hour to 3 weeks). This long delay is explained by the geographical situation of French Polynesia (numerous isolated islands, only one hospital in Tahiti). Intense pain was still present in 36 patients who received pain killers (10 cases with local anaesthesia, 17 cases with morphine). The initial pain was severe for all patients, but none of them had systemic symptoms even several patients who received no treatment other than traditional ones for several days. For 20 patients, the sting was mild. For 23 patients, local necrosis was observed (11 of them needed surgery) and for 3 patients infections were reported (surgery for 2 patients). Outcome was good for 40 patients, but significant necrosis led to 2 amputations (1 finger and 1 toe) and to 4 sequelae. All patients with severe necrosis were managed after a long delay. *Discussion:* The systemic toxicity of stonefish venom is not reported in recent medical reports. Local symptoms were severe; pain was intense during several days without treatment and necrosis (+/- infections) was a frequent complication which can lead to sequelae. When patients cannot be quickly managed in an emergency unit, the use of morphine and/or local anaesthesia is not possible. The authors propose to try in French Polynesia the simple protocol used in the Mediterranean: local heat during 2 minutes immediately replaced by cold application (ice cubes). This treatment has proved its efficacy with Mediterranean fish, and also for stings of the lionfish (*Pterois sp.*) kept in aquariums (initially considered as dangerous too, but found to result in mild envenomation when local temperature variation is quickly performed).

261. Mechanism of Scorpion (*H. lepturus*) Venom Poisoning in Experimental Animals

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Background: Very few reports indicate the manifestations induced by venom of the *Scorpionidae* family. *Hemiscorpius lepturus* is an important scorpion species present in the south and south west part of Iran that causes morbidity and mortality in children and adults. *Method:* For this study *H. lepturus* venom was extracted by electric shock and the venom (6.3 mg/kg) was injected subcutaneously into a group of 6 rabbits. Blood collection was carried out before and 3 hours after venom injection for determination of osmotic fragility, blood sugar ALT, AST, LDH, CPK and alkaline phosphatase. Additionally *in vitro* studies were carried out to investigate the osmotic fragility of RBCs exposed to various concentrations of the venom, ranging from 0–90 µg/2ml of blood. *Results:* Results showed the extreme effect of this venom on lysis of RBCs *in vitro* and *in vivo*. Injection of the venom caused significant ($p>0.001$) increase in ALT, AST, LDH and blood sugar. Although there was an increase in CPK and alkaline phosphatase after venom injection statistically the changes were not significant. All animals died 4 hours after receiving the venom. *Conclusions:* This study reveals that the neurological effect of the venom of *H. lepturus* is more or less similar to the neurological effects produced by scorpions of the *Buthidae f*amily except for the highly significant effect of *H. lepturus* on lysis of RBCs which may be due to presence of a type of phospholipase in its venom.

262. Naturally Occurring Toxins in the Czech Republic

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Objective: Recreational abuse of toxins of natural origin seems popular among young people in our country. The objective of the study was to evaluate the calls to the Toxicological Information Centre (TIC) due to abuse of plants and mushrooms. *Methods:* A retrospective analysis of the calls classified as abuse was performed. Data were extracted from the electronic database from January 1995 to October 2007. *Results:* Total annual inquiries increased during the 13 years from about 5000 to 10000. On the other hand, the number of calls due to abuse was relatively stable, but the proportion of naturally occurring toxins increased (Table 1). Among the calls due to abuse of naturally occurring toxins, 549 calls involved plants (57.2%), and 411 mushrooms (42.8%). Commonly abused substances were *Datura stramonium* (31.7% calls) and marihuana (25.4%); but nutmeg was involved in only 2 calls (0.2%). Datura was eaten raw (seeds, leaves) or prepared as a tea. Thirteen calls involved ingestion of Datura leaves by dogs and cats; the animals were disorientated. Marihuana was smoked or ingested in cakes or in a drink. The most frequently abused mushrooms were *Psilocybe* species (28.9%) (10–150 mushrooms). *Amanita pantherina* and *Amanita muscaria* were used rarely (13.0% and 0.8%, respectively). *Conclusion:* The proportion of naturally occurring toxins amongst all illegal substances during the past 13 years increased from 16% to 27% and documents a favorable trend of using less dangerous agents. The age of abusers was 16–26 years; and the severity of exposure was evaluated mostly as low or mild. *Acknowledgement:* MSM 0021620807.

263. AAPCC – Database Characterization of Native Crotalid Envenomations in the US, 2001–2005

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Background: There are an estimated 6,000 – 8,000 native venomous snakebites a year in the US. Differences in demographics, clinical effects, managements, and outcomes among native crotalid species have not been systematically characterized. *Methods:* The database of the American Association of Poison Control Centers from 2001 through 2005 was analyzed. *Results:* There were 23,372 human exposures to native crotalid snakes reported to US poison centers over the 5-year period (average=4,751/year). Genus and species were identified in 7,799 snakebites (33%). Native crotalids comprised 98% of all venomous snakebites, which occurred in all states except Hawaii. There were significant differences between species in demographics, clinical effects, managements, and outcomes (see Table). Overall, 77% of victims were male, 70% adults, 30% aged less than 20 years, and 12% aged less than 10 years. Rattlesnake and cottonmouth bites were more likely to occur in males; copperheads and cottonmouths more likely to occur in children. Copperheads were more likely to produce local injury; rattlesnakes were more likely to produce systemic, hematologic and neurologic effects. The overall hospital admission rate was 46% of those with a definite outcome code. Major effects and death outcomes were greater with rattlesnake bites than copperheads or cottonmouths. The case fatality rate was 0.06%. *Conclusions:* Native venomous snakebite in the US results in significant morbidity and mortality. Systematic characterization of envenomations may help practitioners evaluate and manage venomous snakebite.

264. Risk Factor for Death Caused by Scorpion Envenomation at the Hospital of Elkelaa Des Sraghna Province (Morocco)

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Objective: This study aims to elucidate some risk factors involved in death caused by scorpion envenomation over a period of 4 years through analysis of data reported in hospital admission forms. *Methods:* A retrospective study was conducted in the medical area of Elkelaa des Sraghna province for the period 2001–2004. All files of hospitalizations due to scorpion envenomation treated at Essalama hospital were systematically analysed. *Results:* This study covers 74 deaths among 984 patients subject to scorpion envenomation. Most of the envenomation happened during the hot season with a high peak during July-August (53.6%). Moreover a sting occurs in 72% of the cases at night between 6 PM and 6 AM. All ages are subject to scorpion envenomation but youngsters of less than 15 years are

Table 1. Calls to the TIC (abuse, abuse of plants and mushrooms)

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007 Jan–Oct
Total calls due to abuse (N)	163	258	282	350	315	366	379	318	260	264	232	190	183
Plants among abuse (%)	8.5	9.7	10.6	18.3	14.0	17.8	14.8	12.9	25.4	16.3	22.0	17.9	12.5
Mushrooms among abuse (%)	7.4	5.0	7.4	10.3	6.7	14.0	11.9	8.2	9.2	20.0	16.0	13.2	14.6

Table: Rates and significance of selected parameters

		Copperheads	Cottonmouths	Rattlesnakes	Significant species differences (*)
Demographics	Female Gender	29%*	18%	20%	Copperheads > rattlesnakes and cottonmouths
	Adults	74%	75%	79%*	Rattlesnakes > than copperheads and cottonmouths
	Age 0–9 yr	10%*	6%	9%*	Copperheads and rattlesnakes > cottonmouths
	Age 10–19 yr	16%*	19%*	12%	Cottonmouths and copperheads > rattlesnakes
Clinical effects	Hypotension	0.9%	1.4%	2.9%*	Increased rate with *C. h. horridus* & *C. adamanteus*
	Edema	72%*	53%	65%	Copperheads > rattlesnakes and cottonmouths
	CPK incr.	0.3%	0.2%	0.7%*	Increased rate with *C. h. horridus*
	Cytopenia	0.1%	0.2%	2.5%*	Increased rate with *C. h. horridus* & *C. v. oreganus*
	PT increased	1.0%	1.8%	7.4%*	Increased rate with *C. adamanteus* & *C. horridus*
	Other coagulation abnormality	0.9%	3.5%	8.0%*	Increased rate with *C. adamanteus* & *C. horridus*
	Muscle Fasciculation	0.1%	0.1%	1.7%*	Increased rate with *C. v. helleri* & *C. v. oreganus*
Managements	Admission (species known)	48%	38%	59%*	Rattlesnakes > copperheads or cottonmouths
	Antivenom use	25%	19%	54%*	Rattlesnakes > copperheads and cottonmouths
	Antibiotic use	23%*	14%	9%	Copperheads > rattlesnakes and cottonmouths
Outcomes	Major effects & Death	3%	3%	8%*	Rattlesnake > copperheads and cottonmouths

commonly affected (61.4%). The rate of intra-hospital death is 7.68%. Statistical analysis indicates that age less than 15 years, envenomation, admission, class and the time of stings are the most important risk factors which have the following relative risk values: 13, 90; 10, 83; 2.61 respectively. *Conclusion:* The role which the health care could have in reducing mortality among patients affected by scorpion envenomation has not yet been given the attention it deserves. Nevertheless health care counts with the other 3 factors among the crucial risk factors for the survival of the affected patients. *Acknowledgement:* This work is within PROTARS III D63/15 program and the national campaign for the control of scorpion stings and envenomation.

265. Grayanotoxin Poisoning from *Pieris japonica*

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Objective: Toxicity from grayanotoxins has been well described in the setting of "mad honey" ingestions along Europe's Black Sea, whereby individuals consume honey made from concentrated rhododendron nectar of the *Ericacae* family (1,2). We report 2 cases of grayanotoxin-induced cardiovascular instability in the United States from ingestion of *Pieris japonica*, another *Ericacae* family member. *Case series:* A 21-month-old female presented with pallor and vomiting after having been observed eating a garden plant. Initial vital signs were significant for a heart rate of 40 bpm; she was treated with atropine. Following intubation and charcoal administration, she was admitted to the ICU where her hemodynamic parameters improved. All toxicology screens were negative; the plant was later identified as *Pieris japonica*. Our 2nd case is a 76 year-old-male who presented with vomiting, bradycardia, and systolic blood pressure of 70 mm Hg. The patient reported symptoms of vomiting, blurred vision and a seizure one hour after ingesting tea made from *Pieris japonica*. His toxicology work-up was negative for co-ingestants; both patients were successfully treated and sent home. Grayanotoxins (GTX) exert their cardiac toxic effects by increasing membrane permeability in sodium-dependent excitable membranes, producing a state of depolarization. Similar effects occur in the skeletal and central nervous system (3). GTX may also produce cardiotoxic effects on muscarinic M2 receptors which mediate vagal effects (4). Of the 18 forms of GTX, GTX-1 occurs in *Ericacae* family members and contains diterpenes responsible for poisoning. *Conclusion:* Grayanotoxin poisoning is extremely rare in the United States; we report a case series of cardiovascular instability from ingestion of Pieris japonica. *References:* 1. Yilmaz O, Eser M, Sahiner A, *et al.* Hypotension, bradycardia and syncope caused by honey poisoning. *Resuscitation* 2006; **68**: 405–8. 2. Ozhan H, Akdemir R, Yazici M, *et al*. Cardiac emergencies caused by honey ingestion: a single centre experience. *Emer Med J* 2004; **21**: 742–4. 3. Kimura T, Yamaoka K, Kinoshita E, *et al*. Novel site on sodium channel α-subunit responsible for the differential sensitivity of grayanotoxin in skeletal and cardiac muscle. *Molec Pharm* 2001; **60**: 865–72. 4. Onat FY, Yegen BC, Lawrence R. Mad honey poisoning in man and rat. *Rev Envir Hlth* 1991; **9**: 3–9.

266. Successful Treatment in Monkshood (Aconitine) Intoxication with Magnesium Sulfate

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Objective: To describe a case of severe deliberate aconite intoxication in which cardiotoxicity responded to magnesium sulfate. *Case report:* A 77-year-old man was admitted to ICU for severe muscarinic syndrome associated with hypotension, bradycardia, wheezing, sweating, nausea and vomiting, only 20 minutes after the intentional ingestion of 5 grams of crushed roots from *Aconitum napellus*. The patient complained of numbness, dizziness and ascending paresthesia. Important features of the ECG consisted of ventricular bigeminism, then severe bradycardia (20 bpm), long QTc (524 msec) and polymorphic ventricular extrasystoles. Saline infusion, atropine (3 mg loading dose, and 0.5 mg/6 hours during 48 hours) and magnesium sulfate (6 g loading dose, and 3 g/24 hours for 48 hours) were administered to treat hypotension, muscarinic signs and arrhythmias, respectively. Plasma magnesium levels remained below 6 mmol/L. Symptoms rapidly disappeared and return to regular sinus rhythm (86 bpm) was observed. Further evolution was uneventful. *Discussion:* Aconitine is the main toxic alkaloid in monkshood. LD_{50} is about 5 mg which represents 2 to 4 grams of crushed roots. Cardiac and neurological toxicities, as well as increased vagal tone, are due to activation of voltage-dependent sodium channels. Cardiotoxicity consists of early and delayed afterdepolarisation. Indeed, during late repolarisation (phase 4 of the action potential) of the Purkinje cells, aconitine-attached Na channels open, allowing sodium influx and depolarization ('delayed afterdepolarization'). This results in increased automaticity (premature ventricular beats). During late phase 2 or early phase 3 (repolarisation), aconitine-induced Na accumulation induces depolarization ('early afterdepolarisation'). This results in long QT interval with a risk of torsade de pointes. Anti-arrhythmic agents have inconstant results in aconite intoxication. Especially amiodarone could promote torsade. The effects of magnesium sulfate on aconitine-induced ventricular arrhythmias have been studied in animal models (1). In contrast to other anti-arrhythmic agents, it abolishes early afterdepolarisation and shortens the prolonged duration of the Purkinje cell action potential. *Conclusion:* To our knowledge, this is the first clinical report of aconitine-induced polymorphic ventricular arrhythmias successfully treated with magnesium sulfate. *Reference:* Adaniya H, Hayami H, Hiraoka M, Sawanobori T. Effects of magnesium on polymorphic ventricular tachycardias induced by aconitine. *J Cardiovasc Pharmacol*. 1994; **24**: 721–9.

267. Systemic Symptoms and Rhabdomyolysis After a *Heteropneustes fossilis* Sting

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Introduction: In recent years the number of exotic fish in private aquarium settings increased. *Heteropneustes fossilis* (Stinging catfish) belongs to the *Heteropneustidae* family and is found in Asian waters. The spines (containing a heat unstable toxin) cause a sting which produces an initial intense pain, followed by an intense inflammatory reaction that can include erythema, swelling, local hemorrhage, tissue necrosis. Systemic reactions are rare but can include nausea, vomiting, weakness, hypotension, syncope, and respiratory distress (1). *Case report:* We report the case of 27 year old patient admitted 40 minutes after he was stung by a *Heteropneustes fossilis* fish spine when he tried moving it into another aquarium. Shortly after the sting he presented with excruciating pain, shortness of breathing, nausea and vomiting, fainting sensation, dizziness. On admission: altered general status, conscious but confused, bradylalia, somnolence, intense pain in the right hand, spontaneous breathing, some sibilant rales on lung auscultation, BP=80/30 mmHg, 112 beats/min. Local examination: puncture wound radial border of finger 5 right hand, with perilesional pallor 0.8/1 cm, erythema of dorsal area, lymphangitis and swelling to the right elbow. The laboratory tests showed elevated values for CK, CK-Mb, LDH and liver enzymes, positive urine myoglobin. The patient received intensive care therapy: aggressive volume replacement, corticosteroids, urine alkalinisation, osmotic diuretics, potent analgesics, antibiotics and tetanus antitoxin. After stabilisation mental status improved, BP normalized, no rales on lung auscultation. The patient underwent a plastic surgery intervention with excision of necrotic tissue, large debridement, drainage. The laboratory parameters showed an increase of muscular enzymes in the next 2 days, normalization in day 7; no signs of renal dysfunction or infection appeared. The wound healed in 10 days. *Conclusion:* In this case, systemic and local symptoms were due to a fish toxin, with neurotoxic and anaphylactoid effects. The rapid swelling of the hand and probably a myotoxic effect of the venom produced rhabdomyolysis. Because of the aggressive action of fish venom it is important to educate the general public about poisonous fish or other animals. *Reference:* 1. Auerback PS. Envenomation by aquatic vertebrates. Wilderness Medicine, Mosby, 2001; 1488–1506.

