

ABSTRACTS

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## 1. Modelling dose-concentration-response

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**Introduction:** It is the aim of modeling to quantitatively describe the relationship between dose, concentration and response and its time course.

**Methods and results:** Pharmacokinetic (PTK) data is information about the entrance and fate within the body of a substance, including its metabolites. The data needed to describe these phenomena can be obtained by *in vivo* experiments. With this approach, modeling means that the concentration-time profile is driven by data and that key data (clearance, half-life) are derived from it (top down approach). Physiologically based PTK (PBPTK) modeling uses results from *in silico*, *in vitro* and *in vivo* studies in a bottom up approach. This PBPTK modeling approach is helpful in estimating target organ doses that can be expected from human external exposure. The fact that PBPTK models are mechanism-based allows them to be “generic” to a certain extent enabling simulations and predictions of the kinetics under special circumstances, e.g. the implementation of age- and disease-dependent physiological changes and also the kinetics in organs which are experimentally difficult to access, e.g. the liver. The need for high-quality *in vitro* and *in silico* data on absorption, distribution, metabolism as well as excretion (ADME) as input for PBPTK models is necessary to predict human concentration-time profile. Pharmacokinetic-pharmacodynamic (PK/PD) modeling means to develop a model for the concentration/AUC-effect relationship which is coupled to the PTK model. Empirical models are non-mechanistic and the parameters may be adequate for describing the longitudinal data at hand (e.g. the time course of an effect), but that may not be biologically relevant. A semi-mechanistic model is a compromise.

**Discussion and conclusion:** The goal of modelling is to describe the time course of xenobiotic actions that are most represented in the (PK/PD) measurements or the responses (the “data”), with simple but adequate complexity. Physiologically-based modeling of pharmacokinetics requires an *a priori* knowledge on the underlying mechanisms causing toxicity or causing the disease.

## 2. Epidemiology of fatal poisonings: National Poison Data System (NPDS) data 2000–2014

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**Introduction:** The American Association of Poison Control Centers (AAPCC) published its first annual report in 1983. Call data from sixteen US poison centers was chronicled in that report. Seven submitted data for the entire year. By July 2000, 63 centers were part of the national poison center system, but only 59 submitted data for the full year. Currently the US poison center system is comprised of 55 regional poison centers serving all 50 states, Puerto Rico, US Virgin Islands, and three Pacific jurisdictions. The centers continuously upload data to the AAPCC's National Poison Data System (NPDS). From 2000 forward, poison center call data including fatality data is available from NPDS online. Since inception of the PC database, exposure-related death analysis has been a priority. Over the years, death report evaluation methodology has evolved. A poison center death is defined as a poison center call resulting in the medical outcome of Death associated with the reported exposure. If no inquiry was made to the poison center, a death is defined as Death, Indirect Report. The singular question that must be answered in reviewing and categorizing deaths is: Did the exposure cause the death? In 2000, only poison center deaths (Death and Death, Indirect Report) judged to be probably or undoubtedly related to the exposure were identified in the annual report as poison-related fatalities.

**Methods:** Beginning in 2006, a new system of evaluating and classifying deaths was implemented. Each death (Direct or Death, Indirect Report) was evaluated by a medical and a clinical toxicologist, reviewed by a medical toxicologist fatality manager and computer scored based on the review results. Deaths and Death, Indirect Reports were assigned to one of six Relative Contribution to Fatality (RCF) categories. RCFs were designated separately by the regional PC and the AAPCC review team with difference resolution part of the review process. The RCFs denote the probability of the exposure substance(s) being responsible for the death: 1) Undoubtedly responsible (Proximate Cause of Death) - beyond a reasonable doubt, 2) Probably responsible - some reasonable doubt remains, 3) Contributory - the substance(s) alone did not cause the death, but combined with other factors, were partially responsible, 4) Probably not responsible - establishes to a reasonable probability, but not conclusively, that the death was not poison related, 5) Clearly not responsible (and Not Contributory) - establishes beyond a reasonable doubt that the substance(s) did not cause the death, and 6) Unknown - insufficient evidence to establish a causative relationship between the substance(s) and the death. The first iteration of this revised process was published in Table 21 of the 2006 NPDS Annual report and included fatalities with RCFs 1-4. Although all deaths received by the poison centers were reported, only those with an RCF of 1-4 were listed in Table 21. This changed with the 2007 report when only deaths with an RCF of 1, 2, or 3 were listed. The reporting process changed again in the 2010 Annual

Report with Death, Indirect Report only being assigned a RCF by the regional center. Thus this scoring process attempts to quantify exposure relatedness to the cause of death. Only deaths with an RCF of 1, 2, or 3 are designated true poison related fatalities.

**Results:** In 2000, 920 deaths (Direct and Death, Indirect Report) were recorded. This number increased to 1728 deaths (Direct and Death, Indirect, includes all RCFs) by 15 December 2014. Although NPDS human exposures peaked in 2008, the proportion of deaths has remained relatively constant from 2000–2014 (15 December). The median number of all deaths was 1544 [range: 920, 2937] or 0.06% [0.04, 0.13] (median [min, max]) of all human exposures. Subtle differences are observed in exposure route and substance count between all human exposures and deaths. Over the 15 year period the top 3 routes for all human exposures were: Ingestion (81.9%), Dermal (7.6%), and Inhalation/nasal (6.0%) compared to all reported deaths: Ingestion (79.4%), Inhalation/nasal (8.8%), and Parenteral (5.3%). Routes for fatalities with RCF 1, 2, or 3 were: Ingestion (83.8%), Inhalation/nasal (9.1%), and Parenteral (4.3%). Although most human exposures were single substance exposures (90.7%), only 42.8% of all fatalities with RCF 1, 2, or 3 were due to one substance. In 2000, the top 5 substance categories associated with human poisoning-related deaths were: Analgesics, Antidepressants, Sedative/Hypnotics/Antipsychotics, Stimulants and Street Drugs, and Cardiovascular Drugs. By late 2014, this ranking had changed to Sedative/Hypnotics/Antipsychotics, Cardiovascular Drugs, Opioids, Stimulants and Street Drugs, and Alcohols, reflecting changing use, abuse and prescription patterns. Detailed analysis reveals increases in opioid, including heroin, deaths. Pediatric deaths are a particular concern. In the 1950s, the awareness of increases in pediatric poisoning deaths stimulated the development of US poison centers. Although the numbers of deaths in children  $\leq 5$  years have decreased since the 1950s, the ratios of pediatric deaths to human exposures and all deaths have been slow to change. In 2000 there were 20 pediatric ( $\leq 5$  years) deaths (2.1% of all deaths). Half were attributable to household products and 4 were related to long-acting opioids (methadone and morphine). In 2013 (the last complete year at the time of writing), there were 29 pediatric fatalities comprising 2.4% of all deaths. In 2013, the leading substances associated with all pediatric deaths (includes Death and Death, Indirect) regardless of RCF score were: Fumes/Gases/Vapors, Analgesics (includes opioids), Unknown Drug, Batteries, and Antidepressants. Year to date in 2014, NPDS lists 31 pediatric deaths equating to 1.8% of all 2014 NPDS deaths with the top 5 substances: Fumes/Gases/Vapors, Analgesics, Cleaning substances (household), Alcohols, and Antihistamines.

**Conclusion:** In terms of absolute numbers, NPDS fatality counts are smaller than other monitoring systems, but the near real-time nature of NPDS makes NPDS a barometer of poison exposure and fatality data in lock-step with other surveillance systems with less rapid reporting timelines. This awareness is important when comparing the relative merits of the poison center-based NPDS system to other monitoring systems. NPDS provides continuously available data for situational awareness and identifies epidemiological trends to enhance decision and policy making.

### 3. Toxic murder 2000–2014

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**Objective:** To review homicidal poisonings in the UK and elsewhere since 2000.

**Methods:** A systematic search of the newspaper database Nexis, together with online indexes of several relevant journals, for the terms “murder” and “poison”. Languages were limited to English, Dutch, and French.

**Results:** Sixty-one separate cases in which murder or attempted murder was alleged or proven were identified in 19 different countries. In one case a man became psychotic after taking 3-methoxyphenacyclidine, and methylenedioxypyrovalerone, and repeatedly stabbed his father; and in another a man was found hanged by his turban after having been poisoned with parathion. Otherwise, all deaths or intended deaths were directly caused by poisoning. The largest number killed was 42, poisoned with tetramine by a restaurateur after a row with a neighbouring restaurant in Nanjing, China. Arsenic, cyanide, and opioids were among the traditional poisons used; and ricin and aconite among the plant poisons employed. A number of cases of poisoning by healthcare workers involved ajmaline, insulin, pethidine, potassium and suxamethonium.

**Conclusion:** Reports of murder by poisoning remain rare, but the wide range of agents used, the potential difficulties of diagnosis, and the lack of systematic reporting make the true incidence of homicidal poisoning difficult to ascertain.

### 4. Toxic deaths: Facts and follies of forensic medicine

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**Background:** It was once believed that blood drawn after death reflected the antemortem drug concentration, assuming circulation and metabolism ceased with death, and therefore few aspects (other than gross decomposition) affected blood concentrations of drugs or poisons. Reports of discrepancies in drug concentrations drawn from different anatomical sites of the same body identified the phenomenon of post-mortem redistribution (PMR), seen particularly with alkaline drugs like tricyclic antidepressants. The sampling source (peripheral blood versus heart blood) is a very important factor influencing the degree of PMR. Several other factors also influence the reliability of whether a particular post-mortem drug concentration is due to PMR: time from death until sampling; manner of death and body condition; refrigeration of the body; sample preparation and storage; and the characteristics of the drug(s), including volume of distribution ( $V_d$ ), lipid solubility, charge and pKa. Toxicologists most frequently become involved in forensic cases when alcohol and drugs of abuse are involved, both in criminal aspects and civil actions. While PMR of alcohol from tissue stores is not an issue, sampling site is important when there is high gastric alcohol after recent drinking, especially when trauma to the thoracoabdominal region can cause gastric rupture and spillage. Decomposition can produce ethanol and gamma hydroxybutyrate (GHB), among other chemicals, which must always be considered in a comprehensive investigation. The following examples highlight various aspects of forensic toxicology, focusing primarily on ethanol and drugs of abuse.

**Case report:** Case 1. A search for a 38-year-old male began a day after he went missing when fishing alone and his empty boat washed up on a nearby shore. The body was found by dredging the

lake and promptly refrigerated. The autopsy revealed a peripheral blood alcohol concentration (BAC) of 0.20 g/dL; other volatiles were negative, vitreous ethanol 0.24 g/dL and urine ethanol 0.24 g/dL. Insurance death benefits were denied due to alcohol intoxication; the family appealed the decision, claiming he did not drink alcohol. Issues: The BAC and the alternative specimens were in agreement that ethanol was present at similar concentrations, and corroborated the BAC results. Case 2. A 38-year-old female left a bar after reportedly having 3 drinks over two hours with a meal; while driving she failed to negotiate a curve, went off the road and struck a light post. She sustained massive thoracoabdominal trauma. The coroner performed an external exam and obtained specimens at the scene. He determined the cause of death (COD) as multiple blunt force traumatic injuries to the head and trunk. The BAC was reported by the State Police lab as 0.268 g/dL. A drugs of abuse screen was negative; no urine or vitreous sampling was performed. The family brought a dram shop lawsuit against the bar for serving too much alcohol, causing intoxication and resulting in her fatal motor vehicle accident (MVA). The bartender testified he served only two standard rum and cokes. Issues: Further investigation revealed the coroner drew blood via a transthoracic approach, with possible needle contamination from spilled gastric alcohol due to severe trauma. No alternative specimens such as vitreous humor or urine alcohol were drawn. Dose calculations of amount of alcohol and BAC did not correlate, and specimen contamination was the most likely explanation. Case 3. A 47-year-old male had been missing for 2-3 days in June when the body was found over a roadside embankment following a motorcycle accident. The autopsy revealed severe decomposition changes of the skin with blisters, yellow-green discoloration, and extensive skin slippage and sloughing. Severe bloating of the body was noted, and all cavities contained gas and foul decomposition fluid. All organs showed extensive decomposition. The COD was C-spine fracture with spinal cord transection. Post-mortem heart blood analysis for volatiles revealed ethanol of 0.09 g/dL, and was positive for n-propanol and acetone. No urine or vitreous sampling was performed. Insurance denied death benefits due to alcohol intoxication but the family appealed. Issues: Post-mortem alcohol production can occur when blood glucose is fermented into ethanol. Other volatiles can be produced, so their presence along with severe decomposition makes post-mortem alcohol production a reasonable explanation for the results. Case 4. A 28-year-old male with chronic pain taking immediate and extended release morphine was found dead in his bed. Autopsy revealed pulmonary edema and pink frothy foam in the tracheobronchial tree. The heart blood cocaine concentration was 0.189 mg/L and benzoylecgonine 0.904 mg/L; the heart blood free morphine concentration was 0.169 mg/L; 6-monoacetylmorphine (6-MAM) was negative. A urine sample was frozen, but not tested. The family filed suit against the pain management doctor for over-prescribing morphine, causing his death. Subsequent urine testing was positive for 6-MAM, indicating heroin abuse was likely COD. Case 5: A 29-year-old male with a history of drug abuse and chronic pain issues treated with fentanyl was found dead at home after recent filling of prescriptions. A 100 mcg fentanyl patch was found on his body and many empty whipped cream cans were found in his room. The post-mortem fentanyl blood concentration was 33 ng/mL, and norfentanyl was 3.3 ng/mL. The medical examiner (ME) concluded that death was due to fentanyl overdose. The family brought a suit against the pain doctor for too-rapid dose escalation. Issues: Fentanyl can exhibit PMR; the heart-to-periph-

eral blood post-mortem fentanyl ratio averages 2.7 (range 0.5-11). An inhalant panel by the ME included only hydrocarbons; nitrous oxide was not assayed.

**Conclusion:** Failure to consider PMR can cause false conclusions as to cause of death. Peripheral blood is preferred for post-mortem analysis, but can still be much higher than antemortem concentrations. Intact heart blood sampling is usually reliable for alcohol. Thoracic and cavity blood and samples obtained via transthoracic needle aspiration are subject to contamination. Post-mortem production of alcohol and other chemicals can occur. Vitreous humor and urine can be useful adjunctive specimens to corroborate BAC values. The presence of parent drug cocaine in any post-mortem blood indicates acute use of cocaine due to its short blood half-life. The presence of the short-lived heroin-specific metabolite 6-monoacetyl morphine in blood or urine indicates acute heroin use.

## 5. A simple prognostic model for predicting mortality in acute aluminium phosphide poisoning

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**Objective:** Aluminium phosphide poisoning is an important cause of morbidity and mortality in India. We have developed a simple 3 point model for predicting mortality, the PGI Score, where P is for pH, G for Glasgow Coma Scale (GCS) and I is for impaired blood pressure. In this study we validated and compared it with the Acute Physiology, Chronic Health Evaluation 2 (APACHE 2), Simplified Acute Physiology Score (SAPS) II & Sequential Organ Failure Assessment (SOFA) scores.

**Methods:** A prospective study including all patients with aluminium phosphide poisoning in the medical emergency at our center from January 2013 to September 2014. At admission, GCS, heart rate, blood pressure, electrocardiogram, blood gases, liver and renal functions were recorded and all these parameters were repeated at 24 hours, 48 hours or death. All patients were followed up until discharge or death. APACHE 2, SAPS II, SOFA and PGI scores were calculated at admission. The primary outcome was mortality. Parametric variables were analyzed by the student's t test. For categorical data relative risk of death was calculated with 95% confidence intervals using a chi-square test. Correlation was carried out by univariate, multivariate and multiple logistic regression analysis. Correlation of all four scores was assessed by Spearman's rho test.

**Results:** A total of 76 patients were enrolled. The majority were male (62.2%) in the age group 15-45 years (88%). Mean age was 28.3 years. The mean dose consumed was 2.33 g. Overall 61% patients died. Important parameters, after multivariate analysis, correlating with mortality were blood pH < 7.2, systolic blood pressure < 90 mmHg, GCS < 13, need for inotropes and mechanical ventilation. The 3 Point PGI Score was calculated by using blood pH < 7.2 (1 point), systolic blood pressure < 90 mmHg (1 point), GCS < 13 (1 point). The PGI score correlated well with mortality with a score of 3 having 85% positive predictive value for mortality and score 0-1 having 92% negative predictive value for mortality. Comparison of PGI score with APACHE 2, SAPS II and SOFA scores was statistically significant with a correlation



coefficient of PGI score with APACHE 2 (0.826), SAPS II (0.844) and SOFA scores (0.814) and  $p$ -value  $< 0.001$  for all the four scores, in predicting mortality.

**Conclusion:** A simple prognostic tool for predicting outcome in acute aluminium phosphide poisoning correlates well with established scoring systems like APACHE 2, SAPS II and SOFA as a predictor of adverse outcome.

## 6. Clinical characteristics of fatal salicylate poisonings

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**Objective:** Death related to severe salicylate poisoning may be preventable with timely correction of metabolic derangement and prompt hemodialysis (HD);<sup>1</sup> however, HD may be delayed or foregone in many cases. Our group's (unpublished) analysis of data from the United States National Poison Data System (NPDS) demonstrates that HD was used less often in patients with salicylate poisoning who died compared with survivors with major clinical toxicity (25.9% versus 36.9%,  $p = 0.018$ ). In order to investigate factors that may influence mortality after aspirin poisoning, fatalities reported to the NPDS were reviewed in detail.

**Methods:** The NPDS was queried for all fatality abstracts from single-agent aspirin poisoning deaths occurring during 2008-2012. Fatality abstracts were explored for sixteen specific patient care characteristics by two trained study investigators. Need for HD was determined according to the EXTRIP workgroup's criteria.<sup>2</sup> Discrepancies in data collection were resolved through independent review by a third investigator.

**Results:** One hundred fatal cases of aspirin poisoning were identified, of which 83 were a direct consequence of aspirin poisoning. Death occurred prior to initiation of HD in 78.3% of cases. Failure to identify the need for and/or attempt to perform HD occurred in 32.5% of cases. There was an identifiable  $> 6$  hour delay in initiation of HD in 8.4% of cases. Intubation was shortly followed by death in 13.3% of cases. Care was withdrawn in patients who had attempted suicide in 8.4% of cases.

**Conclusion:** This study represents the largest cohort of aspirin-related deaths of which we are aware. Factors that likely played a direct role in patient deaths included failure to perform hemodialysis, delay in initiation of hemodialysis, and intubation, among others. Given the large number of cases where the absence or delay of hemodialysis was present, it is crucial that nephrologists, emergency physicians, and intensivists are aware of and act upon indications for emergent hemodialysis in salicylate-poisoned patients.

## References

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## 7. Clinical risk factors in Emergency Department (ED) patients with prescription opioid overdose

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**Objective:** In the US, deaths from prescription opioids exceed deaths from all illicit drugs combined. We identified risk factors for in-hospital severe respiratory depression (SRD) and mortality in ED patients with prescription opioid overdose.

**Methods:** This was a secondary data analysis of a prospective cohort of acute drug overdose patients that presented to two large urban teaching hospital EDs from 2009-2013. From this cohort, we analyzed a subgroup with prescription opioid overdose with the following exclusion criteria: pediatrics ( $< 18$  years), alternate diagnoses (e.g., sepsis), lacking data (e.g., eloped). The following variables were extracted: demographics, vital signs, blood gas, ED endotracheal intubation (ETI), naloxone administration, toxicology screen results and in-hospital mortality. The study outcome was SRD defined by either (a) naloxone administration or (b) ETI. Assuming a 20% prevalence of SRD and predictors, we calculated the need to analyze 300 patients to demonstrate 3-fold risk difference with 80% power and 5% alpha.

**Results:** In total 354 patients were screened; 47 were excluded (25 lack data, 10 alternate diagnosis, 9 pediatrics, 3 prisoners), leaving 307 patients for analysis (mean age 44.7, 42% females, 2.0% mortality). Prescription opioid overdoses involved the following, in decreasing order: oxycodone 124, methadone 116, hydrocodone 31, codeine 27, morphine 12, tramadol 12, buprenorphine 7, fentanyl 4, oxymorphone 3 and, tapentadol 2 (some patients exposed to  $> 1$ ). Demographic associations with specific opioids were: males with methadone ( $p < 0.001$ ), females with tramadol ( $p < 0.05$ ), hispanics with tramadol ( $p < 0.05$ ), and whites with buprenorphine ( $p < 0.05$ ). SRD was experienced by 109 patients (90 naloxone alone, 9 ETI alone, 10 both). Mean age was higher in the SRD group (51.1 versus 41.1,  $p < 0.001$ ), and suicidality was inversely correlated with SRD (OR 0.29, CI 0.17-0.5), while gender had no correlation ( $p = 0.95$ ). Risk for SRD was highly dependent on the type of prescription opioid, with highest relative risks for fentanyl (RR 22.5,  $p < 0.01$ ), and lowest for codeine (3.7% SRD). Six patients died during their hospitalization, and mortality was significantly associated with initial tachycardia ( $p < 0.001$ ), hyperlactatemia ( $p < 0.05$ ) and initial hypotension ( $p < 0.01$ ).

**Conclusion:** In this cohort of patients with prescription opioid overdose, relative risk for severe respiratory depression was significantly associated with age and specific opioid drugs, the highest of which was fentanyl (RR = 22.5) and the lowest was codeine (RR = 1). Clinical risk factors for mortality included initial hemodynamic abnormalities and hyperlactatemia.

## 8. Immunological cross-reactivity and pre-clinical neutralisation of European viper venoms with ViperaTAB antivenom

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**Objective:** ViperaTAB<sup>®</sup> is an ovine-derived Fab immunoglobulin antivenom manufactured to treat snakebite by the European viper *Vipera berus*. This antivenom has been demonstrated to be highly efficacious for the treatment of human snakebite in Scandinavia for the past two decades.<sup>1,2</sup> However, its efficacy in treating snakebite caused by other European vipers remains unknown because the toxic components found in snake venom can vary between species, thereby undermining treatment.<sup>3</sup> The objective of this study was to assess the immunological cross-reactivity and pre-clinical neutralising efficacy of ViperaTAB<sup>®</sup> antivenom against venoms produced by a variety of European vipers.

**Methods:** We first assessed the immunological cross-reactivity of antibodies present in ViperaTAB<sup>®</sup> with venoms from a variety of European vipers, using ELISA and immunoblotting experiments. We next assessed the pre-clinical efficacy of ViperaTAB<sup>®</sup> by testing whether the antivenom protected against venom-induced lethality in murine *in vivo* neutralisation assays. Finally, we compared the results of ViperaTAB<sup>®</sup> cross-reactivity and neutralisation assays with those produced with a different antivenom ('Zagreb antivenom').

**Results:** The ELISA and immunoblotting experiments demonstrated that ViperaTAB<sup>®</sup> antibodies recognise and bind to the majority of toxic components found in the venoms of all European viper species (genus *Vipera*) tested, and at comparably high levels to those observed with the venom used for raising the antibodies (*V. berus*). The results of the *in vivo* neutralisation studies demonstrated that ViperaTAB<sup>®</sup> effectively prevents lethality induced by *V. berus*, *V. aspis*, *V. ammodytes* and *V. latastei* venoms in the mouse model, and at much higher levels than those outlined by regulatory pharmacopoeial guidelines. Notably, venom neutralisation was found to be superior to (*V. berus*, *V. aspis* and *V. latastei*), or as equally effective as (*V. ammodytes*), the anti-*V. ammodytes* 'Zagreb antivenom', which has long been successfully used for treating European snake envenomings.

**Conclusion:** This study suggests that ViperaTAB<sup>®</sup> may be a valuable therapeutic product for treating cases of human snakebite caused by a variety of European vipers found throughout the continent.

## References

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## 9. Australian elapid envenoming and intracranial haemorrhage

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**Objective:** Intracranial haemorrhage (ICH) is a rare but life-threatening consequence of snake envenoming associated with venom-induced consumption coagulopathy (VICC). It is unclear why certain patients haemorrhage and there are few case reports to help understand the timing and potential treatment required. We aimed to provide a clearer description of ICH in Australian snake envenoming based on a national multicentre cohort study, the Australian Snakebite Project (ASP).

**Methods:** All cases of VICC from July 2005 to June 2014 were identified in ASP, a prospective multicentre cohort of snake envenomings across Australia. It collects clinical data, laboratory investigations and measures venom concentrations in snake bite patients. Cases complicated by spontaneous ICH were then individually reviewed.

**Results:** There were 552 cases of VICC from a total of 1,380 recruited cases. The median age of patients with VICC was 40 years (range 2-87 years), 417 (76%) were male, 253 (46%) were due to confirmed brown snake bites and 17 died (3%). Antivenom was given in 523 cases (95%). There were 6/552 (1%) cases of spontaneous intracranial haemorrhage, with a median age of 71 years (range 59-80 years), three were males, five were due to brown snakes, the other a tiger snake. All received antivenom and five of the six died. All six had a past medical history of hypertension, with five taking anti-hypertensive medication. The time to the onset of clinical effects (consistent with an ICH) was about 8-12 hours in four cases, and within 3 hours in the other two. Difficult to manage hypertension and vomiting were commonly documented problems, and two patients complained of headaches. In one case a cerebral CT was done on presentation to ED (due to collapse) which was normal. Following the onset of focal neurological effects (at 7 hours post-bite) the patient had a repeat CT that demonstrated an ICH.

**Conclusion:** ICH remains rare in Australian snake bite victims occurring in just over 1% of patients with VICC. The patients with ICH were older than the main snake bite cohort with VICC and tended to have a past medical history of hypertension. ICH in the setting of VICC was almost universally lethal.

## 10. Development of a new antivenom against *Vipera* species for use in canines throughout Europe

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**Objective:** The objective was to develop a safe, effective, reproducible, stable and affordable antivenom, named ViperaVet, for use in canine victims of envenomation by one of four *Vipera* species

of snake found throughout Europe. Antivenom is the only specific treatment for snakebite which effectively neutralizes the toxic venom components. The incidence of snakebite in dogs is at least eight times that in humans and bites by *Vipera* species can result in morbidity of 97% and mortality of more than 4%.<sup>1,2</sup> To date, the lack of a dedicated veterinary product has resulted in the use of human antivenoms, which have been increasingly difficult to obtain and/or are too expensive for the veterinary market.

**Methods:** Twenty five crossbred sheep were immunized with an equal mixture of venom from four medically important snakes found throughout Europe, namely *Vipera ammodytes*, *V. aspis*, *V. berus* and *V. latastei*. Antiserum was harvested from the flock every four weeks over a period of two years and stored at -20°C until required for manufacture. Specific antibody (SAb) levels were monitored using a small scale affinity chromatography (SSAC) assay.<sup>3</sup> From this pool of antiserum batches of antivenom were manufactured for regulatory testing. The first batch was intact immunoglobulin (IgG), purified using caprylic acid precipitation of non-IgG proteins (albumin), the second Fab fragments obtained by papain digestion, and finally F(ab')<sub>2</sub> fragments produced by enhanced pepsin digestion. All products were passed through a viral filter and the F(ab')<sub>2</sub> product underwent ion exchange (IE) to remove any remaining pepsin. The Fc fragment is digested to smaller fragments which are removed by diafiltration prior to IE. The venoms were separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and binding of antibodies to the different venom components demonstrated using immunoblotting. In addition antibody binding of all four venoms was measured by enzyme-linked immunosorbent assay (ELISA) and SSAC. Efficacy and potency were determined by *in vivo* murine lethality neutralization assays (ED<sub>50</sub>). Safety studies (Phase I clinical trials) were performed in dogs and veterinary practices have been recruited to carry out a phase II clinical trial in envenomed dogs. Stability was monitored at 4°C and room temperature every 6 months.

**Results:** All immunized sheep responded quickly and, despite individual variation, flock SAb concentrations remained remarkably constant at around 6.0 g/L throughout the period of study. Separation of venom components by SDS-PAGE revealed interspecific variation in both molecular mass and quantity (intensity of staining). The immunoblot demonstrated that antibodies from antisera and all three products bound to every major component of each *Vipera* venom. The results of ELISA and SSAC assays demonstrated that all three antivenoms demonstrated extensive immunological cross-reactivity with the four *Vipera* venoms. The *in vivo* preclinical assay (ED<sub>50</sub>) revealed that ViperaVet protected against venom-induced lethality in the mouse model (Table 1). Safety studies in dogs indicated that intact IgG produced a

significant, immediate, but transient hypersensitivity reaction in all test subjects, which did not appear to be related to quantity of protein or rate of administration. Neither the Fab nor F(ab')<sub>2</sub> formulations produced any discernible reaction in the test subjects and it was concluded that these two antivenoms were well tolerated in the target species. Clinical trials were started using the Fab product, which was administered to five envenomed dogs. The outcome was favourable in four dogs. The fifth dog required a second dose of antivenom which halted further progression of oedema. However, the dog was elderly and his owners decided euthanasia was the kindest outcome. After twelve months the appearance of the Fab product changed, with small particles visible. These were almost certainly due to aggregation of Fc fragments and were removed by filtration through a 0.2 micron filter. Consequently the subsequent development and testing of ViperaVet will proceed with the F(ab')<sub>2</sub> formulation in which enhanced pepsin digestion is used to remove all Fc fragments.

**Conclusion:** We have encountered a number of unexpected problems during the development of Europe's first veterinary antivenom, the first being the unpredicted hypersensitivity of dogs to ovine IgG. The Fab product encountered no such problems at Phase I and satisfied the criteria required for an animal trial certificate (ATC) enabling Phase II clinical trials to commence. Due to a subsequent stability problem, ViperaVet has now been reformulated as an F(ab')<sub>2</sub> product. An ion exchange step was introduced to remove contaminants which could compromise stability. Nonetheless our study suggests that ViperaVet F(ab')<sub>2</sub> may be a valuable novel therapeutic to prevent mortality and morbidity associated with veterinary snakebite throughout Europe.

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## 11. A National Serum Depot for antivenoms: The set-up and lessons learned

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**Objective:** The Common Viper (*Vipera berus*) is the only indigenous, venomous snake in the Netherlands. Exotic venomous animals are present in the collections of several zoos, research institutes and amateur herpetologists. They also enter the country as stowaways in luggage or freight. Every year people are bitten or stung by these animals and some develop signs of severe envenomation. In these cases antivenom administration may be necessary and life-saving. As antivenoms are non-registered pharmaceutical products, guidelines of Good Distribution Practice (GDP) are involved. The Dutch Health Care Inspectorate

**Table 1.** Assessment of three different formulations of ViperaVet.

	ELISA (dilution × 1000)	SSAC (Sab: g/L)	Purity by size exclusion chromatography (% principal peak)	ED <sub>50</sub> Potency (Neutralising units/ ampoule)
Pass criteria		>2.5	>85	>125
Reference antiserum	40	6.0	59	N/A
IgG	25	4.8	96	170
Fab	21	4.1	100	364
F(ab') <sub>2</sub>	55	4.8	100	ND



strictly adheres to these GDP guidelines, meaning that antivenom stocks in zoos or other locations of venomous animals are no longer tolerated. This initiated the set-up of a National Serum Depot.

**Methods:** The Dutch National Serum Depot is established in 2008 and is collaboration between the Dutch Poisons Information Center (DPIC) and the National Institute for Public Health and the Environment (RIVM).<sup>1</sup> The Ministry of Health, Welfare and Sport provides permission to import, store and distribute (non-registered) antivenoms to the RIVM. The DPIC has two important roles with regard to this Serum Depot. Firstly, the DPIC advises on the content and amount of antivenom necessary to stock in the National Serum Depot. Extensive contacts with the zoos and many amateur herpetologists, including several site visits to venomous animal fairs and markets, made it clear that almost every venomous animal that can induce a potential life-threatening envenomation is actually kept in the Netherlands. When creating a stock, enough antivenom should be bought to treat at least one severely envenomated patient. The second important role of the DPIC is in advising the physician whether or not antivenom treatment is necessary in case of a bite or sting incident. Indications of antivenom treatment are discussed with the physician, taking into account the severity of the envenomation, relative contraindications and possible adverse effects of the antivenom treatment. When antivenom treatment is indicated, the poison information specialist assists the physician in ordering the correct antivenom at the RIVM and the subsequent delivery to the hospital where the patient is treated. The costs of an Antivenom Depot are related to the antivenoms themselves (approximately 95,000 Euro each year) and the overhead costs, e.g. personnel and a warehouse facility including temperature controlled rooms and refrigerators.

**Results:** In these first 6 years, the National Serum Depot encountered several difficulties, especially in purchasing antivenoms in order to replace used or expired vials.<sup>2</sup> As antivenom production can vary widely<sup>3</sup>, often causing shortage, as well as the fact that in some cases they are extremely expensive, we have created a “shadow” stock of shortly expired antivenom to overcome antivenom shortages. This is done in good cooperation and with approval of the Health Care Inspectorate. At the same time, unused antivenom vials are allowed to be returned to the RIVM if during transport the so called ‘cold chain’ has not been broken. Currently the National Serum Depot contains 20 snake antivenoms, 4 scorpion antivenoms, 3 spider antivenoms and 1 fish antivenom. From April 2008 until April 2014, exotic snake antivenom was delivered in 13 cases, and in 8 cases antivenom was administered to the patient.

**Conclusion:** Although a National Serum Depot is certainly an expensive facility, we believe that for optimal treatment of envenomated patients, it is a necessity in a Western European country. By establishing a governmental approved Serum Depot, antivenom is legally available on a 24/7 basis to treat venomous bites and stings by exotic animals. The cooperation with the Poisons Information Center guarantees up-to-date information and advice on antivenom selection and stock amounts, and on the correct antivenom to be administered in case of severe envenomations.

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## 12. Fomepizole versus ethanol in acute methanol poisoning: A quasi-case-control study

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**Objective:** During an outbreak of methanol poisonings in the Czech Republic in 2012-2014,<sup>1</sup> we compared the effects of two antidotes, fomepizole and ethanol, on short-term and long-term outcomes of treatment.

**Methods:** Data were obtained from a combined retrospective and prospective quasi-case-control study on 50 patients (25 with fomepizole versus 25 with ethanol). All patients treated with fomepizole during the outbreak of poisoning were included in the study. From 70 patients treated with ethanol, 25 patients were selected retrospectively to make the quasi-case-control pairs with the patients treated with fomepizole with similar demographic, toxicological, biochemical, clinical, and therapeutic parameters to make the confounders of the non-randomized study as limited as possible. In 56.4% of survivors the follow-up clinical examination was fulfilled 3-6 months after discharge.

**Results:** The patients treated with ethanol did not differ from the patients treated with fomepizole in age, gender, dose ingested, poisoning severity score, Glasgow Coma Scale, arterial blood pH, bicarbonate, pCO<sub>2</sub>, base deficit, anion gap, serum methanol, ethanol, formate, lactate, glucose, creatinine, time from ingestion and treatment modalities (all p > 0.05). In total 11 patients died, 20 survived with visual and/or CNS sequelae, and 19 survived without sequelae. The difference in the number of patients treated with fomepizole versus patients treated with ethanol who survived without sequelae (9/25 [36%] versus 10/25 [40%]), survived with sequelae (10/25 [40%] versus 10/25 [40%]), and died (6/25 [24%] versus 5/25 [20%]), was not significant (all p > 0.05). All 11 patients who died were comatose on admission. Mortality was 54.5% (6/11) among the patients with coma on admission treated with fomepizole and 45.5% (5/11) among the patients with coma treated with ethanol (p = 0.77). In both groups there were 8/25 (32%) cases with long-term visual damage; the number of patients with CNS sequelae was slightly higher in the group of patients treated with ethanol than in the patients treated with fomepizole, but the difference was not significant (10/25 (40%) versus 8/25 (32%), p = 0.56). The median intensive care unit length of stay was 6 (range 2-22) days in the patients treated with fomepizole and 5 (range 2-33) days in the patients treated with ethanol (p > 0.05).

**Conclusion:** The results of our study cannot promote any of two antidotes as having better short-term or long-term outcomes of treatment. The data did not demonstrate that fomepizole positively affected both the mortality rate and the survival without visual and/or CNS sequelae compared to ethanol.

**Acknowledgement:** A grant to the First Faculty of Medicine, Charles University, P25/ILF/2.

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### 13. Clinical findings in patients receiving physostigmine in a toxicologic ICU: A quality and safety assessment study

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**Objective:** Physostigmine is a cholinergic drug that is used in reversal of anticholinergic syndrome (AChS). At our institution, physostigmine has been used for the last 20 years without severe adverse events. We decided to perform a retrospective quality assessment to judge the safety of our policy and to describe the clinical course of the patients.

**Methods:** We browsed the records of all patients admitted to our toxicologic ICU from January 2011 to December 2012, retrieving 151 patients having received physostigmine. We derived data about the presence of symptoms of AChS, the amount of physostigmine delivered, the clinical results and rates of potential side effects.

**Results:** In total 99 patients (65.5%) were judged as suffering from AChS by the treating physician. The remaining cases (n = 52) received physostigmine for reversal of more unspecific delirium or coma. The AChS-patients had the typical features of AChS more often than patients in the unspecific delirium group (e.g. 30% versus 20% for dry skin/mouth, 45 versus 20% reduced bowel movements, 56% versus 37% slurred speech, and 43% versus 28% agitation). The mean amount of physostigmine administered was 22.7 mg (95% CI ± 86.6) for the AChS group and 16.7 mg (95% CI ± 34.3 mg) in the unspecific coma group, respectively. In classic AChS, 90 of 99 (90.9%) patients experienced resolution of symptoms after administration of physostigmine, as compared to 38 of 56 (67.8%) of patients with non-specific coma. All patients but one survived. In the fatal case the patient had severe prothipendyl intoxication with a QTc of 660 ms, recurrent ventricular tachycardia and hypoxic brain damage after prehospital cardiopulmonary resuscitation. We found no significant bradycardia, atrioventricular block or other conductance disturbance during or after administration of physostigmine; the same was true for bronchorrhoea and diarrhoea.

**Conclusion:** Physostigmine is delivered to our patients in an ICU setting with continuous monitoring in a bolus or infusion manner with bolus dosage about 2 mg and infusion rates of 0.5 to 2 mg/hour. Clinical signs such as bowel movement or grade of delirium guide the dosage and cessation. We consider symptomatic bradycardia with extremely broadened QRS complexes as unfavourable for administration of physostigmine. The administration of physostigmine according to our clinical routine protocol is safe for our patients. Side effects seem to be rare and their nature mild. Typical AChS responded well to physostigmine, and even two thirds of

cases of nonspecific delirium or coma responded to some extent to this therapy.

### 14. Population pharmacokinetics of an Indian F(ab')<sub>2</sub> snake antivenom in patients with Russell's viper bite

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**Objective:** There is limited information on the pharmacokinetics of antivenom. The aim of this study was to investigate the pharmacokinetics of an Indian snake antivenom in patients with Russell's viper (*Daboia russelli*) envenoming.

**Methods:** Patient data and serial blood samples were collected from patients with Russell's viper envenoming admitted to a single hospital in Sri Lanka. All patients received the Indian polyvalent snake antivenom manufactured by VINS Bioproducts Ltd. Antivenom concentrations were measured with a sandwich enzyme immunoassay. Antivenom concentration time data were analysed using the MONOLIX<sup>®</sup> version 4.2 (Lixoft, Orsay, France, www.lixoft.com). One, two and three compartment models with zero order absorption and first order elimination kinetics were assessed. Models were parameterized with clearance (CL), intercompartmental clearance (Q), central compartment volume (VC) and peripheral compartment volume (VP). Between subject variability (BSV) on relative bioavailability (F) was included to account for variations in antivenom dose. The effect of covariates (age, sex, weight, antivenom batch and pre-antivenom concentrations) were explored initially by visual inspection and then in model building.