268. Functional Sequelae Persisting for Months Following Minor to Moderate Local Symptoms After *Vipera berus* Envenomation

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Objective: Vipera berus is the only venomous snake in Norway. Symptoms and signs after bites may be of both local and systemic character. Late sequelae have been reported (1). We present a case with a mild to moderate acute reaction, followed by unusually lengthy convalescence. *Case report:* A 32-year-old woman, with a history of lung emboli and possible coagulopathy 7 years previously, was bitten on her fourth toe by *Vipera berus*. In the course of the first 3 hours, a number of well-known, mild symptoms arose: minor burning sensation, pale red colouring at the bite site, nausea, shiver and pallor. Five hours later there was slight swelling and bruises from the bitten toe up to the ankle. For two days she administered antihistamine and prednisolone. Pain at the lesion site immobilized her. Within three days the bruises affected the entire leg, and the swelling in the foot, although diminished, remained. The fifth day, she menstruated with abnormally strong bleeding. This, combined with the bruises, made her travel to the hospital, and the Poisons Information Centre was contacted. The examination concluded with minor local reaction, and the haematological analysis revealed no abnormalities. Even so, she remained dysfunctional, and had to rely on crutches for 7 weeks. When coming back to the hospital after two weeks, she was still unable to stand on her foot, the leg remaining slightly discoloured and cold. She used NSAIDs for the pain. Circulation, creatine kinase and haematological blood tests were normal. Even after 12 weeks, some discolouration remained, and she could only walk for 30 minutes. *Conclusion:* Initial symptoms were relatively mild, with local development over the next few days, including restriction of patient's mobility. Considering the acute course of envenomation, we find this long convalescence unexpected after a *Vipera berus* bite. *Reference:* 1. Persson H. Clinical toxicology of snakebite in Europe. In: Meier J, White J, eds. Handbook of clinical toxicology of animal venoms and poisons. 1th ed. Florida, USA: CRC press, 1995:413–32.

269. Enquiries Concerning *Daphne mezereum* Exposures to the Finnish PIC

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Objective: All parts of the wild growing plant *Daphne mezereum* except the fruit pulp contain toxins and the plant is considered highly toxic. The yellow berry of *D. mezereum* can be confused with the berry of *Hippophae rhamnoides*, sea buckthorn which is considered a delicacy and healthy. Data on the human toxicity of *D. mezereum* is sparse and old. The aim of the study was to investigate if any given amount of berries can cause systemic symptoms in addition to localized symptoms. *Methods:* A prospective study of calls concerning *D. mezereum* exposures during spring-summer 2006 and 2007. The callers were asked for their consent to a structured telephone interview, which was made a few days later. *Results:* 37 calls concerning *D. mezereum* exposures were received during the study period, 22 interviews were made and were included in the study. 14 patients were under 6 years of age. The number of berries eaten was unknown in 6 cases. Biting of the stem of *D. mezereum* caused intense burning of the mouth, tongue and throat in 3 cases developing in 5–30 minutes after the exposure, progressive and resolving in 5–12 hours. Ingestion of 1–3 berries caused bad taste and burning of the mouth, tongue and throat, diarrhoea and a few small blisters around the mouth. Symptoms developed immediately or about 10–15 minutes after exposure. Symptoms resolved in about 1 hour, but oral irritation lasted over 1 hour if the plant had been bitten. *Conclusion: D. mezereum* exposures caused intense local reactions but no systemic effects in this small number of subjects, but more data is needed to determine the risk of systemic effects.

270. Plant Poisonings: The Tygerberg Experience

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Objective: The objective was to evaluate the spectrum of potentially poisonous plant exposures dealt with by the Tygerberg Poison Information Centre. *Methods:* Telephonic plant-related consultations dealt with by the Centre from 1993–2005 were analyzed. *Results:* During the 13 year study period, the Centre dealt with 39,813 consultations of exposures to poisonous substances, of which 1012 (3%) were plant-related. 800 of these were patient-related consultations: 768 (96%) in humans and 32 (4%) in animals. The breakdown of human exposures was: 544 (68%) children, 149 (19%) adults and 75 (9%) adolescents. All exposures in children were accidental compared to 11% in adolescents and 79% in adults. The most commonly encountered plant exposures were: calcium-oxalate crystal containing plants e.g. *Dieffenbachia amoena*

(dumb cane), *Alocasia macrorrhiza* (elephant's ear) and *Monstera deliciosa* (delicious monster) (132: 17%), syringa tree berries (*Melia azedarach*) (117: 15%), *Datura stramonium* (61: 8%), Oleander (47: 6%), and *Brugmansia species* (37: 5%). Plant dermatitis cases amounted to 71 (9%). Plants in this category included several *Euphorbia, Smodingium* and *Peucedanum* species. 40% of exposures were due to miscellaneous plant species. Four deaths were recorded. With the exception of plants containing atropine-like alkaloids, the incidence of systemic effects after plant ingestions was relatively low (13%). It is important to note that most exposures in adolescents were intentional, and most of these were due to plants containing atropine-like alkaloids (*Datura stramonium* and several *Brugmansia species*). 90% of adolescents presented with systemic symptoms and signs of atropine poisoning. The most common plant ingestions in children were the leaves of plants containing calcium-oxalate crystals and syringa tree berries. Symptoms and signs of toxicity were highest after ingestion of plants containing calcium-oxalate crystals. *Conclusion:* Compared to drug overdose and exposures to household and agricultural poisonous chemicals, the incidence of plant exposures and/or poisonings was low. The amount of plant material ingested by children is usually small, thus the incidence of serious systemic toxicity in this age group was low. Plants containing atropine-like alkaloids were often associated with systemic toxicity. This type of poisoning is prominent in adolescents. Plant dermatitis was a prominent entity in adult exposures.

271. Mass Intoxication with *Datura innoxia*

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Objective: Anticholinergic plants contain a variety of alkaloids that are responsible for poisonings when these plants are consumed (1). The aim of this study was the differential diagnosis of seven intoxicated individuals in the framework of the emergency toxicological analysis. *Case report:* Seven individuals, four women and three men, were admitted to the hospital with anticholinergic symptoms and signs, such as hallucinations, aggression, agitation, amnesia, mydriasis, dry skin, tachycardia, hyperthermia, hypotension, collapse, coma and respiratory depression (2), in two different hospitals of Athens. All patients' symptoms occurred after consumption of boiled blites (vegetables consumed as salad) in their meals. They had bought the blites from a known food market of the town. The investigation of the case revealed that among the blites, there was a dangerous kind of herb, *Datura innoxia*, which seems like blite and was accidentally collected with edible blites. Urine and plasma samples of the seven patients, as well as samples of raw and cooked vegetables, were analysed in the laboratory. Scopolamine and atropine were confirmed by gas chromatography-mass spectrometry in all samples of urine and vegetables, while in the plasma samples neither atropine nor scopolamine was detected, due to the delay in the sample collection. The urine samples of all patients contained atropine in concentration between 67.1 to 532.2 ng/ml, while the concentration of atropine was the same in the raw and cooked vegetables (0.8 ng/mg). All patients recovered completely, although some individuals required mechanical ventilation. *Conclusion:* The investigation and the presentation of this case contribute not only to the differential diagnosis of the mass intoxication with *Datura innoxia*, but also points out the dangers of the similarity between blites and kinds of *Datura*, which are grown in Greece. Moreover, toxicities of herbal origin should always be considered and queried when a patient presents with anticholinergic symptoms. *References:* 1. Pekdemir M, Yanturali S, Akay S, *et al,* Acute anticholinergic syndrome due to Datura innoxia Miller mixed with lime tea leaves. *Vet Hum Toxicol* 2004; **46**: 176–7. 2. Balíkova M, Collective poisoning with hallucinogenous herbal tea. *Forensic Sci Int* 2002; **128**: 50–52.

272. Cell-Phone Camera and Computer Communication can Facilitate Remote Identification of Poisonous Plants

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Objective: Rapid identification of uncommon poisonous plants and animals is a challenge for poison center consultants. Cell-phone camera and computer communication can be used for rapid remote identification of the culprit by on-line transmission of pictures. In the present case report, this tool enabled rapid identification of a rare poisonous plant and assisted in rational patient care. *Case report:* A healthy 12 year old female was admitted to the emergency department (ED) 7 hours after ingesting two fruits of a garden plant. One hour after ingestion, she complained of abdominal pain followed by profuse vomiting and loose stool. Physical examination revealed a fully conscious and oriented adolescent with pulse 92/minute regular, blood pressure 132/64 mmHg, respiratory rate 24/minute, temperature 36.1ºC and epigastric tenderness. No biochemical or hematological abnormalities were detected. When the plant was brought in, description provided by the ED physician to our Poison Center suggested it to be *Thevetia peruviana*. However, when the ED physician compared the plant to a picture of *Thevetia peruviana* e-mailed to him by the Poison Center, the two did not match. Next, the ED physician took pictures of the plant with his cell-phone camera and e-mailed them to the Poison Center. The pictures were forwarded to a botanical consultant who identified the plant as *Jatropha multifida*. The electronic identification process lasted about 10 minutes. The patient was treated supportively and recovered completely the next day. Follow up at 4 months revealed no sequelae. *Conclusion: Jatropha multifida* is a rare cause of plant poisoning. Its toxicity is mainly due to curcin, a toxalbumin. Unless cell-phone camera and computer communication had been used, the working diagnosis in this patient could have been cardiac glycosides poisoning. The inability to view the offending agent is a major limitation in poison center work. On line transmission of pictures to the poison center and if needed, to zoological or botanical consultants is a simple, rapid and useful identification tool. Thus, correct identification can easily be made and rational treatment provided.

273. Intoxication with a Cake Containing *Atropa belladonna*

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Objective: Atropa belladonna (Deadly nightshade, Belladonna) is a plant that commonly grows in Europe. Its black berries, the size of cherries, ripen throughout August to October. Toxicity is mainly due to anticholinergic (atropine-like) effects affecting both autonomic nerve endings and the brain. Common effects include hyperthermia, flushing, dry mucus membranes, mydriasis, tachycardia, decreased gastrointestinal motility, urinary retention, delirium, hallucinations, and mental status depression. We report a case series associated with *Atropa belladonna* ingestion. *Case series:* Five members of a family: mother (aged 59), father (aged 62), grandmother (aged 80) and 2 sons (aged 36 and 31) ate a blueberry cake. The father, having consumed alcohol, picked local berries and baked a cake. It transpired the cake contained *Atropa belladonna* (berries collected). Symptoms of intoxication appeared within 2 to 12 hours after ingestion. The mother developed vertigo, slurred speech, dry mucus membranes, visual hallucinations, transient paranoid delusions and weakness in lover extremities. She was admitted to psychiatric ward. Both sons developed visual symptoms (mydriasis and blurred vision) and dry mouth. Both grandmother and father presented to ICU with unconsciousness, convulsions and mydriasis. Moreover the father had transient hypertension (BP 180/100 mmHg), sinus tachycardia (120/min), dysrhythmias and hyperthermia. The grandmother received three doses of antidote Anticholium (2 mg of physostigmine salicylate) over 36 hours. After that cognition was restored, however decreased gastrointestinal motility and mild elevation of liver enzymes were observed. Both grandmother and father were transferred to a standard department on the 4th day. The mother was discharged from hospital on the 2nd day. All members of the family except grandmother were treated symptomatically. Symptoms of intoxication disappeared within 12 to 48 hours. Father and grandmother who suffered the most which could be a result of 1) amount of ingested cake 2) grandmother's age 3) father's alcohol consumption. *Conclusion:* The clinical features in this case series were as described in the literature. Although this intoxication occurs rarely, it is a necessary consideration in the Czech Republic during summer or early autumn when these fruits are ripening, due to a popular Czech pastime of picking forest berries. *Acknowledgement:* MSM 0021620807.

274. Use of Technology to Guide Treatment of a Patient with an Unknown Botanical Ingestion

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Objective: Consequential and inconsequential botanical ingestions can present with similar signs and symptoms, thus creating a diagnostic challenge. Use of the internet and other information technology has been used for the quick dissemination of information and assistance in multiple disease processes. We report a pokeweed (*Phytolacca americana*) ingestion in which the plant was identified through a digital photograph transmitted through electronic mail to a regional poison control center. *Case report:* A 58 year old man presented to the emergency department with the sudden onset of vomiting, diarrhea, crampy abdominal pain, and lacrimation after ingestion of an unknown plant found in his yard. Onset of symptoms began 3 hours after ingestion. Vital signs were: blood pressure, 110/70 mmHg; respirations, 22 breaths per minute; temperature, 37° C; and a room air oxygen saturation, 99%. The patient had intermittent episodes of bradycardia in the 30s lasting less than 1 minute each, which were followed by vomiting. The patient's baseline pulse in the emergency department was 60 bpm. Physical examination revealed an uncomfortable, diaphoretic, persistently vomiting man with lacrimation. His pupils measured 1–2 mm and were sluggishly reactive. Lungs were clear; abdominal exam revealed hyperactive bowel sounds without guarding or rebound. The patient was treated with intravenous fluids, activated charcoal 1 gram/kg, and parenteral metoclopramide which resulted in some relief. Despite this, the patient continued to have intermittent episodes of bradycardia with recurrent vomiting. An electrocardiogram revealed a sinus rhythm at a rate of 60 bpm with a first degree AV block. Serum digoxin level was <0.3 ng/mL. The patient's complete blood count and chemistries were only significant for a serum potassium of 3.1 mmol/L. The patient's wife was able to take a digital picture of the plant and transmit it to our regional poison center. The plant was quickly identified as *Phytolacca americana*. The patient was observed in the hospital for 48 hours without sequelae. Because of the digital image, no unnecessary organophosphate antidote was administered. *Conclusion:* This case highlights the utility of recent advances in information technology that can guide the management of patients with botanical ingestions in which plant identification is problematic via phone.

275. Anticholinergic Intoxication Due to *Mandragora officinarum*

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Objective: A large number of plants, seeds and berries are used for medicinal, psychotropic or aphrodisiac purposes. In this paper, a case of acute intoxication with *Mandragora officinarum* is presented. *Mandragora officinarum*, a solanaceous plant which contains tropane alkaloids with anticholinergic properties, is widespread in the countryside of Greece, even today. This plant dates back thousand of years and it is traditionally known as an aphrodisiac and closely associated with witchcraft (1,2). *Case report:* A 35-year man was admitted to the hospital with severe anticholinergic symptoms after the ingestion of approximately ten berries of the pharmaceutical plant *Mandragora officinarum*. The diagnosis of this poisoning was based on the clinical signs and symptoms, in addition to a detailed history, during which the patient revealed that he had consumed these berries in order to enhance his homosexual activities. The patient was treated with gastric lavage and activated charcoal. Physostigmine was administered against agitation and severe anticholinergic symptoms. He was hospitalized for 4 days and he recovered without obvious adverse systemic effects. The blood of the patient and the berries were sent for toxicological analysis. The analysis of these berries with GC-MS revealed the presence of tropane alkaloids, hyoscyamine and scopolamine, while the blood sample was negative. This negative result probably was due to the fact that the time elapsed between the consumption of the berries and the blood collection was long, additionally a urine sample was not collected. *Conclusions:* History is extremely important for the investigation of a poisoning with anticholinergic symptoms. In intoxication cases where herbal products have been consumed, it is an absolute necessity that the responsible products are sent to the laboratory for further investigation. A thorough investigation of these cases always contributes significantly to the differential diagnosis of poisonings. *References:* 1. Piccillo G, Miele L, *et al*. Anticholinergic syndrome due to "Devil's herb": when risks come from the ancient time. *Int J Clin Pract* 2006; **60**: 492–494. 2. Piccillo G, Giovita A, *et al*. Six clinical cases of Mandragora autumnalis poisoning: diagnosis and treatment. *Eur J Emerg Med* 2002; **9**: 342–347.

276. Incidence of False Positive 3,4-Methylenedioxymethamphetamine Results in the Syva Emit II Urine Drug Screens

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Objective: We sought to determine the frequency of false positive 3–4 methylenedioxymethamphetamine (MDMA) results in urine drug screens associated with therapeutic use of bupropion and similar drugs. *Methods:* We conducted an IRB approved, retrospective chart review. We searched the database of all urine drug screens performed at our hospital from 1 August 2007 through 5 September 2007. All urine samples were screened using the Syva Emit II Plus reagents on the Dade Behring Dimension analyzer. All positive screens underwent confirmation by gas chromatography using the Hewlett Packard 5890 with an SPB 35 column. We reviewed the medical records of all patients with a positive MDMA result, regardless of whether the results were confirmed or not confirmed by GC. The prescription use of selected drugs including bupropion, other antidepressants, stimulants, antipsychotics, and antihypertensives was recorded as evidence of polysubstance abuse (at least one other positive test for drugs of abuse or ethanol or a documented diagnosis). *Results:* Of 712 urine drug screens performed, 83 (12%) had positive MDMA results. Of these 27 (33%) were confirmed by GC and 56 (67%) failed to confirm. Among the 27 confirmed positives, records reflected polysubstance use in 4 patients (15%), prescription amphetamines in 0 (0%), bupropion in 7 (26%), other antidepressants in 4 (15%), antipsychotics in 3 (11%) and labetalol in 0 (0%). Among the 56 screen positive results that failed to confirm, 9 patients (16%) had documented prescription use of bupropion, 27 (48%) had other antidepressants, 16 (29%) had antipsychotic, 8 (14%) had labetalol, and 2 (8%) had prescription amphetamine. Twenty-two (39%) had polysubstance abuse. *Conclusions:* Bupropion, polysubstance abuse, other antidepressants, antipsychotics, and labetalol are common causes of false positive screening results.