**Results:** There were 75 patients with a median age of 57 years (40-70 years) and 64 were male. There were 510 antivenom concentration data points. A two compartment model with zero order absorption and linear elimination kinetics and a combined error model best described the data. The inclusion of BSV on F and weight on VC improved the model. The inclusion of pre-antivenom concentrations also did not improve the model. Inclusion of different batch numbers on BSV of F did not improve the model. The final model parameter estimates were CL 0.078 L/h, VC 2.2 L, Q 0.178 L/h and VP 8.33 L. The median half-life of distribution was 4.6 hours (90% percentiles 2.6-7.1 hours) and the half-life of elimination, 140 hours (90% percentiles 95-223 hours).

**Conclusion:** Indian F(ab')<sub>2</sub> snake antivenom displayed biexponential disposition pharmacokinetics, with a rapid half-life of distribution and a much longer half-life of elimination. This is consistent with previous small studies. The pre-antivenom venom concentrations did not appear to influence the pharmacokinetics



of antivenom and over this period different batches on average, provided similar doses of antivenom.

## 15. The use of digoxin-specific antibodies in chronic digoxin poisoning

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**Objectives:** Digoxin-specific antibodies (digoxin Fab) are used for the management of digoxin poisoning, however, the indications and dosage of digoxin Fab have not been clearly elucidated.<sup>1</sup> This study aimed to examine the effects of digoxin Fab in chronic digoxin poisoning, and whether this related to dose or patient characteristics.

**Methods:** This was a prospective observational study of patients recruited through the New South Wales (NSW) Poisons Information Centre from September 2013 to October 2014. A standardised data form was used to enter patient information. Serum of patients treated with digoxin Fab was collected from hospitals in NSW and free digoxin assays were performed using ultrafiltration to separate free and bound digoxin. The digoxin concentration was measured using the Multigent Digoxin assay. Free digoxin Fab was measured by enzyme immunoassay.

**Results:** There were 27 patients with chronic digoxin poisoning treated with digoxin Fab. The median digoxin and potassium concentrations were 4.7 nmol/L (3.6 µg/L) (interquartile range [IQR] 3.3 to 6.1 nmol/L) and 5.9 mmol/L (IQR 4.6 to 6.6 mmol/L), respectively. All but two patients had renal impairment with a median serum creatinine of 232 µmol/L (IQR 153 to 306 µmol/L). The median change in potassium and heart rate (HR) post digoxin Fab were 0.2 mmol/L (IQR -0.2 to 0.7 mmol/L) and 10 beats/min (IQR 4 to 21), respectively. The median dose of digoxin specific Fab used was 80 mg (IQR 40 to 80 mg). Bradycardia or slow atrial fibrillation (HR < 60/min) were the commonest presenting rhythms with a median HR of 44 beats/min (IQR 30 to 58). Digoxin Fab was not found to be effective in 16/27 patients (59%) (i.e. HR < 45/min and raised by 10 beats/min within 4 hours of digoxin Fab administration). There were 18 patients recorded to be taking regular beta-blockers or calcium antagonists, 20 patients were taking either spironolactone or angiotensin blocking agents. Gastrointestinal symptoms were present in 14/27 patients (52%). Six patients died in this series, none of the deaths was attributed to digoxin poisoning. Free and total digoxin concentrations and free digoxin Fab were measured in five patients. Free digoxin concentration dropped to almost zero within 1 hour of administering digoxin Fab.

**Conclusion:** In this study of chronic digoxin poisoning, digoxin Fab was not found to be effective in managing bradyarrhythmia. Other medications and diseases often contributed to bradyarrhythmia and hyperkalaemia and this likely explains the lack of response despite the rapid reduction in free digoxin caused by digoxin Fab.

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## 16. The antipsychotic story... an epidemic of prescription and overdose

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**Objective:** A recent study has shown that morbidity and mortality from drug overdose has dramatically decreased over the last 26 years in Australia, which can mainly be credited to safer drugs being more available and therefore taken in overdose (e.g. selective serotonin reuptake inhibitors rather than tricyclic antidepressants). However, there appeared to be an increase in antipsychotic overdoses. We aimed to investigate the changing prescription of antipsychotic medications and the associated epidemiology of antipsychotic overdose for a 26 year period.

**Methods:** All antipsychotic poisoning presentations to a tertiary referral toxicology unit between 1987 and 2012 were reviewed. At presentation data is collected prospectively on a standardised form including demographics, drugs ingested, clinical effects and treatment. Rates of antipsychotic drug use in Australia were obtained from Australian government publications for 1990 to 2011 and compared to the trend in toxicology admissions.

**Results:** There were 3,180 antipsychotic overdose presentations, including 250 lithium poisonings, 1,695 atypical antipsychotic overdoses and 1,235 first generation antipsychotic poisonings. Over the 26 year period there was a 1.8 fold increase in antipsychotic overdoses. First generation antipsychotic overdoses decreased over the 26 years to one fifth of their peak (~80/year to 16/year). These had a median length of stay (LOS) of 18.5 hours, 16% were admitted to an intensive care unit (ICU), 11% ventilated and 0.16% died in hospital. Atypical antipsychotic overdoses dramatically increased over the 26 years to double the peak numbers of first generation antipsychotics (~160/year). Their LOS was 18 hours, 15% admitted to ICU, 11% ventilated and 0.12% died in hospital. Quetiapine and olanzapine made up most of the atypical antipsychotic overdoses, and almost 90% in the last 5 years. There was a 2.3-fold increase in antipsychotic prescriptions over the same period, first generation antipsychotic prescribing declined (from 3.73 to 0.802 defined daily doses [DDD]/1000/day) whereas there was a dramatic rise in atypical antipsychotic prescriptions to 8.842 DDDs/1000/day, mainly olanzapine, quetiapine and risperidone (79%). Lithium prescribing remained relatively constant. There was no decline in the morbidity and mortality of these presentations, despite the reduction in first generation antipsychotic overdose presentations.

**Conclusion:** Over the last two decades there has been an increase in antipsychotic prescribing associated with an increase in antipsychotic overdoses. Although the type of antipsychotics has changed during this time there has been no change in morbidity or mortality. Antipsychotic overdoses are an increasing proportion of the toxicology burden of disease.

## 17. Intentional exposures on school property reported to US Poison Centers

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**Objective:** The purpose of this study was to characterize the epidemiological trends associated with intentional exposures to substances while on school property reported to the US National Poison Data System (NPDS).

**Methods:** NPDS was queried for intentional (abuse, misuse, suspected suicide, and unknown intentional) exposures reported to occur on school property between calendar years 2004 and 2013. Records were restricted to patients 6-18 years of age. Demographic, geographical, exposure, and clinical characteristics were assessed.

**Results:** There were 56,882 substances reported to be intentionally used on school property by 50,379 students. Among the students, 39.8% were females (n = 20,070), 57.7% were males (n = 29,084), and 2.4% were of unknown gender (1,225). While substance abuse or misuse were mostly reported among males (n = 7,129; 55.9% and n = 17,655, 67.1%, respectively), suspected suicide cases were predominantly reported among females (n = 3,676; 76.2%). The most frequent exposures reported included benzodiazepines (2,424; 4.3%), pens/inks (n = 2,062; 3.6%), miscellaneous unknown drugs (1,853; 3.3%), antihistamines/decongestant with dextromethorphan (n = 1,794; 3.2%), and ibuprofen (n = 1,577; 2.8%). Among select illicit substances, there were 752 marijuana or tetrahydrocannabinol (THC) homologs, 183 hallucinogenic amphetamines, 66 cocaine, 30 lysergic acid diethylamide (LSD), and 11 heroin exposures reported. The majority of exposures were managed on site (n = 21,464; 42.6%), followed by treatment at a healthcare facility (n = 20,048; 39.7%). Serious outcomes (moderate or major effects and death) accounted for 9% of all reported exposures.

**Conclusion:** Data from the Centers for Disease Control and Prevention's (CDC) Youth Risk Behavioral Surveillance System provide evidence of the extent of risky or deviant behaviors (e.g. bullying, carrying weapons, smoking cigarettes, taking part in illicit drug trade) that students engage in while on school property. Additional trends in risky behavior may be gleaned by surveillance through poison centers. School personnel and parents/guardians may utilize the poison centers for expertise in management of these substances, and the data gathered by poison center staff serve as a valuable source in identifying key trends in substance use on school property.

## 18. 15 years of vitamin D exposures reported to US Poison Centers

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**Objective:** There has been an increased focus on the potential health benefits of vitamin D. With this increased focus have been significant increases in vitamin D use both by prescription and by

the public as a widely available supplement. We evaluated 15 years of single substance vitamin D exposures to US poison centers.

**Methods:** This was a retrospective analysis of data from the National Poison Data System (NPDS) to evaluate clinical effects, trends and outcomes of all exposures to vitamin D over the period 1 January 2000 through 30 June 2014. Cases were limited to exposures involving vitamin D as a single substance. Inclusion criteria were exposure to vitamin D in a human. Exclusion criteria included exposure to more than one substance (poly-substance), animal exposures and information calls. Multiple vitamin products that may have included vitamin D were not included in this study and would not be included using the search criteria.

**Results:** From 2000 through 30 June 2014 there were 25,397 human exposures to vitamin D reported to NPDS. There was a mean of 196 cases per year from 2000 to 2005, followed by a 1600% increase in exposures between 2005 and 2011 to a new annual mean of 4,535 exposures per year. The mean and median ages were 23.4 years and 10 years. The majority of cases were children under 6 (n = 15,093, 59.4%) and female (n = 14,841, 58.44%). In adults cases (age > 17 years) females accounted for 77% of cases. In adult patients the predominant reasons for exposure were therapeutic error (80.2%), unintentional general (8.6%) and adverse drug reaction (7.8%). There were no fatalities and 8 major effect outcomes (0.03%). Serious medical outcomes (major or moderate outcome) were infrequent, ranging from 2 patients/year to 22 patients/year. Children had similar medical outcomes to adults with 4 major outcomes (0.03% of children) and 45 moderate outcomes (0.3% of children). Clinical effects were primarily gastrointestinal (0.7% to 1.5%) and mild neurological effects (0.2 to 0.4%). The majority of patients were managed on-site at a non-healthcare facility (n = 21,964, 86.5%). There was a decline in the percentage of patients treated in a health care facility and of patients with serious medical outcome.

**Conclusion:** Despite the enormous increase in number of exposures, there was not a significant increase in patients with a serious medical outcome. Rare severe outcomes may occur.

## 19. Nicotine poisoning related to the use of e-cigarettes

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**Objective:** To describe the occurrence and development of possible nicotine fluid-related poisonings and the elucidation of nicotine toxicity from exposure-descriptions

**Methods:** A review of the Danish Poison Center database for enquiries related to e-cigarettes and nicotine, as well as a comparison of poisoning from previously described exposure scenarios of nicotine toxicity.<sup>1,2</sup>

**Results:** Incoming calls to the Poison Center in the last few years have shown an increase in the number of enquiries relating to e-cigarettes, as they become more common within the general population. Within the last year there has been a 25% increase in the number of inquiries regarding suspected nicotine poisoning due to e-cigarettes. The increase covers both queries with limited

and life-threatening risk. Incidents where nicotine liquid has been consumed by accident or during playing, constituted 54.5%, and these account for 75% of all the e-cigarette enquiries in 2014 that were assessed to pose a manifest or life-threatening risk. Toddlers, in particular, accidentally consume the nicotine-containing fluids during play, and children under five years represent 29% of all enquiries. In three adult cases with there was life-threatening exposure, both on dose (760 mg, 30 mg and 120 mg of nicotine) and symptoms

**Conclusion:** Due to the rising popularity of e-cigarettes, there has been a general increase in the total number of enquiries. Children under five years represent a significant proportion of these enquiries, suggesting careless handling of nicotine products. As a result where consumption occurs, an increased number of fatal poisonings with nicotine-containing fluids is expected. Three cases of poisoning shows an unclear dose-response relationship between nicotine and symptoms of poisoning. Insufficient labeling could be part of the explanation. Given the consistent findings, it is reasonable to assume that our knowledge on how low a dose can cause symptoms of poisoning, is not sufficient, and that the toxic dose might be less than anticipated.

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## 20. Acute poisonings in Iceland: Self-poisonings presenting to the Emergency Departments at Landspítali-University Hospital. Comparison between 2001 and 2012

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**Objective:** Self-poisoning due to suicide attempt or drug abuse, is the most common reason for poisoning presentation to Emergency Departments (ED) in Iceland. Drug abuse is known to be a risk factor for suicidal behaviour and differentiation of the intention can be difficult especially in an acute setting; therefore it was decided to look at self-poisonings as a single group. The aim of the study was to compare and determine any changes in the incidence, type and pattern of self-poisonings presenting to the ED at Landspítali, using two 1-year prospective studies.

**Methods:** The first study was performed from 1 April 2001 until 31 March 2002 and the second from 1 January 2012 until 31 December 2012. The studies included all visits due to self-poisonings to the ED. Information collected included age and gender of each patient, previous poisoning history, location and causes of the poisoning, type and amount of poison, route of exposure, clinical manifestations, treatment and outcome.

**Results:** The rate of self-poisonings per 1000 inhabitants was 2.03 in 2012 and 2.05 in 2001. Females outnumbered males in both studies as they were 60% in 2012 and 63% in 2001. The median age

was 35 years (range 12–88 years) in 2012 but 30 years (range 11–83 years) in 2001. Ingestion was the most common route of exposure in both studies and the patient's home were the most common location of exposure. In 2012 43% of patients had a previous history of poisoning but in 2001 this was the case for 37% of patients. In both studies the majority (98%) of ingestions involved drugs and/or alcohol. Alcohol was involved in 49% of cases in 2012 and 38% in 2001. Sedative-hypnotics were the most common pharmaceutical cause of poisoning, with 28% in 2012 and 42% in 2001. Antidepressants were used in 13% of cases in 2012 but 24% in 2001. Paracetamol was involved in 13% of cases in 2012 and 18% 2001. Illicit drugs were used in 16% of cases in 2012 but 14% in 2001. In 2012 6% of patients were treated in Intensive Care Unit and 7% in 2001. Two patients died in 2012 and one in 2001.

**Conclusion:** The rate of self-poisonings requiring emergency medical care remained the same in the two studies periods. Females outnumbered males. There was a marked reduction in the rate of poisonings by sedative-hypnotics and antidepressants. On the other hand alcohol seemed to be more predominant than before. Mortality was low.

## 21. Change over time and severity of antidepressant and antipsychotic medications managed by US poison centers: 2000–2014

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**Objective:** Exposures for antidepressant and antipsychotic medications (AAMs) have been among the largest and most rapidly increasing substance categories managed by US Poison Centers. We examined the medications comprising these 2 categories for their change over time (COT) patterns and severity.

**Methods:** We tabulated closed, human, single substance exposures in the National Poison Data System (NPDS) (1 January 2000 to 31 October 2014) by year for More Severe Exposures (MSE = Medical Outcome of Moderate, Major or Death) and non-severe for AAMs and all substances (All). The AAMs comprised 43 Generic Codes and 3,329 Product Codes. These were mapped to 10 substance groups of interest (Groups). Drug Exposures and % Severe COTs were examined by graphical and statistical (linear and quadratic regressions) using SAS JMP 9.0.0. Odds Ratios (OR) and confidence intervals (CIs) for AAMs versus All were calculated for Age, Gender, Management Site, Level of HCF, Reason, and Route using StatsDirect 2.8.0.

**Results:** 1,068,597 AAM Exposures were extracted, of which 164,395 (15.4%) were MSEs. ORs for AAMs to All for Reason = Suicide were 5.93 [5.85, 6.01], Route = Ingestion 4.90 [4.82, 4.99], Admission to a psychiatric facility [2.72 [2.67, 2.78]. COT (15 year) was statistically significant ( $p < 0.05$ ) for all 10 Groups (8 linear, 6 quadratic). Table 1 summarizes the MSE comparisons across the 10 Groups. Linear regression showed  $p < 0.05$  increase in 7 of the 10 Groups.

**Conclusion:** All outcome AAMs, and particularly MSE outcomes, have increased consistently over the last 14 years, but major Groups show differing COT profiles. There is likewise a distinctive



**Table 1.** The more severe exposures (where the medical outcome was moderate, major or death) for single substance exposures to antidepressant and antipsychotic medications in the NPDS, 2000–2014.

Medication Group	2000 through 2014			2008 through 2014	
	Percent Severe	Severe (total)	Deaths (total)	Exposures/year	Increase [95% CI]
Lithium	34.6%	14712	58	1173	38.6 [17.2, 60.1]
MAOIs	28.7%	294	3	17	-0.9 [-2.81, 1.01]
Tricyclic Antidepressants	28.3%	20543	279	1308	40.5 [20.7, 60.2]
Phenothiazines	24.2%	6929	22	479	5.72 [-4.96, 16.4]
Atypical Antipsychotics	21.4%	47709	130	3850	-49.0 [-98.7, 0.676]
Bupropion	20.4%	14666	62	1079	64.8 [47.1, 82.6]
Tetracyclics	12.7%	11933	26	1028	103 [92.2, 113]
SNRIs	8.8%	6107	41	459	13.2 [2.70, 23.7]
SSRIs	6.9%	20332	56	1638	146 [122, 169]
Buspirone	6.3%	804	0	72	8.02 [5.45, 10.6]

difference in % Severe across these Groups. A better understanding of the changes over time and relative hazards of the medications in this important class should help improve our management and prevention efforts.

## 22. Analysis of telephone enquiries to the UK National Poisons Information Service (NPIS) concerning raspberry ketone weight loss supplements (2011–2014)

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**Objective:** There are few published data regarding the toxicity of raspberry ketone. This ingredient of the red raspberry (*Rubus idaeus*) has been marketed as a lipolytic agent and is taken to promote weight loss. Evidence for the safety of raspberry ketone at the doses used in weight loss supplements is not available. Raspberry ketone is expected to have sympathomimetic activity based on its chemical structure. A 43-year-old male who had taken raspberry ketone for one month reported insomnia, palpitations, sinus tachycardia and jitteriness.<sup>1</sup> We wished to determine the pattern of enquiries to the National Poisons Information Service (NPIS) concerning raspberry ketone.

**Methods:** A retrospective review of telephone enquiries to the NPIS concerning raspberry ketone from 1 January 2011 to 31 March 2014 was undertaken.

**Results:** The NPIS received 56 enquiries relating to 50 patient exposures. Numbers of exposures have increased from 1 in 2011 to 4 in 2012 and 34 in 2013, with a further 11 cases in the first quarter of 2014. Nineteen exposures (38%) involved patients aged between 15 and 24 years. Patients under the age of five years were involved in 17 cases (34%). Most patients (35/50) were female. Most exposures were accidental (n = 24, 48%), but there were also intentional ingestions (n = 12, 24%), adverse reactions (n = 6, 12%), therapeutic errors (n = 6, 12%) and recreational abuse (n = 2, 4%). Of the twenty seven patients who were symptomatic, twenty five (93%) were adults. Nineteen exposures (38%)

were classified as minor in severity (Poisoning Severity Score (PSS) = 1), three (6%) were of moderate severity (PSS = 2) and three patients (6%) were severely poisoned (PSS = 3). Symptoms following ingestion included nausea (n = 7), diarrhoea (n = 5), abdominal pain (n = 5), vomiting (n = 4), dizziness (n = 4), temperature increase (n = 4), shortness of breath (n = 3) and palpitations (n = 2).

**Conclusion:** The NPIS receives a small but increasing number of enquiries relating to exposure to raspberry ketone. Symptoms associated with raspberry ketone ingestion appear similar to structurally related stimulant agents. Consumers should be aware that the use of unregulated weight loss therapies claiming to be natural and safe is not without risk.

## Reference

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## 23. Intentional overdoses and self-harm enquiries in adolescents aged 8–16 years: A retrospective review of enquiries to the National Poisons Information Service in the UK

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**Objective:** The challenges faced by adolescents are becoming more complex as the pressures and demands on our society increases. Sources such as the media and social network sites, in addition to pressures within family and school life, may all contribute to this burden. Appropriate support networks are not accessible to every individual. Subsequently, certain difficult circumstances may not be managed effectively, which can lead to individuals choosing impulsive, consequential alternatives including self-harm by poisoning. We wished to review the pattern of poisons enquiries concerning this group of patients.

**Method:** Enquiries to the National Poisons Information Service (NPIS) between the 1 September 2008 and the 31 August 2014 relating to intentional overdoses and self-harm in children aged 8-16 years were reviewed retrospectively and evaluated to assess trends and patterns of exposure.

**Results:** The NPIS received 8,542 enquiries relating to intentional overdoses or self-harm attempts in children aged 8 to 16 years of age which made up 40% of total enquiries for this age group (n = 21,425). Eighty three percent (n = 7,073) of these enquiries concerned girls and 17% boys (n = 1,428), with 0.5% (n = 41) of unknown gender. This contrasts with only 61% (n = 13,070) girls, 38% (n = 8,245) boys and 0.5% (n = 110) of unknown gender for other enquiries in this age group. Calls relating to children aged 13 to 16 years of age accounted for 95% (n = 8,132) of the intentional exposures in children aged 8-16, with only 5% (n = 410) involving children aged 8 to 12 years of age. The number of enquiries each year were 1,882, 1,493, 1,352, 1,149, 1,280 and 1,386, respectively, from 2008 to 2014. The commonest ingestions were paracetamol (n = 3,447), ibuprofen (n = 917), co-codamol (codeine/paracetamol, n = 405), ferrous sulphate/fumarate (n = 324), fluoxetine (n = 307), aspirin (n = 286), mefenamic acid (n = 186) and citalopram (n = 148). Thirty-nine percent (n = 3,297) displayed features at the time of the enquiry. Thirty percent (n = 2,592) had minor features with a poisons severity score (PSS) of 1, 6% (n = 518) moderate features (PSS2) and 2% severe features (PSS3).

**Conclusion:** The most common agents ingested intentionally by adolescents include those readily available over-the-counter. Intentional overdoses and self-harm attempts in teenage females in particular is a cause of concern.

## 24. Characteristics of the toxicological situation in Sochi during Winter Olympic Games of 2014

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**Objective:** Organization of such a large-scale event as the Olympic Games requires serious preparation for urgent diseases, traumas and poisonings during crowding of a large number of people in the territory of the games. This study of the toxicological situation during the Sochi Olympic Games is of interest from the point of view of such events in future.

**Methods:** Comparison of the number of cases handled by the Sochi Ambulance Station and those admitted to Sochi hospitals with acute chemical poisonings during the periods of January-March 2013 and 2014.

**Results:** According to Wikipedia (free Encyclopaedia), the Sochi population in 2013 was 445,209 and 473,206 in 2014. During the Olympic Games 600,000 visitors were expected, however, the exact number of visitors in Sochi at any one time was unknown. Olympic participants (competitors, trainers, other personnel) were not included in this study, because medical assistance for these people was undertaken by the International Olympic Committee. The total number of poisoning cases handled by the Sochi Ambulance Station was 4,881 in 2011, 4,846 in 2012 and 3,528 in 2013. The type of poisonings

for each year was as follows: ethanol 80.7%, 77.4%, 84.2%, narcotics and hallucinogens 3.9%, 5.9%, 4.4%, hypnotic and psychotropic drugs 2.5%, 2.8%, 1.6% and the rest 12.9%, 13.9%, 9.8%. In January, 2013 this number was 1,139; at the same period of 2014 it was 922 and the type of poisonings in 2013 were (in the same order as above) 81.2%, 6.5%, 2.6%, 9.7% and in 2014 91.9%, 1.2%, 0.1% and 6.8%. Patients admitted with poisoning in January-March 2013 were 50.5% with alcoholic poisoning, 21.2% narcotics and hallucinogens and 28.3% psychotropic and other chemicals. In the same period of 2014 the substances involved were alcohol 64.0%, narcotics and hallucinogens 19.8% and psychotropic and other chemicals 16.2%.

**Conclusion:** The results could be characterized as unexpected, because, despite the considerable influx of people, the total number of poisonings was considerably lower (by 19%) than expected. The structure of poisonings was practically unchanged, however, one could note the lesser number of poisonings by narcotics and hallucinogens, as well as by psychotropic drugs and the increased number of alcohol poisoning (by 10.7%). Possibly it could be explained that Olympic playgoers preferred alcohol to narcotics. Also it could be suggested that effective preventive measures were also a factor.

## 25. Epidemiology of pharmacological poisoning by oral antidiabetic drugs in Morocco

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**Objective:** There are multiple oral agents available for the treatment of diabetes. These include several pharmacological classes: sulfonylureas, biguanides, alpha-glucosidase inhibitors, thiolidinediones, and meglitinides. In one study sulfonylureas were the most frequently observed medication in cases of overdose with antidiabetic agents.<sup>1</sup> We aimed to investigate the epidemiology and outcome of oral antidiabetic drug overdose in Morocco.

**Methods:** Data for this study were extracted from the medical records of Moroccan Poison Control Centre (CAPM). The centre collects reports concerning poisoning cases from different regions of the country. A retrospective review of all reports received from 2004 to 2011, concerning acute poisoning with oral antidiabetic drugs was conducted. The data included circumstances of poisoning, sex, age distribution, symptomatology and outcome.

**Results:** In total 38 inquiries involving acute oral antidiabetic drug exposures were received at CAPM. The sex-ratio was 0.4 (25 females, 11 males). The median of age was 4 years [3-20]; 45.3% of cases were infants (1-5 years) and 25.7% were adults (older than 20 years). In total 27.0% of the cases were suicide attempts and all occurred in females. Accidental exposures occurred in 67.6% of cases, mainly infants (n = 19). Two cases were medication errors. The oral antidiabetics implicated in the largest number of poisoning cases were the sulfonylureas with 73.7% of all cases (glibenclamide 64.3% and glicipiride 17.9% of all sulfonylureas cases), followed by biguanides (metformin in 13.5% of all cases). In 34.2% of the patients, the features were symptomatic (digestive symptoms in 38.7%). No deaths were reported.

**Conclusion:** In Morocco cases of poisoning by oral antidiabetic drugs are rare, and occur mainly in infants in an accidental context. Sulfonylureas were the most frequently observed medication in poisoning cases. Prevention of these poisonings must be focused on parental education, particularly to the storage of medicines out of reach of children.

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## 26. Periodicity of human exposures in suicidal intention reported to the Poisons Information Centre (PIC) Erfurt from 2004 to 2013

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**Objective:** Exposures in suicide attempts are demanding for hospitals and poisons information centres (PICs). Therefore, the time characteristics of their frequency were studied.

**Methods:** A retrospective analysis of all human exposures reported to PIC Erfurt from the beginning of 2004 to the end of 2013 was undertaken according to their frequency in the respective year, season, month, weekday, time of day the PIC was contacted, circumstances of exposure, age and gender.

**Results:** In the study period there were 137,104 exposures of which 59.7% (n = 81,793) were accidental, 23.4% were suicide attempts and 3.3% were substance abuse. Of the suicide attempts 0.3% resulted in death. The number of suicide attempts increased over the study period from 2,422 in 2004 to 3,458 in 2013, but their relative frequency remained almost constant at 23.4%. The highest number of suicide attempts occurred in the spring and summer, with maxima in July and August and minima in February and September. During the week, most suicide attempts were observed between Sunday and Tuesday with the lowest number reported on Friday. The highest rate of suicide attempts was seen at 10 pm and the lowest at 6 am. The median age of patients in this group was 39 years (first quartile 24 years, third quartile 50 years). The female proportion was almost twice as high as the male.

**Conclusion:** Hospitals and PICs should be particularly prepared to deal with exposures due to suicide attempts in the spring and summer (especially in July and August), at the beginning of the week and shortly before midnight.

## 27. Poisoning by carbon monoxide in Morocco: 1991–2012

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**Objective:** The goal of this study is to describe the details related to patient statements, and to evaluate the spatiotemporal evolution of carbon monoxide poisoning reported by all regional health directorates to the Centre Anti Poison et de Pharmacovigilance du Maroc (CAPM).

**Methods:** A retrospective study of all cases of carbon monoxide reported to the CAPM during the period 1991 to 2012. The CAPM has a database of cases derived from two sources: Intoxication declaration forms of poisoning cases received from health delegations throughout the kingdom and toxicological forms completed by doctors during calls received by the center from the public and health professionals working in public facilities. In all cases, the CAPM physician makes a risk assessment and follows the information to completion by regular telephone contacts until the final evolution of patient. The data collected includes the variables: date, time of poisoning, the person who reported the case, origin (province or prefecture), patient (sex, age, weight, pregnancy), toxin/substance suspected (number, name, type), intoxication (isolated or collective circumstances, place, route, symptoms, treatment and evolution). Only cases of carbon monoxide poisoning alone were analyzed. Age groups adopted were those of the International Programme on Chemical Safety (IPCS) of the World Health Organization (WHO). The assessment of the poisoning severity was made using the Poisoning Severity Score (PSS). The descriptive analysis focused on the demographic characteristics and the clinical signs and evolution of carbon monoxide poisoning in Morocco. Data analysis was performed in EpiInfo software and Excel.

**Results:** Between 1991 and 2012, there were 21,356 cases involving carbon monoxide poisoning reported to the CAPM. The average age of patients was  $25.9 \pm 15.7$  years and the male:female sex ratio was 0.48. Poisoning was accidental in 98.8% of cases, mostly in private residences (96.9%) and during winter. Most cases (88.1%) occurred in urban areas. The region of Meknès-Tafilalet, in north-central Morocco, was the most affected with 17.7% of cases. The most common symptoms reported were central and peripheral nervous system disorders (32.7%), gastrointestinal disorders (30.2%) and respiratory signs (18.3%). Deaths occurred in 1.1% of cases.

**Conclusion:** This qualitative and quantitative study allows us to highlight the dangers and risks of carbon monoxide poisoning. Also, it provides us with the opportunity to plan a strategy against the harmful effects of carbon monoxide poisoning in Morocco.

## 28. Tolerance and efficacy of a new antivenom Fab2 variety in the treatment of *Bothrops lanceolatus* bites in Martinique

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**Objective:** Snake bites by *Bothrops lanceolatus* (fer-de-lance) are a common medical emergency in Martinique (30 cases/year). The first specific antivenom (Bothrofav<sup>®</sup>), made in 1993, had reduced mortality; however, a recent increase in cases of ischemic stroke induced by envenomation, despite early serum infusion, suggested a decreasing efficiency.<sup>1</sup> A new specific antivenom (also called Bothrofav<sup>®</sup>) was registered in February 2011. The objective of this study is to evaluate its safety and efficacy in a prospective series of treated patients.

**Methods:** A prospective observational study including all patients admitted due to *Bothrops lanceolatus* bites in the three emergency services and medical-surgical ICUs of Martinique from February 2011 to August 2014. Patients were managed according to a protocol established by the research Group on Snake Bites in Martinique. The intravenous dose of antivenom was adapted to the grade of the bite, defined as a standard score based on clinical and biological criteria. The results were expressed as mean  $\pm$  SD or %.

**Results:** In 40 months, 76 patients were included (age  $47 \pm 17$  years, 56M/20F, past history: hypertension (n = 11), HIV (n = 3) and diabetes (n = 2)). One chronic renal insufficiency patient was bitten on the arm with the fistula for dialysis. The bite was located on the lower (44%) or upper limbs (56%). Edema (96%), pain (96%), bleeding (70%) and elevated troponin (4%) were noted and no patient presented with bleeding disorders. The time between admission and antivenom administration was < 3 hours in 50% of the patients. The outcome was favorable, with no deaths. Three patients (8%) were operated on because of abscesses at the bite site. One case of thrombosis was observed at the arterio-venous fistula in the patient on dialysis. One patient had an aneurysm of the left tibial artery at the site of the bite, supported in vascular surgery. Systematic venous echo-Doppler of the lower or upper limbs showed no other cases of thrombosis. Initial magnetic resonance imaging (MRI) showed no ischemic injury, particularly in two areas of the posterior inferior cerebral arteries (PICA). The duration of ICU stay was  $1.8 \pm 3.0$  days.

**Conclusion:** Our data support the excellent safety and likely effectiveness of early infusion of new antivenom Bothrofav<sup>®</sup> if bitten by *Bothrops lanceolatus* in Martinique. Further studies are needed to optimize its dose regimen, especially in the most severe cases.

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## 29. Hydroxocobalamin and sodium thiosulfate in acute cyanide poisoning

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**Objective:** Hydroxocobalamin is an effective first-line antidote used mainly as monotherapy in cyanide poisoning, while opinion on the effects of its combination with sodium thiosulfate is divided. We report a patient with acute poisoning after ingestion of a lethal dose of potassium cyanide who was successfully treated with both these two antidotes.

**Case report:** A 58-year-old male attempted suicide by ingesting 1200-1500 mg of potassium cyanide. He became unconscious 1-1.5 minutes after ingestion and had an episode of generalized seizures. On admission to the ICU he was acidotic (pH 7.28; HCO<sub>3</sub> 14.0 mmol/L, base excess -12.7 mmol/L, O<sub>2</sub> saturation 0.999) with high serum lactate (12.5 mmol/L). Hydroxocobalamin was administered 1.5 hours after ingestion in two intravenous infusions to a total dose of 7.5 g. The infusion was followed by continuous intravenous administration of 1 mL/kg/h of 10% sodium thiosulfate to the total dose of 12 g. No complications or adverse reactions were observed. The serum lactate decreased to 0.6 mmol/L the same day, and arterial blood gases normalized (pH 7.49; HCO<sub>3</sub> 27.2 mmol/L, base excess 2.2 mmol/L, O<sub>2</sub> saturation 0.994). The follow-up examination 5 months later revealed no damage to the basal ganglia or cerebellum on magnetic resonance imaging; neurological examination revealed no pathological changes. On ocular coherence tomography the retinal nerve fiber layer was normal. In visual evoked potentials there was a normal evoked complex on the left eye and minor decrease of amplitude on the right one.

**Conclusion:** The combination of hydroxocobalamin and sodium thiosulfate can have a positive effect on survival without long-term neurological and visual sequelae in cases of massive cyanide exposure. This may be due to a potentiation or synergism of hydroxocobalamin effects by sodium thiosulfate. This synergism can be explained by the different time points of action of two antidotes: the initial and immediate effect of hydroxocobalamin, followed by the delayed, but more persistent effect of sodium thiosulfate.

## 30. Pre-hospital ethanol administration improves outcomes in mass methanol outbreaks

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**Objective:** Poor outcome (death/sequelae) in methanol poisoning is associated with delayed diagnosis and treatment initiation. Administration of pre-hospital ethanol may improve outcome, but its effects have not been assessed. We studied the effect of

pre-hospital ethanol in patients treated during a large methanol outbreak in the Czech Republic during 2012-2014.<sup>1</sup>

**Methods:** A combined prospective and retrospective case series study of 100 patients with confirmed methanol poisoning.

**Results:** Pre-hospital ethanol was administered by paramedic/medical staff in 30 patients; 12 patients self-administered ethanol before presentation, while 58 received no ethanol. Delay to hospital admission and blood methanol concentrations were similar between groups. Forty-two patients had detectable ethanol on hospital admission before antidote treatment (median concentration 18.3 [IQR 6.6-32.2] mmol/L). The median serum ethanol on admission in patients following pre-hospital administration by paramedic/medical staff (18.3 [7.1-28.1] mmol/L) was lower than in patients self-administering ethanol (30.6 [6.4-81.9] mmol/L;  $p < 0.01$ ). Pre-hospital oral administration of ethanol by paramedic/medical staff had a significant effect on survival without visual/CNS sequelae (OR 19.64; CI 95% 5.38-71.70;  $p < 0.001$ ). Patients receiving pre-hospital ethanol administration from any source more often survived without visual/CNS sequelae than those not receiving ethanol before hospitalization (90.5% versus 19.0%,  $p < 0.001$ ). No patients receiving pre-hospital ethanol died compared to 21 not receiving ethanol (0% versus 36.2%,  $p < 0.001$ ). Positive serum ethanol on admission ( $\geq 1.7$  mmol/L) was a significant predictor for survival without visual/CNS sequelae (OR 40.6; CI 95% 12.0-137.7;  $p < 0.001$ ). Probability of a poor outcome decreased exponentially with increasing arterial blood pH, but the rate of decrease was significantly higher in patients with pre-hospital ethanol administration by paramedic/medical staff.

**Conclusion:** We found a strong association between pre-hospital ethanol administration and good outcome. During methanol outbreaks, conscious adults with suspected methanol poisoning should be given the equivalent of 2 mL/kg body weight of 40% alcohol-by-volume ethanol to reduce morbidity and mortality. Any potential delay before definite diagnosis and treatment further strengthens this recommendation.

**Acknowledgement:** A grant to the First Faculty of Medicine, Charles University, P25/1LF/2.

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## 31. Variations in serum ethanol concentrations during the treatment of acute methanol poisoning

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**Objective:** During an outbreak of mass methanol poisonings in the Czech Republic in 2012, ethanol was the main antidote used. The pharmacokinetics of ethanol makes it difficult to maintain the serum ethanol concentration (S-EtOH) within the therapeutic range of 22-33 mmol/L. We studied the variations in S-EtOH concentrations and investigated the impact on the outcome of methanol poisoning.

**Methods:** A prospective case series in 21 patients with median age 52 years (range 27-79 years), including 13 males and 8 females. Serum ethanol, methanol and formate concentrations were measured every 2-6 hours during treatment. Follow-up clinical examination was performed in 15/18 survivors.

**Results:** The mean period of observation was  $90 \pm 20$  hours. The mean period of consistent maintenance of S-EtOH within the therapeutic range lasted  $27.5 \pm 7.4\%$  of the total time of observation. During  $29 \pm 7.9\%$  of the time the S-EtOH was  $> 33$  mmol/L with peaks up to 76 mmol/L. During  $44 \pm 10\%$  of the time the S-EtOH was  $< 22$  mmol/L. Nevertheless, the mean duration of periods with the sub-therapeutic S-EtOH and serum methanol  $> 6.2$  mmol/L or serum formate  $> 0.4$  mmol/L lasted  $20.3 \pm 9.7\%$  and  $18 \pm 11\%$  of total time of observation, respectively. Adverse events were observed in 14 (67%) of cases including significant fluctuation of S-EtOH ( $n = 9$ ), aspiration pneumonia ( $n = 3$ ) and delirium tremens ( $n = 2$ ). Other adverse events included sepsis, bleeding, rebound acidosis, agitation, intolerance and clotting disturbance. The outcomes were: 11 survivors without sequelae, 7 survivors with sequelae, and 3 deaths. The difference in the duration of periods with sub-therapeutic concentrations of S-EtOH between the 3 groups was not significant (all  $p > 0.05$ ).

**Conclusion:** Despite the difficult pharmacokinetics and significant variations in serum ethanol concentrations during the treatment there was no impact of fluctuations on the outcome of treatment. No adverse drug events which could be directly related to the administration of ethanol were observed. Administration of ethanol according to the present AACT/EAPCCT guidelines was safe and effective in the treatment of methanol poisoning during this mass outbreak. Taking into account a general principle that an antidote should be administered as soon as possible after methanol ingestion, and the general availability of ethanol, both antidotes, fomepizole or ethanol, may be considered for alcohol dehydrogenase (ADH) blockade during mass methanol outbreaks without limitations.

**Acknowledgement:** A grant to the First Faculty of Medicine, Charles University, P25/1LF/2.

## 32. Fomepizole kinetics during intermittent (IHD) and continuous hemodialysis (CVVHD): A case study

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**Objective:** Fomepizole is the antidote of choice for toxic alcohol poisonings. Due to its dialysability, dosing is increased from every 12 to every 4 hours during intermittent dialysis (IHD). During continuous dialysis (CVVHD) blood flow is lower and data on elimination kinetics are lacking. We present a case of ethylene glycol poisoning where both dialysis modalities were used and fomepizole kinetics were evaluated.