277. Incidence of False Positive Amphetamine Results Due to Bupropion in the Syva Emit II Urine Drug Screens

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Objective: Three case reports false positive amphetamine results in urine screens for drugs of abuse associated with bupropion (1,2,3). The frequency of false positive amphetamine results due to bupropion is unknown. We sought to determine the frequency of false positive amphetamine results in urine drug screens associated with therapeutic use of bupropion. *Methods:* We conducted an IRB approved, retrospective chart review. We searched the database of all urine drug screens performed at our hospital from 1 January 2006 through 31 July 2007. All urine samples were screened using the Syva Emit II Plus reagents on the Dade Behring Dimension analyzer. All positive screens underwent confirmation by gas chromatography using the Hewlett Packard 5890 with an SPB 35 column. We reviewed the medical records of all patients with a positive amphetamine result, regardless of whether the results were confirmed or not confirmed by GC. The prescription use of selected drugs including bupropion, other antidepressants, stimulants, antipsychotics, and antihypertensives was recorded as evidence of polysubstance abuse (at least one other positive test for drugs of abuse or ethanol or a documented diagnosis). *Results:* Of 10,011 urine drug screens performed, 362 (3.6%) had positive amphetamine results. Of these 234 (65%) were confirmed by GC and 128 (35%) failed to confirm. Among the 234 confirmed positives, records reflected polysubstance use in 55 patients (24%), prescription amphetamines in 50 (21%), bupropion in 3 (1.3%), other antidepressants in 38 (16%), and antipsychotics in 17 (8%). Among the 128 screen positive results that failed to confirm, 53 patients (41%) had documented prescription use of bupropion, 17 (13%) had other antidepressants, 14 (7%) had antipsychotic, and 9 (7%) had labetalol. None had polysubstance abuse. *Conclusions:* Bupropion is the most common cause of false positive screening results for amphetamine. *References:* 1. Weintraub D, Linder MW. Amphetamine positive toxicology screen secondary to bupropion. *Depress Anxiety* 2000; **12**: 53–54. 2. Nixon AL, Long WH, Puopolo PR, *et al*. Bupropion metabolites produce false-positive urine amphetamine results (letter). *Clin Chem* 1995; **41**: 955–956. 3. Vidal C, Skripuletz T. Bupropion interference with immunoassays for amphetamines and LSD. *Ther Drug Monit* 2007; **29**: 373–375.

278. Falsely Elevated Creatinine and Methanol Following Ingestion of Nitromethane

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Case report: A 15 month old male ingested an unknown amount of Byron remote control car racing fuel which had been decanted into a cup with a straw for use with a model race car. The fuel contains a proprietary mixture of oil, methanol and nitromethane. His parents immediately took him to a local hospital. His initial blood chemistry results included sodium 137 mEq/L, potassium 4.7 mEq/L, chloride 107 mEq/L, bicarbonate 23.3 mmol/L, BUN 19 mg/dL (6.8 mmol/L), creatinine 3.16 mg/dL (280 micromol/L), glucose 92 mg/dL (5.1 mmol/L), measured osmolality 276 mEq/kg H_2O, ethanol < 4 mg/dL (<0.9 mmol/L), methanol 33 mg/dL (10.6 mmol/L). His venous blood gases were pH 7.33, pCO_2 44 mmHg, pO_2 43 mmHg. He received fomepizole 177 mg IV before transfer to our hospital for suspected acute methanol ingestion with renal failure. He was asymptomatic upon arrival. Repeat labs 9 hours later showed: sodium 140 mEq/L, potassium 5.3 mEq/L, chloride 109 mEq/L, bicarbonate 17 mmol/L, BUN 13 mg/dL (6.1 mmol/L), creatinine 0.2 mg/dL (18 micromol/L), glucose 97 mg/dL (5.4 mmol/L), osmolality 290 mOsm/kg H_2O, methanol undetectable. Arterial blood gases were pH 7.35, pCO_2 40, pO_2 115 (ABG). The patient remained asymptomatic during 24 hours of observation. We obtained the remaining original blood samples for repeat analysis at our hospital. The creatinine was 0.7 mg/dL (62 micromol/L) by the modified Trinder reaction. Methanol was below the limit of detection. Nitromethane has previously been shown to interfere with creatinine measurement by the widely used Jaffe reaction (1,2). However, the modified Trinder reaction does not suffer from the same interference. *Conclusion:* This case exhibits another occurrence of false elevation of the creatinine due to nitromethane interference with the assay. We hypothesize that nitromethane also results in a false positive detection of methanol due to similar molecular size, weight, and polarity. *References:* 1. Mullins M, Hammett-Stabler C. Intoxication with Nitromethane-Containing Fuels: Don't Be "Fueled" by the Creatinine. *J Toxicol Clin Toxicol* 1998; **36**: 315–320. 2. Cook MD, Clark RF. Creatinine elevation with nitromethane exposure: a marker of potential methanol toxicity. *J Emerg Med* 2007; **33**: 249–253.

279. Determination of Methadone and its Metabolite, 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) in Umbilical Cord Blood

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Objective: The aim of this study was the determination of methadone and its metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) in plasma samples obtained from venous and arterial umbilical cord blood, since methadone maintenance is the treatment of choice for rehabilitation of opioid addiction in cases of pregnant women. Significant negative consequences have been reported in methadone-exposed newborns, from which 60–90% develop neonatal abstinence syndrome (NAS), while a constellation of symptoms frequently require prolonged hospitalization and treatment (1). *Method:* A validated gas chromatography-mass spectrometric method was used for the determination of methadone and EDDP in plasma samples of venous and arterial umbilical cord blood. The procedure combines protein precipitation and solid phase extraction (2), with minimal matrix effect, leading to absolute recovery of methadone and EDDP higher than 95.6%. This assay uses methadone-d9 as internal standard for the determination of methadone, and EDDP-d3 for the determination of EDDP. *Results:* This method has been used recently in cases like the one presented in this report. Plasma concentrations of methadone of venous and arterial umbilical cord blood samples were 35.7 and 28.7 ng/ml, respectively, while the corresponding concentrations of EDDP were 9.0 and 8.0 ng/ml. The concentrations of methadone and EDDP of the relative plasma sample of the mother were 85.3 and 15.0 ng/ml, respectively. *Conclusion:* Measuring levels of methadone and its metabolite EDDP in plasma of venous and arterial umbilical cord blood might enlighten the methadone-exposure of infants, whose mothers have been under methadone treatment. Methadone and EDDP concentrations in methadone-maintained pregnancies may affect an altered response in fetal central nervous system and changes in fetal behavior induced by methadone. *References:* 1. Jansson L, Velez M, Harrow C. Methadone maintenance and lactation: Review of the literature and current management guidelines. *J Hum Lact* 2004; **20**: 62–71, 2. Cooper G, Oliver J. Improved Solid-Phase Extraction of methadone and its two major metabolites from whole blood. *J Anal Toxicol* 1998; **22**: 389–392.

280. Correlation of Serum Glycolate with Falsely Elevated Lactate in Severe Ethylene Glycol Poisoning

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Objective: In the setting of ethylene glycol (EG) poisoning a falsely-elevated serum lactate is presumed to be an assay cross-reaction with glycolate. We aimed to correlate lactate and glycolate serum concentrations in a case of severe EG poisoning. *Case report:* A 78 year-old man was found unresponsive at home. He was endotracheally intubated by EMS and taken to the ED. His wife reported finding an empty bottle of automotive antifreeze nearby. Initial laboratories revealed: bicarbonate, 12 mmol/L; BUN, 4.3 mmol/L; creatinine, 141.4 mmol/L; anion gap, 25 mmol/L; lactate, 15 mmol/L. The initial serum EG concentration was 20.05 mmol/L. During the hospitalization, he underwent three hemodialyses with concurrent fomepizole therapy and he survived to hospital discharge without permanent sequelae. *Results:* Serial EG (gas chromatography), glycolate (derivatized to methyl glycolate, analysis by gas chromatography), and lactate (spectrophotometry, Quest Diagnostics) concentrations are depicted in the Table. The correlation coefficient (Pearson's R) between lactate and glycolate was 0.984 and was statistically significant ($p<0.01$). The mean lactate:glycolate conversion factor was 2.58 ± 0.95. *Conclusions:* In this patient, a significant correlation was found between lactate and glycolate serum concentrations. Since there was no reason to suspect a truly elevated lactate, our assumption of a falsely elevated lactate was confirmed by the presence of serum glycolate. We demonstrate the correlation between falsely-elevated lactate and serum glycolate concentrations in this case of severe EG poisoning. This finding should be confirmed in other patients.

Table: Serial serum concentrations of EG, lactate, and glycolate

Time after presentation:	Initial	15.5 hr	27.5 hr	30 hr	32 hr
EG (mmol/L)	20.05	5.66	4.58	5.05	3.58
Lactate (mmol/L)	15.0	12.5	2.5	2.0	1.0
Glycolate (mmol/L)	9.00	5.69	0.96	0.88	0.24

281. Rapid Diagnosis of Metabolic Acidosis: Improving Bedside Detection of Urine Beta-Hydroxybutyrate

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Objective: Rapid identification of the etiology of metabolic acidosis is essential. While the urine dipstick detects acetoacetate, it detects acetone poorly and cannot identify beta-hydroxybutyrate at all. Unfortunately, alcoholic, starvation, and severe diabetic ketoacidosis may produce beta-hydroxybutyrate in marked excess of acetone and acetoacetate. This inability to detect beta-hydroxybutyrate might delay therapy for ketoacidosis or provoke unnecessary evaluation or empiric treatment of other causes of metabolic acidosis, particularly toxic alcohols. We tested the assertion that commonly available hydrogen peroxide (H_2O_2) would improve beta-hydroxybutyrate detection (1). Since the reaction of beta-hydroxybutyrate to acetoacetate is favored at

pH > 9.5, we also assessed the effectiveness of alkalinization and use of a silver nitrate ($AgNO_3$) catalyst to improve oxidation (2). *Methods:* Control and urine test specimens containing from 0.5–800 mmol/L of acetone, acetoacetate, and beta-hydroxybutyrate were prepared. Urine specimens were either oxidized with H_2O_2 (3%) 1:9 (H_2O_2:urine), alkalinized with KOH (10%), exposed to $AgNO_3$ sticks, or altered with a combination of these methods in a random fashion. Blinded emergency physicians evaluated Multistix placed in the specimens for "ketones." Inter-rater reliability for each reader was assessed using the kappa statistic for nominal variables and the Spearman rank coefficient (rho) for ordinal variables. *Results:* Inter-rater agreement for presence or absence of ketones (kappa = 0.8, $p < 0.001$) and estimation of ketone quantity (rho = 0.9, $p < 0.001$) were excellent. Multistix detected urine acetoacetate appropriately; acetone only at high concentrations ≥ 600 mmol/L; and failed to measure beta-hydroxybutyrate at all concentrations tested. H_2O_2 improved urinary BOHB detection, although not to clinically relevant levels (40 mmol/L). Alkalinization and AgNO3 sticks did not improve beta-hydroxybutyrate detection beyond this threshold. *Conclusion:* Addition of H_2O_2 (3%), alkalinization, or $AgNO_3$ sticks do not improve urine beta-hydroxybutyrate detection to a clinically meaningful amount. Clinicians should use direct methods to detect beta-hydroxybutyrate when suspected. *References:* 1. Stavile KL, Sinert R. Metabolic acidosis. eMedicine. Available at: http://www.emedicine.com/emerg/topic312.htm; accessed 11/5/07. 2. Zaidi SS. A simple chemical method for the oxidation of beta-hydroxybutyrate; application of the method for the estimation of ketone bodies. *Indian J Biochem Biophys* 1993; **30**: 58–61.

282. Alpha-Fetoprotein Ratio as a Prognostic Marker in Acetaminophen-Induced Hepatic Injury

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Objective: Serum concentrations of alpha-fetoprotein (AFP) have been suggested to be of prognostic importance in acute liver failure. The AFP ratio defined as the day 3 AFP concentration divided by that on day 1 may be a more valid prognostic tool than measurement of single AFP concentrations. We report a case of acetaminophen-induced hepatotoxicity, where the AFP ratio was predictive of hepatic recovery even before other liver function tests began to improve. *Case report:* A 28 year-old female with a history of depression presented after an overdose of five to ten grams of acetaminophen. The time of ingestion was approximately 16 hours prior to her presentation. She was noted to have an acetaminophen level of 10 µg/mL with an ALT of 784 IU/L and AST of 505 IU/L with an initial INR of 1.1. Patient was started on acetylcysteine for her acetaminophen-induced hepatic injury. While in the hospital, the patient's ALT peaked at 23,275 IU/L and AST peaked at 12,274 IU/L on day 3. Patient's INR also peaked at 3.6 on day 3 and then trended down. Her serum alpha-fetoprotein on day 1 was 2 µg/L and her level on day 3 was 22 µg/L with a ratio of 11. Patient had extensive hepatic work-up for other possible causes of liver failure, which were are all negative. Patient improved on acetylcysteine only and was discharged to psychiatric care. *Discussion:* Increase in AFP is a sign of hepatic regeneration following acute liver injury with extensive necrosis. Multiple studies, both on acetaminophen and non-acetaminophen induced hepatic failure have shown that elevations in AFP is associated with a favorable prognosis. *Conclusion:* There have been many prognostic models proposed to predict the outcome of patient who present with acute hepatic failure. An increase in AFP is associated with a favorable outcome in patients with acetaminophen-induced liver injury. Use of the AFP ratio may be useful as a supplement to existing prognostic criteria, and might increase predictive accuracy.

283. Vitamin K–Dependent Factor Activity as Surrogate Marker of Brodifacoum Poisoning

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Background: Ingestion of long-acting anticoagulant rodenticides such as brodifacoum can lead to prolonged and life-threatening coagulopathy Anticoagulant rodenticides inhibit vitamin K (1)-2,3 epoxide reductase and thus the synthesis of vitamin K and clotting factors II, VII, IX and X. Few institutions have timely access to direct measurement of anticoagulant rodenticide levels. As a result, diagnosis sometimes can be delayed and therapy initiated late. We report a case of brodifacoum poisoning where early diagnosis was made based on factor activity. *Case report:* A 59-year old male was admitted with abdominal pain, hematuria and prolonged anticoagulation. There was no history of liver disease, ingestion of drugs or 'rat poison'. Physical examination was unremarkable. On admission PT was greater than 100, INR was greater than 10 and PTT was greater than 150. Hemoglobin was 5.9 and hematocrit was 17.8. Mixing studies were normal and ruled out presence of inhibitors. The patient was treated with fresh frozen plasma, packed red blood cells and vitamin K. Factor II (0.36 U/mL range 0.70–1.50), Factor IX (0.29 U/mL; range 0.60–1.50), Factor VII (0.13 U/mL; range 0.60–1.60) and Factor X (0.43 U/mL; range 0.70–1.50) levels were low. Factor V (1.19 U/mL; range 0.70–1.50) level was normal. This pattern of factor activity was suggestive of Vitamin K inhibition secondary to anticoagulant rodenticides and the patient was continued on large doses of Vitamin K. Comprehensive drug screen was negative for warfarin and brodifacoum levels eventually came back three weeks later at 50 mcg/ml, confirming the initial diagnosis. *Discussion:* Measuring coagulation factor activity will reveal deficient activity in the vitamin K Factors (II, VII, IX, X), while Factor V activity will be normal. *Conclusion:* Brodifacoum poisoning can be identified by analysis of vitamin K–dependent coagulation factor activity and assessment of serum levels. The turn-around time for serum level is several days to weeks, making early and timely diagnosis difficult. Factor activity assays is readily available in-house and enables rapid diagnosis of suspected long-acting anticoagulant rodenticide toxicity.

284. Anion Gap Metabolic Acidosis with Normal Lactate Following Sulfuric Acid Ingestion

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Introduction: The etiology of severe anion gap acidosis following acid ingestion is unclear. The etiology of the acidosis is believed to be related to hyperlactinemia secondary to gastrointestinal tract ischemia. However, there is oral absorption and it may be due to the acid ingestion itself. We report a case of anion gap metabolic acidosis with normal lactate following sulfuric acid ingestion. *Case report:* A 57-year-old male with history of depression presented to the hospital 18 hours following the ingestion of "half a glass" of battery sulfuric acid in a suicide attempt. His vitals were: heart rate, 86 beats per minute; blood pressure, 111/81 mm Hg; and respiratory rate, 40 breaths per minute, and SaO_2 (RA) 100%. Physical examination was otherwise unremarkable without any visible burns to mucus membranes or oropharynx. During his evaluation, he developed hematemesis and mild epigastric pain. Arterial blood gas (ABG) results were: pH 7.016 (7.38- 7.46), PCO_2 19.5 mm Hg (32–46), pO_2 129.1 mmHg (74–108), and HCO_3 4.9 mmol/L 9 (21–29). Initial serum electrolytes were Na^+: 137 mEq/L (136–146), K^+: 5.4 mEq/L (3.4–5.4), Cl^-: 108 mEq/L, BUN: 21 mg/dL (8–23), and Cr: 1.3 mg/dL. The measured anion gap was 28 (<12). The patient was administered two ampoules of sodium bicarbonate IV and started on a bicarbonate infusion. His repeat pH was 7.21, serum bicarbonate 10 mEq/L (21–31). The arterial lactate was 0.9 mMol/L (0.5–1.6). Concomitant measurement of the anion gap was 21 (<12). Serum salicylate, ethylene glycol, methanol, propylene glycol and isopropanol were undetectable. Urgent endoscopy demonstrated necrosis of the stomach and exploratory laparotomy confirmed ischemic and necrotic stomach, duodenum, and proximal jejunum that were all removed. The patient died 11 days after hospitalization following multiple surgeries. *Discussion:* It has been hypothesized that acidosis following acid ingestion is related to tissue necrosis with resultant lactic acidemia. However, in our patient the anion gap acidosis was associated with a normal lactate and appears to be related to direct absorption of the indirectly measured sulfate anion. *Conclusion:* Ingestion of sulfuric acid leads to anion gap acidosis due to direct absorption of sulfate prior to the development of lactic acidosis. Absence of high lactate in the face of anion gap acidosis should not lead toxicologists to rule out sulfuric acid ingestion.