**Methods:** A 42-year-old female was found unconscious outdoors next to an empty bottle of antifreeze containing ethylene glycol, and a half-full bottle of solvent containing isopropanol. On admission her GCS was 3, her arterial blood gas showed a moderate metabolic acidosis, creatinine 102  $\mu\text{mol/L}$ , ethylene glycol 192  $\text{mmol/L}$  (1190  $\text{mg/dL}$ ), acetone 5.7  $\text{mmol/L}$  (33  $\text{mg/dL}$ ), and negative methanol and isopropanol. She was initially dialysed with IHD (blood flow 200  $\text{mL/min}$ ) for 4 hours, then with CVVHD (blood flow 150  $\text{mL/t}$ ) for 18 hours. Fomepizole was dosed every 4 hours during IHD and every 8 hours during CVVHD. The patient had a temporary reduced vision for a few hours during early dialysis, but the symptoms subsided and she was discharged after an otherwise uneventful treatment. Samples were collected from pre- and post-filter blood, as well as the dialysate during the course of the treatment. Fomepizole was measured using high-pressure liquid chromatography with a reverse phase column (sensitivity 5  $\mu\text{mol/L}$ ; coefficient of variation 4.5% at 25  $\mu\text{mol/L}$ ).

**Results:** During treatment, fomepizole was maintained in the therapeutic range. After 4 hours of IHD the lowest fomepizole concentration was 77  $\mu\text{mol/L}$ , whereas the lowest concentration during CVVHD was 116  $\mu\text{mol/L}$ . During IHD, the average dialysance was 216  $\text{mL/min}$  (range 208–223,  $n=2$ ), whereas the average dialysance during CVVHD was 51  $\text{mL/min}$  (range 36–60,  $n=6$ ).

**Conclusion:** This case suggests an alternative dosing strategy for fomepizole during CVVHD. In spite of the dosing regimen being only half of that typically given with IHD, the lowest measured serum fomepizole concentration was 11 times the recommended minimum therapeutic concentration (10  $\mu\text{mol/L}$ ). The CVVHD fomepizole dialysance was approximately a quarter of that found during IHD, hence the present dosing regimen appears safe even before larger trials are undertaken. This may play an important role in times of limitations in fomepizole supplies, such as during out-breaks or in areas where fomepizole availability is limited.

### 33. Comparison of adverse drug reaction rates using a two-bag to a standard three-bag intravenous acetylcysteine regimen for paracetamol poisoning

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**Objective:** A lower incidence of anaphylactoid and gastrointestinal adverse drug events (ADEs) has recently been reported using a modified 12-hour acetylcysteine regimen with a loading dose of 100  $\text{mg/kg}$  over two-hours (50  $\text{mg/kg/h}$ ).<sup>1</sup> We examined the rate of ADEs using patient cohorts treated with i) a two-bag acetylcysteine protocol (200  $\text{mg/kg}$  loading dose over 4 hours followed by 100  $\text{mg/kg}$  infused over 16 hours) implemented in our hospitals in February 2014 and ii) an historical cohort of patients (2009–2013)

reported previously<sup>2</sup> treated with a three-bag regimen (150  $\text{mg/kg}$  over 1 hour, 50  $\text{mg/kg}$  over 4 hours, 100  $\text{mg/kg}$  over 16 hours).

**Methods:** Data from the two groups were analysed including: gender, age, type and time of ingestion, paracetamol dose and serum concentration, and acetylcysteine dose. Nursing and medical notes were examined for description of reactions using key words; rash, hives, urticaria, itch, pruritis, flushing, redness, wheeze, dyspnoea, cough, hypotension for histamine-type reactions and nausea and/or vomiting for gastrointestinal reactions.

**Results:** There were 122 acetylcysteine administrations with the 2-bag protocol; median patient age was 31 years, 76% female, 84% deliberate self-poisoning, 65% presenting < 8 hours post-ingestion. There were 385 administrations with the 3-bag protocol; median age was 22 years, 79% female, 93% deliberate self-poisoning, 70% presenting < 8 hours post-ingestion. Reported median paracetamol dose ingested was 15 g with 2-bag and 18 g with 3-bag protocol ( $p=0.006$ ). Mean initial paracetamol concentration was similar (2-bag 942  $\text{mcmol/L}$  and 3-bag 1063  $\text{mcmol/L}$ ), measured at 5.5 and 5.0 hours, respectively. Median acetylcysteine dose was 19.5 g in both groups administered over median time of 20 and 21 hours, respectively ( $p=0.0001$ ). Three-bag protocol had 40/385 (10.4%) histamine-reactions recorded (11 significant: 7 bronchospasm, 3 facial swelling, 1 hypotension). Two-bag protocol had 5/122 (4.0%) histamine-reactions, all mild and cutaneous (3 facial flushing, 1 rash, 1 itch at infusion site) recorded. (Odds ratio: 2.7 (95% 1.05–7.0,  $p=0.04$ ). Incidence of gastrointestinal reactions was similar (39% v 44%, respectively).

**Conclusion:** Simplification of acetylcysteine administration to a 2-bag protocol with loading-dose over 4 hours at 50  $\text{mg/kg/h}$  was associated with less severe histamine-type reactions in this observational cohort. Although using a retrospective cohort has limitations, further evaluation of different acetylcysteine dosing regimens to improve ADE rates is warranted.

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### 34. A novel infusion protocol for the administration of acetylcysteine

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**Objective:** A 3-phase acetylcysteine (N-acetylcysteine; NAC) infusion is currently used for paracetamol poisoning if the concentration taken 4 + hours post-overdose is above the nomogram. This regimen delivers half the total dose in 15–60 minutes and is prone to adverse reactions. Based on a simulation study we modified our practice to give a novel infusion protocol where the initial two



infusions were combined and given over an extended period. We aimed to determine if the rate of reactions was reduced by a slower initial infusion rate.

**Methods:** This was a quality assurance review of a change in practice for NAC administration in paracetamol poisoning. A new 2-phase infusion protocol was commenced in all patients ingesting > 4 g paracetamol on admission and ceased if the paracetamol concentration was non-toxic. The first infusion was 200 mg/kg given over a duration based on time since overdose, so 11 hours MINUS the time since ingestion (i.e., 9 hours if 1-2 hours post-overdose etc. up until 4 hours if 7+ hours post-overdose). The first infusion was given over 4 hours for staggered, repeated supratherapeutic ingestions and for unknown ingestion time. The second infusion was 100 mg/kg over 16 hours. Pre-defined outcomes were frequency of adverse reactions defined as systemic hypersensitivity reactions (SHR) or gastrointestinal effects; proportion with abnormal alanine transaminase (ALT) in patients administered NAC within 8 hours post-overdose and number of medication errors.

**Results:** There were 596 paracetamol poisonings treated with the new protocol (median age 29 years (15-98 years), 418 were female). There were 537 acute and 59 staggered/chronic ingestions. In 394 overdoses (66%) the NAC infusion was stopped because of non-toxic paracetamol concentrations. In 190 acute overdoses < 10 g (not staggered) none had toxic paracetamol concentrations. An adverse reaction occurred in 208/596 (35%), 155 cases (26%) were only gastrointestinal, 50 (8%) included skin only SHR and three had severe anaphylaxis (hypotension). There were adverse reactions in 97/202 cases (48%) receiving the full NAC treatment compared to only 111/394 (28%) where the infusion stopped. In 190 patients ingesting < 10 g there were 49 reactions. Forty patients developed some degree of toxicity (11 with ALT > 1000U/L); all but one presented > 12 hours post-overdose. There were four medication errors.

**Conclusion:** A 2-phase NAC infusion protocol appeared to result in fewer SHRs and most reactions were gastrointestinal. One quarter of reactions occurred in patients with non-toxic poisoning who would not normally receive NAC. Increasing the treatment threshold to 10 g would reduce the number of patients treated by 32% and prevent 49 reactions.

### 35. Is normobaric oxygen efficient in cyanide poisoning? A systematic review of individual cases

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**Objective:** Assessment of efficiency of oxygen in cyanide poisoning is based on the mechanism of toxicity of cyanide, case reports and expert opinion. To address this question, we systematically reviewed the medical literature providing access to individual data. We present data dealing with normobaric oxygen administered either alone or in combination with supportive treatment; the control group included patients treated with supportive measures but without oxygen, meaning the patient was removed from toxic atmosphere receiving or not artificial ventilation.

**Methods:** The literature was reviewed up to 2010 in PubMed, Embase, Scopus, Toxline, French PCC database and 'Current Awareness in Toxicology'.<sup>1</sup> References providing individual patient data for at least one patient were eligible for the study. The Poison Severity Score (PSS) adapted to cyanide was used for sequential assessment. A sequence was defined as a sequence of events with treatment allowing calculating the PSS before and just after administration of a treatment, a treatment means either a single drug e.g. oxygen, or a combination e.g. nitrite and thiosulfate. Results are expressed using median (25-75 percentile). Wilcoxon matched paired test was performed to compare before and after treatment for sequences including 7 patients and more.

**Results:** From 1847 to 2010, 400 cyanide poisonings were considered, 111 were not included due to the absence of information on treatment. Among the 289 included patients, 23 patients received supportive treatment without oxygen and without any antidotes (control group). Thirty-two patients received oxygen (oxygen group). Oxygen was administered either alone or in combination with supportive treatment. In the control group, sequence 1 and 2 included 23 and 1 patient, respectively. In the oxygen group, sequence 1, 2, and 3 included 32, 5, and 2 patients, respectively. Only the first sequence can be tested. In the control group, the median PSSs before and after were 1 (1-2) and 0 (0-0), respectively ( $p < 0.0011$ ). In the oxygen group, the median PSSs before and after were 3 (1-3) and 1.5 (0-4), respectively ( $p < 0.13$ ).

**Conclusion:** In mild cyanide poisoning, removal of patients from the toxic atmosphere is efficient. In severely cyanide poisoned patients, oxygen, even associated with supportive care, resulted in a non-significant improvement. These data support the need to consider antidote therapy, in addition to supportive treatment including oxygen, in severe cyanide poisoning.

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### 36. Admission characteristics of patients receiving physostigmine in a Toxicologic ICU: A quality and safety assessment study

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**Objective:** Physostigmine is a cholinergic drug used in reversal of anticholinergic syndrome (AChS), however, the safety profile of this drug remains unclear. At our institution, physostigmine has been used for the last 20 years without severe adverse events. We performed a retrospective quality assessment to judge the safety of our policy and as a first step, we characterised the AChS in these patients.

**Methods:** We analysed the records of all patients admitted to our toxicologic ICU from January 2011 to December 2012, retrieving data on patients that received physostigmine. We derived data about medical history, status at admission and presence of symptoms of anticholinergic syndrome.

**Results:** In total 151 patients received physostigmine. Mean age was 37 years and 65.6% were females. The media Glasgow Coma Scale (GCS) was 11 with 23.1% of patients showing GCS < 9. The nature of ingested drugs was amitriptyline (11.9%), chlorprothixene (7.9%), diphenhydramine (12.6%), olanzapine (6%), prothipendyl (11.3%), quetiapine (22.5%) or other (27.8%). Median heart rate at admission was 120 bpm (95% CFI 77-162 bpm), median systolic blood pressure 130 mmHg (28 to 185). In 59.6% of the cases the patients ingested more than one drug. In 26.5% (n = 40) of the cases an ECG was available, the median QTc was 453 ms (95% CFI 344-572 ms), with a maximum of 660 ms. Possible symptoms of anticholinergic syndrome included diminished bowel sounds in 66.2%, disorientation in 61.5%, slurred speech in 56.2%, agitation in 53%, dry skin/mouth in 44.4%, mydriasis in 21.2%, coma with inability to keep airway patent in 19.9%, respiratory failure requiring positive end-expiratory pressure (PEEP) in 17.9%, circulatory failure requiring catecholamines in 10.6%, picking movements in 9.3%, hallucinations in 6.6%, seizures in 7.3% temperature > 37.5°C in 3.3% and extrapyramidal syndrome in 2%. Acute kidney injury was reported in 4% of patients and 7.3% had signs of pulmonary aspiration. In 64% of cases the treating physician judged the presenting symptoms as 'classic AChS', in the remaining 36% the use of physostigmine was an attempt to reverse a more non-specific delirium or coma.

**Conclusion:** The symptoms of peripheral and central anticholinergic syndrome are well described, though there is no score or algorithm leading to a definite diagnosis. The observed symptoms correspond well to those commonly published except for the rate of mydriasis and especially significant hyperthermia, which were surprisingly low. Diminished bowel movements, disorientation, slurred speech and agitation were the most common findings in our patients.

### 37. A 2-year analysis of scorpion envenomations in a regional poison center following new scorpion antivenom introduction to the US market

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**Objective:** Scorpion envenomation is a frequent and important toxicological scenario in the USA. According to the American Association of Poison Control Centers' (AAPCC) 2012 Annual Report, US poison centers reported 19,224 single exposure scorpion cases to the National Poison Data System (NPDS). While all scorpions are inherently venomous, the only systemically poisonous scorpion in the US is *Centruroides exilicauda* (bark scorpion). Prior to 2012, there was no Food and Drug Administration (FDA) approved antivenom available for scorpion envenomations. There was a preparation available in Arizona effective against severe *Centruroides* envenomations, however production ceased and supplies were depleted. In 2011, Rare Disease Therapeutics, Inc announced approval of Anascorp®, an equine-derived antivenom indicated for treatment of patients with clinical signs of scorpion stings, and in the spring of 2012, this new antivenom became available. We sought to evaluate the use of Anascorp following its introduction to the US markets.

**Methods:** We retrospectively reviewed all poison center (PC) charts from our 4-state regional poison center from 1 January 2012

to 31 October 2014 using the AAPCC Generic Code 0205240. Data from NPDS was analyzed according to gender, age, level of health care facility care, clinical effects, and therapies.

**Results:** A total of 3,094 human exposure cases were identified. Of these 56.2% were female (1.5% were pregnant); 2.4% of cases occurred in children ≤ 2 years of age, 4.2% in children aged 3-6 years, 11.5% in 7-18 year olds, 66.4% in patients aged 19-65 years and 14.4% in patients over 65 years of age (0.9% of cases had unknown age). The most common clinical effect was pain (82%), followed by numbness (17.5%) and erythema (12.8%). Most cases (87%) were managed on site (non-health care facility [HCF]), 4.8% were already in a HCF at the time of call and 6.7% were referred to a HCF by the PC. Of those that were evaluated in a HCF, only 20 patients (0.6%), all with severe symptomatology, received Anascorp® antivenom. There were no deaths and no cases of anaphylaxis or serum sickness due to antivenom were reported.

**Conclusion:** While scorpion envenomation is not infrequent in the US, it is a situation that can usually be managed at home with standard supportive care measures. Referral to an HCF may be indicated in severe cases, and in those situations, the need for antivenom therapy must be decided on a case by case basis.

### 38. Intravenous lipid emulsion for amlodipine/benazepril toxicity: A case report

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**Objective:** Intravenous lipid emulsion (IVLE) has been suggested as a potential antidote for calcium channel blocker overdose. Although many mechanisms have been hypothesized, the "lipid sink" theory is most often proposed due to the lipophilic nature of the drug providing an alternative medium for distribution. We report a case of amlodipine and benazepril toxicity with amlodipine concentrations obtained before and after administration of IVLE.

**Case report:** A 12-year-old, 60 kg female presented to the emergency department 2 hours after ingestion of 240 mg of amlodipine and 480 mg of benazepril. Initial vital signs included blood pressure (BP) 116/55 mmHg and heart rate (HR) 118 beats/minute (bpm) with blood glucose of 133 mg/dL. She was given 50 g activated charcoal upon arrival. BP declined to 70/36 mmHg (HR 96 bpm) and the patient was given IV fluid resuscitation, calcium supplementation, epinephrine (0.3 mcg/kg/min) and norepinephrine (0.3 mcg/kg/min) infusions. She had subsequent decline in mental status and was intubated on arrival at the pediatric intensive care unit. Insulin infusion was started (0.03 units/kg/h) but not titrated to goal rate. The patient was given a bolus of 100 mL of 20% IVLE 11 hours post-ingestion. One hour prior to IVLE administration, the amlodipine concentration was 87 ng/mL (BP 86/36 mmHg, HR 122 bpm). Within 1 hour of IVLE administration, the amlodipine concentration was 83 ng/mL (BP 108/42 mmHg, HR 132 bpm). Epinephrine infusion was tapered over the next 9 hours as norepinephrine requirements decreased (0.15 mcg/kg/min). Calcium was maintained at a goal ionized level of 8 mg/dL until 24 hours post-ingestion. Insulin infusion was discontinued

after 12 hours (max rate 0.5 units/kg/h) due to glucose concerns and hyperdynamic left ventricle seen on bedside echocardiogram. The patient was extubated 44 hours post-ingestion and maintained on norepinephrine infusion until 55 hours post-ingestion. She was subsequently treated for aspiration pneumonia and admitted to psychiatry after 4 days.

**Conclusion:** We report a case of combined amlodipine and benazepril toxicity treated with IVLE. Potential treatment modalities include calcium, insulin, vasopressors and IVLE.<sup>1</sup> Despite multiple pharmaceutical interventions, our patient had persistent hypotension that improved after IVLE administration resulting in decreased vasopressor requirements. Pre/post amlodipine serum concentrations do not support the lipid sink theory as the mechanism of benefit in this case. The amlodipine concentration decreased slightly after administration of IVLE in contrast to the increase that would be expected with a lipid sink.

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## 39. Successful management of acute collective hydrogen sulfide exposure

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**Objective:** Hydrogen sulphide (H<sub>2</sub>S) is a highly lipophilic, toxic and irritant gas, usually formed from bacterial breakdown of organic material in the absence of oxygen, such as in swamps and sewers; a process commonly known as anaerobic digestion.<sup>1</sup> H<sub>2</sub>S toxicodynamics consists, similarly to cyanide, in interrupting oxidative phosphorylation by inhibition of cytochrome a3 oxidase, thus producing cytotoxic hypoxemia, decreasing ATP production and enhancing anaerobic metabolism.<sup>2</sup> Moreover, H<sub>2</sub>S activates guanylate cyclase increasing the intracellular concentration of cGMP, inducing vasodilation.<sup>3</sup> We report two cases of exposure treated with sodium nitrite.

**Case series:** In May 2014 two sewer employees experienced acute inhalation exposure to H<sub>2</sub>S. Both of them collapsed within one minute in attempting to help each other without protective equipment. Because of acute respiratory failure, both patients were intubated on-scene and mechanical ventilation started. On Emergency Department arrival they had a Glasgow Coma Scale (GCS) score of 3 and were hemodynamically stable. Both patients showed signs of tissue hypoxia with “arterialized” venous blood (venous blood partial pO<sub>2</sub> 99.9 and 90.1 mmHg, respectively). Both were admitted to the Intensive Care Unit and mechanically ventilated with invasive monitoring. In order to create a false substrate to bind the toxic hydrosulfide anion and to promote detoxification, sodium nitrite was administered. Nitrite-induced methaemoglobin, by competitively binding the toxic hydrosulfide anion, presum-

ably reactivated and protected cytochrome oxidase thus improving patient recovery by enhancing aerobic metabolism. Methaemoglobinemia was closely monitored and restoration of respiratory physiological values gradually occurred. No focal neurological dysfunctions were found and the patients were discharged after 15 days of hospitalization.

**Conclusion:** H<sub>2</sub>S is an extremely toxic gas and severe exposure is life-threatening. Severe cases of H<sub>2</sub>S poisoning could be treated with nitrite-induced methemoglobinemia in addition to vigorous supportive care and, in the future, with inhibitors of guanylate cyclase (i.e. methylene blue) thus reducing the decrease in blood pressure.

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## 40. The impact of new paracetamol treatment guidelines on children who take accidental acute paracetamol overdose

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**Objective:** In January 2013, the Irish Medicines Board introduced new guidelines for paracetamol overdose recommending treatment with acetylcysteine for patients with a plasma paracetamol concentration of > 100 mg/L at 4 hours post-ingestion. This equates to an ingested dose of 75 mg/kg. Previously, doses < 150 mg/kg did not mandate clinical investigation unless the patient had specified risk factors. The aim of this preliminary retrospective study was to assess the impact of the new guidelines on children with acute accidental paracetamol overdose.

**Methods:** We reviewed enquiries to the National Poisons Information Centre (NPIC) for the period January-December 2013 and compared data to the same period in 2012. We identified cases involving acute accidental ingestion of 75-150 mg/kg of single formulation paracetamol products by children < 12 years old. We used NPIC data and a short questionnaire to establish if the patient had blood tests and/or antidotal treatment.

**Results:** The NPIC received 730 enquiries regarding acute paediatric paracetamol overdose in 2013. There was a 2.6-fold increase in the number of patients who required hospital assessment and plasma paracetamol concentrations compared to the same period in 2012 (329 versus 125). In total 198 cases (27%) involved ingestion of 75-150 mg/kg. Of these cases, contact information could not be obtained for 104 patients as they attended a GP or Community Pharmacy therefore 94 cases were included for further analysis. One patient refused to participate in the study. Complete data was available for 44 cases (46.8%). Of these 39 patients had a plasma paracetamol



concentration measured, 2 patients had no paracetamol concentration measured and 3 patients did not attend hospital. Three patients received acetylcysteine: one had a 4-hour paracetamol concentration of 120 mg/L, one received it despite a non-toxic concentration and one had no reported paracetamol concentration measured due to faulty laboratory equipment. No adverse effects were reported.

**Conclusion:** A prospective study with a wider dataset is required but preliminary results suggest the new paracetamol guidelines increase unnecessary hospital attendance and clinical investigation in children without any clear benefit.

#### 41. A new national antidote database: An open online service

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**Objective:** To describe the implementation of a new national antidote database created in order to ensure adequate availability and use of antidotes.

**Methods:** The Swedish Poisons Information Centre is responsible for the national antidote programme. Since 1996 an antidote database is included. To optimize this function a new comprehensive database was implemented in 2012. It is available online and contains updated information on all antidote stocks kept in Swedish hospitals. All 74 hospitals with emergency care units in the country are participating. A centralized antidote store at a pharmacy in Stockholm, open around the clock with transport capabilities, is also included as an extra preparedness for emergency situations. The database contains information on generic and commercial names of the recommended antidotes, appropriate amount to store, current quantity, where in the hospital the store is located, therapeutic indications and administrative aspects (licence obligation, name of manufacturer etc.). Any changes of the stores are reported directly to the poison centre by the hospital staff and are subsequently entered into the database. To facilitate this procedure the hospitals can download and modify a file containing their own local list. The administrator at our poison centre has contact details for the personnel responsible for antidotes at each hospital. This record of email addresses enables the poison centre to instantly inform each hospital about important changes concerning antidotes. A dedicated email address is also linked to the database to be used whenever hospitals have questions regarding antidotes. Both the Swedish poison centre and medical staff at the hospitals have access to data without using a password (<https://antidot.gic.se/antidot-web>). A physician treating an overdose case can directly see the locally available amount of a particular antidote and also if a nearby hospital can provide more if needed.

**Results:** The new database gives access to instant information regarding antidote stock in all hospitals with an emergency care unit in the country. The database also facilitates the collaboration between the Swedish poison centre and the hospitals concerning availability, storage and supply of antidotes. Cost-effectiveness can be improved by joint regional planning. Such an open database can also provide possibilities for cooperation between neighbouring countries.

**Conclusion:** The new antidote database has proven efficient in providing instant information, around the clock, on medical and administrative aspects of antidote use.

#### 42. Chemical instability of glucagon when given as a continuous infusion

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**Objective:** Bradycardia and hypotension are the most common effects in beta-blocker overdose, and severe poisonings can result in cardiogenic shock.<sup>1</sup> Glucagon is recommended as specific therapy against cardiotoxicity in beta-blocker overdoses.<sup>1</sup> Intravenous glucagon is given as a bolus followed by a continuous infusion.<sup>1</sup> There are no clinical studies evaluating the efficacy of glucagon in this setting, and information is limited to case reports. We present a case describing what happened when we administered glucagon as a continuous infusion.

**Case report:** A 59-year-old female was admitted to a regional hospital after two weeks of atrial fibrillation (HR 120-200) and signs of cardiac failure, caused by acute hyperthyroidism. Verapamil 5 mg and metoprolol 5 mg x 3 was given intravenously without effect, followed by propranolol 40 mg orally. She then deteriorated with hypotension, and was transferred to our hospital. She experienced cardiac arrest, return of spontaneous circulation (ROSC) was established almost immediately, but large doses of vasopressors, high dose insulin, calcium and glucagon was needed to maintain adequate circulation. She recovered completely. A glucagon solution of 1 mg/mL was prepared by reconstituting 1 mg powder with water for injection. The initial dose was 10 mg bolus, followed by a second dose after seven hours. Then after 1 hour a continuous infusion of 4 mg/hour was started. After 16 hours a fresh solution for continuous infusion was made but 9 hours after the solution was changed the syringe pump stopped because the solution had coagulated. A literature search revealed that this is a known problem since glucagon is chemically unstable in aqueous solution. Fibrils can form and there is rapid chemical degradation at room temperature.<sup>2</sup> No previous case reports on the use of glucagon as an antidote for beta-blocker overdose have described this as a problem.

**Conclusion:** Due to the chemical instability of glucagon in aqueous solution, caution should be taken regarding the use of glucagon as continuous infusion, and a fresh solution has to be made frequently. After this case, the Norwegian Poison Information Centre changed their recommendations to repetitive intravenous bolus dosing of glucagon instead of continuous infusion.

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#### 43. Doubling the third dose of intravenous N-acetylcysteine survey: An international practice perspective

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**Objective:** N-Acetylcysteine (NAC) has been used highly effectively for acetaminophen toxicity for over 35 years.<sup>1</sup> Due to uncertainties about the quantity needed in massive acute acetaminophen overdose, its original regimen is sometimes modified in this situation.<sup>2</sup> Some Poison Control Centres (PCC) advocate doubling the dose of the third infusion of the standard NAC regimen (12.5 mg/kg/hour from 6.25 mg/kg/hour). There is limited theoretical evidence to support this practice. The definition of a massive ingestion is also lacking and the practice of adjusting the dose of NAC in repeated supra-therapeutic ingestions or in cases treated with extracorporeal treatments (ECTR) has never been described. The goal of this international survey was to assess NAC adjustment practices.

**Methods:** A volunteer online questionnaire containing 10 items was sent to the American Academy of Clinical Toxicology, American College of Medical Toxicology, American Association of Poison Control Centres, Canadian Association of Poison Control Centres, European Association of Poisons Centres and Clinical Toxicologists and the Asia Pacific Association of Medical Toxicology to deploy to their membership. Informed consent was obtained digitally after explanation of the survey and answers collected anonymously. The survey was open for participation from November 4th to 14th, 2014. No reminder was sent.

**Results:** A total of 164 completed responses were received from 19 different countries. In total 61% of participants were PCCs (20%) or Inpatient Medical/Clinical Toxicology Consultant (41%). Most (61%) of all participants consider a high acetaminophen concentration as an indication to increase the dose of NAC and 33% of them choose 3000 µmol/L (450 µg/mL) as the cutoff point. Participants recommended doubling the dose of the third NAC infusion in acute toxicity and repeated supra-therapeutic dosing in 32% and 14%, respectively. Most (68%) also recommended increasing the dose of NAC in cases of acetaminophen toxicity during ECTR. Poison information specialists in 87% of responses are not allowed to recommend adjustment to the NAC infusion without consulting a medical toxicologist.

**Conclusion:** Adjusting the dose of NAC is a highly variable practice. High acetaminophen concentrations and ECTR are the main indications. Doubling the third infusion of NAC is recommended more often in acute compared to repeated supra-therapeutic overdose. Factors underlying this variability should be further explored.

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## 44. Early administration of isosorbide dinitrate improves survival of cyanide-poisoned rabbits

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**Objective:** To evaluate the effectiveness of isosorbide dinitrate compared to sodium nitrite in cyanide poisoning.

**Methods:** A comparative animal study was performed using 18 rabbits, randomized into 3 study groups of 6 animals each. The rabbits were poisoned with potassium cyanide (1 mg/kg intravenously). The first group was not given any further treatment (controls). The second and third groups were treated intravenously 1 minute after poisoning with sodium nitrite (6 mg/kg) and isosorbide dinitrate (50 mcg/kg), respectively. The primary outcome was short-term survival of up to 30 minutes. Secondary outcomes included time to death, a clinical score, mean blood pressure, pulse, blood pH, lactate and methemoglobin concentrations.

**Results:** All rabbits treated with isosorbide dinitrate or sodium nitrite survived while only one untreated rabbit survived. The median time to death of the 5 control untreated animals was 10 minutes. All the animals collapsed soon after poisoning, exhibiting rapidly disturbed vital signs and lactic metabolic acidosis. Treated animals improved gradually with almost full recovery of clinical scores, vital signs and blood gases. Sodium nitrite administration increased the methemoglobin concentration to an average peak of 7.9% while isosorbide dinitrate had no effect on the methemoglobin concentration.

**Conclusion:** Early administration of isosorbide dinitrate improved the short-term survival of cyanide-poisoned rabbits. Isosorbide dinitrate shows potential as an antidote for cyanide poisoning and may exert its effect using a nitric oxide-dependent mechanism.

## 45. Evolution of the antidote treatment in acute poisoning in an emergency department

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**Objective:** The frequency of antidote treatment is linked to the epidemiological poisoning profile but it also depends on the adequacy of its indication. The aim of this study was to analyse the changes in the trends of antidote use in our emergency departments from 1996 to 2012.

**Methods:** Retrospective descriptive study of the use of antidotes and its relationship with the epidemiological profile in the acute poisonings attended in our emergency department. The data have been obtained from the files of our clinical toxicology unit for the 17 years evaluated.

**Results:** Our database includes 18,232 cases with a mean of 1,075 acute poisonings per year. The most frequently involved agents were ethanol (49.2%) and benzodiazepines (18.2%). In the group of abused drugs the second after ethanol was cocaine (6.29%). Focusing on the agents that can be treated with antidotes we find opiates (3.4%), carbon monoxide (1.76%) and paracetamol (1.74%). Acute poisoning by benzodiazepines has followed a rising trend in the years of the study with a higher incidence peak in 2008 with 258 cases and remaining around 200 during the following years. Opioids showed a clear decreasing incidence from 81 cases in 1996 to less than 20 in the last years. Antidote treatment was administered in 2,161 cases (12.2%). The more

frequent antidotes used were flumazenil alone (6.98%) followed by the combination flumazenil-naloxone (1.66%), naloxone alone (1.65%), oxygen (0.8%) and N-acetylcysteine (0.58%). Naloxone and the combination of flumazenil and naloxone presented a clear decreasing trend from 1996 dropping to less than 10 cases in the last years. Flumazenil alone also showed a decreasing trend but much less pronounced. This decrease in flumazenil use does not correlate to a decrease of benzodiazepines poisoning cases, but to better indications for its use. The use of oxygen is well correlated to carbon monoxide poisoning and N-acetylcysteine use showed a slight rising tendency reflecting a slight rise in paracetamol cases. Other antidotes such as ethanol, atropine, oximes and hydroxocobalamin are rarely used due to the very low frequency of poisoning by methanol, organophosphates or cyanide.

**Conclusion:** The use of antidotes in the emergency department is well correlated to the epidemiological profile of poisoning. The most frequently used antidote in our ED is flumazenil whose indication is improving and the use of naloxone has experienced a clear drop in parallel with the extremely low numbers of opioid overdose.

#### 46. Severe cardio-respiratory adverse effects after concentrated and rapid intravenous fomepizole administration: A case report

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**Objective:** Fomepizole (FOM) is a pyrazole derivative antidote that prevents the formation of methanol toxic metabolites through alcohol dehydrogenase inhibition. Commonly adverse effects are characterized by mild symptoms such as venous irritation, nausea, dizziness and vertigo. The minimum methanol toxic dose is approximately 100 mg/kg and severe effects have been reported to occur after ingestion of about 15 mL of 40% methanol. We describe a case of severe cardio-respiratory adverse effects after rapid intravenous fomepizole administration.

**Case report:** A 78-year-old male (94 kg) hospitalised for severe congestive heart failure, chronic atrial fibrillation, type 2 diabetes, obstructive sleep apnoea syndrome and chronic obstructive airways disease (COPD), accidentally ingested one vial (15 mL) of Cytolit<sup>®</sup> (a fixative urine solution) containing 20-50% methanol. Considering the patient's general condition, severe fluid restriction (max 500 mL/day) and the estimated methanol ingested dose (up to 160 mg/kg), fomepizole (15 mg/kg, 1.5 mL diluted with 10 mL normal saline) IV over 2 minutes was administered. Five minutes after fomepizole administration he developed respiratory failure, cyanosis and tachycardia. Arterial blood gases showed respiratory acidosis and non-invasive ventilation support (FiO<sub>2</sub> 30%) was started. Echocardiography showed acute right heart failure with signs of systemic venous congestion (positive airway pressure 71 mmHg; right ventricular diameter 53 mm). Diuretic, low molecular weight heparin and morphine were administered. One hour later the clinical condition rapidly improved, arterial blood gas normalised, a reduction of systemic venous congestion was

reported in a subsequent echocardiography and non-invasive support was stopped after 24 hours. No sequelae occurred. Methanol in the blood sampled 3 hours after ingestion was 4 mg/dL (non-toxic concentration).

**Conclusion:** In this case methanol blood concentrations were not rapidly available and fomepizole by IV bolus was administered due to the patient's pre-existing critical condition, and the estimated methanol dose ingested. The cardio-respiratory effects that occurred after a fomepizole concentrated bolus (15% in 2 minutes) were more severe than the mild reactions expected with less concentrated slower-infused formulations (2.5% in 5 minutes).<sup>1</sup> In our case supportive treatment was associated with complete recovery within 24 hours. Pyrazole and its derivatives have been shown in animal studies to have vasodilating effects that could be involved in hemodynamic disorders resulting from rapid administration or use of concentrated solutions. A less concentrated and a slower IV infusion rate needs to be considered to avoid potentially severe hemodynamic disorders after fomepizole administration.

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#### 47. Safe and effective use of physostigmine for olanzapine overdose

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**Objective:** To describe our experience using physostigmine to treat anticholinergic toxidrome related to olanzapine overdose. Olanzapine is an atypical antipsychotic that, in overdose, typically presents as a combination of sedation and anticholinergic symptoms. Hypotension from alpha-1 blockade and QTc prolongation also occur and, despite antagonism at 5-hydroxytryptamine 2 (5HT<sub>2</sub>) receptors, symptoms consistent with serotonin syndrome have been reported.<sup>1,2</sup>

**Case series:** Case 1: An 18-year-old male with ingestion of an unknown amount of olanzapine, who also admitted to acute use of synthetic cannabinoids presented comatose with severe urinary retention, dry skin and mucous membranes, and hypoactive bowel sounds. Pupils were described as 'pinpoint' and heart rate was 90 beats/minute. He received 2 mg physostigmine with reversal of coma, followed by another 2 mg dose 2 hours later due to recurrent symptoms. No bradycardia, vomiting or seizures occurred. Case 2: A 27-year-old female with reported ingestion of 150-300 mg olanzapine and 1600-2250 mg hydroxyzine presented with agitation, hallucinations, warm/dry skin, hypoactive bowel sounds and tachycardia (150 beats/minute). A dose of 2 mg physostigmine was administered with reversal of symptoms. No adverse effects or recurrent toxicity were reported. Case 3: A 23-year-old male presented with reported ingestion of 900 mg olanzapine and an unknown amount of trazodone. He was initially agitated, hyperthermic, dry, and tachycardic (180 beats/minute) with small pupils. ECG revealed a QTc of 508 ms. A dose of 2 mg physostigmine was administered with improvement in heart rate, but no improvement



in mental status and he was ultimately intubated. The patient had a number of symptoms leading to suspicion of serotonin syndrome (extreme tachycardia, hyperreflexia, clonus, hyperthermia). No adverse effects related to physostigmine were noted.

**Conclusion:** We report three cases of olanzapine ingestion with different coingestions; all were consistent in the presence of anticholinergic toxidrome. Physostigmine was efficacious in reversing all anticholinergic features and completely reversing somnolence, delirium and hallucinations and peripheral anticholinergic symptoms in 2 out of 3 cases. No adverse effects related to physostigmine were noted. Despite patient 1 having a normal heart rate before administration, no bradycardia occurred. We conclude that physostigmine is safe and may be a useful antidote in patients with olanzapine overdose.

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## 48. Antidote treatment of poisoned children before admission to the Toxicology Department

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**Objective:** To assess the antidote treatment of poisoned children before admission to the Toxicology Department, that is, during the transport to the hospital and in the Emergency Department.

**Methods:** We performed a retrospective study of children with severe acute poisoning seen in the Emergency Department before admission to the Toxicology Department, between 9 September 2013 and 30 April 2014. The following criteria were assessed, level of emergency, etiology and type of used antidote.

**Results:** Out of 986 children seen in the Emergency Department during the study period 71 cases (7.2%) were children with acute poisoning. The poisoned children were divided into the following emergency categories: level I emergency - 5 children (7.0%), level II emergencies - 47 children (66.2%) and level III emergencies - 19 (26.7%). Drugs intoxication had an overwhelming prevalence with 37 children (52.1%), followed by poisoning with household products 10 children (14%), alcohol 6 patients (8.4%), mushrooms 2 patients (2.8%), and carbon monoxide 6 children (8.4%); opiates, rodenticides, pesticides and poisonous plants accounted for 10 cases in total (14%). Gastric lavage was performed in 43 cases (60.5%). Out of the 71 poisoned patients, a specific antidote was administered in pre-hospital stage in 3 cases (4.2%) for children with benzodiazepine, carbon monoxide and opiate toxicity. Specific antidote therapy was initiated in the Emergency Department in 15 cases (21.1%). Antidotes used in the pre-hospital phase and emergency department were naloxone, N-acetylcysteine, atropine, vitamin K and 100% oxygen.

**Conclusion:** In our study 18 children (25.3%) were given an antidote, with 3 given an antidote in the pre-hospital stage and 15 in the Emergency Department. Administration of specific antidotes in acute poisoning in children before admission to the Toxicology Department remains quite modest in our country compared with literature data.<sup>1</sup>

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## 49. Is hyperbaric oxygen efficient in cyanide poisoning? A systematic review of individual cases

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**Objective:** Rationale basis for hyperbaric oxygen in cyanide poisoning includes the mechanism of toxicity of cyanide, case reports, and experts' opinion. To address this question, we systematically reviewed the medical literature providing access to individual data. We present data dealing with hyperbaric oxygen administered either alone or in combination with supportive treatment but without any additional cyanide antidote during at least one sequence of treatment.

**Methods:** The literature was reviewed up to 2010 in PubMed, Embase, Scopus, Toxline, French PCC database, and "Current Awareness in Toxicology".<sup>1</sup> References providing individual patient data for at least one patient were eligible for the study. The Poison Severity Score (PSS) adapted to cyanide was used for sequential assessment. A sequence was defined as a sequence of events with treatment allowing calculation of the PSS before and just after administration of a treatment. A treatment means either a single drug e.g. oxygen, or a combination e.g. nitrite and thiosulfate. Wilcoxon matched paired test was performed to compare before and after treatment for sequences including 7 patients and more.

**Results:** From 1847 to 2010, 400 cyanide poisonings were considered, 111 were not included due to the absence of information on treatment. Among the 289 included patients, 6 patients received at least one session of hyperbaric oxygen. In three patients, the session of hyperbaric oxygen was combined with the simultaneous administration of other cyanide antidotes. Therefore, the three patients treated with a combination of treatments were excluded from this analysis. In three patients, the PSS was assessed before and after the hyperbaric session (hyperbaric group). In the hyperbaric group, sequences 1, 2, 3, and 4 included 0, 1, 1, and 1 patients, respectively. The number of patients in each sequence was too low to allow statistical analysis.

**Conclusion:** Owing to the mechanism of cyanide toxicity, a high partial pressure of oxygen is recommended in the treatment of cyanide poisoning. However, the modality of oxygen administration, normobaric high flow versus hyperbaric oxygen, is a matter of debate. Data reported in the medical literature are too scarce to allow any conclusion. Hyperbaric oxygen was used as

second line treatment and even later on in patients with cyanide exposure.

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## 50. N-acetylcysteine treatment of paracetamol poisonings in the Czech Republic and Slovakia: Outcomes and side effects

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**Objective:** Paracetamol overdose is among the most frequent reason for calls to the Czech Toxicological Information Centre (TIC) and the Slovak National Toxicological Information Centre (NTIC). In 2012, the treatment-line for indication of N-acetylcysteine (NAC) in the UK was lowered from 150 mg/L to 100 mg/L paracetamol plasma concentration at 4 hours after ingestion. The aim of the study was to evaluate the indication strategy of NAC administration depending on plasma paracetamol concentration and outcomes in both Central European countries.

**Methods:** Data concerning paracetamol poisoning from TIC and NTIC databases 2000-2013 and discharge reports were analysed retrospectively. In addition, the outcomes and numbers of patients presenting within 24 hours after a single paracetamol overdose were compared in 3 groups with different paracetamol concentration bands of the nomogram (< 100 mg/L, 100-149 mg/L and ≥ 150 mg/L).

**Results:** More than 5,000 enquiries concerning paracetamol were recorded in TIC and NTIC. Data from 196 discharge reports with measured plasma paracetamol concentration were studied. Of these 120 subjects, median age 18 (0.2-86) years who had a single acute overdose with known time of both intoxication and plasma collection until 24 hours after ingestion were included in the study. They were divided into 3 groups according to the plasma paracetamol concentration: 34/61 (55.7%) subjects have been treated with NAC in the < 100 mg/L band, 19/26 (73.1%) in the 100-149 mg/L band group and 32/33 (96.9%) in the ≥ 150 mg/L band group, respectively. Of the 196 patients 8 (4.08%) developed side effects after NAC administration with dyspnoea (n = 5), rash (n = 4), vertigo (n = 2), vomiting (n = 2), flushing (n = 1), cough (n = 1), pruritus (n = 1) and bronchial hypersecretion (n = 1). The median length of hospitalization of NAC-treated patients was 3 (1-27) days. Only 1 death as a result of suicidal attempt with a plasma concentration 407 mg/L, presenting at 20 hours was recorded among 120 patients. Another 2 fatal outcomes due to admission later than 24 hours (n = 1) or staggered overdose (n = 1) were identified in the total of 196 patients. No patient without NAC treatment died due to acute overdose and a plasma concentration ≤ 150 mg/L at 4 hours.

**Conclusion:** Most Czech and Slovak patients with paracetamol ingestion are treated with NAC even at no-risk plasma paracetamol concentrations. Our data support the opinion that NAC is not needed in patients with paracetamol concentration ≤ 150 mg/L in the absence of risk factors because of very low risk of hepatotoxicity, and the possible side effects and high treatment costs.

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## 51. First-line sodium thiosulphate administration – effective in a case of potassium cyanide suicidal ingestion

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**Objective:** Cyanide is a potent and fast acting poison, available in gaseous forms, poorly water-soluble salts and water-soluble potassium or sodium cyanide salts.<sup>1</sup> Cyanide exposure may occur following accidental smoke inhalation or deliberate ingestion of cyanide salts. Hydroxocobalamin represents the first-line life-saving antidote. Sodium thiosulphate (ST) can be administered in association with hydroxocobalamin whereas the delayed onset of clinical response makes ST less suitable for emergency use.<sup>2</sup> We describe a laboratory confirmed case of cyanide intoxication following ingestion of potassium salts. Moreover, we demonstrate the prompt administration of ST improved clinical outcome and lactic acidosis.

**Case report:** A 43-year-old man was admitted to the Emergency Department (ED) after sudden collapse at work. About 30 minutes earlier he had ingested an unknown amount of potassium cyanide, purchased via the Internet, for suicidal purpose. At admission, he presented Glasgow Coma Score (GCS) 3, fixed bilateral mydriasis and bright red skin. Blood pressure 125/70 mmHg and pulse rate 120 beats/min were registered. Orotracheal intubation and gastric lavage were performed and oral activated charcoal given. Arterial blood gas revealed severe lactic acidosis (pH 7.24, pCO<sub>2</sub> 26.6 mmHg, pO<sub>2</sub> 202 mmHg, HCO<sub>3</sub> 13.6 mmol/L and lactate 18 mmol/L). Electrocardiogram demonstrated ventricular conduction delay and brain CT scan was negative. ST was available in the ED and 10 g were infused within 30 minutes. Hydroxocobalamin (Cyanokit®) was provided by the poison center and 5 g given 2 hours after ED admission. Following ST administration the patient became rousable and lactate concentration (9.2 mmol/L) improved; metabolic acidosis completely resolved after hydroxocobalamin administration. The patient was extubated on the second day, moved to the mental health department on day 6 and discharged asymptomatic 9 days later. Blood cyanide concentrations at ED admission were 15 mg/L.

**Conclusion:** Cyanide poisoning is a life-threatening condition. Its lethality is related to the fast onset of toxicity.<sup>3</sup> This case highlights

the role of the Internet as a source of information and purchase of such toxic products. Prompt administration of ST improves lactic acidosis and should be considered when hydroxocobalamin is not available in an emergency setting.

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## 52. Massive paracetamol overdose: Early NAC prevented liver damage but not pancytopenia

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**Objective:** Pancytopenia is a rare but previously reported complication of severe paracetamol poisoning.<sup>1–3</sup>

**Case report:** A 28-year-old woman ingested an estimated 195 g of paracetamol (as evidenced by newly purchased empty packets), but no other drugs. She presented at the emergency department a few hours later with a slightly reduced level of consciousness and a moderate acidosis. Intravenous N-acetylcysteine (NAC) was started immediately and 50 g charcoal was administered. Laboratory tests on admission revealed: paracetamol 586  $\mu\text{mol/L}$ , pH 7.3, base excess -10 mmol/L, AST 2.2  $\mu\text{kat/L}$  (reference < 0.75), ALT 0.9  $\mu\text{kat/L}$  (reference < 0.75), INR 1.5 (reference < 1.3). Hemoglobin, white blood cells (WBC) and platelets were within the normal range. During the following 10 hours the patient deteriorated with increasing acidosis and declining level of consciousness, and was intubated. Artificial ventilation and continuous venovenous hemodiafiltration (CVVHDF) were started. The blood paracetamol concentration was 2146  $\mu\text{mol/L}$  at 5 hours after ingestion, 2489  $\mu\text{mol/L}$  (9 hours), 6346  $\mu\text{mol/L}$  (14 hours), and then slowly declined. An abdominal CT scan on day 4 revealed a suspected pharmacobezoar in the stomach, which was confirmed and removed by suction through a gastroscope followed by instillation of charcoal. On day 3 the blood cell count started to decrease and on day 5 the hemoglobin was 80 g/L (reference 115–147), WBC  $2.9 \times 10^9/\text{L}$  (reference 4–10) and platelets  $41 \times 10^9/\text{L}$  (reference 125–400). Liver function tests normalized slowly. The CVVHDF and ventilator treatment were stopped after one week and the NAC infusion after 8 days. The patient made a full recovery.

**Conclusion:** A direct toxic effect of paracetamol or its metabolites on the bone marrow or peripheral blood cells is the most likely mechanism underlying the development of pancytopenia in this setting.<sup>1,3</sup> This rare complication does not appear to be prevented by early NAC treatment.

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## 53. Severe pediatric cyanide poisoning due to smoke inhalation: Two cases

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**Objective:** Smoke inhalation is a common cause of cyanide poisoning during fires. Clinical data in the pediatric population are lacking. The mortality rate in children found in cardiac arrest at the scene of a fire is very high, despite supportive care and administration of hydroxocobalamin.<sup>1</sup> Early clinical diagnosis and prompt antidote treatment are crucial to counteract the toxic effects of cyanide. We describe two cases involving two sisters (house-fire victims) with confirmed cyanide poisoning.

**Case report:** Case 1. A 17-month-old girl, 17 kg, was carried to a local hospital in cardiac arrest, with return of spontaneous circulation at 10 minutes. Gas exchange showed pH 6.6, PaO<sub>2</sub> 408 mmHg, PaCO<sub>2</sub> 80 mmHg, BE -27.9 mmo/L and lactate 15.5 mmol/L. She was transferred after 3 hours in PICU and presented with areflexia and mydriasis. Her lactate remained high (10.5 mmol/L). Hydroxocobalamin (80 mg/kg) and sodium thiosulfate (500 mg/kg) were given intravenously. The patient died the following day. Case 2. A 4-year-old girl, 20 kg, was transferred together with case 1 to PICU, with GCS 9. Gas exchange showed pH 7.14, PaO<sub>2</sub> 379 mmHg, PaCO<sub>2</sub> 37 mmHg, BE -16 mmo/L and lactate 11.5 mmol/L. The patient was intubated and ventilated for respiratory failure and edema of the upper airways. Hydroxocobalamin (125 mg/kg) and sodium thiosulfate (500 mg/kg) were given intravenously and hyperbaric oxygen therapy was immediately performed. The clinical condition improved and after 4 days she was transferred to the pediatric ward. The follow-up (1 year later) showed attention and language disorders as demonstrated by neuropsychological tests. Blood cyanide concentrations were (4 hours after the fire) 0.258 mg/L (case 1) and 0.29 mg/L (case 2).

**Conclusion:** An early suspicion for cyanide poisoning must be based on clinical data including neurological alterations, hemodynamic instability, respiratory depression, soot particles in airways and blood lactate (> 8 mmol/L). Pre-hospital administration of hydroxocobalamin and sodium thiosulfate is recommended; pediatric patients are at increased risk of severe or lethal poisoning in cyanide intoxications by smoke compared to adults due to their higher respiratory rate, lower body mass and immature metabolism.<sup>2</sup> Neurological sequelae may be present in cyanide fire victims.



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## 54. Antidote availability in emergency departments in the municipality of Campinas, São Paulo state, Brazil

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**Objective:** The lack of adequate and prompt availability of antidotes is a worldwide problem, with potentially disastrous consequences. We evaluated the availability of antidotes used in the treatment of poisonings in public and private emergency departments in the municipality of Campinas, São Paulo state, Brazil.

**Methods:** A structured questionnaire was sent to the pharmacy directors of public and private emergency departments in the municipality of Campinas. The availability, amount in stock, place of storage, and access time in the emergency room (immediately or within the first hour) were investigated for 31 antidotes in 33 pharmaceutical preparations. A stock was defined as at least one full antidote treatment per service per 70 kg adult. The selection of antidotes was based on stock recommendations contained in published international guidelines.<sup>1,2</sup> Antivenoms were not included in the analysis.

**Results:** Questionnaires were completed by 14 of 17 emergency departments (7 public and 7 private) operating at the time, including the public ambulance transport service. No emergency department stocked all of the 31 selected antidotes, and none of them had digoxin antibodies, physostigmine, fomepizole, hydroxocobalamin or pralidoxime. Eight units had an adequate stock of N-acetylcysteine, but in inappropriate presentations for use as antidotes (injectable solution 3 mg/mL for IV use; 100 mg, 200 mg or 600 mg sachets for use orally or by nasogastric tube). Only seven antidotes (atropine, sodium bicarbonate 8.4%, diazepam, phytomenadione, flumazenil, glucose 50% and calcium gluconate 10%) were stocked in all evaluated units, followed by 13/14 units where there was a stock of activated charcoal and naloxone. Only the referral public department for the treatment of poisonings had a stock profile close to that outlined above, with 25 antidotes and 27 pharmaceutical forms, but without digoxin antibodies, physostigmine, fomepizole, hydroxocobalamin, glucagon and pralidoxime. (Before the 2014 FIFA World Cup in Brazil, the referral public service received an additional stock of hydroxocobalamin and pralidoxime).

**Conclusion:** The stock of antidotes in emergency departments in the municipality of Campinas is inadequate and poorly scaled, potentially jeopardizing the treatment of poisoned patients.

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## 55. Naloxone availability in the USA: Bystander versus emergency medical services (EMS) administration

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**Objective:** In the US the age-adjusted rate for opioid-analgesic poisoning deaths nearly quadrupled from 1.4 per 100,000 in 1999 to 5.4 per 100,000 in 2011.<sup>1</sup> Access to naloxone and other emergency treatment is often limited by laws and regulations that pre-date the overdose epidemic. Although a number of states have amended legislation to increase access to emergency intervention many EMS jurisdictions still restrict the availability of naloxone.<sup>2</sup> We sought to document which states (listed below by state abbreviations) while allowing bystander naloxone still have restrictions for trained emergency medical personnel in the administration of naloxone.

**Methods:** Systematic review of the current scope of practice of emergency medical services (EMS) personnel in the USA as well as a systematic review of States that have legislation permitting bystander naloxone administration.

**Results:** States that allow naloxone prescription for lay person administrators (24 states + DC): NY, IL, WA, CA, RI, CT, MA, NC, OR, CO, VA, KY, MD, VT, NJ, OK, UT, TN, ME, GA, WI, MN, OH and DE) and the District of Columbia. States with all level EMS naloxone administration (12): CA, CO, DC, MA, MD, NM, NC, OH, OK, RI, VI, VT. States that allow prescribed (bystander naloxone) but restrict EMS administration: NY, IL, WA, OR, VA, KY, NJ, UT, TN, ME, GA, WI, MN, DE.

**Conclusion:** Although many states have permissible legislation for the administration of bystander naloxone, only half of these states allow all level EMS providers to administer naloxone. Furthermore, many of the states restricting EMS availability have reported significant increases in opiate-related mortalities.<sup>3</sup>

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## 56. Comparison of hyperbaric oxygen treatment reported to poison centers in the US and Israel

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**Objective:** Hyperbaric oxygen (HBO) is the optimal treatment for serious carbon monoxide (CO) poisoning. We sought to evaluate HBO treatment in the US and Israel for a more global perspective. The objectives include investigating trends in HBO use for CO, evaluating circumstances and medical outcomes of HBO as well as its use for other toxic chemicals.

**Methods:** A retrospective evaluation of exposures treated with HBO reported to US poison centers and the Israel Poison Information Center (IPIC) from 2000-2011 was performed. Data on HBO cases were evaluated for toxic fume(s), reason, site and outcome. Total annual case counts for each agent were used to establish frequencies of HBO use.

**Results:** In the US, HBO was performed in 4,052 (2.7%) CO and 142 (0.7%) smoke cases; of these 25 cases also involved cyanide, two hydrogen sulphide (H<sub>2</sub>S) or one methylene chloride (CH<sub>2</sub>Cl<sub>2</sub>). In addition, HBO was used in 5 cyanide, 10 methylene chloride and 17 H<sub>2</sub>S only. The proportion of CO cases treated with HBO doubled from 1.8% (2000) to 3.6% (2011). In Israel, HBO was recommended in 77 CO (26.6%), 35 smoke (3.3%), 4 H<sub>2</sub>S (7.0%) and 10 (0.1%) other toxic fume cases. HBO use in Israel for CO in 2011 was one-third that of 2000. In the US and Israel, respectively, most patients were adults over 19 years (73.0% versus 60.3%), followed by 13-19 years (9.6% versus 17.4%), 6-12 years (8.8% versus 11.9%), and children < 6 years (7.4% versus 10.4%). Most common reasons in US were environmental (62.4%) and suicidal (14.6%) compared to accidental (52.4%) and misuse (21.4%) in Israel. Sites of exposure in US and Israel, respectively, were residence (79.8% versus 81.7%), workplace (9.8% versus 9.5%), public area (3.6% versus 2.4%), other (4.4% versus 2.4%) and unknown (2.2% versus 4.0%). In the US, outcomes were death (1.6%), major effect (23.4%), moderate (46.0%), minor (20.9%), no effect (3.6%) and unknown (4.1%). In Israel, degree of severity assessed by toxicologists was major (0.8%), moderate (43.7%), minor (20.6%), no effect (0.8%) and unknown (19.8%).

**Conclusion:** HBO was used most often for CO and infrequently for other fumes/chemicals in both countries. HBO use increased in the US but decreased in Israel. This drop may be attributed to improved knowledge of emergency medicine physicians as well as changes in triage/treatment protocols. Ages and exposure sites were similar, although Israelis were younger. Reasons and outcomes were different, most likely due to different field definitions and follow-up procedures.

## 57. Accidental laundry pod exposure resulting in first reported US fatality

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**Objective:** Clothing detergent pods or capsules have growing US market share since 2011. Child exposures to these products are

disproportionately reported to Poison Centers compared with other household cleaners and detergents.<sup>1</sup> Significant adverse effects have been reported in Europe and now the US including ocular, skin, gastrointestinal, pulmonary and CNS effects.<sup>2,3</sup> We describe the first US fatality as reported to a Poison Center.

**Case report:** The mother of a 7-month-old called the Poison Center regarding the ingestion of a single All-Mighty Free and Clear® laundry pod. During the call, the child could be heard crying and coughing. The patient was transported to the ED during where he vomited and became drowsy but was otherwise stable. Oxygen saturations of 80% normalized with supplemental oxygen. In the ED over the first 30 minutes the patient became more obtunded, experienced a seizure and was intubated. A post-intubation chest radiograph noted a possible right upper lobe infiltrate. Over the next 30 minutes, the patient developed bradycardia and CPR was initiated. During the resuscitation, arterial venous blood gas indicated pH < 6.6, pCO<sub>2</sub> 70.5 mm Hg and pO<sub>2</sub> 27 mmHg. Bedside cardiac ultrasound noted normal ventricular contractility. Resuscitative efforts were continued for 60 minutes, during which time the patient was administered standard advanced life support medications and therapies but was pronounced dead less than 3 hours post-exposure. Post-mortem examination demonstrated minimal hyperemia of the oropharynx and trachea. There was asymmetric right pulmonary congestion and moderate cerebral edema. Post-mortem analysis measured propylene glycol levels of 33 mg/dL, and 370 mg/dL in blood and gastric content respectively. No ethylene or diethylene glycol was detected.

**Conclusion:** Severe symptoms from laundry pod ingestion were first reported in the US in 2012 and were similar to European observations. We report the first fatality likely caused by progressive CNS and respiratory depression complicated by profound metabolic acidosis in the absence of oropharyngeal injury.

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## 58. Mortality after antipsychotic poisoning

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**Objective:** The objective of this study was to investigate the short- and long-term mortality after antipsychotic poisoning.

**Methods:** All Danish citizens have a personal identification number (CPR), which enables bridging of personalized information to various databases. We merged the Danish Poison Information Centre Database with the National Registry of Death and Migration. For this particular study we included data on 2,927 patients with hospital contacts due to poisonings which involved antipsychotic agents in the period 1 August 2006 to 1 January 2014. Data was

**Table 1.** Mortality after antipsychotic poisoning.

		Short-term mortality			P
		Death	Alive	RR	
Age	Mean SD	35.6 (15.8)	53.4 (25.1)		< 0.001
Gender	F	1871	8	0.34	0.02
	M	1035	13		
Benzodiazepines	Yes	686	3	0.54	0.4
	No	2220	18		
Mixed poisoning	Yes	1648	12	1.02	1
	No	1258	9		
Tricyclic antidepressants	Yes	60	0	0.00	1
	No	2846	21		
SSRI	Yes	307	2	0.89	1
	No	2599	19		
SNRI	Yes	273	5	2.98	0.04
	No	2633	16		
Total		2906	21		

analyzed with Kaplan-Meier statistics and Cox-regression. Patients were only allowed to enter the study once (first contact).

**Results:** The average age of the patients was 35.7 (SD 15.9) years, 64.2% were female and 56.7% of the cases were classified as mixed poisonings. The 30-day mortality was 0.72%. Male gender, increasing age and intake of serotonin-norepinephrine reuptake inhibitors (SNRIs) were statistically significant risk factors of an early death, while co-ingestion of benzodiazepines or selective serotonin re-uptake inhibitors (SSRIs) was not associated with an excess risk. The univariate estimates are shown in Table 1. By the end of follow-up 230 patients were deceased, and after seven years mortality approached 14%. Similar to above, the multivariate Cox regression revealed that males (HR = 1.58,  $p = 0.0006$ ) and elderly patients (HR = 1.060 per year,  $p < 0.0001$ ) had the worst prognosis.

**Conclusion:** This study showed that antipsychotic poisoning is associated with a considerable risk of death. Further studies should elucidate whether it is possible to improve the prognosis.

## 59. Changes in pediatric poisoning mortality: A 20-year retrospective study

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**Objective:** To analyze toxic deaths and establish the main changes produced in pediatric poisoning mortality regarding the rate, etiology, and age distribution.<sup>1</sup>

**Methods:** We performed a 20-year retrospective study, between 1995 and 2014, split into two decades (1995-2004 and 2005-2014), to perform the analysis and make comparisons between groups using the nonparametric tests Mann-Whitney and Kruskal-Wallis.

**Table 1.** Etiology of toxic pediatric deaths in two decades.

Product	Number of cases 1995–2004	Percentage of total poisoning deaths 1995–2004	Percentage of total poisoning deaths	
			Number of cases 2005–2014	2005–2014
Caustics	16	34.78	2	8.33
Mushrooms	12	26.09	1	4.17
Carbon monoxide	7	15.22	1	4.17
Medicines	5	10.87	2	8.33
Alcohols	2	4.35	0	0.00
Cholinesterase inhibitor insecticides	2	4.35	13	54.17
Nitrates	1	2.17	2	8.33
Lead	1	2.17	0	0.00
Hydrocarbons	0	0	2	8.33
Substances of abuse	0	0	1	4.17

**Results:** Although the total number of poisonings did not vary significantly over the two decades (6,667 versus 6,435), death rates from poisoning was significantly lower (0.37% versus 0.69,  $p = 0.04$ ) in the second decade. Regarding the etiology (Table 1) the analysis showed that although the causes of toxic deaths in the two decades were not significantly different, the decrease in the number of deaths by mushrooms, caustics and carbon monoxide is notable (1 versus 12 for mushrooms, 2 versus 16 for caustics and 1 versus 7 for carbon monoxide). An increased number of deaths by poisoning with cholinesterase inhibitor insecticides were noted in the second decade (13 compared to 2 cases, representing 54.17% of toxic deaths). Regarding the age distribution, there was no significant difference between the two periods; the highest rate of deaths being the age group 1-5 years.

**Conclusion:** The death rate by poisoning in children has significantly decreased in the last 10 years but the total number of poisoning cases remained about the same. The number of deaths by mushroom, caustics and carbon monoxide significantly decreased while the number of deaths by insecticides increased, changing the structure of pediatric poisoning mortality in our center.

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## 60. Causality assessment of fatal poisoning: Evaluation of the Gfkt causality score

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**Objective:** Assessing the causal role of a drug in the occurrence of an adverse medical reaction is routine in pharmacovigilance. Various methods are used, including expert opinion and algorithms. Systematic causality assessment in acute poisoning is not generally established. Medical toxicologists of a Gesellschaft für Klinische Toxikologie (GfKT) working group rated fatal poisonings using a score based on the causality categories of the Swiss Toxicological Information Centre (STIC), i.e. probable, certain, possible, unlikely, conditional, none and not assessable. The aim of the study was to determine the inter-rater agreement in the causality assessment of cases with fatal poisoning and the evaluation of the effect of refinement and training.

**Methods:** Initially four experienced clinical toxicologists rated the causality score of 66 lethal poisoning cases. After this, a 6 year training phase followed with regular discussion and rating of new cases during which the system was refined with additional criteria (e.g. likelihood of exposure, qualification of reporters to PC). In the post-training phase the same 66 cases randomly mixed with 66 new cases were rated again by the same raters. The Fleiss' kappa (a statistical measure expressing the concordance of raters assigning categorical ratings) was used. Values can range between 0 (no reliability) and 1 (complete reliability). In order to calculate the Fleiss' kappa and measure inter-rater reliability for the validation of the causality assessment as such (using the new cases) and for the training effect (first versus second assessment of old cases), the criteria were grouped into a level of good evidence for causal relationship (probable and certain) or a level of uncertain evidence for causal relationship (possible, unlikely, conditional, none and not assessable).

**Results:** There was a substantial agreement of the causality assessment with a  $\kappa$  value of Kappa (0.636) even before training. After training, the reliability in these cases improved (Kappa post 0.73). However, while 13 cases were rated more reliable after training, there were 7 cases where the reliability was smaller. The reliability of the new cases in the post-training phase was also better (Kappa new 0.66) than in the pre-training phase.

**Conclusion:** The GfKT causality score is suitable for the assessment of causality between exposure and fatal outcome in human poisoning, with a good inter-rater agreement in untrained experienced clinical toxicologists. Specific training improved the inter-rater agreement even further. The assessment of causality is essential for the reliability of human data on poisoning, for scientific purposes as well as basis for regulatory decisions (in toxicovigilance).

## 61. Poisoning deaths in Poland: Type and prevalence detected on analysis of cases from 6 poison centres during the period 2009–2013

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**Objective:** The aim of this study was to assess the characteristics of acute poisoning deaths in Poland between 2009 and 2013.

**Methods:** The analysis was based on the data obtained from patients' records submitted by poison centres in Lodz, Cracow, Sosnowiec, Wroclaw, Gdansk and Poznan. Toxicological analyses were routinely performed in blood and/or urine. Major toxic substances were classified in the categories medications, alcohols, gases, solvents, drugs of abuse, corrosives, pesticides, metals, mushrooms, toxic plants, venoms and others. Cases were analysed according to the following criteria, year, age, gender, toxic substance category and type of poisoning. The recorded fatal poisonings were classified according to the International Classification of Diseases.

**Results:** The records of 261 deaths were retrospectively reviewed. There were 187 males (71.64%) and 74 females (28.36%) and the male to female ratio was 2.53. The highest poisoning frequency was recorded for the age group 40–60 years (125/261, 47.9%). The most common classes of substances involved in fatalities were alcohols (42.9%), medications (36.4%) and gases (5.7%). Among alcohol poisonings, the highest mortality rate was recorded for ethylene glycol and methanol. Deaths due to alcohols were recorded more frequently for males (102/112, 91.1%). Ingestion was the predominant route of exposure (92.3%), followed in frequency by inhalation and injection. Accidental poisonings and suicidal intent were the most frequent manner of death, 42.5% and 37.5%, respectively.

**Conclusion:** Alcohols were implicated in the majority of accidental poisoning deaths. Epidemiological profile data from investigation of poisoning deaths is very useful for the development of preventive programs.<sup>1</sup>

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## 62. In-hospital mortality after toxic exposures in Spain, the EXITOX project

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**Objective:** Mortality studies in toxicology are a key indicator of poisoning severity. There is no registry of deaths due to toxic exposures in Spain and to fill the gap the Spanish Clinical Toxicology Foundation (FETOC) promoted a multi-center network in 2012 to collect data on in-hospital mortality after toxic exposures, the EXITOX project.

**Methods:** A retrospective analysis of epidemiological, clinical and treatment data was performed for all in-hospital deaths in 10 Spanish hospitals from 2012 until August 2014, as well as the cause-effect relationship between poisoning and death. The in-hospital mortality rate was calculated according to the population of each hospital's area of coverage. A centralized, web-based tool was created with exclusive access for investigators at each hospital. Data was analyzed using Excel 2010.

**Results:** A total of 60 cases were identified. The mean age was 55 years (range 19-93 years); 60% of patients were male (n = 36). The number of cases per hospital ranged from 1-16. The estimated in-hospital mortality due to poisoning was 0.5/100,000 individuals/year. The highest incidence of death was on Tuesday (23.3%) and in the months of February and May (13.3%). Poisoning was considered to be the sole and direct cause of death in 44 cases (73.3%). Suicidal motivation was responsible for deaths (38.3%), overdose for (30%). Primary groups of substances found responsible for the deaths were pharmaceuticals and drugs of abuse in 16 cases (26.6%), caustics in 15 cases (23.3%), methanol in 7 cases (11.3%), gases in 6 cases (10%) and pesticides and mushrooms in 1 case each. The substance responsible for the most deaths was hydrochloric acid in 11 cases (18.3%). Ethanol was present in 9 cases (15%) and benzodiazepines in 8 cases (13.3%). The most common presenting symptoms were altered level of consciousness (50%), cardiac arrest (31%), caustic esophageal burns (23.3%) and cardiovascular shock (20%). Supportive measures included fluids and vasoactive drugs (76.3%), antidotes (36.6%), gastrointestinal decontamination (6.6%) and extracorporeal purification (5%). The most commonly used antidotes were naloxone (10%), N-acetylcysteine (8.3%), hydroxocobalamin and flumazenil (5%). The place of death was the ICU in 66.6% of the cases and in the Emergency Department in 20%.

**Conclusion:** The in-hospital mortality rate due to poisoning in Spain is 0.5 deaths per 100,000 people per year. The most common motivation was suicide. Pharmaceuticals, drugs of abuse and caustic substances were the most common cause of these deaths.

### 63. Toxicologic related deaths: A case series from 1970 to 2014

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**Objective:** Acute poisoning is a leading cause of admittance to health care facilities (HCF) worldwide. The aim of our study was to analyse the mortality rate (MR), class and nature of offenders, demography and timing of death in patients admitted in our Toxicology Unit. A comparison with data from international reports and literature is also included.

**Case series:** We retrospectively analyzed poisoning-related deaths that occurred in patients admitted for acute poisoning between 1970 and 2014. A total of 74,563 patients (47,284 M, 27,279 F) were admitted. Of these, 105 patients died (55 F; 50 M). The overall mean age  $\pm$  SE was 53.7  $\pm$  2.1 years. The distribution by classes

of age (range 2-93 years) were 2.8% (0 to 5 years), 5.7% (6 to 19 years), 32.4% (21 to 50 years), 36.2% (51 to 70 years) and 22.9% over 71 years. The overall MR was 0.14% (0.20% F; 0.11% M). No deaths occurred from 2007 to 2014, and the adjusted MR was 0.194%. Data emerging from AAPCC annual reports (1985-2012)<sup>1</sup> indicate an overall MR of 0.051. However, the value adjusted according to the number of HCF admittances reached 0.298 in 1999-2012. Substances involved in fatal cases were drugs (n = 42; 44.8%), mushrooms (*Amanita phalloides*) (n = 20; 19%), caustics (n = 11; 10.5%), systemic toxic gases (n = 9; 8.6%), pesticides (n = 9; 8.6%), hydrocarbons (n = 7; 6.7%), substances of abuse (n = 6; 5.7%) and animal toxins (n = 1; 0.9%). The average time between admission and death was 5.5  $\pm$  0.63 days (mean  $\pm$  SE) depending by the class of agent involved (caustics 1.8 and pesticides 7.1 days, respectively).

**Conclusion:** The incidence of death due to acute poisoning is low; the overall MR was higher than that in AAPCC reports<sup>1</sup> relative to total calls, but lower considering patients admitted to HCF. A higher MR was observed in patients aged 21-50 and 51-70 years; drugs and mushrooms represent the chief offenders.

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### 64. Characteristics of deaths in subjects with post-mortem detection of cannabis: Preliminary results

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**Objective:** As cannabis is the most used illicit drug in France, the goal of the study was to determine the occurrence of special characteristics in deceased patients in whom cannabis was detected and measured.

**Methods:** A retrospective study between January 2012 and August 2014 on autopsied patients in the medico-legal department of a city in the south-west of France. Medical records of all deaths autopsied in a unique medico-legal unit whatever the cause of the death were collected. Data used for analysis were: circumstances of death (accident, suicide, homicide, none of them called 'natural'), description of the autopsies and toxicology analyses (blood and/or urine). Two groups were then compared: patients with and without cannabis in toxicological analyses. New synthetic cannabinoids were not included. Univariate analysis was performed on the results with an alpha risk of 0.05%.

**Results:** Of the 1,649 autopsies performed in the study period, a subgroup of 502 files were randomly chosen for the study. Of these 188 had no toxic compounds or drugs detected (37.4%, age 54  $\pm$  19 years, 71% men); 157 were positive for cannabis (31.3%) of which 50 were positive for cannabis only (10% out of 502, age 31  $\pm$  10 years, 88% men), and 157 had at least one toxic compound or drug detected (31.3%). Patients in whom cannabis was detected had

tetrahydrocannabinol (THC) in peripheral blood (mean 59.5 ng/mL, range 0-680 ng/mL), 11-nor-9-carboxy- $\Delta^9$ -tetrahydrocannabinol (THC-COOH) (mean 179.7 ng/mL, range 0-1130 ng/mL) and 11-hydroxy- $\Delta^9$ -tetrahydrocannabinol, (THC-OH) (mean 12.9 ng/mL, range 0-170 ng/mL). In 5 victims the absence of THC and the presence THC-COOH > 40 ng/mL (range 4-163 ng/mL) does not rule out the possibility that they were under the influence of cannabis at the time of death. The 50 victims with only cannabis were compared to the 188 victims with no toxic compounds or drugs detected. Patients under cannabis are mainly men ( $p < 0.05$ ) and die more frequently from an accident ( $p < 0.05$ ). There was no difference between the two groups in terms of age of death, "natural cause" of death, suicide or homicide.

**Conclusion:** There is no difference in autopsy findings between patients under cannabis only versus victims with no toxic or medication except for gender and circumstances of death.

### 65. Once upon a time the toxic related deaths: A case series from 1924 to 1960

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**Objective:** The aim of our study was to analyze toxic-related deaths that occurred in the past in our Toxicology Unit. Victims' demography and their distribution by age, class and nature of substances involved in deaths, overall and adjusted by class mortality rate (MR), and time to death were reported.

**Methods:** We retrospectively analyzed available data related to deaths that occurred in patients admitted for acute poisoning between 1924-1960, from our medical record archives.

**Results:** A total of 7,435 patients were admitted over the study period; of these, 260 died. Gender was registered in 254 out of 260 cases (132 female and 122 male, 52% and 48%, respectively). The victims' ages ranged from 2 to 94 years, and overall mean age  $\pm$  SD was 44.1  $\pm$  1.2 years (female 41.2  $\pm$  1.6, male 47.5  $\pm$  1.7). The distribution by age was 1.6% (0 to 5 years), 9.3% (6 to 20 years), 49.6% (21 to 50 years), 32.5% (51 to 70 years), and 7.3% over 71 years. The overall MR was 3.49%. Multiple different xenobiotics were involved in fatal cases. The five most common agents involved in fatal cases were caustics ( $n = 90$ ; 34.6%), barbiturates ( $n = 73$ ; 28.5%), mercuric dichloride (corrosive sublimate) ( $n = 26$ ; 10%), systemic toxic gases ( $n = 25$ ; 9.6%) and arsenic salts ( $n = 11$ ; 4.2%). The MR value adjusted according to the class of toxic compounds show the higher value for arsenic salts (33.3%) followed by mercuric dichloride (32.9%), barbiturates (10.9%), caustics (8.5%) and systemic toxic gases (4.8%). Sex distribution ratio (male/female) was caustics 0.84, barbiturates 1.25, corrosive sublimate 0.3, systemic toxic gases 1.2 and arsenic salts 2.7. Overall mean  $\pm$  SD time (days) between admission and death was 3.03  $\pm$  0.17, varying by the class of toxics as follows 1.1  $\pm$  0.5 days for systemic toxic gases, 1.7  $\pm$  0.2 days for caustics, 2.7  $\pm$  0.8 days for arsenic salts, 3.9  $\pm$  0.3 days barbiturates and 7.4  $\pm$  0.6 days mercuric dichloride.

**Conclusion:** The retrospective analysis of this historical case series on fatal cases of acute poisoning showed a significant higher MR than reported in contemporary studies. To explain these data, we must consider the different substances involved, the lack of supportive care therapy and decontaminating techniques and effective antidotes available at the time.

### 66. Fatal poisonings in Estonia 2002–2013

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**Objective:** The high number of fatalities from acute poisoning is a challenge in Estonia. We present mortality data inside and outside hospital during one year and compare it to total fatality figures from the period 2002-2013.

**Methods:** Data from all acute poisonings in Estonia were registered prospectively from 1 May 2009 until 30 April 2010 in a one-year multicenter study. The fatalities from this study were compared to deaths from poisoning recorded by the National Institute of Forensic Medicine in 2002, 2005 and 2013.

**Results:** In 2009, there were 414 acute poisoning deaths, giving a mortality rate of 38 per 100,000 (Table 1). Median age was 37 years (range 28-76) and 342 (83%) were males. In 384 (93%) cases, death occurred outside hospital and the main cause of death was illicit opioids such as fentanyl ( $n = 137$ ; 36%), ethanol ( $n = 86$ ; 22%) and carbon monoxide ( $n = 83$ ; 21%). There were 30 (7%) deaths in hospital, mainly caused by chemicals ( $n = 7$ ), mostly acetic acid ( $n = 5$ ), ethanol ( $n = 5$ ) and fentanyl ( $n = 4$ ). Comparing data from 2002 with data from 2013, shows that the overall mortality decreased (432 versus 278). More males than females died of acute poisoning in the 12 years 2002 to 2013 (3,265 versus 865). The mortality decreased for both ethanol (140 versus 72,  $p < 0.001$ ) and carbon monoxide poisoning (109 versus 37,  $p < 0.001$ ), while the mortality increased for illicit drugs (100 versus 118,  $p < 0.001$ ).

**Table 1.** Fatal poisonings in Estonia 2002–2013.

	2002	2005	EstTox 2009	2013
Ethanol	140 (32%)	120 (31%)	91 (22%)	72 (26%)
Illicit drugs	100 (23%)	70 (18%)	178 (43%)	118 (42%)
Medicines	21 (5%)	19 (5%)	15 (4%)	15 (5%)
Other toxic alcohols	25 (6%)	31 (8%)	24 (6%)	32 (12%)
Carbon monoxide	109 (25%)	135 (35%)	86 (21%)	37 (13%)
Others	37 (9%)	14 (4%)	18 (5%)	4 (3%)
<b>Total</b>	<b>432</b>	<b>389</b>	<b>414</b>	<b>278</b>

**Conclusion:** There has been an overall decline in fatalities caused by poisoning in Estonia between 2002-2013, especially concerning ethanol and carbon monoxide poisonings. This may reflect a change in drinking habits and increased alcohol prices. However,



the mortality by illicit drugs increased from 2002-2013, which is concerning and probably reflects increased availability.

## 67. Fatal iron poisoning in an adult

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**Objective:** Numerous cases of fatal iron poisoning, mostly in children, were reported during the last half of the 20th century.<sup>1</sup> Nowadays, these cases are rare, even though reports on fatalities are published occasionally.<sup>2</sup> We report the first lethal case of iron poisoning in Sweden in 20 years.

**Case report:** A 20-year-old woman with a psychiatric illness was found semiconscious on the floor in a pool of black diarrhoea with an empty jar of 100 slow release ferrous sulfate tablets beside her (100 mg Fe<sup>2+</sup>/tablet, 160 mg/kg). There were also a few packages of pharmaceuticals with low toxicity. She was brought to the hospital an estimated 4 hours after ingestion and presented with irritability and a fluctuating CNS depression (GCS 11-13). Her blood pressure was 190/85 mmHg and pulse 130 bpm. An arterial blood gas analysis showed pH 7.17, pCO<sub>2</sub> 5.4 kPa, pO<sub>2</sub> 16.7 kPa and BE -14 mmol/L. Deferoxamine was started immediately with a dose of 15 mg/kg/h intravenously. The patient was intubated and an abdominal CT-scan displayed several suspected tablet conglomerates in the small intestine. Whole bowel irrigation was performed in the ICU with a moderate result. Due to technical problems with the venous blood sampling (blood samples had shown hemolysis), a correct measurement of the serum iron concentration was not available until 15 hours post-ingestion and showed 131 µmol/L (reference 9-34). At that point, after a stable period of normalized blood gases, her condition deteriorated with circulatory instability, increasing acidosis, hepatic failure, coagulopathy and renal insufficiency. Liver transplant was considered, but not performed because of her psychiatric disease. Despite full treatment including prompt antidote administration and dialysis she died after 4 days.