285. Determination of Anticholinesterase Insecticides in Biological Fluids Using a Gas Chromatographic Method. Applications in Clinical and Forensic Toxicology

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Objective: Anticholinesterase insecticides are widely used in most countries and as a result they are accused of being responsible for numerous acute and even fatal poisonings. Therefore, they must always be considered when investigating relevant forensic and clinical cases (1). The aim of the study was the development of a rapid, specific, sensitive and accurate method for the determination of eleven anticholinesterase insecticides (aldicarb, methomyl, methamidophos, carbofuran, diazinon, terbufos, chlorpyrifos, malathion, methidathion, azinphos, dialifos) in blood. *Method:* A gas–chromatographic method combined with nitrogen-phosphorus detector (NPD) was developed, optimized and validated for the determination of the above pesticides. Only a small amount of blood (0.5 ml) is needed for the isolation of analytes by liquid-liquid extraction with solvent mixture of toluene: chloroform (4:1). The organic phase was evaporated and the residues were reconstituted by addition of hexane, before of the injection (1 µl) onto GC-NPD. Mevinphos was used as internal standard. *Results:* The recoveries were more than 80% for all the analytes. The calibration curves were linear in the corresponding dynamic ranges with correlation coefficient more than 0.996. For all analytes, the limits of detection were found between 1–15 ng/ml with S/N (3:1) and limits of quantitation were 3–50 ng/ml with S/N (10:1). Accuracy and precision were also calculated and were found to be less than 13%. The method was successfully applied to 6 insecticide poisoning cases where the organophosphates were determined. The identification results were confirmed by GC-MS. *Conclusion:* The method is simple, sensitive and specific and measures the levels of the insecticides in question in blood or other biological fluids. Therefore it could contribute to the investigation of both forensic and clinical toxicological cases of accidental and suicidal poisoning. *References:* 1. E. Lacassie, P. Marquet, J-M Gaulier, *et al*. Sensitive and specific multiresidue methods for the determination of pesticides of various classes in clinical and forensic toxicology. *Forensic Sci Int* 2001; **121**: 116–125.

286. Analytical Mix-Up of Lactate and Glycolate in Ethylene Glycol Poisoning

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Objective: Poisoning with ethylene glycol is associated with metabolic acidosis principally attributed to the accumulation of glycolate and oxalate. Some bedside analytical instruments are unable to distinguish between glycolate and lactate due to their molecular resemblance. Consequently, a high "lactate" level may in reality be a sign of glycolate accumulation. Two cases with suspected lactic acidosis are reported where knowledge of this analytical mix-up gave correct diagnosis. *Case 1:* A 20-year-old man presented semiconscious to hospital. He suffered from vomiting and diarrhoea. Arterial blood gas analysis demonstrated pH 6.96, pCO_2 1.7 and BE -33. Blood pressure was 115/85 mmHg, pulse rate 120/min and respiratory rate 37/min. The lactate level in blood was 36 mmol/L and creatinine moderately elevated. Continuous dialysis was initiated to treat a suspected septicaemia-induced lactic acidosis. Eleven hours following admission, a toxicological screen showed an ethylene glycol value of 1 mmol/L. The poison centre was contacted and suggested that the lactate value probably was an artefact and that late stage ethylene glycol poisoning should be considered. A change to haemodialysis was recommended as well as microscopy of the urine. The presence of calcium oxalate crystals (and the patient's history) later confirmed the diagnosis. *Case 2:* A 58-year-old man was admitted unconscious to hospital. Arterial blood gas analysis showed pH 6.91, pCO_2 2.1 and BE -27. Blood glucose and creatinine levels were normal and methanol and ethanol analyses were negative. The lactate concentration was 18 mmol/L and the osmolal gap 58 mosm/kg. The poison centre proposed that the elevated lactate value should be considered false and that treatment for ethylene glycol poisoning should be given. Ethanol infusion and dialysis were started promptly. The diagnosis was later confirmed by a high serum ethylene glycol value. *Conclusion:* Lack of obvious reasons for a clearly elevated lactate should raise suspicion of a false lactate level and possible ethylene glycol ingestion. If lactate additionally is measured by a method able to distinguish between lactate and glycolate and is found to be low, the diagnosis is most probably established. A large difference between two consecutive lactate values is named "lactate gap".

287. Prediction of Severity in Glyphosate Poisoning by Ingestion

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After glyphosate ingestion, patients may present to the Emergency Department (ED) with a wide range of symptoms, not necessarily reflecting the potential severity of the poisoning. *Objective:* To evaluate early indicators of severity and clinical evolution in glyphosate poisoning by ingestion. *Methods:* A retrospective analysis of all cases of glyphosate ingestion referred to the Pavia Poison Center over a period January 2002 - September 2007 was performed; among them, human cases with confirmed poisoning were included in the study. Three potential indicators were evaluated at ED admission for their ability to predict subsequent clinical worsening: ingestion of large amounts (>200 ml) of glyphosate, presence of leukocytosis, increase in pancreatic enzymes. According to the specific criteria proposed in the literature for glyphosate poisoning (1,2), the severity of poisoning (PS) was assessed at admission and during the clinical course, moreover the difference between initial and overall poisoning severity (delta-PS) and the time elapsed between ED evaluation and worsening were calculated. *Results:* Twenty-five patients met the inclusion criteria. At admission, 10 patients were asymptomatic, 8 were graded as mild, 5 as moderate and 2 as severe. Nine patients worsened (delta-PS≥1) after 6.7 ± 6.5 hours (range 0.5–19.7 hours), 2 from asymptomatic to moderate, 3 from mild to moderate, and 4 from moderate to severe; they all had at least one positive indicator of clinical worsening. Among the 16 patients who did not worsen (delta-PS=0), 14 (87.5%) were negative for all the parameters evaluated, whereas 2 cases, both of increased severity since ED presentation, had 2 and 3 positive indicators respectively. *Conclusion:* In glyphosate poisoned patients, ingestion of large amounts, leukocytosis and increased pancreatic enzymes at admission may be useful in predicting subsequent worsening, possibly allowing choice in advance of the proper clinical management. *Reference:* 1. Tominack RL, Yang GY, Tsai WJ, *et al*. Taiwan National Poison Center survey of glyphosate-surfactant herbicide ingestions. *J Toxicol Clin Toxicol* 1991; **29**: 91–109.

288. Carbon Monoxide: Our Experience

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Objective: To describe the characteristics of subjects with acute carbon monoxide (CO) intoxication attended by the emergency department and to assess the presence of a late syndrome. *Methods:* Retrospective study of all cases of CO intoxication presenting during 2004. A follow-up telephone survey at 40 days and 1 year after intoxication was conducted. *Results:* Acute intoxications accounted for 1.2% (1531 cases) of all patients (131,997) attended during the year 2004. A total of 19 cases of CO intoxication were collected, which accounted for 1.25% of all acute intoxications. The mean age was 40 (± 19.2) years. A total of 36.8% were men, and 84.2% were transferred to the emergency room in ambulance with a high flow O_2 mask fitted. Most subjects presented during the winter season (47.4%), and 68.4% between 21:45 p.m. to 7:30 a.m. In 73.7% of cases, more than two people with CO intoxication due to the same cause presented. In 100% of cases oxygen saturation was > 95%. Respiratory rate was > 20 breaths/min in 75% of cases. In 61.6% of cases, heart rate was > 90 beats/min. Causes of CO intoxication included accidents in the household (31.6% fire, 10.5% brazier, 42.1% heater, and 15.8% stove). Symptoms were present in 100% of patients (digestive 42.1%, cardiovascular 21.1%, respiratory 26.3%, cutaneous 10.5%, mild neurological manifestations 84.2%, and behavior disturbances 5.3%). The Glasgow coma scale was 15 in 94.7% of patients. Mydriasis was observed in 10.5% of cases. The mean (SD) pH was 7.4 (0.03), HCO_3 24.5 (2.6) mEq/L, and 20% showed elevated CK levels. The mean COHb was 10%.A total of 21.1% of subjects were discharged from the emergency department within the first 12 h, 63.2% remained in the emergency room for more than 12 h, and 15.8% were transferred to a hyperbaric chamber. These three patients had COHb level > 16%. At 40-day follow-up, 78.9% of patients did not show late syndrome, 10.5% presented headache, 5.3% visual impairment, and 5.3% lethargy. All patients were symptom-free after 1 year. *Conclusions:* CO intoxication should be suspected when two or more patients from the same household present to the emergency department with non-specific symptoms, mainly mild neurological manifestations. In the present clinical series, all patients were symptom-free one year after CO intoxication. It is important to educate the population on the need for appropriate servicing of domestic heating and/or water-heater equipment, as well as to make official administrations aware of their duties in remodeling old houses to avoid the use of braziers.

289. S-Formate as a First-line Diagnostic Feature in Methanol Poisonings

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Introduction: A good diagnostic tool should ideally have a high sensitivity and high specificity, in addition to be fast, cheap, and easy to perform. S-formate analysis for the diagnosis of methanol poisonings by an enzymatic/spectrophotometric method has it all. Methanol itself is not toxic, and a metabolic acidosis of unknown origin cannot be caused by methanol without the presence of formate. Therefore we suggested the following method to be distributed worldwide, with a special utility for developing countries and rural areas; but its time and money saving features will apply for developed areas as well. *Method:* The enzyme FDH is highly specific, and by reducing NAD+ to NADH, a spectrophotometer will give a fast and quantitative answer. The NADH has a 1:1 mole ratio to S-formate, and the concentration of S-formate is hence given. We suggest making a small kit containing one vial of FDH, one vial of NAD+, one vial of a positive control with a known S-formate concentration, and one method sheet. This should then be distributed worldwide, for production costs only to the developing world. *Results/Conclusion:* The main reason for methanol poisonings' high morbidity and mortality is delayed diagnosis and initiation of treatment. This is often due to lack of diagnostic facilities in remote places and in developing countries, and/or due to often comatose patients, where the condition mimics other causes of metabolic acidosis. The fact that large outbreaks often occur where resources are limited, makes a simple and cheap diagnostic test attractive: This enzymatic method is well defined and tested. It has been used for several years, although never as a diagnostic tool before this was suggested and tested upon during a methanol outbreak in Norway recently (1). The test appeared very useful, and we have now initiated cooperation on a more global basis to try to distribute the method as a kit to different parts of the world. We are at present testing the method by running a pilot study in different parts of the world, namely in Latin America (Nicaragua), the Baltics (Estonia), USA, and in Asia. *Reference:* 1. Hovda KE, Urdal P, Jacobsen D. Increased serum formate in the diagnosis of methanol poisoning. *J Anal Toxicol* 2005; **29**: 586–588.

290. Paraquat Poisoning: 14 Years of Cases Recorded by the Pavia Poison Centre

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Paraquat (P) is one of the most toxic poisons: several strategies have been applied in the management of this poisoning, but the mortality remains high. *Objective:* To examine all clinical records in order to evaluate PSS at first evaluation, clinical evolution, laboratory tests, treatment and outcome of P cases recorded by the Pavia Poison Centre (P-PC). *Methods:* A retrospective analysis of all human cases of P exposure referred to P-PC from 1st January 1993 to 30th September 2007 was performed. All human cases were considered eligible. History, clinical presentation, serum/urine P levels, management of specific therapy and outcome were evaluated. *Results:* 50 patients were included in the study. In the oral ingestion group, twenty-three patients (23/28, 82.1%) were considered poisoned; accidental and deliberate ingestions were 5/23 (21.7%) and 18/23 (78.3%), respectively. In the accidental-group (5/23), three patients recovered fully, one patient died after two months and one was lost to follow-up. In the deliberate-group 18/23, one patient recovered and seventeen (17/18; 94.4%) died; in particular 3/17 (17.6%) patients died during the first 12 hours, 8 patients (8/17; 47%) died between 12–48 hours. Quantitative P determinations were assessed in 18 cases, the results ranged from 0.5 to 55 micrograms/ml in a period of 1–93 hours. PSS at first evaluation was 0, 1, 2, 3 in 4, 8, 4, 7 cases respectively; all patient worsened except three patients. Vomiting, gastrointestinal lesions, hypoxemia, respiratory failure, leucocytosis were the most common signs at presentation. All patients received massive gastrointestinal decontamination, NAC was administered in 19/23 (82.6%), vitamins C and E in 16/23 cases (69.6%), forced diuresis in 7/23 patients (30.4%), charcoal hemoperfusion in 12/23 cases (52.2%), haemodialysis in 6/23 cases (26%), dexamethasone in 8/23 cases (34.7%), cyclophosphamide in 3/23 (13%) and a pulsed cyclophosphamide-methylprednisolone therapy in 4 cases (17.4%). *Conclusion:* P poisoning is a rare poisoning in Italy and associated with high mortality in deliberate ingestion. No cutaneous and inhalational exposures resulted in systemic manifestations. Usually, in absence of a standardized treatment, our clinical toxicologists apply different therapies according to both the clinical evaluation and the presumptive severity of exposure resulting from the blood levels of paraquat.

291. Clinical Manifestations After Exposure to a "Not Dangerous" Product in Two Patients

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Triethoxyoctylsilane / 2-butoxyethanol aqueous emulsion (Pulvistop Geal®) is a water-repellent product used particularly in the building trade. According to European dispositions it is considered a "not dangerous" product and no indications about use with compressor-machines are mentioned in technical issues. *Objective:* We describe two cases of chemical alveolitis after inhalation of Pulvistop Geal® emulsion nebulized through a compressor-machine. *Case series:* Case 1 – A 34 year old man was admitted to the Emergency Department (ED) eight hours after exposure to a silane aqueous emulsion; the product was nebulized with a compressor-machine and inhaled for two hours. At admission the patient presented with chest pain and dyspnoea; gas analysis revealed arterial hypoxia so oxygen was immediately administered. The chest radiograph was normal and a CT scan subsequently performed revealed a bilateral alveolo-interstitial infiltrate in the medium-upper lung areas. CPAP was started and corticosteroids and antibiotics were administered. A complete clinical recovery was obtained in three days without sequelae. Case 2 – A 50 year old man presented to the ED after inhalation of a silane emulsion sprayed from a compressor-machine in the morning. After exposure he manifested chest tightness, upper airways burning sensation and expiratory whistle. At presentation the patient presented with mild upper airways irritation and neutrophilic leukocytosis. Vital parameters and gas analysis were normal. Chest radiograph showed thickening of peribronchovascular interstitium at medium-upper lung areas and CT scan confirmed a diffused chemical alveolitis with interstitial consolidation. Oxygen, bronchodilators and corticosteroids were administered and a complete clinical recovery occurred during the next day. CT scan repeated seven days later showed a complete *restitutio ad integrum*. *Conclusion:* Exposure to "not dangerous" products may be associated with negative effects on health when the product is used in an incorrect way. After these cases the producer was alerted and product documentation was altered to include the phrase "do not use with compressors" and to both the product documentation and Safety Data Sheet were added the caution phrase "do not breathe vapors/aerosol". Poison Control Centres can play a key role in toxicovigilance and in detection of newly emerging poisonings.

292. A Comprehensive Review of Diethylene Glycol Toxicity in Humans

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Objective: The recent tragedy of diethylene glycol contamination of pharmaceutical products in Panama in 2006 demonstrated to the world the lethality this toxic industrial chemical. This review

article provides a comprehensive review of all DEG case reports and epidemiologic studies, which reveals a fairly predictable pattern of toxicities that occur in four stages: GI, Hepatorenal, Neurological, and Recovery. *Discussion:* The reports from Panama, prior worldwide epidemic poisonings, along with several recent cases of severe toxicity due to DEG were reviewed. This reveals that poisoning by this toxic diol can be conceptualized as having three distinct clinical stages, which may be followed by a recovery phase; there may be considerable overlap. Stage I: Gastrointestinal stage: Day 1–2 after poisoning - nausea and/or vomiting, an anion gap metabolic acidosis, as well as an osmolar gap. Patients with significant poisoning have more vomiting and more severe acidosis, and will progress to the next stage. Early treatment with fomepizole may be useful. Stage II: Hepatorenal stage: Day 1–3 days post-ingestion. Patients have elevated anion gap acidosis, renal impairment, and hepatocellular injury. Emergent hemodialysis is mandatory; most will develop renal cortical necrosis and permanent dependence on dialysis. The severity of the renal injury seems to be a predictive marker for development of subsequent neurologic injury. Stage III: Neurologic stage: Day 5–10 days post-ingestion - Most patients with renal failure requiring hemodialysis will progress to stage III. Neurologic abnormalities can consist of cranial and peripheral demyelinating sensorimotor polyneuropathies, flaccid paresis, and encephalopathy. Stage IV: Recovery phase: With prolonged good supportive care, patients can survive to Stage IV, the recovery phase. Milder neurologic abnormalities recover more quickly and more completely, but the more severely injured may be left with permanent deficits. However, moderate functional recovery from flaccid paralysis, encephalopathy, and complete unresponsiveness has been reported. Renal injury is permanent, however. *Conclusion:* DEG is a common industrial solvent found in numerous consumer and industrial products. Historical contamination of pharmaceuticals has caused epidemic poisonings. Poisoning by DEG follows a predictable course through three stages of toxicity - GI, Hepatorenal, Neurological, followed by a Recovery phase (which can last months). The development of renal failure seems to be a predictive marker of subsequent neurological toxicity. Prolonged supportive care can allow a relatively good recovery even in cases with a seemingly dismal initial prognosis.