**Conclusion:** The peak serum iron concentration after an overdose of a slow release preparation is reached approximately 4-8 hours after ingestion, and a concentration above 180 µmol/L is strongly associated with liver failure and fatal outcome.<sup>1,3</sup> Severe iron poisonings have become rare during the latest decades, but they still occur.

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## 68. Toxic deaths: Data from the Poison Control Centre of Morocco (CAPM)

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**Objective:** A retrospective review of toxic deaths received by the Moroccan poison control centre (CAPM), to determine the relationship between the emergence of these deaths and various determinants.

**Methods:** Fatal cases were extracted from CAPM data received by telephone or by intoxication reporting from hospitals between 1980 and 2011.<sup>1</sup> Demographic features, frequency, incidence, lethality, mortality, circumstances, management delay after intoxication and symptomatology were studied. Scorpion envenomation cases were excluded. Statistical analysis was made on Epi-Info 3.3.2 complemented by bivariate analysis using Chi2 test.

**Results:** Among 107,716 cases of intoxications received during the period of study, 1,528 deaths were collected (1.4%). The geographic distribution of deaths showed that all regions of the country were affected with a predominance of Souss Massa Daraa (in the south of Morocco) with 195 deaths. In 94.7% of cases, the deaths were reported by health facilities. The sex ratio male/female was 1. The mean age was 22.9 ± 17 years (range less than 1 month to 91 years). The study of the age groups showed that adults represented 56.1% followed by children (17.3%). The most common circumstance was accidental in 43.8% and suicidal in 40.5%. The specific lethality was highly significantly ( $p < 0.0000001$ ) for all of these products: cosmetics with 12.1%, represented exclusively by paraphenylenediamine (PPD), plants (4.7%), snakes bites (3.9%) and pesticides (3.7%). The risk factor was also highly significantly for suicidal circumstance ( $\text{Chi } 2 = 423.4, p < 0.0000001$ ).

**Conclusion:** Despite underreporting to the toxicovigilance system of the Poison Control and Pharmacovigilance of Morocco, this study showed that poisoning in Morocco is serious. Several actions have been undertaken by the CAPM. The implementation of a national registry of toxic deaths remains the solution for a good assessment of the magnitude of this problem.

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## 69. Fatal intoxication with pharmaceutical agents: A 5-year epidemiological study

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**Objective:** To present a retrospective analysis of fatal cases of intoxication with pharmaceutical agents in our toxicological department between 2009 and 2013.

**Methods:** The records of the Toxicology Clinic, Emergency University Hospital NI Pirogov, Sofia, Bulgaria were reviewed retrospectively for all poisonings in adults during a 5 year period, from 1 January 2009 to 31 December 2013. The fatal cases from pharmaceutical agents were analyzed with regard to gender, age and type of medicine. The main reasons for the unfavourable outcome as well as the treatment interventions were analyzed.

**Results:** A total of 9,194 patients were hospitalized in the Toxicology Clinic over the study period, and 75 patients died. Of these, 21 deaths (28%) were caused by pharmaceutical agents and 54 (72%) by other agents. In ten cases (47.6%) the fatal drug intoxication involved a single agent and 11 patients (52.4%) took a mixed drug overdose. Nine fatal intoxications involve two, three or four medicines. One patient took multiple substances, including methanol with medicines, and another ingested methanol, benzodiazepines and cannabis. Male mortality was slightly higher ( $n = 11$ , 52.4%) compared to females ( $n = 10$ , 47.6%). All of the exposures were intentional. The patients with fatal intoxication from pharmaceutical agents were aged between 31 and 88 years. Most deaths occurred in patients over 70 years (71-88 years, 42.9%), followed by patients aged 51-70 years (33.3%) and those aged 31-50 years (23.8%). The most commonly implicated drug groups were benzodiazepines, antihypertensives, antidepressants, neuroleptics and analgesics. Death from pharmaceutical agents was the highest in 2010 (33.3%) and lowest in 2009 (4.7%).

**Conclusion:** The analysis of the data of the fatal poisonings with pharmaceutical agents revealed that over the study period, the incidence of a fatal outcome was stable with little variation throughout the years. The risk of death from intentional poisoning persists. Health programmes should be continued especially to promote well-being in families and to prevent suicides.

## 70. A fatal case of consumption of beta-methylphenylamine, caffeine and dexamphetamine

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**Objectives:** Beta-methylphenylamine is a component of some commercially available "fat burner" formulas increasingly used by body builders. Some of these formulas also contain high amounts of caffeine (150 mg of caffeine per cap). In treatment of adult patients with attention deficit hyperactivity disorder (ADHD) a licensed preparation of amphetamine has become common in Sweden. Mixtures of fat burners and central stimulating drugs may induce profound adrenergic activity leading to agitation, muscular rigidity, hyperthermia, seizures, rhabdomyolysis, confusion and finally circulatory collapse. We report a case of agitation and confusion after ingestion of multiple fat burners when on treatment with several psychiatric medications. A possible interaction was likely leading to a hyperadrenergic syndrome finally leading to cardiovascular collapse and death.

**Case report:** A 31-year-old man, 140 kg, with history of ADHD, panic disorders and substance abuse was on treatment with clomipramine (375 mg/d), lisdexamphetamine (130 mg/d) and flunitrazepam (1 mg/d). He was experienced in body-building and on his own webpage he declared a regular consumption of fat burners containing caffeine and beta-methylphenylamine. He was admitted to the Emergency Department (ED) after being found convulsing at home. At the ED he was disorientated, confused and aggressive. A drug screen was positive for benzodiazepines, buprenorphine, tetrahydrocannabinol (THC) and tramadol. The patient presented with extreme stress, tachycardia, hyperthermia, sweating and high creatine kinase (CK) concentration. He required heavy sedation

with propofol and opioids, and was intubated and ventilated. Dantrolene sodium was administered without any apparent positive effect. Treatment was instituted with dexmedetomidine, propofol, transdermal opioids and high doses of benzodiazepines. He was transferred to the psychiatric ward after 2 days but again became agitated and confused and was brought back to the ICU. Shortly after arrival to the ICU he collapsed and CPR was immediately instituted but this time he was unresponsive to resuscitation and finally expired.

**Conclusion:** Medical treatment with amphetamines, tramadol and antidepressants in a patient with a regular consumption of fat burners may induce a hyperadrenergic syndrome with agitation, confusion, rigidity, hyperthermia, hypertension and tachycardia that may become extremely stressful to the cardiovascular system resulting in cardiovascular collapse and death. Warning to the public of several new fat burners containing different biogenic amines such as beta-methylphenylamine and caffeine seems to be appropriate as well as information to the medical profession of the dangers and risks of mixing licensed amphetamine preparations with some fat burners.

## 71. Characteristics of deaths with detection of opioids in the body: Preliminary results

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**Objective:** As opioids are increasingly common in fatalities in USA, we have studied the characteristics in deceased patients in whom opioids are detected and measured in a city of south-west France.

**Methods:** Retrospective analysis between January 2012 and August 2014 on autopsied patients in the medico-legal department of a city in the south-west of France. Medical records of all deaths autopsied in a unique medico-legal unit whatever the cause of the death were collected. Data used for analysis were: circumstances of death (accident, suicide, homicide, none of them called 'natural'), description of the autopsies and toxicology analyses (blood and/or urine).

**Results:** Of the 1,649 autopsies performed in the study period, a subgroup of 659 files were randomly chosen for the study. Of these 41 were positive for opioids (6%, age  $53.7 \pm 18.4$  years, 53.3% males) of which 1 was positive for opioid alone, and 37 were associated with other medications (92.5%): anxiolytics ( $n = 13$ ), neuroleptics + anxiolytics ( $n = 5$ ), anxiolytics + antidepressants ( $n = 5$ ), these 3 medications ( $n = 5$ ), only antidepressant ( $n = 1$ ) or unknown ( $n = 8$ ). Other substances also detected were blood alcohol ( $n = 12$ , with mean level of 0.63 g/L), cannabis ( $n = 8$ , age 31.5 years), cannabis + cocaine ( $n = 3$ , age 34.4 years). No amphetamine derivatives were discovered. The opioids found were morphine (fentanyl patches or morphine sulphate,  $n = 11$  of which 8 had a toxic concentration), tramadol ( $n = 9$  of which 3 had a toxic concentration), pholcodine ( $n = 5$ ), codeine ( $n = 4$  of which 1 had a toxic concentration) and oxycodone ( $n = 1$  had a toxic concentration). In 8 cases an illness was found: 2 pneumonia, 2 cancers, 1 diabetes, 1 interstitial nephritis, 1 cerebral ischemia and 1 had a

jejunostomy of unknown origin. On the 41 victims, the causes of death were suicide (n = 24), 'natural' (n = 9), accident (n = 6) and homicide (n = 2). As 92.5% of the 41 victims with opioids had also taken another drug it was not possible to compare those positive for 'opioids' with other patients.

**Conclusion:** Of the 41 victims where opioids were detected, 13 (31.7%) were found at a toxic concentration which suggests that opioids took part in the cause of death.

## 72. Drug-facilitated sexual assaults in Italy: Final data of the VARD (Violence And date Rape Drugs) project

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**Objective:** The aims of the VARD project (Violence And date Rape Drug) are to evaluate the cases of DFSA (Drug-Facilitated Sexual Assault) in Italy and to identify the profile of substances involved.

**Methods:** In a prospective study (November 2011 to September 2014), patients seeking health care after sexual assault and for which the Pavia Poison Control Centre (PPC) was contacted from the emergency departments or sexual assault centres all over Italy, were included. The inclusion criteria were partial/complete amnesia for the alleged assault and/or (i) suspicion of covert drug administration and/or (ii) voluntary intake of substances and/or (iii) signs/symptoms of intoxication. In each case, the PPC evaluated the characteristics of the DFSA and the clinical picture, and collected the victims' biological samples which were subsequently analysed (Institute of Legal Medicine, Catholic University, Rome). The study had the approval of the ethical committee of every participating centre, and informed consent was obtained in all the recruited cases.

**Results:** In total 90 patients were included (mean age 26 years, 98% females). Sixty patients (66%) reported the suspicion of covert drug administration, and 11 patients (12%) admitted voluntary consumption of drugs of abuse (excluding alcohol). The assailant was a person known to the victim in 39% of cases. Sixty-nine patients (77%) presented signs or symptoms at hospital admission (genital lesions in 22 cases, injury to the body except the genitals in 46 cases, signs/symptoms of intoxication in 22 cases). Samples were collected between 3 and 72 hours after violence (median 21 ± 20 hours). Laboratory analyses were negative for all substances investigated in 27 cases (30%). Ethanol (mean concentration 1.08 ± 0.84 g/L) was found in blood in 33 cases (37%) and ethyl-glucuronide in the urine (mean value 298.4 ± 468.7 µg/mL) in 54 cases (60%). In 24 cases (27%) the analysis was positive only for ethanol and/or ethyl-glucuronide. Other detected substances were benzodiazepines (n = 16), cocaine and metabolites (n = 16), other drug of abuse (n = 14) and drugs (n = 10). Hair analysis (1 month after the event) was performed in only 1 case and was negative.

**Conclusion:** Ethanol, drugs and drugs of abuse are frequently detected in samples collected from victims of suspected DFSA. The absence of injury or signs and symptoms of intoxication at the time of the medical examination do not exclude a DFSA.

**Acknowledgement:** Study carried out with the support of the Department of Antidrug Policy, Presidency of the Council of Ministers.

## 73. Use of incapacitating substances to commit robberies: The Italian experience

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**Objective:** The covert administration of substances can be used not only to commit acts of sexual violence, as well known, but also robberies. The aims of the VARD project (Violence And date Rape Drug) robberies section, are to evaluate the cases of robberies in Italy performed after the administration of substances to victims and to identify the profile of substances involved.

**Methods:** In a prospective study (November 2011 to September 2014), patients admitted to emergency departments all over Italy after a robbery in which it was suspected that administration of incapacitating substances had occurred, and for which the Pavia Poison Control Centre (PPC) was called, were included. The inclusion criteria were partial/complete amnesia for the robbery and/or (i) physical incapacity during the crime and/or (ii) suspicion of covert drug administration and/or (iii) signs/symptoms of intoxication. In each case, the PPC evaluated the modality of the robbery and the clinical picture, and collected the victims' biological samples for subsequent analysis (Institute of Legal Medicine, Catholic University, Rome). The study had the approval of the ethical committee of every participating centre, and informed consent was obtained in all cases.

**Results:** In total 45 patients were included (mean age 47 years, 44% females). Fourteen patients (31%) reported physical incapacity during the crime. The hypothesized method of administration was ingestion in 10 cases and a forced inhalation in 8 cases. Robberies were committed at the home of the victim in 22 cases (49%). Body injuries were present in 3 cases, signs/symptoms of intoxication in 36 cases; the most frequent were drowsiness (n = 14), confusion (n = 10), headache (n = 9), gastrointestinal symptoms (n = 7) and irritation to the eyes, mouth and throat (n = 7). Samples were collected between 1 and 96 hours after robbery (median 14 ± 17 hours). Benzodiazepines (clonazepam, alprazolam, lorazepam, bromazepam) and zolpidem were the most frequent substances detected in blood and/or urine (n = 18, 40%). Laboratory analysis was negative for all substances investigated in 20 cases (n = 44%). Hair analysis (1 month after the event) was performed in 2 cases (in 1 of which clonazepam were detected).

**Conclusion:** Drugs, mainly benzodiazepines and zolpidem, may be administered in order to commit robberies. The detection of these substances should be included in the management of victims of robbery admitted in the emergency departments.

**Acknowledgement:** Study carried out with the support of the Department of Antidrug Policy - Presidency of the Council of Ministers.



#### 74. The prevalence of marijuana in fatalities involving operators of motor vehicles in Denver County, Colorado, USA

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**Objective:** The effect of marijuana on driving impairment is not clear. Currently, Colorado is one of two US states to decriminalize both recreational and medical marijuana use. Medical marijuana use was legalized in 2000 in Colorado, however, amendments to laws resulted in a 10-fold increase in medical marijuana cardholders in 2009. In late 2012, recreational marijuana was decriminalized with the first recreational retail stores opening on January 1, 2014. Therefore, the objective of our study was to assess the effect of marijuana legalization on the prevalence of marijuana detection in fatalities involving operators of motor vehicles.

**Methods:** All fatalities involving operators of motor vehicles in Denver County, Colorado, USA (the largest county in Colorado) testing positive for marijuana (tetrahydrocannabinol carboxylic acid, THC) at coroner autopsy between July 1, 2007 and June 30, 2014 were examined. Descriptive statistics were generated for demographic data and concomitant substances detected.

**Results:** Over the study period 42 fatalities reported to the Denver County Coroner were identified. The majority of fatalities were male (81%, n = 34). Ages ranged between 17-73 years with a mean of 36.0 years. In the 18 months from July 1, 2007 to December 31, 2008, there were 0.28 fatalities/month (n = 5). From January 1, 2009 to December 31, 2012 there were 0.5 fatalities/month (n = 24). In the 18 months from January 1, 2013 to June 30, 2014 there were 0.56 fatalities/month. The most common concomitant substances detected were cocaine (21.4%, n = 9) and ethanol (19.0%, n = 8). THC was detected as a single substance in 52.4% (n = 22) of fatalities.

**Conclusion:** Since the significant increase in Colorado medical marijuana cardholders in 2009, there has been an increase in fatalities per month of operators of motor vehicles testing positive for THC at autopsy in Denver County. Additionally, there was a further increase in fatalities per month after recreational marijuana decriminalization in late 2012.

#### 75. Characteristics of telephoned poisons information enquiries arising from British prisons: A report from the UK National Poisons Information Service (NPIS)

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**Objective:** The prison population in the UK has increased to almost 95,000<sup>1-3</sup> with a male: female ratio of 21:1. This study was performed to measure the incidence and describe the nature of NPIS telephone enquiries originating from prisons, using non-prison NPIS enquiries for comparison.

**Methods:** NPIS enquiries received from prisons between 1 January 2008 and 31 December 2013 were compared with non-prison NPIS enquiries for the same time period, restricted to persons aged 15 years and over.

**Results:** During the study period, 305,354 enquiries were received, 5,993 (1.96%) originating from prisons. Of these, 4,965 (83%) involved males and 959 (17%) females. There were 4,865 (81%) intentional exposures, 489 (8.2%) therapeutic errors and 117 (2.0%) arising from recreational misuse. Of prison enquiries, 4,769 (79%) were made by nurses and 3,351 (56%) were received between 2pm and 9pm. Of 7,495 substances implicated in enquiries from prisons, the most common were paracetamol (17%), non-steroidal anti-inflammatory drugs (13%), antidepressants (12%), antipsychotics (7.0%) and opioids (6.7%) and all these were more commonly involved in prison enquiries than in NPIS enquiries overall (p < 0.001 for each). Drugs of abuse (1.4%) and cardiac medications (2.7%) were less commonly involved in enquiries originating from prisons (p < 0.001). Overall, 47.6% of prisoners required hospital referral following discussion with NPIS, often for assessment of psychiatric status following self-harm. Observation in prison was advised in 42.1% of cases.

**Conclusion:** Enquiries from prisons constitute a small but important component of NPIS workload. Most are made by nurses and occur during daytime hours; the majority concerning intentional exposures. Substances implicated are commonly available or prescribed within the predominantly male prison population, with its high prevalence of mental health disorders. The low frequency of enquiries relating to drugs of abuse may reflect lack of availability of traditional recreational drugs or underreporting of use. A high proportion of patients are referred to hospital, often for assessment of mental health. Such referrals may be avoided by better use of prison health services for psychiatric assessment following self-harm attempts.

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#### 76. Poison center utilization by law enforcement personnel

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**Objective:** The purpose of this study was to assess the utilization of a single poison center (PC) by law enforcement personnel over a 10-year period.

**Methods:** The database of Blue Ridge Poison Center, Virginia, was queried for all human exposures between calendar years 2004 and 2013 where the caller was recorded as police/sheriff/law enforcement or correctional facility nurse. Additional records were searched using free text queries for terms pertaining to police or

law enforcement. Data extracted from records included whether the patient was in custody, and the characterization and type of exposures (illicit, pharmaceutical, and non-pharmaceutical). Records were further analyzed for temporal, geographical patterns, clinical outcomes, and management site.

**Results:** In total 647 records were identified as calls from law enforcement personnel, corresponding with an average of 64.7 exposures per year (range 25-232). The majority of exposures recorded involved non-pharmaceutical substances ( $n = 376$ , 58%), followed by pharmaceutical substances ( $n = 311$ , 48%) and illicit substances ( $n = 18$ , 3%). Benzodiazepine and atypical antipsychotic exposures were the most frequent pharmaceutical substances reported to the PC. Among non-pharmaceutical substances, a mass Freon exposure in a prison resulted in 183 exposures, while alcohol ( $n = 36$ , 6%) and bleach ( $n = 16$ , 2%) were commonly reported exposures. Approximately half of all exposures were intentional use of a substance ( $n = 310$ , 48%), of which 64% were suspected suicides. Almost two-thirds of exposures involved patients who were already in or taken into police custody. Fifteen percent of exposures ( $n = 100$ ) resulted in a serious outcome (i.e. major clinical effects, death) or were judged to be potentially toxic, and predominantly involved a pharmaceutical substance ( $n = 82$ , 82%).

**Conclusion:** Law enforcement utilized PC resources to help guide management for significant outbreaks in prisons (e.g., Freon exposure). Forty-two percent of exposure calls from law enforcement were managed on site, avoiding significant costs in transportation to a healthcare facility. PCs should pursue outreach efforts to law enforcement to educate those personnel on the capabilities of the centers. Limitations to this study included its retrospective nature, review of notes with varying styles among PC nurses, and ability to capture the proportion of this population where the exposures occurred in prisons/jails. Prospective studies in the future could capture these data, providing the ability to assess the costs saved by the government through increased utilization of PCs.

## 77. Utilization of uniform crime reports and poison center data to identify patterns in substance abuse

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**Objective:** The purpose of this study was to compare trends in drug arrests as reported through the state Uniform Crime Reporting Program and drug exposures from a Poison Center Network.

**Methods:** Data were extracted from the annual state crime reports to reflect all drug arrests from calendar years 2008 through 2012. The data were tabulated by type of drug, and by age group (10-17, 18-24, 25-34, 35-44, 45-54,  $\geq 55$  years). Select drug exposures (amphetamine/methamphetamine, cocaine, heroin, LSD, marijuana, phencyclidine (PCP), tetrahydrocannabinol (THC) homologs, and other/unknown street drugs) from state Poison Center Network annual reports were extracted for calendar years 2009 through 2012. Changes in annual arrests and exposures were evaluated by linear regression.

**Results:** There was an annual average of 34,747 arrests due to drugs in the state of Virginia between 2008 and 2012, with an

annual increase of 1,408 arrests per year. On average, marijuana accounted for approximately 62% of arrests and was predominantly responsible for the overall increase in rates of drug arrests with 1,031 additional arrests per year. Other drugs frequently resulting in drug arrests included cocaine ( $n = 24,505$ ; 14.1%), other/unknown drugs ( $n = 23,633$ ; 13.6%) and other narcotics ( $n = 7,826$ ; 4.5%). Amphetamines/methamphetamines and other/unknown drugs increased by 101 and 398 arrests, respectively, per year. Arrests due to cocaine, however, appeared to decrease with 458 fewer arrests per year. Drug arrests varied by age group, over half of marijuana arrests (52%) were among adults 18-24 years of age. Those aged 25 to 34-years-old accounted for the majority of arrests due to amphetamines/methamphetamines, cocaine, heroin, other narcotics, and PCP. When compared with state poison center data, similar annual increases were seen for amphetamine/methamphetamine exposures (64 more exposures per year). Cocaine exposures decreased by 16 cases per year, while heroin and PCP appeared to be stable during this time frame.

**Conclusion:** This study highlights how data from unique sources such as those from the state police and poison centers may be merged to identify the public health burden of a problem (e.g. substance abuse) in a community. Limitations to this study included variable practices in categorization of drugs between law enforcement and poison center for select substances. Reviewing drug arrest data allows poison centers to prepare for the changing trends and prevalence of substances, and may also drive collaborative efforts between law enforcement and poison center personnel.

## 78. Penetrating trauma and overdose: An uncommon combination in complex suicide attempts

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**Objective:** Complex suicide, the use of two or more concurrent methods of self-harm, is reported in 1.5-5% of all suicides.<sup>1,2</sup> Since complex suicide is often discovered at post-mortem, reports of complex suicides are rare, and few describe concurrent penetrating trauma and intentional overdose.<sup>3</sup> We report two cases of complex suicide attempts.

**Case series:** During a 3-month period, two patients presented to the same Level I trauma center after complex suicide attempts. The first, a 57-year-old woman with a history of depression, initially presented with a self-inflicted left chest stab wound necessitating tube thoracostomy on arrival. Ten hours after arrival, she became obtunded, and was intubated for airway protection. Ten minutes later, she suffered an asystolic cardiac arrest with return of spontaneous circulation after five minutes of cardiopulmonary resuscitation, administration of epinephrine and sodium bicarbonate and defibrillation of ventricular tachycardia. Her serum aspirin concentration at the time of the arrest was 100 mg/dL. She was treated with a sodium bicarbonate drip, hemodialysis and therapeutic hypothermia. The patient improved and was discharged to an inpatient psychiatric facility on hospital day 46. The second patient was a 32-year-old man with a history of schizoaffective disorder, who presented from an outside hospital with a self-inflicted neck stab wound and untimed acetaminophen (APAP) overdose. His initial APAP concentration at the outside hospital was 60 mcg/mL. He

was started on a N-acetylcysteine infusion for 21 hours per hospital protocol. The patient's superficial neck injury was repaired by the trauma surgery service. He showed no signs of hepatic injury, and was transferred to inpatient psychiatry after 3 days of treatment.

**Conclusion:** These cases illustrate complex suicide attempts involving self-inflicted penetrating trauma, as well as analgesic ingestion. Complex suicide attempts may be underreported in the current literature. In these patients, a history of intentional ingestion may be overlooked in the setting of overt injuries, or be unobtainable from the critically ill patient. These cases highlight the necessity to consider concomitant overdose when treating patients with self-inflicted penetrating trauma.

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## 79. Severity of cholinergic side-effects after therapeutic use of the organophosphate diazinon (dimpylate) to combat flea infestations in cats and dogs

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**Objective:** Diazinon (dimpylate) is an organophosphate insecticide which is used in The Netherlands as treatment for cats and dogs against flea infestations. In other European and non-European countries (e.g. Austria, Germany, USA) the use of this organophosphate is either forbidden, or severely restricted. This restriction is firstly due to its potent cholinergic properties, and secondly due to impurities of diazinon (tetraethyl pyrophosphate or TEPP variants) that mostly form during prolonged storage of the substance and cause significant increased toxicity. In the past 3 years the Dutch Poisons Information Center (DPIC) observed a steady rise of information inquiries about diazinon. The aim of this study is to prospectively record signs and applied treatments after the therapeutic use of diazinon.

**Methods:** From 1 August 2014 onwards, all veterinarians who contact the DPIC regarding diazinon exposures to cats and dogs are asked to fill out a questionnaire.

**Results:** Thus far, over a 2-month period, 15 questionnaires were sent out, 80% of these were filled in and returned. Of the reported exposures 81% concerned cats. In 27.3% of the cases the owner had accidentally used suprathreshold dosages; in the remaining cases the correct dose was applied. Signs were classified as mild, moderate or severe; all animals showed at least mild cholinergic effects and 83% showed additional moderate signs while 9% displayed severe effects including seizures. The signs usually developed either within 4 hours of exposure (54%) or after 12–48 hours (46%).

Treatment of the animals varied from washing with a detergent (45.5%), to IV fluids (45.5%) and pharmacological intervention such as diazepam, atropine or metoclopramide (36.4%). Recovery time also varied; in 55% of cases recovery took > 48 hours, 33% recovered between 12–48 hours after exposure, while only 11% recovered swiftly within the first 4–12 hours after exposure. All animals were treated with diazinon products that were within their sell-by date, suggesting that the symptomatology was not due to the presence of the chemical impurities of TEPP variants.

**Conclusion:** The data support the notion that even when diazinon is used therapeutically, moderate and severe cholinergic signs can occur that require veterinary intervention. More than half of the animals with reported signs did not recover until > 48 hours after exposure. In conjunction with the Dutch veterinary registration authority, steps are being taken toward increasing the warnings on these products, or, if deemed necessary, restricting the sale of this compound.

## 80. Be aware of renal toxicity in dogs following a small ibuprofen overdose

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**Objective:** Ibuprofen intoxication in dogs occurs relatively frequent in veterinary practice. The literature concerning ibuprofen intoxications thus far indicates that doses > 70 mg/kg cause gastrointestinal disturbances and doses > 175–200 mg/kg may lead to renal damage. The Dutch Poisons Information Center (DPIC) however, has occasionally encountered renal dysfunction including acute renal failure at lower doses than 175 mg/kg. The aim of this study is to prospectively study the dose-effect relation for renal toxicity in ibuprofen intoxicated dogs.

**Methods:** From January 2012 to December 2013, a questionnaire was sent by email to all veterinarians who consulted the DPIC concerning a single, acute ibuprofen overdose in a dog.

**Results:** In the study period 104 acute ibuprofen exposures in dogs were reported, and 98 questionnaires were sent. In 6 cases the enquirer information was missing. A total of 44 questionnaires (45%) were returned and 42 (43%) met all inclusion criteria. The ibuprofen-dose as estimated by the owner ranged from 11–1035 mg/kg body weight (median 89 mg/kg). Emesis was induced and/or repeated dose activated charcoal was administered in 18 cases (43%). A total of 11 dogs developed signs that may be related to nephrotoxicity such as polydipsia/polyuria. In 9 out of 11 cases renal function was tested and in 7 cases elevated creatinine and urea values were found. In 8 out of these 11 cases, less than 175 mg/kg body weight ibuprofen was ingested; in one dog the estimated ingested dose reported (14 mg/kg) was most likely incorrect and it is likely that more ibuprofen was ingested. Seven dogs developed elevated creatinine and urea concentrations at a dose between 25 mg/kg (12.5 mg/kg twice with a 12 hour interval) and 125 mg/kg. The mean age of these dogs was 2.7 years (range 7 months to 10 years). There were no German Shepherds, a breed considered to be more sensitive. One dog was a crossbreed Shepherd and this 10-year-old dog (ibuprofen dose 109 mg/kg body weight) was



ethanized because of persistent renal dysfunction. All other dogs recovered within days to weeks.

**Conclusion:** Veterinarians must be aware that, in non-sensitive dog breeds, mild renal damage can be observed at ibuprofen doses less than 175 mg/kg.

## Reference

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## 81. Common toxic exposures of animals in the Netherlands: A report from the Dutch National Poisons Information Center

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**Objective:** The Dutch National Poisons Information Center (DPIC) can be contacted 24/7 for queries about acute intoxications. Although the center is originally directed toward human toxicology, veterinary toxicology related information requests are also answered. On average 10% of the information requests made to the DPIC from 2009 to 2013 were from veterinarians. The aim of our study was to investigate the most common toxic health risks to pets in the Netherlands by studying the most frequently encountered toxic exposures as received by the DPIC in the past 5 years.

**Methods:** All information requests made to the DPIC are registered in a database. Using the programme QlikView (version 11) the DPIC database was analysed retrospectively concerning information requests made by veterinarians from 2009 to 2013.

**Results:** From 2009 to 2013 the DPIC received 19,405 information requests from veterinarians. These concerned 19,526 animals exposed to one or more potentially toxic substance. The majority of cases concerned dogs (68%) and cats (23%). The most common substance classes were medications registered for human use (22%), pesticides and disinfectants (20%), and plants, fungi and encounters with other (venomous) animals (20%). At the top of the list of exposures to human medications were ibuprofen (n = 343) and paracetamol (acetaminophen) (n = 310). The highest scoring pesticides were the insecticides (1,835 cases; e.g. non-cyanopyrethroids n = 702, imidacloprid n = 262, organophosphate compounds n = 251 and fipronil n = 111) and rodenticides (1,285 cases; e.g. anticoagulants n = 1,081). Plants that were most commonly associated with toxic ingestions were *Vitis vinifera* (the grape) (n = 180), and *Lilium* species (lily) (n = 165). Toads (*Bufo* species) were responsible for 124 of the 239 animal to animal encounters.

**Conclusion:** The most common toxic health risks to animals involve different substance classes. Many of the information requests made to the DPIC concern substances to which animals can react differently in comparison to humans (such as ibuprofen, paracetamol and various foods and plant species). Veterinary toxicological knowledge about the differences in reaction between species to these substances is vital. Given the number of enquiries, further steps to improve this veterinary information service are necessary. Sharing international experiences and strengthening relations with dedicated veterinarian consultants are the first steps in this process.

## 82. Is *Vipera berus* antivenom needed for pet treatment?

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**Objective:** Every year dogs are bitten by the Common Viper (*Vipera berus*), the only native venomous snake in the Netherlands. For decades antivenom was readily available to treat viper bites in humans. Since April 2008, with the establishment of a National Serum Depot (NSD), antivenom can be delivered to veterinarians for the treatment of dogs and cats provided it does not deplete human stock. Currently, the NSD is switching from the Viper venom antiserum, European (equine) Institute of Immunology, Croatia to the very expensive VIPERFAV<sup>®</sup> (Sanofi Pasteur) making this antivenom less affordable to animal owners. The aim of this study was to assess whether viper antivenom for veterinary practice is useful and whether antivenom for animal use should be kept in storage.

**Methods:** As viper antivenom is only available via the Dutch Poisons Information Center (DPIC), we analysed the DPIC database for the veterinary use of viper antivenom between April 2008 and October 2014.

**Results:** In the study period, the DPIC was consulted about 52 viper bites in the Netherlands (range 5-14 information requests each year). All bites were in dogs. In 17 cases antivenom was delivered to the veterinarian (range 0-6 times each year) and 15 dogs were treated with antivenom. Ten of these dogs were bitten in the muzzle, four in a leg and in one case the bite site was unknown. Beside local oedema (severe), most dogs developed signs of shock, central nervous system depression and some experienced coagulopathy. None of the antivenom treated dogs died. One dog developed symptoms of an adverse reaction caused by the antivenom administration. In dogs not treated with antivenom, the intoxication grade varied from 'dry bites' to severe intoxications (grade 3). Two dogs died as a result of the viper bite, one within hours after the bite and the other after a few days. In this last case antivenom treatment was considered too expensive by the owners.

**Conclusion:** Viper antivenom can be lifesaving for pets. Antivenoms are non-registered pharmaceutical products and in the Netherlands veterinarians are not allowed to buy these for the treatment of severely envenomated animals. A cheaper viper antivenom registered for veterinary use so veterinarians are allowed to buy this antivenom, is preferred. Meanwhile, in our NSD, it is worthwhile to keep the relative cheap European Viper venom antiserum (equine) for veterinary use.

## 83. Toxic effects due to ingestion of *Tradescantia spathacea* (Sw.) leaves by an adult dog

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**Objective:** *Tradescantia spathacea* (Sw.) (Commelinaceae), originated from Central America, and is now widespread in tropical areas as an ornamental plant. In many places it is known as boat lily, oyster plant, or Moses-in-the-cradle, due to its peculiar flower appearance. We report a case of toxic effects due to ingestion of *Tradescantia spathacea* leaves by an adult dog.

**Case report:** An adult pitbull dog was seen 4 hours after having chewing and swallowed an undetermined number of *Tradescantia* leaves. The dog has vomited several times, and became abnormally aggressive, and agitated. At examination he presented tachycardia, tachypnea, abdominal pain, muscle tremors and hypersalivation with hyperemic oral mucosa. The aggressiveness worsened despite receiving metoclopramide and ranitidine, and it became necessary to use benzodiazepine IV. Three hours later he was much improved; he accepted water and some food, but the symptoms only receded completely 2 days later. As little information about the substances present<sup>1,2</sup> in the plant and responsible for the dog's ailments was available, microscopic preparations of its leaves were made and examined. Calcium oxalate raphides and prismatic structures were neatly visualized.

**Conclusion:** The plant in question, first wrongly identified by the dog's owner as *Sansevieria trifasciata*, was classified as *Tradescantia spathacea* by a botanist working with our PCC. The sap of *Tradescantia* is considered irritating, but there is little information about the real substance responsible for that effect.<sup>3</sup> A few cases of gardeners developing hyperemic skin effects and conjunctivitis after contact with it have been described.<sup>1</sup> A flavonoid, rhoenine, was isolated from this plant species, however it has not been shown to be toxic. Raphidic and prismatic calcium and potassium oxalate had been described in other *Tradescantia* species, but not in *T. spathacea*.<sup>4</sup> No systemic effects have been described after skin or mucosal contact with the plant. The psychomotor agitation and aggressive behavior presented by the dog are attributed to the local oral mucosal and gastrointestinal tract ailments secondary to calcium oxalate raphides, shown to be present in microscopic preparations.

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## 84. Ingestion of *Amanita pantherina* in a dog

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**Objective:** *Amanita pantherina* contains the isoxazol derivatives ibotenic acid and muscimol. They exert their effect on the central nervous system where ibotenic acid acts on glutamate receptors and muscimol is a GABA receptor agonist. We present a veterinary

case reported to the National Poisons Information Centre resulting in severe symptoms.

**Case report:** A Golden retriever, 9-years-old, 26 kg, ingested approximately two mushrooms. About three hours after the ingestion the dog had vomited, was ataxic and collapsed. Parts of mushroom were seen in the vomitus. The mushroom was identified as *Amanita pantherina* by a mycologist based on the appearance of the mushroom, the habitat and the geographic area of Norway. Four hours post-ingestion the dog was brought to a veterinary hospital, where examination showed confusion, tachycardia, ataxia, myoclonic jerking and partial paresis. The dog was treated with intravenous fluids, diazepam, an enema and repeated doses of intravenous diazepam over the next hour. She was subsequently placed under general anesthesia and gastric lavage was performed. Activated charcoal was deposited after the final rinse and an antiemetic agent was given. When the dog was weaned from anesthesia anxiety, nystagmus, dilated pupils, muscle twitching, paddling and apparent hallucinations commenced. The signs abated following the administration of phenobarbital and diazepam. Glucose values declined steadily to subnormal values (probably due to increased muscular activity), and one bolus dose of glucose was administered six hours after admission. Over the next seven hours the dog was treated with repeated injections of phenobarbital and diazepam at the recurrence of the signs. After injection of midazolam and acepromazine 15 hours after ingestion the signs abated. Approximately 24 hours after ingestion, the dog still had an unsteady gait, but was able to walk without assistance. By the second day of hospitalization, she appeared clinically normal and was discharged without sequelae 40 hours after ingestion.

**Conclusion:** There are few case reports of canine poisoning from mushroom ingestion. Ingestion of *Amanita pantherina* by dogs can result in potentially severe neurologic signs. The symptoms can persist for 24–48 hours and treatment is symptomatic.

## 85. Lethal mushroom poisoning in a dog

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**Objective:** Amatoxic mushroom poisoning is characterized by delayed gastrointestinal effects and hepatotoxicity. These poisonings are rare in dogs in Norway. There is no specific antidote and treatment is supportive. We describe a case of fatal *Amanita virosa* toxicity in a dog.

**Case report:** An English springer spaniel, 10-years-old, 18 kg was discovered by the owner playing with a white mushroom in the forest. When the dog vomited 8–9 hours after the ingestion, it subsequently ate parts of the vomitus before the owner was able to prevent it. The dog vomited again 8 hours later and developed loose stools. The condition deteriorated over the next 6 hours and the dog was found lying in his own vomit with profuse, watery diarrhoea. At 26 hours after ingestion the dog was brought to a veterinary clinic recumbent with abdominal pain, hyperthermia (40°C), tachycardia, dilated pupils and a weak pulse. First blood analysis revealed acute hepatitis with a very high alanine aminotransferase concentration (above the measurable range of the blood biochemistry analyzer) and elevated alkaline phosphatase, gamma glutamyltransferase, bilirubin and a high neutrophil count,

consistent with *Amanita virosa* poisoning. Symptomatic treatment with intravenous fluids, antiemetics, analgesics, antibiotics and glucose was given. Despite supportive care, the condition deteriorated. By 48 hours post-ingestion the dog was in lateral recumbency with increased pancreatic enzymes, gastrointestinal bleeding and severe hepatitis including coagulopathy. The dog was euthanized 22 hours after initial presentation. From the owners' description of the mushroom, the habitat and the geographic area of Norway together with the clinical presentation, the mushroom is tentatively identified as *Amanita virosa*. This is a relatively common mushroom in Norway, causing severe poisonings in humans every autumn. The owner estimated the ingested amount to be about a tablespoon. The re-ingestion of the vomitus and late presentation to the veterinary clinic may have contributed to the fatal outcome of this case.

**Conclusion:** There are few case reports of canine poisoning from mushroom ingestion. Ingestion of *Amanita virosa* by dogs can result in potentially lethal symptoms. To our knowledge, this is the first report of a poisoning with *Amanita virosa* in a dog.

## 86. Toxic deaths in cats and dogs reported to the Veterinary Poisons Information Service (VPIS)

Nicola Bates, Nick Edwards

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**Objective:** To establish the common causes of death in cats and dogs with suspected poisoning reported to the VPIS in the UK.

**Methods:** Retrospective analysis of cases reported to, and successfully followed up, by the VPIS between 2000 and 2013.

**Results:** In cats there were 828 fatal cases in the study period (Table 1). The most common agents implicated in poisoning resulted in 559 fatalities (67.3% euthanised and 32.7% died). Ethylene glycol was the most common agent, followed by pyrethroids, lilies and paracetamol. Euthanasia was more common in these cases than natural death. In dogs there were 1,151 fatal cases. The most

common agents implicated in poisoning resulted in 488 fatalities (48% euthanised and 52% died). *Vitis vinifera* (sultanas, raisins etc) was the 3rd most common agent in dogs that were euthanised but 10th in dogs that died, whereas vitamin D derivatives were the 4th most common agent in dogs that died and 9th in dogs that were euthanised. Where the agent was known, metaldehyde resulted in the highest number of deaths but vitamin D derivatives had the highest case fatality rate.

**Conclusion:** In the UK the most common reported cause of death in cats from poisoning is ethylene glycol but vitamin D and metaldehyde are common in dogs. Fatalities in dogs were equally likely to have resulted from euthanasia or natural death, whereas two thirds of the feline fatalities were euthanised. The unknowns may include a non-toxic event or unusual presentations of toxins. Limitations include lack of confirmatory laboratory analysis and inclusions of only cases reported to VPIS (a subscription service). It is certain that there are additional cases of toxic deaths in cats and dogs that go unreported (e.g. animals that die before arrival at a veterinary surgery).

## 87. Liquid detergent capsule exposure in cats and dogs

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**Objective:** To determine the clinical signs and outcome in cats and dogs exposed to laundry capsules, which contain a small volume of concentrated detergent.

**Methods:** Retrospective analysis of cases of liquid detergent exposure in cats and dogs reported to the Veterinary Poisons Information Service (VPIS) between January 2001 and September 2014.

**Results:** In 19 cats exposure was commonly via oral (89.5%, n = 17%), dermal (26.3%, n = 5) or ocular (5.3%, n = 1) routes. Multi-route exposures were reported in 4 cases (21%). The most common effects were gastrointestinal signs (52.9%, n = 9), respi-

**Table 1.** The top agents involved in fatal feline and canine cases reported to the VPIS 2000–2013.

Toxic deaths in cats							
Agent	Euthanised (% of total cases with that agent)	Rank	Died (% of total cases with that agent)	Rank	Total cases in cats with known outcome	Total fatal cases (% fatality)	Overall rank by % fatality
Ethylene glycol	159 (74.6%)	1	38 (17.8%)	3	213	197 (92.5%)	1
Pyrethroids [permethrin]	118 (10.6%)	2	60 (5.4%)	2	1116	178 (15.9%)	4
	[98 (10.2%)]		[56 (5.8%)]		[963]	[154 (16.0%)]	
<i>Lilium</i> species	43 (7.5%)	3	15 (2.6%)	4	571	58 (10.2%)	5
Unknown	39 (16.9%)	4	58 (25.1%)	1	231	97 (42.0%)	2
Paracetamol	17 (12.5%)	5	12 (8.8%)	5	136	29 (21.3%)	3
<b>Total (% of total deaths)</b>	<b>376 (67%)</b>	–	<b>183 (33%)</b>	–	<b>2267</b>	<b>559 (24.7%)</b>	–
Toxic deaths in dogs							
Unknown	84 (16.9%)	1	104 (21.1%)	1	496	188 (37.9%)	1
Metaldehyde	48 (5.9%)	2	54 (6.7%)	3	808	102 (12.6%)	3
<i>Vitis vinifera</i>	36 (4.0%)	3	11 (1.2%)	10	896	47 (5.3%)	4
Anticoagulant rodenticides	33 (1.9%)	4	55 (3.2%)	2	1695	88 (5.2%)	5
NSAIDs	30 (1.0%)	5	20 (0.7%)	5	2974	50 (1.7%)	6
Vitamin D	13 (8.7%)	9	24 (16.1%)	4	149	37 (24.8%)	2
<b>Total (% of total deaths)</b>	<b>244 (48%)</b>	–	<b>268 (52%)</b>	–	<b>7018</b>	<b>512 (7.3%)</b>	–



ratory signs (41.7%, n = 8) and hyperthermia (35.3%, n = 6). Of the 19 cases, 2 cats (10.5%) remained asymptomatic, 17 (89.5%) developed signs and of these, 15 (78.9%) fully recovered. One elderly cat (17-years-old) presented 2 days after ingestion with severe gastrointestinal signs and died; a 14-year-old cat was electively euthanized, following tachycardia, hyperthermia and frothing at the mouth after ingestion of detergent capsules. In 72 dogs, ingestion was the most common route of exposure (94%, n = 68), followed by dermal (5.6%, n = 4), ocular (4.2%, n = 3) and buccal (4.2%, n = 3); multi-route exposure occurred in 5 dogs (6.9%). Eleven dogs remained asymptomatic. Vomiting (66.7%, n = 48) and coughing (23.6%, n = 17) were the most common signs. Of the 61 symptomatic dogs, 55 (90.2%) had gastrointestinal, 27 (44.3%) respiratory, 5 (8.2%) dermal and 3 (4.9%) ocular signs. In total 56 dogs (91.8%) recovered fully and 1 dog was still coughing at follow up. Two died (3.3%), 2 were euthanised; all four presented with gastrointestinal and respiratory signs. One dog presented at 22 hours and died 2 hours later. The other dog, an epileptic, presented 1 hour after ingestion, developed seizures and died 10 hours later. Both dogs had vomiting and aspiration pneumonia. Both euthanized dogs presented 12 hours after ingestion with gastrointestinal and respiratory signs; 1 dog was euthanized when it failed to improve after 24 hours and the other was euthanized 15 hours after ingestion.

**Conclusion:** Exposure to liquid detergent capsules can result in gastrointestinal, dermal and respiratory signs in cats and dogs. In this series cats and dogs had a similar incidence of respiratory (47.1% versus 44.3%) and dermal signs (11.8% and 13.1%), while dogs showed a higher susceptibility for gastrointestinal effects compared to cats (90.2% versus 52.9%). Based on this case series, the fatality rate in dogs was 6% (n = 4), and 10.6% (n = 2) in cats, although the total number of feline cases was small.

## 88. Lipid infusion: An analysis of cases reported to the Veterinary Poisons Information Service (VPIS)

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**Objective:** Lipid infusion is increasingly used in toxicology, where one of its proposed mechanisms involves acting as a "lipid sink" for lipophilic agents. The VPIS began recommending lipid infusion in 2009 and the objective was to summarize cases, determine the efficacy of lipid infusion and early indications for treatment.

**Methods:** Retrospective analysis of cases where lipid infusion was used with follow-up (with known poisoning agent) reported to the VPIS between March 2009 and October 2014. In some cases lipid was given before discussion with the VPIS.

**Results:** Results were available for 69 animals; 47 dogs and 22 cats (Table 1). Responses were variable. Whilst a lack of a control group limits conclusions about efficacy, where lipid seemed to be effective the response was usually rapid (average 1.5 hours, range 0.5-6 hours from the last infusion) and recovery quicker than would generally be expected given the poisoning agents involved and treatment with standard supportive measures. Additionally, in some cases where clinical improvement was not reported the treating veterinary surgeon believed it halted progression of clinical signs. Comments on mortality could not be made as the numbers were small and originally lipid was only recommended in severe cases. In three cases it was reported by the treating veterinary surgeon that lipid infusion saved the life of the animal. Repeat doses may be required and, of the cases with

**Table 1.** Lipid infusion in cats and dogs in cases reported to the VPIS.

Agent	Number of animals	Full recovery	Number where lipid was effective/beneficial	Time until improvement after last lipid infusion, where given (hours) per case	Number where lipid appeared ineffective	Deaths (%)
<b>Lipid infusion in feline poisoning cases</b>						
Permethrin	16	13	4	0.66, 0.33	1	3 (18.75)
Ivermectin	2	2*	2	0.5	0	–
Moxidectin	2	2	–	–	–	–
Baclofen	1	1	1	1	0	–
Milbemycin	1	1	1	2	0	–
<b>All agents in cats</b>	<b>22</b>	<b>18 (81.8%)</b>	<b>8</b>	<b>0.9 (n = 5)</b>	<b>1</b>	<b>3 (13.6)</b>
<b>Lipid infusion in canine poisoning cases</b>						
Baclofen	14	12	6	2, 0.5	3	2 (14.2)
Ivermectin	13	12	7	2, 6, 1	2	1 (7.7)
Moxidectin	13	12	8	1, 1, 2.5, 0.5, 2	2	1 (9.1)
Doramectin	2	1	–	–	–	1 (50)
Calcipotriol	2	2	–	–	–	–
Lamotrigine	1	1	–	–	–	–
Metaldehyde	1	1	–	–	–	–
Pyriprole	1	1	–	–	–	–
<b>All agents in dogs</b>	<b>47</b>	<b>42 (89.4%)</b>	<b>21</b>	<b>1.0 (n = 10)</b>	<b>7</b>	<b>5 (10.6)</b>
All animals						
<b>All agents</b>	<b>69</b>	<b>60 (87%)</b>	<b>29</b>	<b>1.5 (n = 15)</b>	<b>8</b>	<b>8 (11.6)</b>

\*1 ongoing but improving at follow up

clinical improvement, it was usually after the second administration. Further doses were sometimes needed after deterioration of signs. Only one adverse event was reported; mild swelling and pain where extravasation occurred.<sup>1</sup> In animals with fatal outcome, most (87.5%, n = 7) had uncontrolled seizures and were euthanized.

**Conclusion:** Lipid infusion was rapidly effective in several cases. Fatalities occurred in animals with uncontrolled convulsions which were euthanized. Rapid efficacy, low cost and low risk of adverse effects mean lipid can be recommended early in treatment, even before onset of signs in large exposures.

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## 89. Palm oil ingestion in dogs

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**Objective:** Palm oil is an edible vegetable oil, which is semi-solid at room temperature. It is used in processed foods, toiletries and as a biofuel. Palm oil from transport ships washing out their tanks off the coast of Britain regularly washes up on some beaches; however, in the winter of 2013-2014 severe weather resulted in large quantities appearing around the coast which lead to ingestion by dogs walked on beaches. Warnings were widely publicised in the press with reports of fatal exposure attributed to palm oil ingestion.

**Methods:** Retrospective analysis of cases of palm oil ingestion in dogs reported to the VPIS in the winter of 2013 to 2014.

**Results:** Information was available on 41 individual cases. Of these, 31 dogs (78%) remained asymptomatic. The dose ingested in most cases was unknown but up to 1.7 kg of oil was reported in one case. Of the 10 symptomatic dogs (24%), all had vomiting. Other signs were diarrhoea (n = 3), hypersalivation (n = 2), lethargy/dullness (n = 2), cough (n = 2), belching (n = 2) and inappetence (n = 1). One dog had a mild cough lasting 3 days. There were only 2 dogs with complications. One had aspiration pneumonia after ingestion of palm oil (and administration of an emetic) with a strong diesel odour. It recovered over 7 days. Another dog had significant gastrointestinal signs and elevated liver enzymes but recovered. Of the 41 cases, 10 dogs received no treatment; 6 received an emetic, 6 gut protectants, 4 intravenous fluids and 3 antiemetics. All dogs recovered. In addition a practice in South-West England collectively reported more than 10 cases. All were seen within 30-60 minutes and given apomorphine emetic and activated charcoal. Some had gastrointestinal signs but none required IV fluids and all recovered uneventfully.

**Conclusion:** In over 50 cases reported to the VPIS of palm oil ingestion in dogs most remained asymptomatic. Vomiting occurred in all symptomatic dogs. There was no evidence to suggest that palm oil ingestion in dogs can be fatal. In addition, there is no place for the use of emetics in the management of palm oil ingestion in dogs as it may result in complications.

## 90. Canine exposure to jellyfish

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**Objective:** True jellyfish belong to the phylum Cnidaria (formerly Coelenterata), class Scyphozoa. They are marine pelagic organisms that display a wide variety of shapes, colours and sizes. Species found in the North Atlantic and North Sea includes *Pelagia*, *Chrysaora*, *Cyanea* and *Physalis*. There is little information in the veterinary literature on canine exposure to jellyfish.

**Methods:** Retrospective analysis of cases of "jellyfish" exposure in dogs reported to the VPIS from 1992 to September 2014 to determine clinical signs reported, treatments given and outcome. Only cases with returned veterinary surgeon follow-up (via postal questionnaire) are included. The jellyfish were not formally identified.

**Results:** Information was available on 32 cases. The route of exposure was most commonly ingestion (n = 18) and then buccal exposure (n = 7), sting (n = 5) and sting and ingestion in 2 dogs. Only 2 dogs remained asymptomatic; one dog remained well, even though it had reportedly eaten 4 jellyfish. Of the 30 symptomatic dogs the most common signs were vomiting (63% of symptomatic dogs), facial, lip, limb or laryngeal oedema (20%), hypersalivation (17%), retching (13%) and oral or buccal irritation (13%). Onset of effects was reported in 7 cases and ranged from 2 minutes to 3 hours (median 0.5 hours). Six dogs received no treatment; 16 were given steroids and 11 received antihistamines. Other treatments included analgesia (n = 14), antibiotics (n = 6), antiemetics (n = 4), IV fluids (n = 4) and oral fluids (n = 3). The time to recovery was reported in 10 cases and ranged from 2-48 hours (median 7.5 hours). One dog had recurrence of facial and lip oedema at the time of follow up but all other dogs recovered fully.

**Conclusion:** Canine exposure to jellyfish on the coast of Britain typically causes vomiting and local swelling. Signs are rapid in onset and resolve within a few hours. The most common treatments given in cases reported to the VPIS were steroids and antihistamines. Most cases involved ingestion rather than stings. Severe cases in dogs are uncommon but this may be because their fur provides some protection from dermal exposure.

## 91. Diclofenac ingestion in dogs: What are the risk factors associated with clinical signs?

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**Objective:** Diclofenac is a non-steroidal anti-inflammatory drug (NSAID); it is generally not used in dogs as they are at risk of gastrointestinal and renal effects from NSAIDs. The objective was to analyse canine cases of diclofenac ingestion, particularly the prevalence and risk factors associated with clinical signs.

**Methods:** Retrospective analysis of diclofenac ingestion in dogs (with outcome) reported to the VPIS between April 1987 and February 2014.

**Results:** There were 443 cases; 254 dogs (57.3%) remained asymptomatic and 189 (42.7%) developed signs, including 5 that died or were euthanized (2.6%). Dose ingested ranged from 0.7 to

**Table 1.** Signs, onset, duration and dose range in symptomatic dogs after diclofenac ingestion.

Sign	Number of cases (% of symptomatic)	Onset average (mode) Hours	Duration average (mode) Hours	Dose range (average) mg/kg
<b>Gastrointestinal</b>				
Vomiting	<b>149 (78.8)</b>	25 (24) n = 77	47 (48) n = 39	0.7–115.4 (12.25) n = 96
Haematemesis	19 (10.1)	36 (48) n = 9	60 (–) n = 2	0.83–60.6 (12.5) n = 11
Diarrhoea	<b>59 (31.2)</b>	31 (24) n = 38	60.8 (48) n = 22	0.77–90 (21) n = 39
Haemorrhagic	22 (11.6)	36 (48) n = 18	48 (24) n = 8	2.9–60.6 (8.5) n = 13
Melaena	<b>22 (11.6)</b>	40 (24) n = 9	148 (168) n = 6	3.2–71.4 (12.5) n = 13
<b>Behavioural</b>				
Dull/depressed	<b>29 (15.3)</b>	32 (48) n = 11	12 (–) n = 1	0.93–115.4 (22.7) n = 15
<b>Renal</b>				
Renal signs	<b>14 (7.4)</b>	56 (–) n = 3	–	0.9–115.4 (29.6) n = 10

Signs with < 10 cases not shown.

115.4 mg/kg. In total 184 dogs recovered (97.3%) within 4 hours to 6 days (average 61 hours, n = 15). Time to presentation/treatment was on average 44 minutes in asymptomatic treated dogs (n = 83) and 38 hours in symptomatic animals (n = 128); however, 47 dogs remained asymptomatic without treatment despite reported doses similar to those in symptomatic dogs. Signs, duration and severity did not appear to be dose-related (Table 1). Non-tablet formulations (gels/suppositories) or sustained release preparations had a higher representation in symptomatic (14.3%) compared to asymptomatic (2%) dogs, but this did not affect presence of renal signs. Renal signs were rare (7.4% of symptomatic cases) and associated with delayed presentation (average 80 hours, n = 11) and prolonged gastrointestinal signs (contributing to dehydration). Age and severity had mild correlation and renal impairment was more likely in older dogs, but occurred at all ages. Although most dogs with renal signs recovered fully (85.7%), renal impairment was reported in 40% of fatal cases.

**Conclusion:** Diclofenac in dogs is associated with gastrointestinal signs; renal effects are rare and related to delayed treatment and clinical signs resulting in dehydration. Prompt treatment is associated with reduced incidence of clinical signs. A more guarded prognosis is appropriate for dogs that present late rather than those that develop renal signs.

## 92. Electronic cigarette ingestion in dogs

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**Objective:** To determine the clinical signs and outcomes associated with ingestion of electronic cigarettes and refill liquid in dogs. In the UK at least one canine death in a press report was attributed to ingestion of electronic cigarette liquid although the cause of death was not stated.<sup>1</sup> Electronic cigarettes are part of a broad product group (electronic nicotine delivery systems; ENDS), which includes cigarette-like products and pipe-like objects and their liquid refills.<sup>2</sup> They claim to contain high concentrations of nicotine.

**Methods:** Retrospective analysis of cases of electronic cigarette ingestion in dogs reported to the Veterinary Poisons Information Service (VPIS).

**Results:** There were 20 cases with follow up including 7 asymptomatic dogs (35%) and 13 dogs (65%) that developed signs. In the symptomatic dogs the most common sign was vomiting (69%), followed by hypersalivation (38%), lethargy (15%), diarrhoea (15%), hyperthermia (15%) and ataxia (15%). There was one report each of tachycardia, mild, shallow respiration, twitching and drowsiness. The concentration of the solution was known in 15 cases: 8 mg/ml (n = 1), 11 mg/ml (n = 1), 16 mg/ml (n = 1), 18 mg/ml (n = 6) and 24 mg/ml (n = 6). The dose of nicotine ingested was estimated in 7 cases and ranged from 0.1 to 18 mg/kg. All these dogs developed clinical signs but there was no dose-relationship. Treatments used included emesis in 5 cases and activated charcoal in 8 dogs. No treatment was given in 8 animals (5 remained asymptomatic). The time to recovery was recorded in 7 cases; 6 dogs recovered within 0.5 to 2 hours and the 7th recovered within 12 hours. Of the symptomatic dogs 12 recovered fully and one with only mild signs was given no treatment but euthanized due to financial constraints.

**Conclusion:** Ingestion of electronic cigarettes or refill liquid does not appear to be associated with severe toxicity in dogs. This is consistent with reports of human exposure to these products. The amount of nicotine in these systems is variable and uncontrolled at present.<sup>2</sup> Vomiting and hypersalivation are the most common signs reported in dogs and recovery is usually rapid.

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## 93. Nitroxylin causes severe hyperthermia in dogs

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**Objective:** Nitroxylin is a veterinary anthelmintic drug used mainly in cattle and sheep. It is also used in some countries in dogs (10 mg/kg subcutaneous injection or 15 mg/kg orally). Nitroxylin is related to the herbicides ioxynil and bromoxynil and uncouples oxidative phosphorylation in mitochondria resulting in a hyper-metabolic state. There is limited information on canine cases of nitroxylin exposure in the veterinary literature.

**Methods:** Retrospective analysis of cases of nitroxylin exposure in dogs reported to the Veterinary Poisons Information Service (VPIS) to determine clinical signs reported, treatments given and outcome.

**Results:** Information was available on 7 incidents involving 8 dogs and all occurred between 2011 and 2013. The same product (nitroxylin 34%), intended for subcutaneous injection in cattle and sheep, was involved in all cases. In 4 dogs the source was an animal carcass and in 1 dog it was meat, both used, illegally, for control of pests such as foxes. One dog had reportedly scratched and eaten a dried residue from a spill, another drank from the container and in the final case the owner had given 2-3 ml of a 34% solution subcutaneously (42.5-62.6 mg/kg) to treat a tick infestation (instead of ivermectin). This was the only case where the dose known. All the dogs were symptomatic; the most common signs were panting (n = 7), hyperthermia (n = 7) and vomiting (n = 5). Body temperature was reported in 6 dogs and varied from 39.3 to 42.9°C (mean 40.7°C). Signs generally started within 4 hours. One dog received no treatment (and recovered); 7 received IV fluids and 5 received cooling measures. Of the 8 dogs, 4 died, and 4 recovered. Time to death was recorded in 3 cases and was within 1 hour of admission, another at 15.5 hours post-ingestion; the dog given the SC injection died at 9 hours. The median time to recovery in the 4 survivors was 48 hours (range 24-72 hours).

**Conclusion:** Nitroxylin causes severe hyperthermia in dogs. In 8 dogs reported to the VPIS, half the dogs died; death typically occurs within 24 hours.

#### 94. Adder antivenom: The experience and opinions of veterinary professionals in the UK

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**Objective:** To seek information from UK veterinary professionals on their use of adder antivenom, particularly following the cessation of production of the Croatian antivenom (commonly known as Zagreb antivenom).

**Methods:** An online questionnaire (using SurveyMonkey®) sent to all email addresses in the VPIS database (> 3,200).

**Results:** In total 112 responses were received (response rate 3.5%). In a typical year the number of cases treated with antivenom was none (38%), 1-5/year (53%), 6-10/year (7%) and 11+/year (<1%). The majority treated no cases with antivenom (56%); 13% respondents treated all cases and 12% about three-quarters. Adverse effects to antivenom were rarely (rare 10%, very rare 11%) or never seen (70%). Reactions were reported as common (< 2%) or uncommon (8%) by a few respondents. Where applicable the reasons for not treating a case with antivenom were unavailability (29%), mild effects (21%), concern about adverse effects (6%), late presentation (15%) or cost (2%). Only 35% of respondents stocked

the antivenom (29% held 1-2 vials and 6% held 3-5 vials). Only 1 respondent held > 5 vials. In an emergency, most respondents who did not stock antivenom would contact another practice (30%); 17% would contact a local hospital and some did not know (11%). If they held antivenom, 86% of respondents would supply to another practice in an emergency. Most respondents were familiar with the Zagreb antivenom (59%); 18% had heard of the BIOMED (newly available from Poland) antivenom and 13% of ViperaVet® (a UK product in development); 41% were not familiar with any particular antivenom. The main issues obtaining antivenom were availability (36.6%) and the time-consuming process of obtaining an import licence (7.1%). Cost was an issue in two cases. Most respondents expected to pay £50/63 euros (38%) or £100/125 euros (34%) for antivenom. A few expected to pay £20/25 euros (8%), £150/187 euros (14%), £250/312 euros (4%) or >£250 (3%).

**Conclusion:** Few responses were received, but it appears that most UK veterinary practices do not stock antivenom and rely on other practices in an emergency. The perceived unavailability of antivenom and the procedure for obtaining an import licence are barriers to obtaining and stocking antivenom in the UK.

#### 95. A multicentre cohort study of snake envenoming defines clinical syndromes and influences clinical practice

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**Objective:** Australian snake envenoming is rare and mainly occurs in rural/regional hospitals. Limited clinical exposure and lack of large studies or controlled trials has resulted in treatment being based on anecdotal experience. We aimed to determine the effect of a national multicentre cohort study, the Australian Snakebite Project (ASP), on improving our understanding and treatment of snake envenoming.

**Methods:** ASP is a prospective multicentre collaborative study of hospital clinicians, poison centres and clinical toxicologists across Australia. It uses predefined data collection, laboratory investigations and venom assays to describe envenoming, antivenom effectiveness and dose. Data collection sheets and laboratory protocols are faxed to clinicians who return them by fax. Blood samples are transported to a central laboratory for venom enzyme immunoassays. All snakebites recruited to ASP from 2004 to February 2014 were included.

**Results:** There were 772 definite snake envenomings from 1,454 snakebites; the median age was 41 years (1-88 years) and 581 (75%) were males. Snake types and clinical effects are in Table 1. Coagulopathy was the commonest clinical effect, then neurotoxicity, renal toxicity and myotoxicity. There were 18 deaths but no change in case-fatality. Antivenom was administered in 665 envenomed patients (86%). Nine publications over 5 years showed that one vial of antivenom was sufficient and repeat doses are not required based on measuring venom concentration measurement pre- and post-antivenom. There was a reduction in median antivenom dose from 5

**Table 1.** Snake types and clinical effects in cases of snakebite collected by the Australian Snakebite Project.

Data collected	Number of cases	%
<b>Snake type</b>		
Brown snake ( <i>Pseudonaja</i> spp.)	274	35%
Tiger snake ( <i>Notechis</i> spp.)	88	11%
Red-bellied black snake ( <i>Pseudechis porphyriacus</i> )	104	14%
Rough-scale snake ( <i>Tropidechis carinatus</i> )	55	7%
Taipan ( <i>Oxyururus</i> spp.)	33	4%
Mulga snake ( <i>Pseudechis australis</i> )	29	4%
Death adder ( <i>Acanthophis</i> spp.)	24	3%
<b>Clinical syndromes</b>		
Coagulopathy	560	73%
Complete VICC	429	56%
Partial VICC	131	17%
Anticoagulant	86	11%
Major haemorrhage	10	1%
<b>Neurotoxicity</b>	84	11%
Mild	48	6%
<b>Myotoxicity</b>	73	9%
<b>Thrombotic microangiopathy</b>	58	8%
<b>Renal toxicity</b>	89	12%
Acute renal failure	42	6%
Abnormal creatinine	47	6%

VICC = venom-induced consumption coagulopathy.

to 1 vial, decreased repeat dosing from 65% to 24%, associated with a slight decrease in antivenom reactions, over 10 years.

**Conclusion:** A national multicentre collaboration systematically described clinical syndromes and antivenom effectiveness in snake envenoming. Laboratory support was critical, providing objective evidence based on venom concentrations. The collaborative nature allowed immediate dissemination of research results into clinical practice, rapidly influencing and improving treatment. Reduced antivenom use means decreased cost and less risk of anaphylaxis.

## 96. Novel ciguatera shellfish poisoning (CSP) cluster after consumption of *Tectus niloticus*, a gastropod, in Nuku-Hiva, French Polynesia

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**Objective:** Recently, a new pathway of ciguatera-like syndrome, also known as ciguatera shellfish poisoning (CSP), associated with the consumption of marine invertebrates (giant clams, sea-urchins) has been highlighted.<sup>1</sup> This is the first report of a cluster of CSP after consumption of troca (*Tectus niloticus*, a gastropod), although a few unofficial reports are already known among local populations of South Pacific.<sup>2</sup>

**Case series:** In June 2014, 9 sailor tourists (2 French, 2 Dutch, 5 Italian) were poisoned after the consumption of troca in Nuku-Hiva island (French Polynesia). Seven of them were evaluated at the local hospital for severe gastrointestinal and neurological manifestations. Two patients were evaluated in our centre 1 week after the poisoning. Case A (45-years-old) presented mainly with severe gastrointestinal manifestations (vomiting/diarrhoea), asthenia/myalgia, paresthesias/dysesthesias/thermoalgia and intractable hiccups. Esophagogastroduodenoscopy showed esophagitis. Specific investigations for neuropathological alterations and genetic predisposition for chronic disease were conducted. The patient was treated with mannitol. A 5-month follow-up documented the persistency of mild temperature-related dysesthesias of the upper extremities. Case B (72-years-old) presented mainly with slight gastrointestinal manifestations (vomiting/diarrhoea) associated with asthenia/myalgia during the 1st week. Neuropathological tests (after 1 month) were normal and the 5-month follow-up documented complete clinical resolution. Most of other victims are still symptomatic with gastrointestinal and/or peripheral neurological symptoms. Investigations based on specific clinical questionnaires were submitted to them. Preliminary toxicological analysis of troca specimens confirmed the presence of lipophilic ciguatoxin-like compounds. Moreover, unidentified hydrophilic toxins have also been detected and are currently being analyzed for identification.

**Conclusion:** Our investigations confirm the implication of *Tectus niloticus* in a CSP cluster. Additional investigations are ongoing in order to specify the toxic source (organisms and toxins involved), to characterize the clinical features of this CSP form, including the occurrence of potential chronic effects and to recommend effective treatments. Moreover, these data would be useful to health authorities to improve the risk management of seafood poisonings, especially in Pacific islands, where *T. niloticus* constitute a significant subsistence and economic resource.

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## 97. Viper envenomation in Italy: Clinical course, laboratory investigations and antivenom treatment in a case series (2002-2012) from Pavia Poison Centre

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**Objective:** Viper envenomation may be characterized by local and systemic symptoms with an estimated mortality up to 1%. Clinical and laboratory disorders and antivenom administration are often debated<sup>1</sup> Poisoning severity, laboratory alterations and antidote

administration in viper-envenomed patients referred to the Pavia Poison Centre (PPC) are described in order to evaluate predictable clinical and laboratory factors in viper envenomation management.

**Methods:** All viper bitten patients referred to PPC from 2002–2012 were retrospectively studied. Clinical manifestations and evolution were evaluated according to a Grading Severity Score (GSS)<sup>2</sup> and related to laboratory parameters and antidote treatment.

**Results:** During the 11-year study period, 482 viper bitten patients were evaluated (44 ± 23 years; male 65%). At hospital admission 43.2% had only fang-marks (GSS0), 39% local edema (GSS1), 15.8% regional edema and/or mild systemic manifestations (GSS2) and 2% severe local and/or systemic manifestations (GSS3). Among GSS0-admitted patients, 38/208 (18%) developed GSS ≥ 1, and 10/208 (5%) required antivenom because they progressed to GSS ≥ 2. Among GSS1-admitted patients, 73/188 (38.8%) developed GSS ≥ 2, and 59/188 (31.3%) needed antivenom. Most GSS2–3 (63–100%) admitted patients received antivenom. Among 482 patients, 170 (35%) had dry bites and 312 (65%) developed envenomation. Systemic symptoms were mainly gastrointestinal (118/312; 38%), hemodynamic (37/312; 11.8%), neurotoxic (36/312; 11.5%) and local thrombosis (24/312; 8%). Seven patients developed hemodynamic shock and three had splenic, myocardial or cerebral ischemia, respectively. No fatal cases occurred. Mean onset time of local manifestations was 11.8 hours and 27.5 hours for mild and extensive edema, respectively; gastrointestinal and hemodynamic disorders developed within 5–7 hours and neurotoxic effects within 10.7 ± 6.2 hours. Increase in leukocytes, D-dimer, INR and decreased thrombocytes and fibrinogen were statistically related with GSS ≥ 2. Antivenom was required in 44% of patients and administered with a mean time of 15.5 hours. Most patients (76%) improved after antivenom. In those (24%) where GSS ≥ 2 was present within a few hours edema worsened despite antivenom administration.

**Conclusion:** Viper bite is potentially serious and requires immediate hospital care. GSS0-patients at hospital admission may worsen and require antivenom within 12–24 hours. Leukocytosis and increased D-dimer occur with severe envenomation. Prompt antivenom administration is important and further administration may be evaluated in patients that develop severe envenomation.

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## 98. A novel strategy for identifying *Naja atra* species-specific venom antigen C3 for developing cobra snakebite confirmation test in Taiwan

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**Objective:** Taiwan, a subtropical island has more than 40 snake species, and 6 of them play a clinically significant role in snakebites. They are *Deinagkistrodon acutus*, *Viridovipera stejnegeri*, *Protobothrops mucrosquamatus*, *Daboia russelii siamensis*, *Bungarus multicinctus* and *Naja atra*. Due to lack of specific tests misdiagnosis of the culprit snake is common (nearly 10%). This is especially true when patients are bitten by *Viridovipera stejnegeri*, *Protobothrops mucrosquamatus* or *Naja atra*, because they have similar clinical presentations in the early phase. As a consequence administration of the wrong antivenin is frequently seen. We combined immunologic and mass spectrometry methods to develop a new strategy to determine snakebite biomarkers. In this study, we tried to identify *Naja atra* species-specific antigen by a novel strategy. As a model, the identified proteins can be further used as candidates for developing venomous snakebites detection kits.

**Methods:** *Naja atra*-specific antibodies (NA-SSAbs) were purified by affinity chromatography. *Naja atra* venom immunized horse plasma was allowed to flow through the 5 columns which contained beads coating with the other 5 venomous snakes, respectively.<sup>1</sup> After this step, we could produce NA-SSAbs. Secondly, the specificity of NA-SSAbs was analyzed by immunoblotting and ELISA. Then, the NA-SSAbs corresponding antigens of *Naja atra* venom were obtained by immunoprecipitation. After trypsin in-gel digestion, liquid chromatography-mass spectrometry (LC-MS/MS) analysis and Swiss-Prot database searching the target protein identifications were obtained. Lastly, species-specific antigen C3 was verified.

**Results:** A *Naja atra* species-specific antigen C3 was identified (Table 1).

**Table 1.** The list of target antigens of *Naja atra* species-specific antibody with high confidence.

Bands	Name	Score	Coverage	Unique Peptides	Peptides	PSMs	MW [kDa]
A	NA species-specific antigen A1	391.12	58.9	3	6	11	16
	NA species-specific antigen A2	132.24	28.57	1	3	4	14
	NA species-specific antigen A3	277.33	28.08	1	3	5	16.1
B	NA species-specific antigen A1	792.74	74.66	5	8	20	16
	NA species-specific antigen A3	505.17	52.05	2	5	10	16.1
C	NA species-specific antigen 3	198.41	22.22	1	2	9	9
	NA species-specific antigen C5	169.45	28.4	2	3	8	9
	NA species-specific antigen C6	135.92	34.57	2	3	6	9
	NA species-specific antigen C9	194.49	50	2	4	7	7
	NA species-specific antigen C8	123.72	34.94	1	3	5	9.3
	NA species-specific antigen C7	160.17	30.49	1	2	4	9.1
	NA species-specific antigen C3	427.07	61.73	1	8	28	9
D	NA species-specific antigen C4	681.74	67.9	2	9	36	9.1
	NA species-specific antigen C6	379.87	65.43	3	7	25	9
	NA species-specific antigen C1	654.64	70	2	6	32	6.7



**Conclusion:** A novel strategy was developed to discover *Naja atra* species-specific antigen that not only has a unique sequence but also specific immunogenicity. A novel *Naja atra* envenoming biomarker, NA species-specific antigen C3, was identified and could be used to diagnosis *Naja atra* envenoming from the other clinical significant venomous snakebites in Taiwan.

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## 99. Incidence and clinical characteristics of lionfish poisoning in Martinique

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**Objective:** Lionfish (members of genus *Pterois*) invasion in the French overseas departments represents one of the most important marine invasions by alien species in the history. Since its arrival in Martinique in February 2011, the presence of lionfish has strongly advanced and it is responsible for increasing number of poisonings affecting fishermen and aquarists. The objective of this study was to analyze the clinical characteristics.

**Methods:** A prospective study led by the emergency department at the University Hospital of Martinique, general practitioners, and the department of the pre-hospital emergency medical service. All the patients admitted from November 2011 to February 2014 for one or several stings by the lionfish were included, with a strongly suggestive clinical presentation associated with severe local pain and edema. Treatment included immersion of the affected area in hot water at 35–40°C for 60 minutes, analgesics, tetanus toxoid and antibiotics. Data are presented as median [25–75th percentiles] or percentages.

**Results:** In total 117 patients (98/19F, age 42 years, range 13–89 years) were included. Of these 19 patients (16%) had significant past history including diabetes, cardiac failure, chronic alcoholism, allergy, hypertension, hepatitis C, Hodgkin's lymphoma and breast cancer. The group included 5 children and 4 elderly men. On admission, the patients presented with cardiovascular (22%) and respiratory failure (3%). Clinical manifestations were characterized by severe pain and local edema (100%), paresthesia (90%), abdominal cramps (62%), extensive edema (53%), skin rash (32%), gastrointestinal disorders (28%), fainting (27%), paralysis (24%), hyperthermia (9%), hypophosphotemia (12%), elevated aspartate aminotransferase (AST) (10%), and thrombocytopenia (3%). Other complications included sepsis (17%), cutaneous necrosis (6%), right-side hemiplegia (1%), abscess (5%), cellulitis (3%) and arthritis (2%). In total 26 patients (22%) were hospitalized requiring

surgery (6%). The stings were single (81%) or multiple (19%) and localization was preferentially in the upper (67%) or lower limbs (32%). Hot water was used in 52 patients (44%), and was started within less than 3 hours in approximately 36% of all cases.

**Conclusion:** Lionfish stings represent a major public health problem in Martinique. The increasing number of cases remains difficult to estimate in the absence of a national register. The mortality rate is almost non-existent if the initial management is prompt and appropriate.

## 100. Severe envenomation by *Bothrops venezuelensis*

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**Objective:** *Bothrops venezuelensis* is a venomous snake of the viperidae family. Typical symptoms of bothropic envenomation are local and severe systemic effects, mainly coagulopathy, but information about the clinical course caused by *Bothrops venezuelensis* is scarce. We describe a case of life-threatening envenomation by *Bothrops venezuelensis*.

**Case report:** A 55-year-old man presented to the Emergency Department (ED) after a bite by a juvenile *Bothrops venezuelensis* in the distal phalanx of his left thumb. He immediately treated himself with prednisone (50 mg) and clemastine (4 mg). At admission (1.5 hours after the bite) his hand was swollen and severely painful. The neurological and cardiopulmonary status was unremarkable. The initial laboratory findings revealed incoagulable blood (INR > 12, aPTT 136 s, fibrinogen < 0.3 g/L) without signs of disseminated intravascular coagulation (DIC). After 2400 IU of prothrombin complex concentrate (coagulation factors II, VII, IX, X, protein C and S), fibrinogen (6 g) and 10 vials of polyvalent equine anti-viper serum (Antivipmyn<sup>®</sup>), administered 4.5 hours after the bite, the coagulation parameters improved progressively. On day 2 microangiopathic hemolysis and severe thrombocytopenia appeared, and signs of compensated DIC were present (Table 1). Fresh frozen plasma was administered (10 mL/kg/d) for 7 days, and erythrocyte concentrate on day 7. Furthermore the patient developed acute renal failure with macroscopic hematuria and fluid overload, including peripheral tissue edema, pleural effusion and pulmonary edema, which was associated with respiratory insufficiency requiring intermittent ventilation. The patient developed fever, without microbial growth in blood cultures and bronchoalveolar fluids. Echocardiogram and ECG were normal. Fluid overload was treated with furosemide. The patient recovered and was discharged with moderately elevated creatinine (238 µmol/L) 16 days after hospitalisation. Creatinine level normalised within one week.

**Conclusion:** *Bothrops venezuelensis* appears to have a similar envenomation profile as other *Bothrops* species. Early treatment with the polyvalent antivenom had a beneficial effect, but patients

**Table 1.** Laboratory parameters during hospitalization of a patient with *Bothrops venezuelensis* envenomation.

Parameter	Day of hospitalisation									
	0	1	2	3	5	7	9	11	14	16
<b>Coagulation</b>										
INR (<1.3)	>12	1.2	1.2	1.1	1	1.2	1.1	1.2	1.2	1.2
aPTT (25-34 s)	136	27	27	26	22	26	25	22		26
Thrombocytes (150-450 G/L)	190	188	39	25	29	78	293	615	894	938
Fibrinogen (1.7-4 g/L)	<0.3	1.3	1.8	2.8	4.2	6.7	8.4	7.2	6.6	6.7
D-Dimer (<0.5 µg/ml)			>20		15	6.5	5.4			
Factor V (70-120%)	27	109	120							
<b>Hemolysis</b>										
Hemoglobin (140-180 g/L)	148	140	118	95	57	62	69	67	69	90
LDH (135-225 U/L)	255	803	1882	2787	3312	1557	901	663	414	395
Bilirubin total (<24 µmol/L)	13	22	34	46	96	34	24	19	12	13
<b>Renal values</b>										
Creatinine (49-97 µmol/L)	93	193	366	509	760	955	947	729	368	238
Urea (3.4-8.7 mmol/L)	3	7	16	25	37	48	49	40	18	13
<b>Other parameters</b>										
Creatine kinase (50-200 U/L)	181	181	330	639	806	159	42	30		58
AST (11-34 U/L)	42	88	113	141	160	46	44			36

should be closely monitored for venom-induced complications requiring specific treatment.