293. Chemical Skin Burns Caused by a Biphasic Nail Polish Remover Containing Ethyl Acetate.

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Objective: Ethyl acetate and butyl acetate are widely used in nail polish removers. In contact with water they may decompose (1,2) with formation of acetic acid. Our aim is to describe a case of skin injury caused by a decomposed biphasic nail polish remover. *Case report:* Three hours after using a nail polish remover, a 74-year-old woman felt a burning sensation in her fingers. The following hours, she complained of increasing burning pain. She was examined by a general practitioner one day later. There was erythema with blisters at the top of the fingers, suggestive of a second degree burn. The lesions were treated with a silver sulfadiazine ointment. She recovered without sequelae. The original product existed in two phases: a solvent phase containing 59.4 % of ethyl acetate, 20.0 % of butyl acetate and 20.0 % of dimethoxymethane and an aqueous phase consisting of 99.2% of water with trace amounts of other ingredients. At presentation, one month after opening, there was only an aqueous phase left with a pH of 2.47. Analysis by HPLC-UV revealed 40% of acetic acid. *Discussion:* Ethyl acetate and butyl acetate are widely used in nail polish removers, normally in one phase formulations. If mixed with water, there will be an apolar solvent phase and a polar aqueous phase. Ethyl acetate (1) and butyl acetate (2) in biphasic solvent systems may slowly decompose into acetic acid and ethanol. In the literature we found no cases of skin burns caused by nail polish removers containing ethyl acetate or butyl acetate. We believe that the polar phase promoted decomposition of ethyl acetate by trapping acetic acid. This resulted in a solution with 40% of acetic acid and a pH of 2.47. Acetic acid is known to cause skin burns in concentrations as low as 5% (3). *Conclusion:* Decomposition of ethyl acetate or butyl acetate in biphasic phase nail polish removers can lead to the formation of a highly concentrated acetic acid solution, causing second degree skin burns. *References:* 1. Berthod A. Operating a countercurrent chromatography machine. In: Berthod A ed. Countercurrent Chromatography. Amsterdam, The Netherlands: Elsevier Science, 2002:21–48. 2. Butyl Acetates: Concise International Chemical Assessment Document 64. Geneva, Switzerland: WHO, 2005: 1–49. 3. Korkmaz A, Sahiner U, Yurdakök M. Chemical burn caused by topical vinegar application in a newborn infant. *Pediatr Dermatol* 2000; **17**: 34–36.

294. Portal Venous Air Embolism Due to Intentional Ingestion of Dilute Hydrogen Peroxide

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Objectives: Ingestion of household (3%) hydrogen peroxide (H_2O_2) is generally assumed to be benign. H_2O_2 is available in a variety of grades and concentrations, and the household-grade 3% concentration is generally considered to be safe when ingested. By comparison, more concentrated forms are severely caustic. The mechanism of air embolism following ingestion of H_2O_2 involves absorption of H_2O_2 across the gut lumen, followed by degradation into water and liberation of oxygen gas while in the vascular space. Portal venous gas is diagnosed radiographically by the appearance of tubular lucencies branching from the porta hepatis to within two centimeters of the peripheral liver margin. It has the potential to cause local ischemia or systemic embolus. We report a case of portal venous air embolism due to intentional H_2O_2 ingestion. *Case report:* A 32 year-old woman with a history of peptic ulcer disease presented to the ED with epigastric abdominal pain and shortness of breath after intentionally ingesting several mouthfuls of household (3%) H_2O_2. In the ED, her vital signs were: temperature, 36.7 C; blood pressure, 120/97 mmHg; pulse, 110/min; respirations, 20/min; pulse oximetry, 97% on room air. Her physical examination was completely unremarkable. Electrocardiogram revealed sinus tachycardia with normal intervals. Routine laboratory evaluation was unremarkable. Abdominal CT revealed portal venous air embolism. After consultation with the regional Poison Center, the patient was placed in left lateral decubitus position, administered 100% oxygen by nonrebreather mask, and was transferred for hyperbaric oxygen therapy. After hyperbaric treatment for one hour, the patient became asymptomatic and remained medically stable. *Conclusions:* We report the uncommon occurrence of CT-confirmed portal venous air embolism due to ingestion of dilute hydrogen peroxide. Management of portal venous air embolism using hyperbaric oxygen has theoretical benefit. While its use was associated with a favorable outcome in this patient, its efficacy remains unproven.

295. The Main Cause of Death in Deliberate Self Poisoning, Aluminium Phosphide

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Objective: Aluminium phosphide known as “rice tablet” in Iran is an important grain insecticide which is popular among farmers due to its low cost, easy application, high efficacy, lack of persistence and harmless decomposition products (1,2). This is one of the lethal poisons that have achieved added attention in recent years. The Iranian Ministry of Health has forbidden its sale. The present study was designed and conducted to investigate consumption and mortality of “rice tablets” in Loghman-Hakim Poison Hospital, the largest inpatient clinical toxicology complex of the Middle East and probably the world (3). *Methods:* This descriptive study was carried out from March 2005 through March 2007. All inpatients where there was suspicion of ingestion of botanic (garlic extract based) or chemical “rice tablets” were included and sex, age, month of admission (1–24), length of stay and outcome evaluated. Patients’ data were collected by questionnaire using observational methods. SPSS software version 15 was used for statistical analysis and $P<0.05$ considered as significant. *Results:* During the 24 months of the study 12,169 patients in the first year from March 2005-March 2006 and 14,061 patients in the second year from March 2006-March 2007 were hospitalized. Of these 340 subjects were included in the study; 232 (68.2%) of them were admitted in the second year. One hundred (29.4%) died and most of these were female (59%). There was no significant correlation with sex, age and outcome. With 74 mortalities this was the first cause of intentional death in the second year. *Conclusion:* Usage and mortality of ALP is rising in our community. Prohibition of distribution and marketing of this product did not reduce its consumption, and perhaps even caused a rapid rise due to increased awareness in those at risk of self-harm. *References:* 1. Bogle RG, Theron P, Brooks P, *et al*. Aluminium Phosphide poisoning. *Emerg Med J* 2006; **23**: e3. 2. Dua R, Gill KD. Aluminium phosphide exposure: Implications on rat brain lipid peroxidation and antioxidant defence system. *Pharmacol Toxicol* 2001; **89**, 315–319. 3. Hassanian-Moghadam H, Pajoumand A. Characteristics of acute adult and adolescent poisoning admitted to Loghman Hospital, Tehran; is this largest clinical toxicology center of the world!? Eleventh International Congress of Toxicology (ICT XI). July 15–19 2007 Montréal, Canada.

296. A Case of Acute Intentional Ethyl Acetate Ingestion with Severe Metabolic Acidosis

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Objective: Ethyl acetate is generally considered of limited toxicity. We aim to describe a near fatal poisoning after ingestion of approximately 80 grams of ethyl acetate. *Case report:* A 78-year-old woman intentionally ingested 100 ml of nail polish remover containing 85% ethyl acetate and minor percentages of methylpyrollidone, dimethylsuccinate, dimethylglutarate and dimethyladipate. On admittance, one hour later, she presented in cardiovascular shock with pronounced bradycardia (25 beats/minute) and blood pressure of 45/30 mm Hg. Blood gas results under 40% FiO_2 were pH 6.39, pCO_2 25 mm Hg, PO_2 440 mm Hg, bicarbonate 6 mEq/L and a anion gap of 45 mEq/L. Serum ethanol was 1.2 g/L, methanol 0.15 g/l and osmolality 352 mOsm/kg. The patient was intubated, transferred to the ICU and hemodialysis was started for 3 hours. After dialysis arterial pH was 7.40, bicarbonate 23 mEq/l with an anion gap of 29 mEq/l. On day 2, a marked toxic hepatic injury became apparent (aspartate aminotransferase 6339 U/L, alanine aminotransferase ALT 3733 U/L). Lactate normalised on day 4 but there was persistent hemodynamic instability. She was extubated on day 8, transferred to a medical ward on day 11 and recovered without sequelae. *Discussion:* Little is known about human toxicity of ethyl acetate. From animal data it is known that it is easily absorbed orally and can be hydrolysed by liver and plasma esterases into ethanol and acetic acid (1). Based on the clinical course, ethyl acetate was apparently rapidly absorbed and readily hydrolysed with a pronounced acidosis accompanied by cardiovascular shock. There was severe toxic hepatic injury which has been described in animals (1) but not in humans. In the literature we found one report of fatal ethyl acetate poisoning (2). The low ratios of ethyl acetate to ethanol in post mortem tissue samples confirmed the rapid biotransformation of ethyl acetate which fits with our observations. *Conclusion:* Ingestion of small amounts of nail polish removers containing ethyl acetate is a common accident and is usually considered not toxic. However, if ingested in large amounts it can lead to rapid and massive release of acetic acid with a life threatening acidosis and hepatocellular damage. *References:* 1. Specifications for the identity and purity of food additives and their toxicological evaluation: some flavouring substances and non-nutritive sweetening agents. FAO Nutr Meet Rep Ser 1968; **44**: 1–18. 2. Coopman V, Cordonnier J, De Meyere C. Fatal workplace accident involving ethyl acetate: a distribution study. *Forens Sci Int* 2005; **154** : 92–95.

297. Organophosphate Poisoning in Tehran 2003

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Objective: Acute pesticide poisoning has become a major public health problem worldwide. Organophosphate insecticides (OPs) are a common cause of poisoning in developing countries but less so in developed countries (1). A recent published study that was done in Loghman-Hakim Poison Hospital (LHPH) indicated that 18.5% of total mortality was due to pesticides, and of this, 11.94% was due to OPs (2). This study aimed to review the epidemiology, initial clinical abnormalities and management of patients with organophosphate poisoning admitted to the LHPH, Iran, over a 6-month period in 2003. *Methods:* This was a cross sectional prospective study. The population was patients aged >12 year with OP poisoning admitted to LHPH in 2003. Demographic data included age, sex, route of exposure, intentional or accidental poisoning, type of admission, place of intoxication, length of hospitalization, symptoms, signs, treatment and outcome were reviewed for each case. SPSS Version 11.5 was used to analyse the data. *Results:* In total 121 acute OP poisoning cases were referred to LHPH in the mentioned period. These represented nearly 1% of all poisoning emergency admissions. 71.2% cases were self poisoning, 23.1% accidental and 1.7% unspecified. The majority of patients were young (mean age 29.3), male (51.2%) and from a rural area (81%). 80% were hospitalized. 82% of poisoning happened at home. Miosis was the most common sign (60%), followed by tachycardia and

sweating (48%) while nausea and vomiting (18%) were the most common symptoms, followed by abdominal pain (13.7%). Atropine and pralidoxime was given to 36% of patients in the ED. The majority of patients (80%) stayed in the hospital for approximately 4 days. Average hospital stay per patient was 4–5 days. Seven patients died (5.8%). *Conclusion:* Methods of prevention to reduce the number of poisonings with these agents, should be carried out. *References:* 1. Moghadamnia AA, Abdollahi M. An epidemiological study of poisoning in northern Islamic Republic of Iran. *East Mediterr Health J* 2002; **8**: 88–94. 2. Shadnia S, Esmaily H, Sasanian G, *et al*. Pattern of acute poisoning in Tehran-Iran in 2003. *Hum Exp Toxicol* 2007; **26**; 753.

298. Pulmonary Aspiration of a Polyethylene Glycol (PEG) – Electrolyte Solution (Klean-Prep)

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Objective: Klean-Prep is used for intestinal cleansing before diagnostic and therapeutic interventions as well as for whole bowel irrigation after toxic ingestions. We report a case of aspiration pneumonia after administration. *Case report:* A 17-year-old female patient suffering from recurrent convulsive abdominal complaints was administered Klean-Prep solution in preparation for colonoscopy via gastric tube. A total volume of four litres should be given in quarter-litres, with the first two litres being instilled within two hours. The conscious patient was not intubated for this procedure. Slight coughing and dyspnoea occurred after administration of the third portion (total 750 mL; 30 min after start of the procedure). Symptoms improved after removing the gastric tube and further drinking of the solution. Nevertheless, symptoms reappeared three and a half hours later. Pneumonia was visualised in chest roentgenogram (particularly right lower and left paracardial areas) confirmed by pathological laboratory findings (arterial oxygen saturation 84%; C-reactive protein max. 50 mg/L; white blood cell count max. 18.8 Gpt/L). A foamy secretion was siphoned off by bronchoscopy. Intensive bronchoalveolar lavage was carried out to remove remaining aspirated solution. Patient was treated with cefuroxime and supplementary oxygen was given. She recovered under this treatment within 7 days. *Conclusion:* The nasogastric infusion of PEG - electrolyte solution is more often complicated by pulmonary aspiration than oral administration (1). This complication must be taken into account in whole bowel irrigation when the patient cannot or will not take the solution orally (2). The aspiration of PEG causes a diffuse mucosal inflammation and interstitial oedema. The absorption of the solution by pulmonary tissue may be delayed as a result of its isotonic constitution. Bronchoalveolar lavage should be carried out immediately after aspiration to prevent life-threatening respiratory failure by toxic lung edema (1,2). *References:* 1. de Graaf P, Slagt C, de Graaf JL, *et al*. Fatal aspiration of polyethylene glycol solution. *Neth J Med* 2006; **64**: 196–198. 2. Marschall HU, Bartels F. Life-threatening complications of nasogastric administration of polyethylene glycol-electrolyte solutions (Golytely) for bowel cleansing. *Gastrointest Endosc* 1998; **47**: 408–410.

299. Left Abdominal Wall Abscess Through Elemental Mercury Injection

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Introduction: Elemental mercury injection is a rare condition and is seen mostly in psychiatric patients. Injected metallic mercury (extravascular) causes sterile, inflammatory and necrotic reactions resulting in abscesses and granulomas. *Case report:* We present the case of 20 year old female patient transferred to our department as a case of mercury poisoning. She gave a history of swollen and tense formation in the left abdominal wall that appeared by night 6 months ago. She constantly denied any self injection. She was admitted to a regional hospital 3 weeks earlier and she suffered a surgical intervention for abscess drainage under local anesthesia; the wound remained open and presented leakage of mercury droplets. On admission general examination was unremarkable. Local examination revealed a sutured surgical wound, 10 cm long, in the course of healing with the exception of 1 cm open area in superior pole with leakage of foreign metallic droplets. X-ray examination confirmed the presence of radiopaque multiple foreign bodies in the deeper part of the left abdominal wall. The laboratory tests were normal. Analytical toxicological tests performed on AAS: urine mercury concentration was 20 micrograms/l (normal adult level < 50 micrograms/l) and serum mercury level was zero. Neurological and psychiatric exams were normal. No other signs of systemic mercury toxicity were detected. A surgical intervention under X-ray control was performed for complete removal of the remaining mercury, with second wound closure after 4 days. All clinical and biological parameters remained normal in the course of hospitalization. The patient was discharged after 10 days, but the circumstances of mercury injection remained a mystery. We repeated the analytical toxicological tests after 1 month and these were normal. *Conclusion:* In this case, despite an apparent large volume of injected mercury, no systemic toxicity appeared. Some authors report abnormal serum mercury levels suggesting that there is some lymphatic and vascular migration following extravascular mercury injection. We did not find any abnormality with the exception of local abscess, but our tests were performed 6 months after the exposure.

300. Lipoid Pneumonia Due to Inhalation of a Household Insecticide Spray

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Objective: Lipoid pneumonia is an infrequent but severe disease caused by the aspiration or inhalation of mineral, vegetable or animal oils. The lipid component of the oil emulsifies and cannot be hydrolyzed by the pulmonary lipases. This triggers an intense inflammatory response to the foreign bodies in the pulmonary parenchyma. Lipoid pneumonia may also be due to micro-aspiration of the lipidic vehicle of some drugs, occupational exposure to some industrial processes and even accidents suffered by fire-eaters. We report a case of lipoid pneumonia due to direct inhalation of an insecticide spray. *Case report:* A 68-year-old man was sent to the emergency department after attempting suicide by ingesting a quantity of benzodiazepine tablets and directly inhaling (about 10 puffs) a domestic insecticide spray containing pyrethrins and carbamates. The patient smoked about 45 packets of cigarettes a year and had been diagnosed with bipolar disorder and had made two previous suicide attempts. At admission, the patient was drowsy, tachypneic and stable hemodynamically. Crackling rales were auscultated in the right pulmonary base. The rest of the physical examination was normal, with no muscarinic or nicotinic signs. The arterial blood gas test showed mild hypoxemia (basal pO_2 70 mmHg). Toxicological analysis by enzyme immunoassay was positive for benzodiazepines and the concentration of serum pseudocholinesterase was normal (10.8 mg/dl). The chest X-ray showed an increase in the density of the right base. The patient was admitted to hospital. After 24 hours he presented fever and progression of the pulmonary infiltrates with images of cavitation. Blood and sputum cultures were negative. A thoracic CT showed multiple low-density nodal images and cavitation in the right pulmonary parenchyma, compatible with lipoid pneumonia. Treatment with methylprednisolone resulted in clinical recovery, although the pulmonary images were slow to resolve. *Conclusion:* Intentional inhalation of a domestic insecticide can cause respiratory disease that is not a direct consequence of the insecticide itself but rather of the mineral oil that acts as a vehicle for the insecticide. The lipoid pneumonia results in a more severe poisoning than exposure to the insecticide alone.

301. Endosulfan Poisoning

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Objective: Endosulfan is an organochlorine insecticide, used in agriculture in many countries, including Iran. It has health hazards for human beings, namely potential toxicity to the CNS, cardiopulmonary system, liver and kidney (1). *Case series:* The following cases were observed in the emergency department of Ali-ebne-abitaleb hospital in Rafsanjan, Iran involving suicidal patients with endosulfan ingestion: Case 1: An 18 year old man was admitted to the emergency department with a history of endosulfan ingestion. The patient was initially alert but showed *status epilepticus* later which did not respond to benzodiazepine and phenytoin. This status was finally controlled by thiopental. The patient was discharged in good condition after 5 days. Case 2: A 22 year old man with a history of endosulfan poisoning (ingestion) was admitted to the emergency department with *status epilepticus*. Initial treatments were carried out. Thiopental was prescribed but this was not completely successful. Four hours after admission, the patient developed GI-bleeding and low blood pressure. PTT and PT were over 90 and 60 respectively. Blood pressure was 70 mm/Hg. In spite of all the efforts (fluid and dopamine), the patient died. Case 3: A 23 year old woman was admitted with *status epilepticus*. Seizure was controlled by thiopental and phenytoin, but the patient's blood pressure dropped and arrhythmia and anuria occurred. Blood pressure was 60 mm/Hg and EKG showed junctional rhythm. Unfortunately, the patient died. For all the patients, endotracheal intubation, NGT and gastric lavage with normal saline were carried out. They were transferred to ICU. They all had *status epilepticus* and hyperthermia. Laboratory tests showed hyperglycemia (except case 1) and electrolyte disorders. *Conclusion:* Generalized seizure is the most common presentation of endosulfan toxicity. Hence, when observing seizure and status epileptics in agricultural areas, endosulfan poisoning should be considered.

302. High Lead Levels with Minimal Signs of Encephalopathy

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Objective: Although it is generally accepted that children with whole blood lead concentrations (BLC) above 4.80 µmol/L (100 mcg/dL) should be severely symptomatic, data to support this contention are lacking. We report two children with markedly elevated BLC, who initially showed minimal signs of encephalopathy. *Case report:* A 3-year old girl with sickle cell disease was brought to the ED for abdominal pain, persistent vomiting and generalized weakness for 3 days. Vital signs were: BP, 160/90 mmHg; pulse, 76/minute; respirations, 20–24/minute; afebrile; and pulse oximetry, 98% on room air. Laboratories showed: hemoglobin, 8.7 gm/dL; hematocrit, 26.5% (baseline 30%); MCV, 73.0 fL. Abdominal radiograph showed radiopaque 'flecks' and a BLC was 10.90 µmol/L (227 mcg/dL) – normal < 0.48 µmol/L (<10 mcg/dL). Multiple clinicians felt that she was cognitively normal. A 3-year old boy was being followed for a swallowed toy that had not passed over 30 days. Two days prior to presentation a BLC was 5.90 µmol/L (123 mcg/dL). He was discharged prior to the BLC result because he was asymptomatic and clinically well. He was brought to the ED for progressive lethargy. A repeat BLC was 9.75 µmol/L (203 mcg/dL). In the ED, he was lethargic, had multiple episodes of vomiting and was writhing with abdominal pain. His hemoglobin was 9.4 gm/dL with a hematocrit of 27%. Both patients were decontaminated and chelated with BAL and EDTA, followed by oral succimer and improved (1). *Conclusion:* Prior to chelation the mortality of untreated elevated BLC was reportedly >60% (2). Varying BLC are associated with death, 4.35–39.85 µmol/L (90–825 mcg/dL) (2), and no markers predict which patients with high BLC will develop encephalopathy, coma and death. In the cases we report, both children initially showed no signs of encephalopathy with profoundly elevated BLC. This may result from the relative acuity of the exposures. *References:* 1. American Academy of Pediatrics: Treatment guidelines for lead exposure in children. American Academy of Pediatrics Committee on Drugs. *Pediatr* 1995; **96**: 155–60. 2. Gordon RA, *et al*. Aggressive approach in the treatment of acute lead encephalopathy with an extraordinarily high concentration of lead. *Arch Pediatr Adolesc Med* 1998; **152**: 1100–4.

303. Chronic Carbon Monoxide Poisoning in the Elderly

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Carbon monoxide (CO) poisoning is an underdiagnosed cause of morbidity. The elderly often experience multiple different problems and so it may appear to be even less reason to look for a further toxic cause despite this group being at higher risk (1). *Objective:* To find out whether CO poisoning was a possible contributor to illness in the elderly. *Method:* Descriptive study investigating elderly patients attending the outpatient geriatric clinic during 9 months. Carboxyhemoglobin levels (COHb) were measured using a portable breath analyser. High levels were confirmed on a blood sample. Information on household and smoking risk factors was assessed

by questionnaire. Patients were investigated for CO poisoning compatible history/symptom. A COHb greater than 2% was considered abnormal for a non smoker, and greater than 5% for a smoker. *Results:* 156 patients (112 female, 44 male) attended. Mean age 76.3 +/– 7.6 years (min 61, max 95). One hundred patients (64%) had a history/symptoms compatible with CO poisoning: 64 cognitive disorders, 24 fall/malaise, 9 headache, 1 vertigo, 2 post-stroke. The breath-test was performed by 146 patients (94%) whereas 10 patients were unable to use the device. Mean COHb was 0.98% +/– 0.66% in the whole group, 2.88% +/– 1.70% in smokers (n=8), and 0.87% +/– 0.31% in non smokers (n=138). Mean COHb was 1.11% +/– 0.9 % in CO-compatible group and 0.84% +/- 0.22% in non-compatible group. COHb was abnormal in two patients, both belonged to the CO-compatible group (2%). One was a non-smoking 82 year old man with COHb of 2.8% attending for post-stroke evaluation. Another was a 71 year-old woman smoker (15 cigarettes/day) with COHb of 11.6% attending for headache. Three household CO sources (gas heater, gas boiler, gas cooking) were identified for both. *Conclusion:* CO was found to be a possible contributor to illness in 2% of elderly patients with CO compatible history/symptoms. COHb measure can be performed by breath-test in ambulatory elderly patients and should be encouraged for identification and prevention of chronic CO poisoning contribution to illness. *Reference:* 1. Harper A, Croft-Baker J. Carbon monoxide poisoning: undetected by both patients and their doctors. *Age and Ageing* 2004; **33**: 105–09.

304. Clinical Relevance of Oxime and Sodium Bicarbonate Therapy for Acute Organophosphate Poisoning - Still a Dilemma

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Objective: To evaluate the efficacy of oxime and sodium bicarbonate therapy in organophosphate poisoning, and to correlate it with objective endpoints such as AChE status, survival, need for mechanical ventilation and atropine consumption. *Methods:* Retrospective study of 109 patients with OP poisoning, treated in the National Poison Control Centre, Belgrade (January 2003-June 2007) was performed. The patients were analyzed according to the class of OP (96 had dimethylphosphoryl and 13 diethylphosphoryl compounds poisoning) and the applied therapy: Group I - atropine and bicarbonate (17); Group II - atropine, oxime and bicarbonate (10); Group III - atropine and oxime (40); Group IV - atropine (42). Pralidoxime methylsulphate (4 g/day) and bicarbonate (5 mEq/kg/day) were administered as long as OP was present in biological samples. *Results:* The majority (59.6%) of patients had severe and fatal poisoning (PSS 3 and 4). According to their AChE status patients were divided to 4 groups: A. No significant inhibition; B. 21–50%; C. 11–20%; D. ≤10%. The lowest rate of AChE inhibition was registered in patients from Group IV ($p<0.05$). Reactivation of more than 50% was registered in Group I and Group II, but the difference between these groups was not significant. Mechanical ventilation was more frequent in patients from Group IV (46%) than in other groups (14%) ($p<0.05$). Atropine consumption was the highest in Group IV (2330 mg), and lowest in Group II (318 mg) and the differences were significant ($p<0.01$). Eighteen (16.5%) patients died, but none of them with diethylphosphoryl OP poisoning. *Conclusion:* Assessment of these therapeutic regimens is difficult when stratification of patients according to the level of poisoning, initial AChE, the poison load, time to therapy is not possible. Reactivation of AChE and survival were not different between therapeutic groups, so one might assume that oxime and bicarbonate should not be used. However the difference in atropine consumption, and the need for mechanical ventilation between the patients on atropine regimen only and other therapeutic groups was significant. *Reference:* Eddleston M, Szinicz L, Eyer P, *et al*. Oximes in acute organophosphorus pesticide poisoning: a systematic review of clinical trials. *Q J Med* 2002; **95**: 275–283.

305. Multicentre Data Collection on Paraquat Poisoning in Europe

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Objective: Paraquat has been used as a herbicide worldwide since 1962. The aim of this study is to collect adverse health incident data to a common standard in Europe, using paraquat as model substance. *Methods:* Interim analysis (after 18 months) of a Poisons Centre-based prospective multicentre cohort study in 9 European countries where paraquat is marketed during 2006–2008. In the first months of 2006 data were collected in a retrospective pilot study. Patient and exposure characteristics were recorded and likelihood of exposure, symptoms, severity, causality, and outcome were assessed. Only cases with a high likelihood of exposure are included here. *Results:* Total reported cases n=211 (Portugal 70; Spain 64; Greece 62; Italy 6; Belgium 3; Netherlands 2; Cyprus 1; Germany 2; Slovakia 1). 156 had a high likelihood of exposure. Patient characteristics: Adults n=144, mean age 53.5 y (S.D. 17.9, range 17–92), children (age <16 years) n=9, mean age 7.0 y (S.D. 4.3, range 1.5–15), unknown n=3. Severity and outcome according to circumstances of exposure are listed in the table. The route of exposure was oral in 79, dermal 35, inhalation 18, ocular 7, mucosal 2, combined 15. Paraquat could be analytically detected in 38 cases (47% of all cases tested). Symptoms were mainly gastrointestinal, pulmonary, renal (from oral ingestion), and dermal. *Conclusion:* It is feasible to collect data from different poisons centres using predefined criteria. Paraquat poisoning is particularly prevalent in Southern Europe. Severe or fatal poisoning is more frequent in intentional than in accidental/occupational exposure ($p<0.0001$).

306. Reversible Nephrotic Syndrome and Minimal Change Disease Related to Mercury Exposure in a Fluorescent Light Bulb Worker

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Background: There are previous reports of minimal change and membranous glomerulonephritis from mercury exposure in skin-lightening creams, but no previous reports of significant nephrotoxicity related to mercury exposure in fluorescent light bulb manufacture. *Case report:* A 25 year old man presented with a two week history of lethargy and increasing peripheral and peri-orbital oedema. His blood pressure was 160/110 mmHg (there was no previous history of hypertension). He had no rashes, abdominal symptoms or abnormal neurological signs. Investigations revealed a nephrotic syndrome: 6.9 g/24 hr proteinuria, serum albumin 20 g/L. Renal function was normal, he had no haematuria, renal ultrasound was normal and an immunology screen was negative. Renal biopsy revealed minimal change glomerulonephritis. He had worked in a fluorescent light bulb factory for nine months, "blowing" heated elemental mercury into the light bulbs. Blood and urine mercury were 58 nmol/L and 642 nmol/L (1925 nmol/24 hrs; 44.5 nmol/mol creatinine). He was treated with prednisolone 60 mg daily, ramipril 5 mg daily, furosemide 80 mg daily and DMPS (2,3-dimercaptopropane-1-sulphonate) initially intravenously 250 mg four-times a day for 3 days, followed by 250 mg IV three-times a day for 3 days and then 200 mg orally twice daily for three weeks and 200 mg orally once daily for three weeks. His nephrotic syndrome gradually settled and three months later he had no significant proteinuria, a normal serum albumin and a normal blood (12 nmol/L) and urine mercury (4.1 nmol/mol creatinine). *Conclusions:* We report a case of minimal change nephropathy and nephrotic syndrome related to elemental mercury exposure in the fluorescent light bulb industry that was successfully treated with steroids and DMPS chelation. Toxicologists and occupational physicians should be alert to the possibility of significant mercury exposure and neprotoxicity in individuals working in this industry.

Table: Severity and outcome according to circumstances of exposure in paraquat poisoning

Severity	Occupational	Accidental	Intentional	Unknown	Total
Asymptomatic	7	8	2	1	18
Minor	40	17	7	2	66
Moderate	5	4	4	2	15
Severe			6	2	8
Fatal		2	38		40
Unknown	2	1	2	4	9
Total	54	32	59	11	156

307. Encephalopathy and Peripheral Neuropathy Secondary to 1-Bromopropane Toxicity

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Objective: 1-bromopropane is increasingly popular as an alternative solvent to ozone depleting chlorofluorocarbons. Preliminary reports suggest neurologic toxic effects in exposed workers. We report the acute effects of 1-bromopropane in an electrician who developed encephalopathy and peripheral neuropathy after exposure. *Case report:* A 50 year old male presented to the ED complaining of confusion, dysarthria, and dizziness as well as weakness, paresthesias and ataxia for 24–48 hours. He worked as an electrician and had been soldering at his job recently. Physical examination: vital signs BP 167/77 mmHg, T 37° C, Pulse 88 beats/ min, RR 21/min; mental status was alert but with slowed mentation, mild confusion and tremors, cranial nerves and motor strength were intact, gait was wide based and ataxic. Laboratory results were significant for a negative anion gap (-31) and a serum chloride of 146 mmol/L. An extensive neurologic and infectious workup were unrevealing. The patient had improved at the time of toxicology evaluation but had persistent slowed mentation and ataxia. The initial hyperchloremia and toxic symptoms suggested a possible bromide exposure but was not documented until OSHA investigated his workplace and measured 100 x levels of 1-bromopropane in air samples. A bromide level obtained from the patient two weeks post hospitalization was elevated at 48 mg/dl (6 mEq/L). His peripheral neuropathy persists 6 months later. *Conclusions:* 1-bromopropane toxic exposures may be occurring and are not easily recognized. Unexplained hyperchloremia suggests possible bromide exposure and was a clue to the possible etiologic agent in this case. *References:* 1. Raymond LW, Ford MD. Severe illness in furniture makers using a new glue: 1-bromopropane toxicity confounded by arsenic. *J Occup Environ Med* 2007; **49**: 1009–19. 2, Ichihara G, Li W, Shibata E, *et al*. Neurologic abnormalities in workers of a 1-bromopropane factory. *Environ Health Perspect* 2004; **112**: 1319–25.

308. Increasing Use of Swimming Pool Disinfectants at Home – A Potential Hazard

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Objective: Inquires to the SPIC concerning pool disinfectants in home settings have increased five-fold during the last five years. Many swimming pool products are considered hazardous due to their corrosive properties. The documentation concerning these accidents is scanty. Only a few case reports and one study about exposure to chlorine gas generated by pool disinfectants were found (1). The aim of this study was to collect information about the frequency of exposures, severity of symptoms and need for medical interventions. *Methods:* All inquiries concerning swimming pool disinfectants in home settings during a six months period were included. Follow up interviews were performed and hospital case records were collected. The severity of symptoms was assessed using the Poisoning Severity Score (PSS). *Results:* In total 61 cases were studied. Interviews were performed in 48 cases and hospital records were received concerning 13 patients. The most common routes of exposure were inhalation (n=28) and ingestion (n=26), whereas eye exposure was rare (n=4). The majority of exposures resulted in none (PSS 0) or mild (PSS 1) symptoms. In 10 cases moderate symptoms (PSS 2) occurred after inhalation. Severe eye damage (PSS 3) was seen in one patient and a moderate reaction (PSS 2) was noted in an additional case. Pulmonary symptoms usually resolved spontaneously, but in some cases treatment was given with oxygen, bronchodilators and corticosteroids. Pulmonary oedema was not observed, nor was corrosive injury after minor ingestion. Inhalation while opening packages was mainly seen among adults and teenagers. In small children ingestion was dominant. *Conclusions:* Despite the potentially hazardous contents of pool disinfectants, exposures seem to imply a relatively low risk. Most patients had none or mild symptoms.

Table 1. Eight cases of poisoning with ethylene glycol

	Case I	Case II	Case III	Case IV	Case V	Case VI	Case VII	Case VIII
Gender	Male	Male	Male	Male	Male	Male	Female	Male
Type of poisoning	intentional	accidental	accidental	accidental	accidental	accidental	intentional	accidental
Chronic alcohol abuse	no	no	no	no	no	yes	no, but co intake of ethanol	yes
Period between ingestion and hospitalization	App. 5 h	App. 7 h	App. 1 h	App. 1 h	App. 7 h	App. 7 h	App. 5 h	App. 24 h
Blood ethylene glycol level	0.68 mg/ml	0.075 mg/ml	0.32 mg/ml	0.2 mg/ml	0.74 mg/ml	0.32 mg/ml	0.68 mg/ml	0.13 mg/ml
Dysmetabolitic syndrome	No	Yes	No	No	No	Yes	No	Yes
Kidney damage	No	Yes	No	No	No	Yes	No	Yes
Depurative haemodialysis	Not done	Done	Not done	Not done	Done	Done	Not done	Done
Hospital stay	5 days	39 days	6 days	6 days	5 days	20 days	7 days	17 days

Inhalation and eye exposures appear to be more hazardous than ingestion. Moderate symptoms occurred after inhalation in a limited number of patients and a severe eye injury in one case. Medical attendance is recommended for any exposure that results in pronounced or persisting symptoms. *Reference:* 1. Lo Vecchio F, *et al*. Outcomes of chlorine exposure: a 5-year poison centre experience in 598 patients. *Eur J Emerg Med* 2005; **12**: 109–10.