### 101. Treatment of black widow spider (*Latrodectus mactans*) envenomation: A review of 53 cases

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**Objective:** Female *Latrodectus mactans* (black widow spider) cause serious envenomation; they are commonly found in dark environments like outhouses and garages. The venom contains alpha-latrotoxin, a neurotoxin which causes opening of nonspecific cation channels, leading to an increased influx of calcium, resulting in release of neurotransmitters like acetylcholine and norepinephrine. Most clinical effects are secondary to acetylcholine causing several pain, muscle cramps, abdominal pain, back pain and norepinephrine causing hypertension and tachycardia.<sup>1</sup> We present cases of symptomatic black widow spider envenomation and evaluate the efficacy of treatment suggested by the Greek Poison Center.

**Methods:** All *Latrodectus mactans* exposures reported to the National Poison Center between 1 January 2010 and 30 September 2014 were studied retrospectively.

**Results:** A total 53 *Latrodectus mactans* exposures occurred in the study period. Exposure peaked in July and fell to a nadir in January. The age of patients ranged from 2 to 74 years (mean 37.9 years). Only minor clinical effects occurred in 56.6% of patients and no hospitalization was needed. Mild to severe symptoms presented in 43% of patients who were hospitalized. There were no deaths. Symptoms typically lasted for 1-3 days and included abdominal pain 52.1%, muscle rigidity/cramping 43.4%, diaphoresis 43.4%, hypertension 34.7%, chest pain 30.4%, limb pain 50%, back pain 26%, salivation 26%, myalgia

21.7%, tachycardia 17.4%, respiratory failure 21.7%, myocarditis 8.7%, cardiac failure 4.3% and acute pulmonary edema 4.3%. There was leucocytosis in 21.7%, troponin increase in 30.4% and creatine kinase increase in 34.7% of the patients. Physicians treated moderate or severe symptoms with IV benzodiazepines (n = 6), IV opioids (n = 5) or a combination of IV opioids with benzodiazepines (n = 12). Antivenin IV was administered in 5 patients with severe systematic findings. Treatment relieved pain in 47.7% of patients taking opioids or benzodiazepines alone, and in 52.1% using both opioids and benzodiazepines. All 5 patients who received antivenin reported complete symptom resolution after an average of 80 ± 30 minutes and the need for hospitalization was reduced.

**Conclusion:** Treatment ranged from administration of opioids and benzodiazepines to specific antivenom. Opioid analgesics combined with muscle relaxants, such as benzodiazepines, are generally effective at symptomatic control. In selected severe cases antivenom is the most efficacious therapy available.<sup>2</sup>

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### 102. Coral snake bites in Brazil: A review

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**Objective:** Coral snakes (*Micrurus* spp.) are the main representatives of the family Elapidae in the Americas. We reviewed the reports of coral snake bites in Brazil from 1933 to 2014 to determine the species involved, the clinical manifestations of envenomation, the treatment used and the outcome.

**Methods:** Twenty four reports in English or Portuguese describing case series and case reports of coral snake bites were identified by searching Internet databases (EMBASE, PubMed, Scielo and LILACS), books, abstracts published in congress proceedings, academic dissertations and personal communications. Since three reports dealt with the same cases, subsequent analysis was restricted to 21 reports (6 articles, 9 abstracts, 3 books, 2 academic dissertations, 1 personal communication) describing 150 cases.

**Results:** Of the 150 cases, 60% were from Santa Catarina state (southern Brazil). The snakes were brought for identification in 82 cases (*Micrurus* spp. n = 22, *M. corallinus* n = 37, *M. frontalis* n = 12, *M. lemniscatus* n = 5, *M. filiformis* n = 1, *M. hemprichi* n = 2, *M. surinamensis* n = 1, *M. spixii* n = 1, *M. ibiboboca* n = 1). Of the 134 cases in which the bite site was recorded, most involved the hands (46.3%) and feet (26.1%). The main clinical features described were local numbness/paresthesia (52%), local pain (47.3%), palpebral ptosis (45.3%), blurred vision (20%), weakness (16.7%), dysphagia (14.7%), myalgia (9.3%), inability to walk (9.3%), dyspnea (8%), and salivation (8%). Fang marks were present in 45.3%, and 14.7% were classified as asymptomatic. A slight increase in total blood creatine kinase was reported in two cases (1,766 IU and 1,354 IU). Therapeutic procedures included the use of anti-*Micrurus* antivenom raised against *M. corallinus* and *M. frontalis* venoms (76%; F(ab')<sub>2</sub>, Instituto Butantan, Brazil), anticholinesterase drugs (7.3%) and mechanical ventilation (4.7%). Two patients (reported in 1933), developed respiratory failure/paralysis and died 6 hours and 17 hours post-bite, respectively.

**Conclusion:** Neuromuscular blockade (pre- and/or post-synaptic) is the hallmark of systemic envenomation by *Micrurus* spp. Systemic neurotoxic envenomation was detected in 47.3% of patients (respiratory depression in 6%), similar to data reported by Wood et al.<sup>1</sup> Local features, such as paresthesia and pain, were also frequently reported. The two reported deaths were described in a situation where mechanical ventilation support was unavailable. Envenomation by *Micrurus* spp. in Brazil is uncommon. Although many patients developed systemic neurotoxicity, few required respiratory support.

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## 103. Multidisciplinary proposal of loxoscelism management: A clinical case

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**Objective:** Loxoscelism is caused by envenomation by spiders from *Loxosceles* genus; the clinical treatment is still controversial<sup>1</sup> and not always effective<sup>2</sup>. Clinical symptoms can evolve in local reactions, such as severe dermo-necrotic damage, and systemic reactions, with risk of death. *Clostridium*<sup>3</sup> and Methicillin-Resistant *Staphylococcus aureus* (MRSA)<sup>4</sup> can be present in the microbial flora of the fangs, hence the need for aggressive treatment against the risk of infection. We describe a case of loxoscelism in the light of recent scientific literature about the risk of infection from this spider bite.

**Case report:** A 39-year-old man presented to Emergency Department 4 days after a spider bite complaining of headache, ear and eyeball pain associated with nausea and diarrhoea. On examination he had a swelling and red area of probable necrotic nature in the right zygomatic region with ear swelling and periorbital edema. Systemic therapy with cortisone and amoxicillin/clavulanic acid was administered, with no response. A few days later the patient returned with retro-orbital pain with no vision defects, right headache and a lesion with dermonecrotic damage. After running a swab for intralesional culture, high dose antibiotic therapy with ciprofloxacin and hyperbaric oxygen therapy (HBOT) were started. No retro-orbital and periorbital phlegmons were shown by magnetic resonance imaging (MRI). Swab culture confirmed the presence of multi-resistant *Staphylococcus haemolyticus*. No lesions were detected by MRI. After 4 days of HBOT and specific antibiotic therapy, the lesion was significantly improved with resolution of the edema and pain.

**Conclusion:** *Loxosceles* injury should not be underrated especially if a necrotic lesion is present. We recommend performing a bacterial culture to better focus the antibiotic treatment; also hyperbaric oxygen therapy may be useful to treat infection caused by anaerobic bacteria inoculated during the spider bite and to treat necrotic tissues.

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## 104. A snake bite by Dinniki's Viper

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**Objective:** Dinniki's Viper (*Vipera dinniki*) is a venomous snake endemic to the Caucasus. A bite can lead to similar symptoms seen with bites by other European vipers. The venom probably contains procoagulants and haemolytic factors and can cause severe envenoming with potentially lethal outcome. No specific antivenom is available. To our knowledge, this is the first documented case of a snake bite by Dinniki's Viper.

**Case report:** A 43-year-old male was bitten by a Dinniki's Viper on his thumb and developed severe local swelling, leading to hospital admission. During transport he developed gastrointestinal symptoms, hypotension, a feeling of tightness of the throat and swelling of the nasal mucous membrane. He consequently received pre-clinically intravenous steroids, dimetindene and dimenhydrinate. On admission cardiac and respiratory functions were stable, but he had fever and progressive swelling to the middle of the upper arm accompanied by erythema. Due to the local and systemic symptoms European Viper Venom Antiserum was administered intravenously 120 minutes after the bite along with prednisolone. The patient had a history of multiple previous snake bites and had previously received antivenom, raising the risk of immunisation. Therefore, we injected diluted antiserum subcutaneously to test for possible allergic reactions prior to administration. During the infusion of the antiserum the swelling decreased visibly. Immobilisation and cooling were applied and oral diclofenac given. The swelling subsided almost completely and the patient was discharged with no visible signs of possible sequelae.

**Conclusion:** Bites by Dinniki's Viper have so far been unreported with no known antivenom available. We chose not to use the antivenom ViperaTAB<sup>®</sup>, because it was developed specifically for bites by Central and South European vipers, especially *Vipera berus*. Instead, we preferred to administer the European Viper Venom Antiserum that was developed against bites by snakes from Eastern Europe and Turkey such as *Vipera ursinii*. The latter regions are geographically closer to the Caucasus, which makes the antiserum more likely to be effective against bites by Dinniki's Viper than ViperaTAB<sup>®</sup>. As administration of the European Viper Venom Antiserum appeared to be clinically beneficial in this case, it may be a therapeutic option for future cases.

## 105. Viper bites on the left and right hand side of the River Rhine: Comparison of experiences in the poisons centres in Freiburg and Strasbourg

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**Objective:** The poisons information centres (PCs) of Freiburg and Strasbourg are rather similar with regard to the geographic and climatic characteristics. Nevertheless the population in the area served by PC Freiburg is 3.5 times larger than that served by PC

**Table 1.** The characteristics of *Vipera* snake bites reported to the Poison Centres of Strasbourg and Freiburg.

	PC Strasbourg	PC Freiburg
Bite of presumably endemic snakes	55	106
Viper identified or suggested by fang marks and symptoms	13	75 (two involved vipers kept at home)
Severity of viper bites	No symptoms 1 (8%) Minor 1 (8%) Moderate 9 (70%) Severe 2 (15%)	No symptoms 5 (7%) Minor 53 (71%) Moderate 13 (17%) Severe 1 (1%) Unknown 3 (4%)
Cases where antivenin was given	10	9 (of 37 cases with follow up information available)
Cases of children presumably bitten by endemic snakes	52%	38%

Strasbourg. We wanted to compare the frequency of calls related to bites by native vipers, the severity of symptoms and the treatment strategies.

**Methods:** Retrospective analysis of the databases of both PCs regarding snake bites between April 2007 and June 2014. Inclusion criteria were human cases of bites by *Vipera aspis* or *Vipera berus*, the only endemic poisonous snakes in France and Germany. The snakes were identified by morphology or by fang marks and characteristic symptoms.

**Results:** See Table 1.

**Conclusion:** Accidents with endemic vipers are relatively rare events in the regions served by the PCs Freiburg and Strasbourg. In relation to the population served, viper bites are more frequent in Freiburg compared to Strasbourg, whereas moderate or severe cases are more frequent in Strasbourg than in Freiburg. In Strasbourg the proportion of pediatric patients with snake bites is higher than in Freiburg. Antivenin is more likely to be given in the area of Strasbourg than in the area of Freiburg.

## 106. Specific issues of the clinical picture and evolution in acute toxic methemoglobinemia in children

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**Objective:** To assess the specific aspects of the clinical picture and evolution in cases with acute toxic methemoglobinemia admitted to a pediatric emergency hospital.

**Methods:** We performed a retrospective study of cases with acute toxic methemoglobinemia admitted in our hospital during a 5 year period (2010 to 2014). The following criteria were taken into

consideration, etiology, age, gender, symptoms and evolution under treatment.

**Results:** Out of the total number of 3,087 poisoned children (aged 0-18 years) admitted to our hospital in the study period, 61 cases (2.0%) were reported with acute toxic methemoglobinemia (13.4% to 86%). The children were aged between 22 days and 16 years. We noted a high incidence in two age groups, children less than 1-year-old (45.9%, n = 28) and children aged 1 to 5 years (42.6%, n = 26). The rate of male patients was slightly higher than female (55.7% versus 44.3%). Well water contaminated with nitrates used in the preparation of food was implicated in the majority of cases (83.6%, n = 51). A new entity was noted; acute severe methemoglobinemia in patients with severe burns treated with topical benzocaine occurred in 9 cases (16.4%). Pentaerythritol tetranitrate poisoning was implicated in 1 case. Generalized cyanosis, chocolate-brown blood obtained from venipuncture and impaired clinical status was noted in all cases. Other clinical signs included acute respiratory failure in all cases with serum methemoglobin above 50% (16.4%), seizures in 2 cases (3.3% with methemoglobin above 70%), vomiting 8 cases (13.1%) and tachycardia 10 patients (16.4%). Methylene blue was administered in all cases. The clinical condition and serum concentration of methemoglobinemia normalized after one dose in 51 children (83.6%). Multiple (two or three) administrations of methylene blue was required in 10 patients (16.4%) with methemoglobinemia above 50%. One death was reported in 6-week-old premature infant who was admitted 12 hours after onset of symptoms.

**Conclusion:** Acute toxic methemoglobinemia is a rare but potentially fatal event in children.<sup>1,2</sup> Acute toxic methemoglobinemia due to topical benzocaine is particularly severe and was reported in children with extensive burns. Methylene blue, the antidote, is very efficient if given in time, sometimes requiring repeated administration.

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## 107. Unintentional medication errors in children under the age of 1 year reported to the National Poisons Information Centre of Ireland

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**Objective:** To characterise the epidemiology of unintentional medication errors in children under 1 year of age, reported to the National Poisons Information Centre (NPIC) of Ireland.

**Methods:** A retrospective observational study of cases reported to the NPIC was conducted from 1 January 2009 to 31 December 2013. The NPIC database was searched for cases of inadvertent medication errors in children aged < 1-year-old. Data on patient demographics, enquiry source, pharmaceutical agents involved, the reasons for the medication error and the treatment recommended were collated.

**Results:** During the 5-year study period, the NPIC received a total of 748 enquiries relating to medication errors in infants less than 1-year-old. Of these cases, 10.16% of infants (n = 76) were aged less than 4-weeks-old. Enquiries originated from members of the public (n = 246, 32.89%), primary care facilities (n = 369, 49.33%), acute hospitals (n = 94, 12.57%), community pharmacists (n = 35, 4.68%), and other sources (n = 4, 0.53%) including paramedical staff and public health nurses. A total of 808 medication exposures occurred; a single medication was involved in 695 cases, 2 separate medications were administered in 50 cases and 3 or more medications were involved in 4 cases. Non-prescription (over-the-counter) pharmaceuticals accounted for 68.32% of cases (n = 552), prescription medications were implicated in 27.72% of cases (n = 224) and non-medication items were administered erroneously instead of a medication in 3.96% of cases (n = 32). The principle classes of medications involved were analgesics and antipyretics (n = 231), vitamins (n = 116), anti-inflammatory and anti-rheumatic agents (n = 115), antibiotics for systemic use (n = 77) and cough and cold preparations (n = 39). Paracetamol (n = 220), ibuprofen (n = 107) and vitamin D (n = 105) were the most common ingredients present in single pharmaceutical formulations. The predominant reasons for the medication errors were wrong dose (n = 396, 52.94%), wrong medication (n = 223, 29.81%), wrong time (n = 21, 2.81%), wrong route (n = 27, 3.61%), dispensing error (n = 16, 2.14%), double dosing by both parents (n = 57, 7.62%) and the medication administered to the wrong child (n = 8, 1.07%). The majority of cases did not require medical treatment (n = 451, 60.29%), 75 cases (10.03%) required oral fluids only, 59 (7.89%) were referred to an emergency department, 26 (3.48%) were referred to a General Practitioner, supportive care was recommended for 61 cases (8.16%), 55 cases (7.35%) were advised to seek medical advice if symptoms developed and other advice was provided for 21 cases (2.8%).

**Conclusion:** The majority of medication errors in children < 1 year of age involved non-prescription medication and dosing errors were prevalent.

## 108. Self-poisoning in the elderly: A 10-year observational study

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**Objective:** Deliberate self-harm in older people is more likely to result in completed suicide compared to a younger population. Contributing factors are complex, including social isolation and greater susceptibility to poisoning due to co-morbidity and frailty. Drug ingestion patterns vary between age groups, reflecting prescribing practice; older patients were more likely to ingest tricyclic antidepressants and cardiovascular drugs and less likely to ingest selective serotonin reuptake inhibitors or recreational drugs.<sup>1</sup> We studied all patients over 65 years admitted between 2003 and 2013 to our regional toxicology unit with self-poisoning, to characterise the group and compare outcome with their younger counterparts.

**Method:** All patients 65 years or greater presenting to the Royal Infirmary of Edinburgh (RIE) with intentional self-poisoning (2003-2013) were included. A control cohort of younger patients (less than 45 years old) with intentional self-poisoning, were matched to the study group by admission date.

**Table 1.** Destination at discharge from acute medical services following episode of self-poisoning (\* $p < 0.05$  versus younger population).

Outcome	Older population (n, %)	Younger population (n, %)
Home	285 (74.80%)*	342 (89.76%)
Inpatient psychiatry	86 (22.57%)*	39 (10.23%)
Died	10 (2.62%)*	0 (0%)

**Results:** In the study period 629 patients aged 65 years or greater presented to the RIE with self-poisoning. This included 480 intentional acts (76.3%) but 99 episodes were excluded as repeat presentations leaving a study group of 381. Older patients admitted with intentional self-poisoning had a longer length of hospital admission (mean days  $\pm$  SD:  $4.10 \pm 9.50$  versus  $0.76 \pm 0.84$ ,  $p < 0.05$ ) and greater co-morbidities ( $1.58 \pm 1.14$  versus  $0.27 \pm 0.57$ ,  $p < 0.05$ ) than their younger counterparts. Older patients also demonstrate a higher incidence of transfer to inpatient psychiatry services (Table 1).

**Conclusion:** Older patients presenting with self-poisoning have a longer length of hospital stay and a greater burden of co-morbidity, which may be a contributing factor. A higher referral rate to inpatient psychiatry services is also evident. This suggests an increased severity of psychological illness and a need for targeted outpatient psychiatric support in this vulnerable population.

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## 109. Analysis of enquiries about antiretroviral therapy (ART) involving neonates, as reported to the UK National Poisons Information Service (NPIS)

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**Objective:** In 2012, of 675,800 pregnant women screened in England, 1,310 (0.19%) were HIV positive. Of all children born to HIV-infected women in the UK between 2005 and 2011, an estimated 2% became infected with HIV, although the transmission rate of HIV among children born to women with diagnosed HIV infection was under 1%.<sup>1</sup> In order to prevent vertical transmission, neonates born to HIV-positive mothers should be given post-exposure prophylaxis with zidovudine. Combination antiretroviral therapy should be given to neonates whose mothers have a high viral load or undiagnosed infection at delivery. Prophylaxis is continued for 4 weeks<sup>2</sup> and drug regimens may be complex. This study assessed the features of toxicity of antiretroviral agents in children under 1 year, as reported to the NPIS.

**Methods:** NPIS telephone enquiry records involving ART exposure in children under 1 year of age were reviewed for the period February 2004 to July 2014, analysing the circumstances of poisoning and reported features of toxicity.

**Results:** Of 557 enquiries relating to ART in all age groups, 49 cases related to children less than 1 year of age and 38 of these to neonates less than 1-week-old. Most enquiries arose from accidental exposures/therapeutic errors, with incorrect dosing frequency a common scenario. Exposures took place outside hospital in five cases. The most common agents involved were zidovudine ( $n = 36$ ), with 10-fold overdosing frequent ( $n = 16$ ) and clinical features reported in four exposed neonates (vomiting, loose stools, jitteriness, minor ALT activity rise to 53 IU/L), nevirapine ( $n = 9$ , all patients asymptomatic) and lamivudine ( $n = 2$ , one child with hyperkalaemia and one asymptomatic). One child may have been intentionally administered unknown quantities of Atripla® (Efavirenz, emtricitabine and tenofovir) and other drugs but remained well. A 6-month-old child accidentally took a ritonavir 100 mg tablet belonging to their mother and remained well.

**Conclusion:** Young children are at risk of medication errors involving ART, especially 10-fold dosing errors for zidovudine, possibly due to the small volumes of solution involved. Adverse clinical consequences were uncommon. Measures to reduce medication errors within and outside hospital, including clear advice on drug dosing, are required.

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## 110. Paracetamol toxicity in an extremely preterm neonate after an inadvertent intravenous overdose: A case report

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**Objective:** To describe a paracetamol overdose in an extremely preterm infant, born H23 + 6/580 g.

**Case report:** A 4-day-old prematurely born girl (H24 + 3, weight 585 g) required treatment in a neonatal intensive care unit (NICU) including mechanical ventilation after early surfactant, and total parenteral nutrition with minifeeding. Blood pressure, ECG, oxygen saturation and temperature were constantly monitored. As part of the NICU routine, IV paracetamol was prescribed 8.5 mg (14.5 mg/kg) 3 times daily. The first dose was given correctly, but the second dose was mistakenly administered too early leading to a cumulative dose of 29.1 mg/kg (17 mg) within 3 hours. After the error was noted, the serum paracetamol concentration



was monitored. The concentration at 0.5, 4, 7.67, 14, 31 and 38 hours was 338, 286, 237, 180, 17, and < 15  $\mu\text{mol/L}$ . The slow elimination of paracetamol (estimated half-life 14.8 hours) suggested that concentrations considered hepatotoxic were to be reached. Lacking reliable information of the risk of hepatotoxicity in this age group, N-acetylcysteine (NAC) was initiated 15 hours after the second paracetamol dose. A loading dose of 150 mg/kg IV (in 30 minutes), followed by 50 mg/kg in 4 hours and 100 mg/kg in 16 hours were administered. No adverse events were observed, until 5 hours after the onset of NAC, hypotension (mean arterial pressure below 24 mmHg), acidosis (pH 7.02; base excess -14.7) and increased oxygen requirement (from 30% up to 80%) were noted. These were corrected by vasopressor-inotropes (dopamine and dobutamine) and high-frequency ventilation. Concurrently, a misplaced intubation tube had to be corrected with subsequent correction of hypoxia and acidosis. No elevation of thromboplastin time, INR, ALT, gamma-GT, or other signs of liver toxicity were observed. The baby recovered fully.

**Conclusion:** Pharmacokinetics of paracetamol have not been studied in extremely premature newborns, and it is not known, whether production of the hepatotoxic N-acetyl-p-benzoquinoneimine (NAPQI) metabolite or its detoxification in extreme premature newborns is different from other age groups. The hypotension observed may have been an adverse effect of NAC, but could also be explained by the intubation complication with hypoxia, or the basic problems of prematurity, which required treatment at the NICU in the first place. A modest paracetamol overdose in an extremely premature newborn treated with NAC did not lead to signs of liver toxicity. NAC treatment was tolerated, but it is unclear if it contributed to hypotension that was, however, managed with standard treatment.

### 111. Child poisonings with methadone in France: A 6-year prospective national survey since the availability of capsules in 2008

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**Objective:** Before 2008, methadone used in France for opiate substitution was only available as syrup. In 2007 the French Health Authorities permitted the availability of solid forms. A national survey was performed in order to evaluate the modification of child poisonings induced by such a new pharmaceutical form.

**Methods:** A prospective study was set up (15 April 2008 to 15 April 2014) with the analysis of cases of ingestion of methadone by patients under 18 years.

**Results:** In total 87 cases of child poisonings with the 2 forms were reviewed (syrup 56 patients, capsules 31 patients). The patients were similar for both forms (no significant difference concerning age [median 2 years], sex ratio [M/F 0.85], previous history and ingested methadone quantities). There was a similar severity profile with both forms showing that methadone can lead to lethal paediatric poisoning (1 death with capsule, 4 with syrup). The relative risk of paediatric accidents was also the same

with the 2 forms, leading the health authorities, in collaboration with the laboratories, to design and distribute flyers. The aim was to inform patients who are also parents about the high dangers for children of their treatment, whatever the form of methadone present in the home. The study of the circumstances of child methadone poisonings before and after the distribution of the flyers showed that it was efficient for the population treated with capsules (e.g. better informed parents, immediate and adequate reaction in case of child ingestion, faster medical care during the second part of the survey), but surprisingly not for the population treated with syrup.

**Conclusion:** The results of this survey were similar to those of another national study by the French Poison Centres about adult suicide attempts with methadone.<sup>1</sup> Both prospective studies concluded that methadone must be considered as a dangerous drug for patients and their families. The recent availability of a solid form in France did not change the profile of poisonings in children with this opiate substitution treatment.

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### 112. Cluster of naphazoline and phenylephrine intoxications in children due to a compounding pharmacy error

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**Objective:** We present 7 cases of intoxication after inadvertent use of a naphazoline and phenylephrine preparation for the reconstitution of oral antibiotic solutions.

**Case series:** By mistake, a pharmacist used a self-prepared nasal decongestant solution (naphazoline 1 mg/ml, phenylephrine 2.5 mg/ml, chlorbutol, eucalyptol, menthol, niaouli oil, sodium EDTA, glycerin, propylene glycol) as a diluent to reconstitute 7 individual antibiotic suspensions. He contacted the parents as soon as he discovered the mistake. Six children presented on the same day for medical assessment at the emergency unit of a local hospital. The Belgian Poison Centre received the hospitalisation reports for 6 children and limited information for the seventh case. They received between 2 to 12 doses (4–5 ml). Ages ranged from 16 months to 12 years of age. Patient characteristics, number and volume of doses received, total quantity of naphazoline and phenylephrine, symptoms and duration of medical observation are summarized in Table 1. Bradycardia, pallor and somnolence were the most frequent symptoms. An 8-year-old boy (case 2) who ingested 55 mg naphazoline and 137.5 mg phenylephrine over a 3–4 days period (11 doses) and his older sister (case 7) both presented with headache and photophobia. He was kept under medical observation for 5 days. In the other documented cases, all symptoms resolved within 24 hours. All the children recovered.

**Conclusion:** Intoxication with naphazoline may occur after oral intake of 0.1 mg/kg in infants (0.3 mg/kg over 2 years of age; 0.05 mg/kg by intranasal route). The 3 younger children were repeatedly exposed to doses 4 fold higher than the estimated

**Table 1.** Patient characteristics, number and volume of doses received and symptoms and duration after accidental exposure to naphazoline and phenylephrine following a compounding error.

	1	2	3	4	5	6	7	Total (by symptoms)
Sex	M	M	F	M	M	M	F	–
Age	19 m	8 y	16 m	6 y	1 y	12 y	≥9 y	–
Weight	13	41	11	?	10	44	?	–
Number of doses	2	11	8	10	4	12	?	–
Volume (ml)	5	5	5	5	4	5	?	–
Naphazoline (total, mg)	10	55	40	50	16	60	?	–
Naphazoline mg/kg/dose	0.4	0.1	0.5	?	0.4	0.1	?	–
Phenylephrine (total, mg)	25	138	100	125	40	150	?	–
Bradycardia	1	1	1	1	–	1	1	6
Pallor	–	1	1	1	1	1	1	6
Somnolence	1	–	1	1	1	1	–	5
Vomiting	–	1	1	–	–	1	–	3
Diaphoresis	1	–	–	–	–	1	–	2
Headache	–	1	–	–	–	–	1	2
Photophobia	–	1	–	–	–	–	1	2
Ataxia	–	–	1	–	–	–	–	1
Duration (days)	1	5	1	1	1	1	?	–

toxic dose (0.1 mg/kg). Unexpectedly, they only developed mild symptoms.

## Reference

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### 113. Long-term effects of vitamin D poisoning in children

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**Objective:** Mass poisoning with vitamin D were recorded in Russia in late 1990s, which were related to household use of vegetable oil enriched with vitamin D that was designed for application in agriculture. There is a considerable amount of information in the literature about the clinical signs of this disease at the acute stage and about the remedial methods, but we have encountered virtually no data about long-term consequences of this illness. So the research task was to conduct a retrospective analysis of clinical, laboratory and instrumental data obtained when following up the affected children 5 years later.

**Methods:** A total of 25 children aged 4-14 years with vitamin D poisoning were followed up. For all children, the concentration of calcium in blood serum and urine was measured. Routine

urine tests and biochemical parameters of blood were studied and ultrasonic study of kidneys and radiography were undertaken. The blood concentration of vitamin D was measured by a high-efficient liquid chromatography method.

**Results:** The vitamin D blood concentration was 96-360 ng/mL (normal 20-50 ng/mL). The calcium blood serum concentration was 3-4.5 mmol/L (normal 2.2-2.7 mmol/L). This was accompanied by asthenic syndrome, anorexia, nausea and vomiting, spine and bone pains and polyuria, daily loss of protein up to 0.20 g, leucocyturia, erythrocyturia, and sustained isosthenuria and elevated creatinine and urea blood concentrations. At ultrasonic examination, thinning of the cortex layer of the kidneys and consolidation of the collecting system were observed. On the ECG, prolongation of QRS, length of T wave and prolongation of P-Q interval were visible. Bradycardia was reported in 40% patients. During a year and more, hypercalcaemia (2.7-3.1 mmol/L) and hypercalciuria were noted. Radiography signs of washing of calcium out of diaphysis and its intensive depositing in epiphysis of tubular bones were detected. Ultrasonic study of the kidneys revealed the development of nephrocalcinosis. During the 5-year period, laboratory data showed restoration of the concentration function of kidneys; however, glomerular filtration remained at a decreased level for a long time. Currently, kidney function is undamaged in 15 patients, but metabolic nephropathy together with oxaluria 30-46 mg/day (versus the normal 1 mg/day) is still reported in 5 patients without a change in their general condition and without complaints.

**Conclusion:** A gradual improvement of the renal function in the affected children was shown. However, due to the risk of unfavorable somatic dysfunctions, this category of patients should remain under medical supervision for a long time.

### 114. Methemoglobinemia due to dapson in a child: Follow up after therapeutic intervention using non-invasive pulse co-oximeter

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**Objective:** To present a clinical case of methemoglobinemia in a child monitored with non-invasive pulse co-oximeter after therapeutic intervention, until normalization of methemoglobin (MeHb) concentrations.

**Case report:** An 18-month-old girl accidentally ingested 7 pills of dapson 100 mg regularly used by her grandmother. Two hours after the ingestion the girl she was agitated with “blue” lips. Taken to an emergency department (ED) nearby, our poison center was called, and we asked for the child to be transferred to our ED. A blood sample was analyzed for MeHb using a bench co-oximeter and the result showed MeHb 36.9%. At the time the child was agitated and moaning, and the main clinical features were nausea, tachypnea (66 breaths/minute) and tachycardia (153 bpm). Considering the MeHb concentration, and the clinical features, a single dose of 1.2 mL (0.1 mL/kg) of methylthioninium chloride (methylene blue) was given IV. After 2 hours the MeHb level dropped to 8.2%, and increased again to 27.8% 4 hours later. No more methylene blue was given. Dapson has a very long half-life due to its enterohepatic recirculation, and a multiple dose activated charcoal (MDAC)

regimen every 6 hours was instituted over a period of 42 hours. During that follow up period, instead of drawing blood samples for MeHb analysis, a pulse co-oximeter (Rad-57 CO-Oximeter) was used to monitor the rate of decrease of the MeHb concentration. For the whole period pulse measurements were performed regularly showing an average rate of decrease of 0.68% each hour. The child was discharged with a MeHb concentration of 2.6%. A checking analysis using the bench co-oximeter, at 35 hours of the follow up, showed a result of 3.4% against a 3.3% result from the pulse co-oximeter. Method validation studies have already shown a good correlation between the two methods.<sup>1</sup>

**Conclusion:** In the management of methemoglobinemia in children, monitoring of MeHb concentrations during treatment and follow up, can be safely and accurately done using a pulse co-oximeter. Our results also show the efficacy and usefulness of MDAC during dapsone methemoglobinemia therapeutic management.<sup>2</sup>

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## 115. Chronic ayurvedic medicine use in pregnancy associated with fetal abnormalities

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**Objectives:** Although there are potential associations between lead exposure during pregnancy and adverse pregnancy outcomes, there is limited data to whether *in utero* lead exposure is associated with major congenital abnormalities. We describe a case of major congenital abnormalities associated with maternal chronic lead ingestion throughout pregnancy.

**Case report:** A 28-year-old primigravida female was referred to a maternal-fetal specialist obstetrician because a fetal ultrasound at 20 weeks showed anhydramnios, absence of one kidney and agenesis of the other. She had a history of lethargy throughout her pregnancy. She had normocytic anaemia with a haemoglobin of 95 g/L at 24 weeks and 88 g/L at 30 weeks gestation; with a normal white cell count and platelets. Liver and renal function, vitamin B12, folate and ferritin were within normal limits. A blood film performed at 30 weeks gestation showed basophilic stippling. The blood lead level (BLL) was 67 mcg/dL (3.2 mcmol/L) at 30 weeks. The toxicology unit was consulted and chelation with oral succimer was commenced (10 mg/kg three-times daily for 5 days followed by 10 mg/kg twice-daily for 14 days). Three weeks after chelation her BLL was 14.4 mcg/dL (0.7 mcmol/L). The patient had been taking an Ayurvedic medicine prescribed by a practitioner in India and had purchased sufficient stock to self-import this to Australia. She had been taking two tablets a day for the previous

six months. Analysis of the tablets showed a lead content of 47%; small amounts of mercury (1.7%) and arsenic (<0.01%) were also detected but urine arsenic and mercury concentrations were within normal limits. No other sources of lead were found. Three days prior to an elective caesarian section at 39 weeks she received IV calcium disodium edetate 40 mg twice-daily to decrease her lead concentrations prior to delivery. She gave birth to a baby with pulmonary hypoplasia, a pneumothorax and minimal kidney tissue. The cord blood lead concentration at delivery was 8.0 microg/dL (0.37 mcmol/L). Unfortunately, the baby died 2 days later from respiratory failure. Three weeks postpartum the mother's BLL was 17.3 microg/dL (0.8 mcmol/L).

**Conclusion:** This case suggests that maternal lead toxicity during pregnancy may be associated with major congenital abnormalities.

## 116. Poisoning exposures in infants: Data from the Tygerberg Poison Information Centre, Cape Town, South Africa

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**Objective:** To describe the characteristics of acute poisoning exposures in infants (0-1 year) presenting to the Tygerberg Poison Information Centre, Cape Town, South Africa.

**Methods:** A 3-year retrospective study (2011-2013) was conducted based on Tygerberg Poison Information Centre's consultations. Data about the infant's demographics and causes of poisoning were collected and analysed.

**Results:** During the study period Tygerberg Poison Information Centre processed a total of 17,434 consultations. Of these 1,101 (6.3%) cases involved infants of which 46 cases (0.3%) were neonates. Of the calls related to infants, 661 (60%) were made by health care professionals (public and private sector) with 429 (39%) of calls coming from family members (unknown n = 11, 1%). Most poisonings were accidental, except 9 cases (0.8%) where there were a clear intention to harm the infant. Exposures were categorized into pharmaceutical agents (n = 168, 15.3%), non-drug chemicals (n = 824, 74.8%) and biological agents (n = 113, 10.3%) (4 infants took a combination of drugs). Analgesics (n = 49, 29.2%) were the commonest drug involved of which 23 (46.9%) cases related to paracetamol. In the non-drug chemical exposures, pesticides were most frequently involved (n = 184, 22.3%); rodenticides accounted for 56 (30.4%) of these exposures. Of the rodenticides 16 (28.6%) were related to aldicarb and 40 (71.4%) to anticoagulant rodenticides. Ninety four (11.4%) cases relating to non-drug chemicals were categorised as low or minor toxicity substances; 52 (55.3%) of these cases involved silica gel. From the total of 113 biological exposures, plants and mushrooms were responsible for 80 (70.8%) exposures. Most infants (n = 987, 90%) presented with no or minor symptoms, while no deaths were reported. Sub-analysis of the neonatal group indicated that 17 (37%) presented with symptoms of moderate to severe toxicity and 6 (35%) were exposed to complementary and alternative medicines.



**Conclusion:** Less than 7% of all cases related to infants. Aldicarb is commonly used in developing countries as an illegal rodenticide, but our study had more infants exposed to commercial anticoagulant rodenticides. Complementary and alternative medicines can be potentially toxic, though parents often believe that they are safe. Neonates are at increased risk as a result of their small size and differences in pharmacokinetics; it is thus important to monitor the safe use of these medicines in neonates. The detection of intentional poisoning is worrying as this is a rare phenomenon. Socioeconomic factors might play a role and require further investigation.

### 117. Cardiac ischemia and rhabdomyolysis associated with 2,4-dinitrophenol misuse for weight loss and body building in a pediatric patient

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**Objective:** 2,4-Dinitrophenol (2,4-DNP) uncouples oxidative phosphorylation and may be used as a dietary supplement aid for weight loss and body building. We report a case of severe toxicity in a pediatric patient resulting in cardiac ischemia and rhabdomyolysis.

**Case report:** A 15-year-old male presented to the Emergency Department (ED) complaining of nausea, vomiting, sweating and decreased urine output for 24 hours. He was alert and vital signs (VS) were HR 137, BP 92/60 mmHg, respiration rate 36 and T 38.8°C. The patient was restless with diaphoresis and mydriatic reactive pupils of 4-5 mm. Physical examination was otherwise unremarkable. Initial ECG showed sinus tachycardia, QRS 86 ms, QTc 559 ms, with diffuse ST depressions in all leads, most notably > 1 mm depression in V3, V4, V5, and an inverted T-wave in aVL. Laboratory values included a WBC 8,700/microliter, hemoglobin 16.5 gm/dL, hematocrit 46.7%, platelets 39,000/microliter, anion gap 15 mmol/L, BUN 15 mmol/L, creatinine 1.31 mg/dL, creatine kinase (CK) 304 U/L and thyroid stimulating hormone (TSH) 1.01 mU/L. Serum/urine toxicology was negative for salicylates and drugs of abuse, including amphetamines and cocaine. Acetaminophen orally and piperacillin-tazobactam IV were given for fever and possible sepsis in addition to 5 L of IV 0.9% saline. Repeat VS were HR 120, BP 110/60 mmHg, respiration rate 36 and T 38.8°C. He was admitted to the ICU. The patient subsequently admitted to taking approximately 40 x 250 mg capsules of 2,4-DNP intermittently in 1 g doses over the previous 30 days for weight loss and body building and tolerated it well; however, 24 hrs before presentation he took 500 mg every 6 hours for 3 doses (1.5 g) and became acutely symptomatic. He confirmed the DNP capsule by photograph. Fluid resuscitation totaled 8.85 liters of saline in the first 24 hours. His serum CK peaked at 9520 U/L, and troponin-I at 0.85 ng/mL; consistent with rhabdomyolysis and demand myocardial ischemia. His ECG, laboratory values and VS normalized over 4 days and he was discharged without sequelae.

**Conclusion:** This pediatric patient manifested hyperthermia, hypotension, QTc prolongation, rhabdomyolysis and cardiac ischemia associated with 2,4-DNP misuse. Previous reports have shown that metabolic acidosis, seizures, muscle rigidity, pulmonary edema, cerebral edema, hepatic injury, ventricular arrhythmias and

death may occur. The cardiac effects and rhabdomyolysis appear to be unique in this pediatric case.

### 118. Levetiracetam intoxication in a preterm infant due to a medication error

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**Objective:** To describe a levetiracetam overdose in a preterm infant.