309. Early Haemodyalysis in Acute Ethylene Glycol Poisonings?

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Objective: To re-evaluate the accepted practice in this country for performing early haemodialysis in acute ethylene glycol poisoning based only on the blood ethylene glycol level. *Methods:* We have studied 18 cases with acute ethylene glycol poisoning treated in the Toxicology Clinic of the Emergency Medicine Institute "Pirogov", Sofia for the period 2005-June 2007. Eight of these cases are described in detail with regard to severity of poisoning, severity of metabolic acidosis, kidney damage, blood ethylene glycol level and haemodialysis treatment. *Results:* 8 cases of acute ethylene glycol poisoning have been closely studied. There is a male prevalence (7:1), as well as a prevalence for accidental poisonings (75%). All patients received antidotal treatment with ethanol solution, given in an individualised dose and mode, while monitoring strictly the condition of the patients, the presence/severity of metabolic acidosis, blood ethanol and ethylene glycol levels. All patients were discharged after different durations of hospital stay. None of the patients showed kidney dysfunction at discharge (table 1) *Conclusions:* 1) No correlation between blood ethylene glycol level and kidney damage was detected. 2) No correlation between blood ethylene glycol level and metabolic acidosis was observed. 2) However we did see a marked correlation between severity of metabolic acidosis and kidney damage. 3) We consider the severity of metabolic acidosis as the most important criterion for performing early haemodialysis in ethylene glycol poisonings.

310. Mass Poisoning with Hydrogen Sulfide. What Happened? A Case of Mistaken Identity

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Objective: Identification of the offending agent(s) involved in hazardous materials accidents sometimes presents a challenge both for rescue workers on site as well as for toxicologist on call. The advent of new economy in some Eastern and Central European countries adds to the problem. By hiring cheap unskilled and untrained personnel, employers are trying to cut down production costs, but this in turn can lead to inappropriate and/or delayed hazmat response as witnessed in the presented case. *Case report:* We received a call from an emergency medical team on site in a textile processing plant, on mass poisoning with an unknown agent, affecting ten workers. The circumstances surrounding the event were unclear. The workers fell ill within seconds of inhaling an unknown gas. Four of them were unconscious, six more suffered from dyspnea, dizziness, ataxia, vertigo, headache and near-collapse. The inexperienced plant's safety engineer was not able to provide the toxicologist with adequate information for an extended period of time, misinterpreted the offending agent as sulfur dioxide and directed the medical team which was without any personal protecting equipment into the "hot zone". Clinical presentation and the time-frame of the event clearly suggested that a different agent was involved (1) and the medical team was prevented from entry. We suspected that the agent at hand must have been hydrogen sulfide, and our estimation was later confirmed when the MSDSs of the chemicals used in the plant were sent to the PCU and the events leading to its release were reconstructed. All patients recovered without sequelae after a brief hospital stay. *Conclusion:* New economy's paradigm of "cutting production costs at all costs" went awry in presented case. A string of events involving untrained workers unfamiliar with hazmat procedures and an inexperienced safety engineer, almost lead to potentially disastrous situation (2). *References:* 1. Munday SW. Hydrogen Sulfide. In: Olson KR ed. Poisoning & Drug Overdose. 4th ed. McGraw-Hill, 2004: 224–5. 2. Kage S. Fatal and nonfatal poisoning by hydrogen sulfide at an industrial waste site. *J Forensic Sci* 2002; **47**:652–5.

311. Pediatric Ingestion of Ant Bait Gel Results in Arsenic Toxicity

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Objective: An ant insecticide trap may contain arsenic trioxide 0.46% in a sweet tasting sugar and protein gel base that attracts ants. Each trap contains approximately 9.9 grams of gel (45 mg arsenic trioxide). The gel is enclosed in a metal container with a small hole for insect access and designed to prevent children from ingesting the contents. The objective of this report is to describe the clinical effects associated with six pediatric exposures to ant traps containing arsenic trioxide. *Case series:* Six children (mean age, 24 months; range, 8 months-4 years) ingested all or part of the contents of an arsenic ant trap found in each child's home (estimated dose range, 5–45 mg AsO_3). In four cases the gel had been removed by an adult for easier ant access, one child opened the container with his teeth, and the method of access was unknown in one case. All children vomited shortly after exposure and were referred to the hospital; one had diarrhea. Initial spot or 24-hour urine total arsenic concentrations before chelation ranged from 2,040 mcg/L to 13,981 mcg/L (mean, 8,546 mcg/L; reference range 0–35 mcg/L). Three patients received a 19-day course of succimer therapy, two patients received a 10-day succimer course and one was started on succimer but was lost to follow-up. Post-chelation urine total arsenic concentrations ranged from 26 mcg/L to 54 mcg/L in 5 patients (mean 41.2 mcg/L). None of the 5 patients who were followed developed alopecia or neuropathy at 2–5 weeks post exposure. All six patients had potentially dangerous urine concentrations of arsenic. *Conclusion:* Ingestion of the gel base contents of an arsenic ant bait by six children resulted in very elevated urine arsenic concentrations. Vomiting was a consistent initial symptom and no long-term toxicity was noted. The effectiveness of chelation therapy for these exposures is unknown.

312. Suicidal Attempt with 99.8% Methanol: An Unusual Case

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Objective: To report an intentional 99.8% methanol (analytical reference material) acute exposure. *Case report:* A 52 year old non drinker male was admitted 3 h after the ingestion of 150 mL 99.8% methanol, presenting nausea, vertigo and 6 episodes of vomiting, without other complaints. He had been under irregular psychiatric treatment for depression, using bupropion, clonazepan and oxicarbazepine for the last 4 months. This was his second suicidal attempt. Physical examination showed no remarkable features. The first methanol serum result (70 mg/dL) was obtained 10 h after the ingestion. A loading dose of 10% ethanol solution (7 mL/kg iv) was given, followed by a maintenance dose of 0.9–1.0 mL/kg/h/iv during the next 42 h (2.1 mL/kg/h during hemodialysis). Folinic acid was administered during 48 hours. An eight hour course of hemodialysis was started 19 h after ingestion. The table below summarizes the main laboratory results according to time post-ingestion. Ophthalmologic evaluation and cerebral CT scan 4 days after admission revealed no changes. The patient was discharged at day four. *Conclusion:* Suicide attempt with high concentrated methanol (99.8%) is not common. A possible low alcohol desidrogenase activity phenotype, in a chromic alcohol abstinent person, may explain the lack of relevant acid-basic disturbances during the first 20 h from ingestion, despite the high methanol serum level. The good outcome may be attributed to the prompt admission, ethanol administration, and hemodialysis performed in the first 24 h after ingestion. *Reference:* Barceloux DG, Bond R, Krezenlok EP, *et al.* AACT Practice Guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol* 2002; **40**: 415–446.

313. Inhalational Methanol Exposure in an Occupational Setting

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Objective: Methanol which is widely used as a solvent can cause severe symptoms even with small ingested doses. Toxicity after inhalation is rare and mainly described after inhalational abuse. Little is known about accidents in an occupational setting (1,2). *Case report:* 3 workers were exposed to methanol vapor in an enclosed room of 600 cubic meters for 60 minutes. They were repairing a leakage, due to which 300 liters of methanol were spilled. All patients had only minor symptoms (nausea, blurred vision, dizziness, dyspnea, burning feeling with inspiration) during the exposure. All symptoms resolved within minutes of cessation of exposure. None developed any delayed symptoms. For methanol blood levels and arterial or venous blood gas analysis see table. Blood was drawn about 3 hours after exposure. *Conclusion:* Despite a prolonged exposure in an enclosed, ill-ventilated room with a large methanol spill, no toxic methanol blood levels resulted, although the levels were clearly elevated compared to naturally occurring levels (0.03–0.2 mg/dL (3)). Such accidents might be managed safely without measuring methanol blood levels which are not routinely available and without antidotal

Table: Laboratory results according to time post-ingestion

	Time from ingestion						
Laboratory parameter	**4h**	**10h**	**19h**	**27h**	**35h**	**52h**	**76h**
Blood pH (RV=7.35–7.45)	7.38	7.42	7.42	7.42	7.49	7.44	
sLac (mmol/L) (RV=0.5–1.6)	1.9	1.8	3.3	3.4	1.8	–	
Anion gap (mmol/L) (RV=12–16)	12.8	10.4	15.2	9.7	8.2	–	
sMethanol (mg/dL)		70	–	20	12	5.7	ND
sEthanol (mg/dL)				99	90	80	12
Ethanol infusion		X	X	X	X	X	
Hemodialysis			X	X			

therapy. *References:* 1. Van Kampen RJ, *et al.* Serious intoxication after inhaling methanol. *Ned Tijdschr Geneeskd* 2006; **150**: 1298–302. 2. Aufderheide TP, *et al*. Inhalational and percutaneous methanol toxicity in two firefighters. *Ann Emerg Med* 1993; **22**: 1916–8. 3. Ernstgard L, *et al*. Uptake and disposition of inhaled methanol vapor in humans. *Toxicol Sci* 2005; **88**: 30–8.

Table: Three patients exposed to methanol vapor

	Methanol					BE
	mmol/L	mg/dL	pH	pCO_2 mmHg	HCO_3 mmol/L	mmol/L
Patient A	0.45	1.4	7.41	36	23	–1
Patient B	0.11	0.35	7.42	43	27	3
Patient C	0.96	3.07	7.38	51	29	3

Blood gas analysis: patient A and B arterial, patient C venous.

314. Reducing Unintentional Adult Exposures to Chemicals: What Messages and to Whom?

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Objective: Poison Centres infrequently focus poison prevention messages to adults since unintentional poisonings in adults are often considered to be an uncommon occurrence. We undertook to characterize the nature and frequency of adult unintentional chemical exposures with a view to identifying poison prevention messages targeted to the adult population in Saskatchewan. *Methods:* All adult unintentional poisonings due to chemical exposures reported to the Saskatchewan Poison Centre from April 1, 2006 to September 30, 2006 were retrospectively identified. Only those cases with sufficient narrative to determine circumstances were included. *Results:* Of the 458 cases identified, 379 (83%) met the inclusion criteria, 79 (17%) cases were excluded due to coding errors (2), insufficient narrative (5), symptoms unrelated to suspected exposure (24), food/animal or plant poisoning (45), or irretrievable (3). The majority of chemical exposures occurred in the 20–39 age group (50%). Routes of exposure were equally distributed among ingestion (28%), inhalation (24%) dermal (22%) and ocular (18%). The most common circumstances resulting in chemical exposure were occupation-related (20%) with a frequency reflecting the agricultural (29%) and oil and gas (11%) nature of the local economy. These occurred in the 20–39 age group, during routine use (38%), involving a procedure breach (20%) or equipment failure (20%). For those cases where documentation of use of PPE was recorded, 73%, 55%, and 80% were not wearing ocular, dermal or respiratory protection, respectively. Over half were managed in a health care facility. The second most common circumstance was mistaking a chemical for an edible product (19%), usually related to transferring the chemical into a drink container (48%). This was a common practice in both the 60+ age group (48%) and the 20–39 age group (31%). Household chemical exposures were primarily inhalational (55%) related to using a product in a confined space. *Conclusion:* Three areas of targeted poison prevention messages were identified, (1) proper use of functioning PPE among young adults in the workplace, (2) dangers of transferring chemicals into drink containers (3) precautions when using household cleaners in an enclosed space.

315. Glyphosate Poisoning

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Objective: Glyphosate, a non-inhibiting aminophosphonate (non-cholinesterase inhibitor), is a widely use herbicide. There are some different formulations that contain a salt of glyphosate and a surfactant, which seems to be the causative agent of poisoning effects. Glyphosate has a high grade of toxicity since an ingestion of more than 200 ml is associated with a high morbidity and mortality. *Case report:* We present the case of a 39-year-old male patient who consumed intentionally more than 200 ml of glyphosate (Roundup©). He presented with profuse vomiting. Clinical evaluation was normal and the complementary tests showed: EKG with sinus tachycardia, K 2.8 mmol/L, creatinine 2.75 mgr/dl, arterial blood gases: pH 7.12, pCO_2 26 mmHg, PaO_2 96 mmHg, HCO_3 8.6 mEq/L, EB - 20.7. Gastric lavage was carried out. Four hours after ingestion he developed neurological deterioration, respiratory difficulty and arterial low blood pressure treated with dopamine, bicarbonate and mechanical ventilation. In the second radiography there was a congestive bilateral pattern. He developed oliguria with a renal failure. Seven hours after ingestion he developed cardiovascular refractory deterioration, acute respiratory failure, elevation of liver enzymes and refractory hypoglycaemia. He died because of multiorgan failure thirteen hours after ingestion. *Conclusions:* Cases of death have been described in the first hour after the ingestion of 50–150 ml. The most common symptomatology after ingestion includes throat pain and dysphagia, ulcerations of the oral mucous membrane, vomiting. Shock happens in serious cases, with arterial low blood pressure and oliguria. In addition to the usual measurements endoscopy is recommended in patients with symptoms of gastric irritation after consumption. Hemodialysis was indicated. In our patient but the rapid evolution and deterioration did not allow this procedure.

316. DNA-Damaging Potential of Carbon Monoxide in Acute Poisoning (Case Report)

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Objectives: Carbon monoxide exposure continues to be one of the leading causes of poisoning in Poland. Although CO-induced mortality is on the decline, there is an increasing concern regarding delayed sequelae in poisoned patients. The aim of this study was to investigate cytotoxic and genotoxic effects of acute carbon monoxide poisoning on human leukocytes and to determine the possible relation between DNA damage and apoptosis in an otherwise healthy 25-year-old woman. *Methods:* Fenech method (1) was used to obtain material for micronuclei (MN) analysis and to count MN in binucleate cells (BNC). Nuclear division index (NDI) was calculated to determine the proliferation rate. Apoptosis was revealed as sub-G1 events in flow cytometry analysis of DNA content stained with propidium iodide in lymphocytes. Annexin V (FITC) was used to recognize translocated phosphatidyloserine in membrane of apoptotic cells. Negative control sample was analyzed in parallel with the test sample. *Results:* Decrease of the total number of leukocytes from 7.5x10ˆ3/mm^3 to 3,38x10ˆ3/mm^3 was observed in the first three days. Initially, the number of apoptotic cells in the studied sample did not differ from the control sample. Significant changes in a subset of leukocytes were observed on the third day: monocytes (90.68% versus 44.63% in the control sample), neutrophils (87.25% vs. 23.16%), lymphocytes (2.39% vs. 0.39%). MN test results at 3 MN in 71 BNC, while NDI comes to 1,044. *Conclusion:* Presented *in vitro* and *in vivo* studies confirmed the genotoxic and cytotoxic potential of CO. Carbon monoxide drastically reduces the number of cell capable of proliferation, which might result in resistance to stimulation, permanent cell cycle arrest or apoptosis. Leukopenia reported after CO intoxication and changes in the subset of leukocytes may result from DNA damage - a well-known apoptosis-inducing agent. A decrease in the number of leukocytes until 48 h after the intoxication would suggest that either the apoptotic signal lasts for several hours or that leukocytes activated as a result of stress connected with external CO are removed by apoptosis once the stress factor is no longer present. *Reference:* 1. Fenech M. The *in vitro* micronucleus technique. *Mutation Res* 2000; **455**: 81–95.

317. The BfR–ESPED Study 2000–2006: Dangerous Lamp Oils

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The particular health risk for young children posed by dangerous lamp oils has been known in Germany since about 1970. Even very small quantities (often less than a sip) can result in severe health damage. Numerous risk minimization measures have been initiated and promoted by the BfR and predecessor institutes. Coloured and scented lamp oils containing petroleum distillates or paraffin for use by private consumers were banned (from 1 January 1999 in the Federal Republic of Germany and from 1 July 2000, in EU Member States). The effects of the ban are reviewed. *Results:* Since 1 March 2000, altogether 765 cases of lamp oil ingestion have been reported by the participating paediatric hospitals through the ESPED centre in Düsseldorf. The 65% response rate to questionnaires on clinical data (494 cases) can be regarded as a good. The total number of cases of lamp oil poisoning reported by the participating paediatric hospitals has clearly shown a decreasing trend. A similar trend has also been recorded by the German PCCs. Prior to the study, the ratio of coloured/colourless lamp oils was about 80%/20%, and this ratio has become completely inverted from 2005 onwards. As cases of lamp oil poisoning decreased, the rate of cases of pneumonia was reduced to the same extent, which can be regarded as successful in benefiting the health of children. According to the study results and information submitted by PCCs, lamp oil substitutes have not shown any risk potential so far. *Conclusions:* The annual numbers of cases and the incidence of pneumonia, caused by lamp oils in Germany have been reduced to less than 40% of the level in 2000. This means that the risk due to lamp oil ingestion has shown a clearly decreasing trend. Additionally, if in the near future child-proof burners, according to the CEN standard for decorative lamps and garden lamps initiated by the BfR, are used by parents, oil lamps and their fuels will soon cease to pose any relevant risk for children.

318. The Cardiovascular Toxicity of Glyphosate-Surfactant (Case Series)

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Background: Glyphosate-surfactant herbicide (GlySH) is used widely as a non-selective herbicide. Accidental ingestion of GlySH is generally associated with only mild and transient gastrointestinal features but ingestion of more than 200 mL is prognostic of a poorer outcome. Shock occurs in most severe cases. Hypovolemia has been observed as the cause of shock, but recurrent hypotension refractory to fluids and vasopressors is noted. Cardiogenic shock probably occurs because of transient suppression of the cardiac conduction system and contractility. Major poisoning could lead to decelerating contractility and heart rate, which might be chiefly attributed to the added surfactants. The purpose of this study is to review the clinical presentations and the management of cardiovascular toxicity of GlySH. *Methods:* The patients were collected from Jan 2006 to Mar 2007 in one 1500-bed hospital in the central part of Taiwan. We included patients who had unstable vital signs, or shock requiring resuscitation. We use T-test for variation analysis. *Results:* There were 26 patients with GlySH intoxication (41% isopropylamine and 15% polyoxyethyleneamine) via ingestion in our study period. Six cases with unstable vital signs needed resuscitation and intubation. The incident rate of shock after poisoning was 24%. The average age was 60 years in these four male and two female cases. Three patients expired, two with ischemic bowel. The average amount of GlySH ingested was about 270 mL (200–500). Sinus tachycardia was recorded in 4 cases on electrocardiogram and bradycardia was noted in others. Fluid resuscitation was administrated (more than 3000 mL in all) with vasopressors but recurrent hypotension was noted. One female suffered bradycardia with diffuse intraventricular conduction defect after drinking 500 mL of GlySH and torsade de pointes occurred later. She recovered after treatment with magnesium sulfate in intensive care. The other case of note presented with junctional bradycardia after ingestion of about 200 c.c. and hemodialysis (HD) was carried out, after which cardiovascular status improved. Electrolytes including magnesium, potassium, sodium and calcium in 5 cases were within normal range except for one male patient. *Discussion:* Shock occurs in most severe cases. In spite of hypovolemic shock, cardiogenic shock is mandatory because of transient suppression of the cardiac conduction system and contractility. Several types of dysrhythmias have been recorded in our cases, so intensive acute cardiac life support is indicated. Hemodialysis is not only for patients with renal failure, but also played an important role in overcoming the cardiovascular toxicity of GlySH intoxication.

319. Unusual Acute Exposure to Urea – A Case Report

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Objective: According to the best of our knowledge there are no reports in the medical literature about massive and acute exposure to carbamide. We have described a man who has fallen into a wagon car full of 100% of granulated urea. *Case report:* A 34-year-old worker slid down from the loading platform and fell into granulated carbamide during the reloading of the wagon. He was completely covered up with urea for about ten minutes until his co-workers were able to get him out. At the time of admission the patient was in deep coma (GCS 4) with BP 100/40 mmHg, MAP 60 mmHg, pulse 110 b./min, RR 25 breaths/min, and T 37.0 C. The biochemical results showed elevation of creatine kinase to 660 U/L (norm <190 U/L), and hemolysis with the level of free hemoglobin to 79.8 mg/dl (norm 2.4–11.5 mg/dl). From the chest X-ray acute lung injury (ALI) was diagnosed. The arterial blood gasometry was as follows pH 7.32; CO_2 40 mmHg; pO_2 51 mmHg; HCO_3 20.6 mmol/L; BE -5,5; and SO_2 82%. There were numerous foci of burns seen in the vocal cords, epiglottis, neighbouring mucous membranes, tongue, velum, and skin especially in places which were not covered with the overall. After initial improvement of the patient's health strenuous non-productive cough, and dyspnea appeared. In HRCT there was a sign of allergic alveoli reaction. The spirometry showed the obturative respiratory insufficiency. Four months follow up discovered the resolution of all abnormalities seen in the first chest X-ray, and HRCT. The spirometry, however, showed persistent obturative respiratory insufficiency accompanied with cough and gasping during any exertion. The same results were obtained also after one year of observation. *Conclusions:* Carbamide is known as a nontoxic agent and there are little data about its toxicity in the medical literature. Massive carbamide exposure, however, resulted in chronic health diminution as persistent obturative respiratory insufficiency in the described case. *References:* 1. Brooks SM. Occupational asthma. *Toxicol Lett* 1995; **82**: 39–45. 2. Edjtehadi M, Szabuniewicz M, Emmanuel B. Acute urea toxicity in sheep. *Can J Comp Med* 1978; **42**: 63–68. 3. Andersen FA. Final report of the safety assessment of urea. *Int J Toxicol* 2005; 24 Suppl 3: 1–56.

320. Evaluation of Plasma Nitric Oxide Level and Total Thiol in Acute Organophosphate Induced Poisoning

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Objective: Organophosphates (OPs) are acetyl cholinesterase (AChE) inhibitors (1) and may induce nitrosative stress leading to generation of nitrogen free radicals (NFR) and alterations in scavengers of free radicals in many biological systems (2,3). The aim of this study was to examine whether OPs might induce nitric oxide (NO) production and total thiol molecules alteration (as a marker of scavengers of free radicals) in acute OP induced patients. *Methods:* Patients (n=21) with acute organophosphate poisoning according to case history and clinical diagnosis were selected. Whole blood and plasma samples from patients and healthy volunteers as control group (n=26) were collected. AChE activity was assayed by the Ellman method (4) and NO in plasma was determined by Greiss method (5) and plasma total thiol was determined by UV-VIS spectrometry (6). Data from patients were analyzed and compared with controls. *Results:* The presented data shows: 1. The AChE activity (4.36 ± 3.24 U/L) in patients was significantly lower than control (10.02 ± 1.42 U/L) (P<0.001). 2. In patients, the plasma NO concentrations (3.72 ± 2.01 mcg/L) had no significant difference in comparison with control (4.06 ± 2.39 mcg/L), but the plasma total thiol amounts in the intoxicated group (0.48 ± 0.19 mM/L) were significantly less than control (0.85 ± 0.44 mM/L) (P<0.001). *Conclusion:* We concluded that in OP poisoning, depression of AchE may be accompanied by induction of oxidative stress which is not caused by NO production. *References:* 1. Khurana D, Prabhakar S. Organophosphorous intoxication. *Arch Neurol* 2000; **57**: 600–602. 2. Chan JY, Chan SH, Chang AY. Differential contributions of NOS isoforms in the rostral ventrolateral medulla to cardiovascular responses associated with mevinphos intoxication in the rat. *Neuropharmacol* 2004; **46**: 1184–94. 3, Mantione K. Pesticides may be altering constitutive nitric oxide release, thereby compromising health. *Med Sci Monit* 2006; **12:** RA235–40. 4. George PM, Abernethy MH. Improved Ellman procedure for erythrocyte cholinesterase. *Clin Chem* 1983; **29**: 365–68. 5. Griess Reagent System, Instruction for product G2930, Promega, USA, 2005. 6. Hu ML, Dillaerd CJ. Plasma SH and GSH measurement. *Method Enzymol* 1994; **233**: 35–7.

321. Favorable Gastrointestinal Outcome in Severe Systemic Toxicity after Concentrated Acetic Acid Poisoning (Case Report)

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Objectives: Concentrated acetic acid ingestion results in upper gastrointestinal tract caustic injuries and systemic effects. We present a case with early development of hemolysis, acute renal failure, hyperthrombotic condition but without significant caustic gastrointestinal sequelae. *Case report:* A 48-year old women was admitted to the hospital with a history of concentrated acetic acid ingestion about an hour and a half before in a suicidal attempt. She had no medical history. The first sign of the poisoning was massive haematemesis occurring at home. The patient presented with BP 100/70 mm Hg, HR 105/min, ECG with flattened T waves, leucocytosis, normal BUN and creatinine, bilirubin rise: total 81 g/l, dir 53g/l, indirect 28 g/l, and AST 126 U/l, fibrin-degradation products more than 2030 ng/ml (ref range 250 ng/ml), prolonged activated partial thromboplastin time 51 sec (22 sec) and urine sample with haematuria. Physical examination revealed epigastric pain, metrorrhagia, and anuria at admission. Toxicological analysis did not reveal ingestion of other toxins or medications. Diagnostic oesophagogastroduodenoscopy performed on the second day of admission showed oesophagitis and gastritis corrosive gr IIa and IIb (Kikendall), echotomography revealed enlarged kidneys. Because of anuria with increased urea nitrogen 15.6 mmol/l and creatinine up to 823 micromol/l (normal 130 micromol/l) the patient underwent 10 periods of hemodialysis with heparin 5000 IE in the first and the following with 500 IE due to the intensive hematemesis after each one. Echo color-doppler-investigation showed phlebothrombosis illeofemoralis l.sin. Conservative treatment included parenteral proton pump inhibitor, antacids, broad-spectrum antibiotics, methylprednisolone, fresh frozen plasma and blood substitution, heparin during dialysis, low molecular heparin, total parenteral nutrition. The patient was discharged after 30 days stay at the hospital with regulated hypertension but no upper gastrointestinal complications on control oesophagogastroduodenoscopy and regular diuresis, degradation products, electrolytes and blood count. She was advised to take antihypertensive therapy and anticoagulant therapy until controlled. *Conclusion:* Glacial acetic acid poisoning with marked systemic complications usually causes severe GI lesions. The favorable GI outcome in our patient with severe hemolysis and renal failure may indicate an individual response to the toxin and may indicate a possible role for heparin in preventing GI strictures in this kind of poisoning. *Reference:* Bingol-Kologlu M, Tanyel FC, Muftuglu S, *et al*. The preventive effect of heparin on stricture formation after caustic esophageal burns. *J Pediatr Surg* 1999; **3492**: 281–4.

322. Highly Concentrated Hydrofluoric Acid Digital Burn Treated with Radial Intra-arterial Calcium Infusion

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Objective: To present and discuss a clinical case of digital burn due to highly concentrated hydrofluoric acid treated with intra-arterial calcium infusion. *Case report:* A 41 year old Caucasian male was seen at ED 35 minutes after skin contact with 70% hydrofluoric acid in an occupational accident when cleaning a slate floor around a pool. Despite using gloves to do the job, he had touched the bottle cork without protection shutting it up. By phone he was advised by PCC staff to wash up the lesions profusely with water for 15 minutes and come to the ED. At the ED the skin of the right middle finger was already blanched and swollen with the nail bed injured. Patient complained of severe local pain. 2.5% calcium gluconate ointment was applied over the lesions using surgical glove fingers. He was asked to apply the ointment every two hours for the following 12–24 hours. After 24 hours he was still under severe pain and the lesions had worsened. Serum calcium=9.5 mg/dL (RV=8.6–10). 10% Calcium gluconate (10 ml) was administered intravenously without any improvement of pain. Considering the high concentration of the HF solution; the early start and severity of pain 24 hours after the accident; the blanched and swollen lesion suggesting progression to necrosis; and the impossibility of subcutaneously administer calcium gluconate, it was decided to give him the drug intra-arterially through the catheterization of the radial artery at wrist level. 50 ml of a 2% solution of calcium gluconate in 5% dextrose was given during 4 hours with a pump, and repeated each 4 hours for 48 hours until pain subsided (1). No adverse effects were seen during the procedure, and the catheter was withdrawn without local problems. 28 days later, lesions were stable with no sign of necrosis. *Conclusion:* Intra-arterial calcium gluconate can safely be used in digital burns due to high concentrated HF, when topical treatment showed to be useless, or intradermal and subcutaneous calcium injections can not be performed. *Reference:* 1. Vance MV, *et al*. Digital hydrofluoric acid burns: treatment with intraarterial calcium infusion. *Ann Emerg Med* 1986; **15**: 890–6.

323. Withdrawn

324. A Cluster of Unexpected Severe Phosphine Poisonings in Spain

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Introduction: Phosphine and phosphides are used as insecticides in agriculture as well as fumigants in warehouses and storerooms of ships. Phosphides when in contact with water are able to produce phosphine, a life-threatening toxic substance which causes a poisoning difficult to manage. In some instances, phosphide containers are inappropriately stored and as a result, non occupational intoxications have been described. Between March 2005 to April 2007, 25 toxic exposures were detected in our centre: aluminium phosphide (12 cases), phosphine (11), magnesium phosphide (2) and aluminium phosphide plus other fumigants (1). The aetiology was occupational in 15 cases and the home was the scenario in 10 occasions. Our purpose is to highlight the toxicity of these compounds with a case series of non occupational intoxication registered in our PCC. Two of the victims died. *Case series:* In 2006 our centre was consulted by the emergency department of a hospital about the clinical symptoms of 3 children and their parents. The two smaller children and their mother presented with vomiting and nausea, while the other child and the father remained asymptomatic. The clinical manifestations were the following: nausea, vomiting, headache, dizziness, drowsiness, mucous irritation, chest pain, and in the severe cases coma, arrhythmias, hypokalaemia, metabolic acidosis, and hypoglycemia. Several substances were initially suspected such as mushrooms (ingested the previous night), methanol, carbon monoxide and cyanide. Two days later, the one-year-old child died and so did the three-year-old child the following day. Phosphide was detected in the liver sample of one of the babies. It was finally discovered that the neighbour stored aluminium phosphide in his damp basement. Phosphide was found after a sublimation of the rest of the product. *Conclusion:* The vast majority of phosphide and phosphine poisonings are severe. Although the exposure occurred more frequently at work, we must take account of household intoxications especially because children can be involved and they are more severely affected. There are specific laws and regulations governing the handling, storing, dispersing and disposal of toxic agents. The health authorities and other institutions have an important role in alerting and implementing prevention, and banning measures.

325. The Polonium-210 Incident: The Dutch Perspective

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Introduction: On November 23 2006 ex-spy Alexander Litvinenko died in a London hospital after being poisoned with radioactive polonium-210 (Po-210). As a result of this assassination, various places became contaminated with Po-210, including the bar of a hotel in the middle of

London where Litvinenko met two Russians prior to his sickbed. Because of this contamination of public places foreigners of many different countries were potentially exposed to this highly radioactive material, resulting in a large-scale international follow up. For this reason the British Health Protection Agency set up an overseas team as part of their extensive investigation into the public health risks. *Case report:* In the Netherlands, the Dutch National Poisons Information Centre (NVIC) of the National Institute for Public Health and the Environment (RIVM) was contacted to asses the possibility of a contamination with Po-210 of a group of Dutch hotel guests. The NVIC is officially embedded in the response network for radiological incidents. Its radiation specialists are available 24/7 for medical advice in case of exposure to radioactive material or ionizing radiation. Eleven of 24 individuals that were assessed, had visited the contaminated bar. They agreed to participate in a further investigation. The Laboratory of Radiation Research of the RIVM measured the Po-210 in urine samples collected over 24 hours. In one person an increase of the Po-210 level in urine was determined, indicating contamination with Po-210. It is not expected that this slight increase will cause any health concern to the individual. *Conclusion:* The poisoning of Litvinenko not only affected the UK, but required an extensive international follow-up to check foreigners who visited contaminated places. In the Netherlands, one person proved to be contaminated in relation to this incident.

326. Rapid On-Site Sulfur Mustard Detector for Emergency Medical Teams

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Objective: Attacks with sulfur mustard (2,2'-bis-chloroethyl sulfide) are regarded as a huge threat to civilian and military personnel. Experience from the Iran-Iraq war showed that medical personnel were unexpectedly exposed to significant amounts of sulfur mustard (SM) during treatment of victims thus leading to the development of injuries and long term effects. Our aim was to develop a feasible and sensitive on-site test-strip system for Emergency Medical Teams in order to detect active SM on the skin of victims and prevent involuntary exposure. *Methods:* SM quickly alkylates DNA. This reaction was utilized to develop a sensitive small size immunochromatographic test-strip system (SM-Detector). For the detection an antibody (2F8) produced by the Netherlands Organization for Applied Scientific Research (TNO) was used which shows high specificity and sensitivity to those SM-DNA-adducts (1). The SM-Detector was evaluated by the German Medical Corps in laboratory experiments and in the field. The latter was conducted in military training scenarios during NATO exercises in Canada. For example, in order to test the SM-Detector for direct measurement, SM (1 mM) was spread on pig skin. Another scenario included a soldier exploring a cave filled with SM vapor. The SM-Detector was fixed to a side pocket of the individual protective suit. *Results:* During several on-site applications the detector showed immediate positive results within few minutes. Surprisingly, a positive test result could also be observed after indoor contact with only slight traces of sulfur mustard in the ambient air, proving high sensitivity to SM vapor in the environment. *Conclusion:* Great advantages of this out-of-the-pocket SM-Detector are instant availability, fast analysis and no need for sophisticated technical equipment (2). Furthermore the high sensitivity for SM detection makes it a valuable tool for all Emergency Medical personnel. *References:* 1. van der Schans GP, Mars-Groenendijk R, de Jong LP, *et al*. Standard operating procedure for immunoslotblot assay for analysis of DNA/sulfur mustard adducts in human blood and skin. *J Anal Toxicol* 2004; **28**: 316–9. 2. Noort D, Benschop HP, Black RM. Biomonitoring of exposure to chemical warfare agents: a review. *Toxicol Appl Pharmacol* 2002; **184**: 116–126.