**Case report:** A 37-day-old neonate (born very preterm H28 + 5/1045 g, Apgar 9/9/9) received erroneously 1 ml of 100 mg/ml levetiracetam oral solution in hospital (another patient's medicine). The dose of 100 mg (56 mg/kg in a 1780 g infant) was 5.6 times the maximum therapeutic dose recommended. The medicine was given after feeding 40 ml milk. The patient's own medication was caffeine solution 5 mg/kg for apnoea prevention. The medication error was noticed 60 minutes later and a nasogastric tube was placed and gastric contents were aspirated from the tube yielding 20 ml of milky fluid. The stomach was also rinsed with 30 ml of water. Activated charcoal was not given due to risk of aspiration. At 2.5 hours after administration the oxygen saturation decreased to 60% and heart rate decreased to 50 bpm. The baby needed assisted ventilation and the breathing was supported with nasal continuous positive airway pressure (CPAP) for 2 minutes, until spontaneous breathing recovered. Due to risk of apnoea attacks, the infant was transferred for intensified monitoring. Physical examination revealed drowsiness, lethargy and non-responsiveness for 4 hours. No other neurological symptoms were observed. Apnoea attacks lasted for 3-4 hours, and 5-6 hours after the medication error the patient was eating normally and recovered. The serum levetiracetam concentration 3 hours after ingestion was 18 mg/L. The glutamyltransferase (GT) was slightly increased (81 u/L); the baby also had anaemia (Hb 98 g/L) due to blood sampling and erythrocytes were administered. By 24 hours after ingestion, the patient was asymptomatic and intensified monitoring was ceased. At 3 months follow-up no abnormalities were found, except minor asymmetry in following objects. At six months follow-up this asymmetry had been resolved, and the patient had grown and developed normally.

**Conclusion:** Administration of 5.6 times the maximum therapeutic dose of levetiracetam caused moderate poisoning in a preterm infant.

### 119. Effects on the neonate of maternal abuse of drugs during pregnancy

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**Objective:** The abuse of drugs during pregnancy has potential deleterious effects on the fetus and the neonate. A large number of studies have shown late effects in the mental development with

behavioral consequences, learning performance and other neurological long-term effects. This has mainly been described in cocaine abusers.<sup>1,2</sup> To prevent these effects a strategy of pregnancy control has been recommended. One of the main indicators of maternal drug abuse is the neonatal withdrawal syndrome. The aim of this study is to describe the neonatal evolution of the newborn from drug abuse mothers attending our neonatology service.

**Methods:** A retrospective study from the last 10 years of the clinical files of newborns of drug abuse mothers to analyze the neonate's characteristics and morbidity during the neonatal period. The inclusion criterion was a neonate with a positive urinary drug screen test.

**Results:** From 43 mothers with drug abuse habits studied during this period (0.16% of total attended mothers), the newborn urine analysis was positive for drugs in 33 cases (76.5%) including 19 males (57.6%) and 14 females (42.4%). Gestational age was  $36.6 \pm 3.5$  weeks, lower compared with a normal period ( $39.2 \pm 1.3$  weeks). Fetal weight was  $2507 \pm 634$  g, lower than the medium normal weight ( $3250 \pm 300$  g). The drugs used by the mothers during pregnancy were opioids (heroin, morphine and methadone, 48.5%,  $n = 16$ ), cocaine (45.5%,  $n = 15$ ) and cannabis (27.3%,  $n = 9$ ). In 24% of cases more than one substance was used and half of the total cases were associated with cigarette smoking. Of the 33 total cases 16 (48.5%) presented a clinical picture of withdrawal syndrome during the first days. All but 2 neonates had scores in the Finnegan modified scale equal or over 8 requiring sedative treatment with phenobarbital and support measures, and one neonate had seizures. The withdrawal syndrome duration was  $16 \pm 9$  days.

**Conclusion:** Newborns of drug abuse mothers are more prone to prematurity and a lower weight at birth. Nearly 50% of them presented a clinical picture of withdrawal syndrome in the neonatal period requiring pharmacological treatment and support measures.

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## 120. Head injury or intoxication? Unidentified eye drop ingestion resulting in naphazoline toxicity in a toddler

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**Objective:** Over the counter (OTC) eye-drops and nasal sprays containing imidazoline vasoconstrictors can cause clonidine-like toxicity when ingested. These are often sold without child-resistant caps. We describe a toddler with, initially unrecognised, naphazoline intoxication after ingestion of OTC eye-drops.

**Case report:** A healthy 2-year-old, 14 kg, female presented to a regional emergency department (ED) with drowsiness. Prior to

presentation, she had an unwitnessed fall without head-strike or loss of consciousness. Twenty minutes later, she fell asleep. On rousing, she was pale, lethargic and drowsy with an unsteady gait. In the ED, her Glasgow Coma Scale (GCS) fell to 3 and she was urgently transferred to our tertiary paediatric ED with suspected head injury. En route, her conscious state fluctuated between drowsiness and agitation. On arrival to our ED, GCS was 6 and she was intubated. Vital signs showed a fluctuating heart rate (45-140/min) and BP (75/- to 200/- mmHg) and hypothermia (34.8°C). Intracranial injury was suspected but cerebral magnetic resonance imaging (MRI) was normal. Empiric treatment with IV antibiotics was commenced for suspected meningoencephalitis. Three hours later she self-extubated in the PICU but remained drowsy for several more hours. During this period, pulse ranged from 75-120/min with BP 90/40. Further questioning of her parents revealed that 4 hours before presentation, she was playing with a full 15 ml bottle of eye-drops containing naphazoline hydrochloride 0.25 mg/mL and pheniramine maleate 3 mg/mL (Naphcon®). Suspected naphazoline intoxication was identified at this point. She made a full recovery over the next 24 hours.

**Conclusion:** Naphazoline and other imidazoline agents, applied topically, produce peripheral alpha<sub>1</sub>-sympathomimetic vasoconstriction. The typical volume of nasal/ophthalmic products is 15-30 mL. Ingestion of as little as 3 mL can cause toxicity mimicking clonidine intoxication in toddlers. Initial peripheral alpha<sub>1</sub>-sympathomimetic stimulation leads to transient hypertension. Subsequent central nervous alpha<sub>2</sub>-sympathomimetic stimulation causes miosis, drowsiness/coma, hypothermia, bradycardia, hypotension and respiratory depression. Intoxication with naphazoline can occur with ingestion of less than 0.05 mg/kg (0.7 mg or 3 mL in this child). Management is supportive. In this case, lack of history of ingestion resulted in investigation of suspected closed-head injury and treatment for CNS infection. In cases of sudden unexplained coma in toddlers, associated with bradycardia and alternating hypo/hypertension, exposure to imidazoline decongestants and clonidine should be considered in the differential diagnosis.

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## 121. Acute poisoning in patients with mental disorders

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**Objective:** To present the results of an assessment of actual psychiatric characteristics of persons with acute poisoning in our toxicological department over a one year period.

**Methods:** The study includes 257 patients with acute exogenous intoxication, hospitalized in the Toxicology Clinic, Emergency University Hospital Pirogov, Sofia, Bulgaria for the period 1 January 2013 to 31 December 2013. The demographic features, circumstances, symptomatology, and psychiatric state were analyzed. Each patient was assessed by a consultant psychiatrist, performing

a psychiatric interview, leading to a diagnosis according to DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders IV Text Revision) criteria and responsible for treatment. Various psychological tests including the Pierce Suicide Intent Scale, Hamilton Rating Scale for Depression and Mini Mental State Examination were applied.

**Results:** In total 257 patients between the ages of 18 and 90 with acute poisoning were included; 86 (33.46%) were male and 171 (66.54%) female. Of these, 112 (43.58%) involved a single agent and 145 (56.42%) were combined intoxications, with two or more medicines, alcohol, etc. Intentional poisoning as a result of a suicide attempt occurred in 186 cases (72.37%) whereas 71 (27.63%) were due to an accident. Past suicidal behaviour was reported in 12 (6.45%) subjects. Medicines were the leading cause of self-poisoning and 178 patients (69.3%) had taken various medicines; 92 (35.8%) were intoxicated by hypnotics, neuroleptics, antiepileptics, antidepressants and 44 (17.12%) by cardiovascular medicines. Other medicines (n = 42, 16.34%) included NSAIDs, antihyperglycaemics, antibiotics, etc. Domestic products and pesticides were taken in 20 patients (7.78%), alcohol in 44 (17.12%) and psychoactive substances in 15 (5.83%). The most important motives for suicide attempt were severe physical illness, conflicts with parents or spouse, separation problems and loneliness. A psychiatric history was known in 104 (55.91%) patients who attempted suicide. Other diagnoses were major depressive disorder, recurrent in 10 subjects (5.38%), major depressive disorder, single episode in 28 (15.05%), bipolar disorders in 19 (19.21%), anxiety disorders in 22 (11.83%) and schizophrenia in 25 (13.44%). Alcohol dependence was registered in 38 subjects (14.79%), alcohol withdrawal delirium in 4 (1.55%), other substance-related disorder in 15 (5.84%), personality disorders in 2 (0.78%) and cognitive disorders in 12 (4.67%).

**Conclusion:** A significant quantity of poisoned patients have mental disorders. Patients should be offered interventions according to their specific problems.

## 122. Toxic coma in children and related mortality: A retrospective study of 9 years in a Pediatric Emergency Department

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**Objective:** To study the prevalence of coma and mortality due to acute poisoning in children.

**Methods:** We analyzed all the pediatric cases with coma that presented to the Emergency Department and were admitted to ICU and the Toxicology Department in our hospital during a 9 year period (2003 to 2011). We studied all cases of toxic coma using the following criteria: etiology, depth of coma, type of poisoning and distribution by age, gender and intention.

**Results:** In the 9 year study period there were 5,761 cases of acute poisoning in children in our hospital; 750 with coma (Table 1). Of these, 445 cases were due to toxicity (59.3%) and 305 were due to non-toxic causes (40.7%). In 294 toxic coma cases (66.1%) exposure was voluntary and in 149 cases (33.5%) exposure was accidental; in 2 cases (0.4%) the etiology was not determined. The mean age of patients with toxic coma in the study group was 10.9 years. Of the children with toxic coma 23 died (5%); 19 deaths

**Table 1.** Children with poisoning and coma over a 8 year period in a pediatric emergency department, Romania.

Year	Cases of poisoning	Cases with toxic coma	% Toxic coma	Deaths in children with toxic coma	% Deaths from toxic coma
2003	663	20	3.01%	2	10.0%
2004	615	42	6.82%	3	7.14%
2005	529	32	6.04%	3	9.37%
2006	570	37	6.49%	5	13.5%
2007	518	45	8.68%	1	2.22%
2008	634	58	9.10%	2	3.44%
2009	726	62	8.50%	2	3.22%
2010	718	71	9.80%	3	4.22%
2011	788	78	9.89%	2	2.56%
Total	5761	445	7.72%	23 (0.39%)	5.16%

(82.6%) were due to non-pharmaceutical toxicants and involved organophosphorus insecticides (diazinon, n = 7), carbamates (carbofuran, n = 2), caustic substances (n = 6), mushrooms (n = 2), hydrocarbons (n = 1) and carbon monoxide (n = 1). There were 3 drug related deaths from antidepressants (carbamazepine, n = 1), drugs of abuse (heroin, n = 1) and Dentocalmin (lidocaine/menthol/phenol, n = 1). The etiology was unknown in 1 case.

**Conclusion:** Despite low prevalence, mortality associated with acute poisoning in children is one of the leading causes of accidental death in childhood (0.39%). Non-pharmaceutical toxicants are the leading cause of death by poisoning in children.

## 123. Accidental hashish ingestion in children: A Pavia Poison Centre case series

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**Objective:** Hashish is made from the resin of the flowering tops of the *Cannabis sativa* and contains a considerable higher tetrahydrocannabinol (THC) content than does marijuana (13-20%).<sup>1</sup> Accidental ingestion of small pieces of this substance may cause severe cardiac and neurological effects in pediatric patients; however data concerning pediatric accidental exposure is lacking. The aim of the study is to evaluate toxic effects of accidental ingestion of hashish in a pediatric cases series.

**Methods:** Retrospective analysis of selected pediatric patients (age 0-5) referred to Pavia Poison Centre (PPC) from January 2007 to November 2014 for accidental ingestion of hashish was performed. Patients were assessed for clinical manifestations, toxicological investigations and outcome.

**Results:** Ten cases were included (mean age 2.5 years; 50% male). Eight patients (80%) presented toxic effects whereas 2/10 (20%) did not develop signs of poisoning. Among symptomatic patients, clinical manifestations developed after about 2 hours after ingestion. Seven children (87%) presented stupor, drowsiness, muscular hypotonia, and 2 patients also manifested tachycardia, psychomotor agitation, inconsolable crying and mydriasis. Among these seven cases, all received activated charcoal and one was also given a gastric lavage. Benzodiazepines were administered to treat psychomotor agitation. Clinical manifestations completely resolved



within 24 hours in all patients. One patient (13%) presented coma and required oro-tracheal intubation for 2 days with mild sedation with midazolam, gastric lavage and activated charcoal. A urinary qualitative test was positive for tetrahydrocannabinol (THC) in all symptomatic cases and negative in asymptomatic patients. Quantitative measurement was performed in one case and showed THC concentrations above 200 ng/mL. In one symptomatic case, gastric content was obtained and the presence of THC was confirmed. All patients were discharged asymptomatic within 24-48 hours from hospital admission, except the comatose patient.

**Conclusion:** Our case series emphasizes the need for a greater awareness of the potential poisoning due to accidental hashish ingestion. Clinicians should be aware of the possibility that significant cannabinoid ingestion in children is capable of causing prolonged coma.

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## 124. Accidental ingestion of Portion snus may cause delayed onset of symptoms

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**Objective:** Portion snus is a tobacco product commonly used in Norway and Sweden. Information about accidental ingestion by children is limited in the literature. There is a suspicion that ingestion of this packed form of tobacco causes a delayed onset of symptoms compared to other tobacco products (OTP) which include cigarettes, loose snus, chewing tobacco and regular tobacco. Accidental ingestion of tobacco products by children rarely merits medical attention, but more information is needed.

**Methods:** A call back survey involving 276 exposures to nicotine containing products reported to the National Poisons Information Centre was performed. Data was collected about the time of onset and duration of symptoms.

**Results:** Of the 276 cases reported, 170 involved children (< 5 years) who had ingested or tasted a nicotine product. Of these, 19 exposures were excluded due to ingestion of nicotine-containing pharmaceuticals. The onset of symptoms was > 1 hour for 16.7% of the exposures to Portion snus compared to 6.6% of the exposures to other tobacco products (Table 1). In 8.9%

**Table 1.** Onset and duration of symptoms after exposure to Portion snus compared to other tobacco products (OTP).

	Onset of symptoms		Duration of symptoms		
	Portion snus	Other tobacco products	Portion snus	Other tobacco products	
No symptoms	34	33	No symptoms	34	33
0-1 h	40	22	0-2 h	47	26
1-3 h	11	2	2-4 h	5	-
> 3 h	4	2	> 4 h	3	1
Unknown	1	2	Unknown	1	1
<b>Total</b>	<b>90</b>	<b>61</b>	<b>Total</b>	<b>90</b>	<b>61</b>

of the exposures to Portion snus the symptoms lasted over 2 hours, compared to only 1.6% of the exposures to other tobacco products.

**Conclusion:** The results show that ingestion of Portion snus causes a delayed onset of symptoms and also prolonged duration of symptoms compared to other tobacco products.

## 125. Poisoning by substances of abuse among children: Data from the Moroccan Poison Control Center, 2008-2012

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**Objective:** Poisoning by substances of abuse among children is increasingly frequent. It represents a real public health problem given the increasing number of these substances and their availability.<sup>1,2</sup> The aim of our study was to describe the epidemiological features of poisoning by substances of abuse in children reported to the Moroccan poisoning control center (CAPM) between 2008 and 2012.

**Methods:** This was a five year (2008-2012) cross-sectional retrospective study including all records from CAPM and involving substances of abuse among children (0-15 years). We performed a descriptive analysis using EpiInfo 3.5.3 software.

**Results:** During the study period, 160 cases were recorded. Among them, 57.7% concerned children aged 5-15 years, followed by toddlers aged 1-5 years (35.4%), infants aged 1-12 months (4.9%) and newborns up to 4 weeks of age (1.8%). The most common substance involved was "Maajoune" (a mixture of addictive plants) in 55% of cases, followed by cannabis (21.2%), tobacco (8.1%) and "karkoubi" (1.8%), a counterfeit benzodiazepine. Most exposures were unintentional (80%), however, 12.5% of cases were related to addiction, 3.1% were criminal (child abuse) and 1.8% resulted from suicide attempts. All addiction and suicide cases involved children in the 5-15 years of age group. One death was recorded (lethality of 0.6%), and concerned an 18-month-old toddler who was poisoned by cannabis within an unintentional circumstance.

**Conclusion:** Poisoning by substances of abuse among children remains a frequent issue. These substances can be a cause of toxic death,<sup>3</sup> especially among vulnerable populations such as children. This is even more dramatic when it comes to suicide attempts or substance abuse. Thus, it requires extra vigilance and adoption of risk reduction measures adapted to these specific populations.

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## 126. Severe acute poisoning in children: A 5-year retrospective study

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**Objective:** We analysed the etiology of acute poisoning in children complicated with shock and death. Shock is a clinically defined entity that can have multiple etiologies, including acute poisoning, and can be fatal.<sup>1,2</sup>

**Methods:** We analysed all cases of acute poisoning in a 5-year period that where complicated with shock and death. Shock criteria were the presence of tachycardia, tachypnoea, prolonged capillary refill time, low blood pressure and irritability. All patients were admitted in ICU and received supportive care and antidote therapy where appropriate.

**Results:** In total 78 cases were identified. The etiology of acute poisoning complicated with shock was: drugs 57 cases with naphazoline (n = 13), drugs of abuse (n = 12; opioids/opiates n = 6, heroin n = 3, cannabis n = 3). Dentocalmin (1% lidocaine) (n = 8), beta-blockers (n = 8, Distonocalm, propranolol, metoprolol), tricyclic antidepressants (n = 6, amitriptyline, imipramine), clonidine (n = 3), digoxin (n = 2), and 1 case each of phenobarbital, bromazepam, salbutamol, isosorbide dinitrate, theophylline), insecticides (n = 6, diazinon n = 5; carbofuran n = 1), nitrites (n = 7), alcohol (n = 4) and carbon monoxide (n = 1). Also 3 cases with mushroom poisoning were classified as hypovolemic shock. Of the 78 cases 13 patients died with an etiology of drugs 7 cases (Dentocalmin n = 6 and amitriptyline n = 1), pesticides (n = 5), nitrites n = 1) and 2 cases developed severe neurological complications post-resuscitation.

**Conclusion:** Due to the rapid initiation of supportive and antidote treatment most of the children recovered fully. Acute poisoning in children is still a public health problem in our country, some of them with severe complications and even death.

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## 127. Pharmacovigilance in pediatrics: Medication errors reported to National Milan Poison Control Center

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**Objective:** Although it is well known that children are more at risk for medication errors (MEs) than adults<sup>1,2</sup>, a steady and specific

epidemiological surveillance of these types of error is still lacking. Our aim is to describe and classify MEs in pediatrics, in order to provide informative bases for active and preventive strategies.

**Methods:** A descriptive statistical analysis of all consulting requests received by the National Milan Poison Control Center (NMPCC) involving children (0-18 year-old) was performed. A period of two years of activity of the NMPCC was considered (May 2012 to May 2014). A standard form to collect the following main categories of information was used: patient characteristics, method of administration, the pharmaceutical agent, type of ME, signs/symptoms (scored according to Poisoning Severity Score).<sup>3</sup>

**Results:** During 24 months, the NMPCC managed 3,386 requests for advice related to MEs and ADRs in pediatric patients (MEs n = 3,303, 97.5%; ADRs n = 83, 2.5%). Age class distribution was: 22.5% less than 1-year-old, 44.2% between 1-4 years, 21.9% between 5-9 years, 7.9% aged 10-14 years, 2.1% aged 15-18 years and 1.2% unknown (males n = 1,824, females n = 1,478, unknown n = 1). Symptoms observed were: absent in 3,000 cases, mild in 240, moderate in 57, severe in 5 and unknown in 1 case. Most of the MEs (92.3%) were caused by wrongful administration by others; other categories included, self-administration (3.8%), iatrogenic error (2.7%) and not specified (1.2%). The drugs most frequently involved were analgesics/antipyretics (24.4%, n = 828), for which contributing factors were excessive dosage (n = 723) and medication exchange (n = 78); antibiotics (19.5%, n = 660) of which 463 excessive dosage, 125 reconstitution errors; antihistamines (7.1%, n = 242) dosage errors n = 161, drug exchange n = 60.

**Conclusion:** The data collected allowed us to focus on some issues concerning pediatric drug therapy; over-the-counter liquid medications present a specific risk of MEs, mainly because of issues with the proper use of dosing devices. Preparation errors are frequent, in particular problems with the reconstitution of powdered antibiotics and confusion in matching mg/kg and mL of the preparation. There is a clear need to improve communications between patients and doctors and recommendations by healthcare providers.

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## 128. Suicidal adolescents: Examining self-poisonings within the pediatric population

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**Objective:** Suicide is a major public health problem in the USA, and listed as third-leading cause of death in 10-24 year-olds. Among adolescents, the lifetime prevalence of suicidal ideation and attempt is 12.1% and 4.1%, respectively. Poisonings are a common method of self-harm encountered in the ED. Our

objective was to characterize ingestions and outcomes in adolescents with self-harm attempts reported in the ToxIC database.

**Methods:** We retrospectively searched ToxIC (Toxicology Investigators Consortium), a national case registry, to identify cases categorized as “Intentional Self-Harm” among 13 to 18-year-olds. Cases reported as “Unlikely tox related” were excluded. All cases fitting criteria from creation of the database in 2010 through 1 November 2014 were included in the analysis.

**Results:** There were 2,226 cases of toxicologic exposures in ages 13-18 reported in ToxIC. Of these 783 were categorized as “Intentional pharmaceutical overdoses”, with 604 subcategorized as “Attempt at self-harm”. There were 466 cases of “suicide attempt” (77.2%), 26 cases of “No suicide intent” (4.3%), and intent was not reported or unknown in the remaining cases. Of patients with suicide attempt, 442 (94.8%) had signs/symptoms, 344 (73.8%) were given toxicologic treatment, and 163 (34.9%) were admitted to the ICU. Among patients with no suicide intent, 25 (96.2%) had signs/symptoms, 16 (61.5%) required toxicologic treatment and 7 (26.9%) were admitted to the ICU; there were no significant differences between groups in these three categories. Patients presenting with suicide attempt were predominantly female (76.8% versus 23.2%,  $p < 0.05$ ). A single agent was ingested in 276 (59.2%) of attempts and 188 (40.3%) cases involved multiple agents ( $p < 0.05$ ) (data missing in two cases). The top three most commonly ingested pharmaceutical classes were analgesics, antidepressants and anticholinergics/antihistamines, with 201, 161, and 119 exposures, respectively, in the suicide attempt group and 18, 4 and 7 exposures, respectively, in the no suicide intent group.

**Conclusion:** Females presented after attempted suicide more frequently than males, consistent with previous studies. Comparisons between suicide attempt and no suicide intent groups suggests that patients without intent have similar risk for illness severity. The most common classes of agents ingested did not differ between those with suicidal intent and those without. This study describes characteristics of adolescents with toxicologic exposures. Continued research is needed to prevent pharmaceutical overdose in this population.

## 129. Uncommon indications for extracorporeal removal of toxins

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**Introduction:** While enhancing toxin clearance is intuitively associated with improved clinical outcomes, in fact, there is a paucity of evidence to support this observation. The use of extracorporeal removal to increase clearance has been considered and recommended for a large variety of toxins with very little supporting evidence. For most toxins, the arguments for extracorporeal removal are based on either futility (all other therapies were failing and something must be tried), clinical parameters (awaking, improvement of hemodynamics, etc., during extracorporeal treatments) or toxicokinetic parameters (e.g. decreased drug concentration or half-life). Unfortunately, during acute poisoning plasma toxin concentrations are the result of competing and ever changing variables, including ongoing absorption and total body clearance, the latter comprising the sum of renal, hepatic and other potential routes of

elimination. Likewise, clinical improvement may relate to falling toxin concentrations, but can also result from the many other therapies given simultaneously with the extracorporeal removal technique. Thus improvements ascribed to extracorporeal removal techniques may be true, coincidental or completely erroneous. This lecture uses a systematic approach to evaluate the role of extracorporeal removal for a few uncommon indications. Several recent reviews on the subject of extracorporeal treatments in poisoning are available.<sup>1-3</sup>

**Discussion:** There are three fundamental properties of a toxin to be evaluated when contemplating hemodialysis: 1) molecular mass - the toxin must fit through the filter pores; 2) protein binding - only the water compartment of the blood can be filtered and thus bound toxins are not available to be filtered; 3) volume of distribution - only the blood compartment is passed through the extracorporeal circuit such that toxins with large volumes of distribution are not efficiently dialyzed. It is important to recognize that for many toxins these parameters are not evaluated at toxic concentrations and while protein binding may decrease, volume of distribution can increase in overdose. Other extracorporeal removal techniques can overcome some of these limitations such as the ability of hemoperfusion to overcome limitations of protein binding and molecular size. An additional variable, endogenous clearance, must be considered; extracorporeal removal is unlikely to contribute significantly when toxins have a rapid endogenous clearance. The “gold standard” for assessing efficacy of an extracorporeal treatment is an analysis of the toxin concentration in a known volume of the waste compartment of the technique (such as dialysate). This is the only true assessment of the total amount removed during the procedure and can be compared to the total body load of the toxin or the amount taken if known. A falling blood concentration may be useful if the apparent half-lives are compared before during and after extracorporeal treatments as these three comparisons will help correct for endogenous clearance. However, it should be noted that pre-procedure apparent half-lives may be prolonged by ongoing absorption and post-procedure apparent half-lives may be shortened by changing elimination kinetics (e.g. a change from zero order to first order elimination). Another assessment is the evaluation of an extraction ratio, which is the relationship between the concentrations across the technique. While a low extraction ratio is usually associated with minimal removal of the toxin, high extraction ratios are often misinterpreted as a marker of significant extracorporeal effect. However, if the volume of distribution is high or the blood flow rate is poor, the amount of toxin removed will be minimal, even if the extraction ratio is very high.

**Examples:** Amatoxin: MW about 900 Da; minimal albumin binding; Vd 0.15-0.29 L/kg (in dogs). Sabeel reported on the treatment of 41 patients with *Amanita* poisoning stating with a complex regimen that included hemodialysis and hemoperfusion and concluded that it was efficacious although no actual data were presented.<sup>4</sup> Mullins reported two patients with confirmed *Amanita* poisoning who underwent delayed (23 hours post-ingestion) hemoperfusion and survived despite developing hepatotoxicity.<sup>5</sup> Blood concentrations of amatoxin were undetectable at the initiation of therapy. Faulstich demonstrated that less than 1% of IV administered amatoxin was recovered in the blood of dogs 5 hours after administration.<sup>6</sup> As patients rarely develop symptoms before 5 hours post-ingestion, the benefits of extracorporeal removal seem minimal. While other authors have demonstrated persistent blood concentrations of amatoxin for hours to days after ingestion, these



concentrations are usually trivial. Caffeine: MW about 194 Da; low protein binding; Vd 0.4-0.6 L/kg. Ishigaki and colleagues present clinical and visual evidence to support combined hemodialysis and hemoperfusion, but no clearance data are reported.<sup>7</sup> A similar case is presented by Holstege to support the use of vasopressin and hemodialysis.<sup>8</sup> Fluoride: MW about 19 Da; probably low protein binding; Vd 0.6 L/kg. Berman showed a favorable comparison between dialysance and renal clearance of fluoride in a patient with an intentional ingestion.<sup>9</sup> Usada measured dialysate in patients undergoing hemodialysis to suggest that nearly half of fluoride could be removed in a 5 hour session with low blood flow rate (200 mL/min).<sup>10</sup> Data from a recent manganese case and other toxins will be presented if time allows.

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## 130. Refractoriness of drug-induced hypotension: Prediction and management

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**Objective:** Despite significant improvement in critical care, drug-induced cardiovascular failure remains a leading cause of death. Among the 2,686,673 exposures in adults reported to the American Association of Poison Control Centers in 2012, cardiovascular drugs were involved in 3.87% of the cases but accounted for 12.18% of the fatalities, representing the second toxicant category responsible for death.<sup>1</sup> In this register, calcium channel blockers (CCB) and beta-blockers (BB) accounted for 35% of cardiovascular drug exposures, while CCBs represented the first cause and cardiac glycosides the second cause of cardiovascular agent-related death.

**Methods:** Based on the published data, this presentation will review the predictive factors for failure of pharmacological treatments of drug-induced cardiovascular failure and define the place of lipid emulsion, ECMO and albumin dialysis in poisonings.

**Results:** Severe cardiotoxicity usually appears rapidly after exposure with the sudden onset of hypotension, high-degree atrioventricular block, asystole and pulseless ventricular arrhythmia. Other critical features generally result from cardiovascular failure including mental status deterioration, seizures, hyperlactacidemia, and renal, liver and respiratory failure. Determination of the mechanism of cardiovascular failure based on the usual devices available in the intensive care unit (including echocardiography) is mandatory to improve management. Overdoses with CCBs, BBs, and membrane-stabilizing agents (MSA) result in myocardial negative inotropic effects as well as arterial dilatation. Prognostic factors remain poorly investigated, except for digitalis, colchicine, theophylline and antidepressants. They are specific for a class of toxicants. Interestingly, the prognostic value of blood concentrations remains to be determined.<sup>2</sup> Despite optimal supportive and antidotal treatments, management of drug-induced cardiovascular failure is difficult. Ventricular arrhythmia, sudden cardiac arrest, and refractory cardiovascular failure may cause death, despite tight monitoring and aggressive resuscitative measures and vasopressors. Prognosticators of refractoriness to conventional treatments are lacking. Due to large volumes of distribution and high protein binding ratios, extracorporeal elimination enhancement techniques are not feasible options, although a recent case series has highlighted the possible contribution of albumin dialysis using Molecular Adsorbent Recirculating System in the management of CCB-poisoned patients with refractory vasodilatation.<sup>3</sup> Lipid emulsion has been extensively used to treat severe symptoms attributed to cardiotoxicants. However, due to the lack of randomized controlled studies, this treatment should be used only in local anesthetic systemic toxicity and lipophilic cardiotoxin intoxication with an immediate threat to life and ineffectiveness of other therapies.<sup>4</sup> ECMO for reversible cardiac toxicity has a sound basis but clinical experience is also still limited in toxicology with insufficient evidence to conclude for its recommendation (grade C).<sup>(5)</sup> The purpose of ECMO is to take over the heart function during refractory cardiac shock until recovery can occur, thus minimizing myocardial work, improving organ perfusion, and maintaining the renal and biliary elimination of the toxicant. By contrast, ventricular pacing can only be considered if the inotropic heart function is preserved. Interest of intra-aortic balloon pumps appears also limited due to the need for intrinsic cardiac rhythm for synchronization and diastolic augmentation.

**Conclusion:** Supportive and antidotal treatments are usually efficient to treat drug-induced hypotension. However, due to a persistent high-rate of mortality, there is a need for more aggressive management in patients not responding to conventional treatments. Clarification of prognosticators of refractoriness to conventional treatment is mandatory. Usefulness of lipid emulsions, albumin dialysis and ECMO remains a matter of debate and recommendations from the scientific societies are expected.

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### 131. Long-term outcome of poisoned patients in the ICU: Determinants and prediction

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**Background:** One of the most important indicators of quality of Intensive Care Unit (ICU) treatment is outcome. Outcome is defined as changes in the state of a patient's health that can be attributed to an intervention or to the absence of an intervention.

**Discussion:** Traditionally physicians have looked at in-hospital mortality as their most important outcome measure. In the Netherlands the ICU mortality was 1.2% and the in-hospital mortality was 2.1%. However, hospital mortality is potentially confounded and, therefore, long-term mortality might be more important. The mortality 1, 3, 6, 12 and 24 months after ICU admission was 2.8%, 4.1%, 5.2%, 6.5% and 9.3%, respectively. There is a difference in long-term mortality according to the type of intoxication. Street drugs had the highest mortality two years after ICU admission (12.3%) and a combination of intoxications the lowest (6.3%). A second very important outcome, apart from mortality, is health-related quality of life (HRQoL). The self-reported HRQoL, measured with the EQ-5D was lower than the average HEQoL of the general ICU population.

**Conclusion:** The rather poor long-term outcome combined with a lower than average HRQoL clearly shows that patients with intoxication are a group of patients that that need more attention.

### 132. A comparison of vasopressor utility for drug overdose-induced shock

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**Objective:** Deaths in the US from drug overdose are steadily rising, and increasingly patients present to emergency department (EDs) in circulatory shock after a drug overdose. There remains little consensus on the ideal selection of adrenergic agent (vasopressor) in this growing patient population. Although high-dose insulin

eglycemia (HIE) for beta-blocker (BB) and calcium-channel-blocker (CCB) overdose has become a first-line treatment based on excellent animal data, there remains little human evidence to support this practice. This study investigates the relationship between vasopressor choice, HIE use (when applicable) and mortality in drug overdose-related shock.

**Methods:** This study was a secondary data analysis of a prospective cohort of consecutive ED patients presenting with suspected drug overdose to two urban teaching centers between 2009 and 2014. Inclusion criteria were all adult patients also circulatory shock requiring vasopressors or HIE. Pediatric patients (age < 18 years) and caustic ingestions were excluded. Independent variables were the choice of initial vasopressor (both drip and push-dose), as well as a subgroup analysis of BB and CCB overdose and HIE use. Subgroup analysis compared ICU length-of-stay and total pressor time in the BB/CCB subgroup.

**Results:** In total 55 overdoses qualified by inclusion/exclusion criteria, and 15 of these included a component of either BB/CCB overdose. For all patients, there approached a mortality benefit when norepinephrine was the initial drip given ( $p = 0.097$ ). There was significant mortality benefit when phenylephrine was the initial push-dose medication given ( $p = 0.008$ ). Risk of mortality was significantly higher when epinephrine was the initial push-dose medication given ( $p < 0.05$  24 hour mortality,  $p < 0.05$  in-hospital mortality). In the BB/CCB subgroup, there was no significant benefit for HIE regarding mortality, ICU length-of-stay or total vasopressor time.

**Conclusion:** This data suggests that push-dose phenylephrine is safe, effective, and superior to push-dose epinephrine as the initial medication in undifferentiated drug overdose patients with circulatory shock. This was not a randomized study, so there could be provider bias in vasopressor choice. For example, sicker patients may have been more likely to receive epinephrine rather than phenylephrine (e.g., for cardiac arrest). We were underpowered to demonstrate mortality benefit for HIE, and thus do not suggest cessation of HIE for CCB and BB overdose patients.

### 133. Chemical and biological terrorist attacks identified through the Global Terrorism Database

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**Objective:** The purpose of this study was to characterize biological and chemical terrorist attacks reported to the Global Terrorism Database (GTD).<sup>1</sup>

**Methods:** The GTD was queried for biological or chemical terrorist attacks occurring between calendar years 1970 and 2012. Biological agents were classified as anthrax, botulinum toxin, and salmonella. Chemical agents included acid/alkaline corrosives, arsenic, cyanide, heavy metals, irritants, organophosphates, ricin, and vesicants. Unknown substances included unknown, unknown gas, or other. The frequencies of terrorist attacks, non-fatalities, and fatalities were each calculated geographically, temporally, and by agent.

**Results:** In total 223 terrorist attacks were identified involving chemical ( $n = 191$ , 85.7%) and biological agents ( $n = 32$ , 14.3%),

accounting for 416 deaths and 10,358 non-fatal casualties. One-third of the attacks ( $n = 74$ ) utilized unknown gases or chemical agents, followed by irritants ( $n = 39$ , 17.5%), acid/alkaline corrosives ( $n = 32$ , 14.3%) and cyanide ( $n = 24$ , 10.8%). Among known agents, irritants resulted in the largest proportion of fatalities ( $n = 82$ , 19.7%). Biological agents accounted for 2.2% of all fatalities, and were predominantly identified among North American attacks (anthrax,  $n = 12$ , 40.0%; salmonella,  $n = 4$ , 13.3%). Acid/alkaline corrosives were most frequently reported in South Asia ( $n = 12$ , 37.5%) and Western Europe ( $n = 8$ , 25.0%), while irritants were the dominant agent in Western Europe ( $n = 15$ , 38.5%) and South America ( $n = 8$ , 20.5%). Unknown gases were frequently used in South Asia ( $n = 9$ , 37.5%) and East Asia ( $n = 8$ , 33.3%). Countries with most reported incidents included the USA ( $n = 29$ , 13.0%), Afghanistan ( $n = 26$ , 11.7%) and Germany ( $n = 14$ , 6.3%). Japan accounted for 65.1% ( $n = 6,744$ ) of all wounded individuals, while Uganda ( $n = 200$ , 48.1%) and Columbia ( $n = 71$ , 17.1%) reported the majority of fatalities.

**Conclusion:** Limitations of the GTD originate from the open media resources used to identify attacks and confirmed weapon type, resulting in a significant proportion of unknown chemical or biological agents. The GTD reports only successful attacks, and underestimates the true burden of intended attacks. Although chemical and biological agents are a small subset of GTD, they have contributed to significant morbidity and mortality. As identified through this study, agents used in these attacks varied by region, and identifying these patterns may aid local and international authorities in preparation and response to terrorist attacks. The epidemiological trends found within the GTD provide insight into the regional variation of chemical and biological attacks that may assist in terrorism preparedness endeavors.

### 134. Surveillance of hazardous exposures to liquid laundry detergent capsules in Italy: A preliminary evaluation of the impact of preventive measures

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**Objective:** Liquid laundry detergent capsules (LLDCs) are unit dose fabric washing products consisting of about 32-35 mL of concentrated liquid detergent wrapped in a water-soluble membrane. Previous studies have shown that these products have the potential to cause corrosive eye damage, pulmonary toxicity and serious laryngopharyngeal injuries. In Italy, LLDCs were launched in July 2010. Since then, the National Poison Control Centre in Milan (NPCCM) has documented a series of cases of LLDC-related injuries of moderate severity in children. Considering these evidences, in August 2012 the main LLDCs manufacturer (Brand 1) decided in to sell its product in opaque containers to reduce pediatric exposure. This is a preliminary evaluation of the impact of this measure.

**Methods:** All cases of exposure to Brand 1 that occurred between 1 September 2010 and 31 July 2014 were extracted from the NPCCM

database. There were two periods: Period I (from 1 September 2010 to 30 November 2012), when Brand 1 product was sold in see-through containers, plus a four month period when the product was available both in see-through or opaque containers; Period II (from 1 December 2012 to 31 July 2014), when the product was only available in opaque containers. The mean number of cases of exposure/month (mean monthly rate) were calculated, as were the 95% confidence intervals (95% CI), assuming a Poisson's process. The mean monthly rates observed in Period I were assumed to be constant over time and used to estimate the expected number of cases in the Period II. The ratio of observed to expected cases (O/E) was used as a measure of the association between exposure and the adopted prevention measure. The 95% CIs of the O/E ratio were derived assuming a Poisson's process for the observed cases. **Results:** In Period I 871 cases of accidental exposure to Brand 1 were identified, accounting for 32.2 cases/month (95% CI: 21.9-45.2) and 2.03 cases/million units sold (95% CI: 1.38-2.34); in Period II 226 cases of exposure to Brand 1 were identified, accounting for 11.9 cases/month (95% CI: 6.2-21.0) and 0.97 cases/million units sold (95% CI: 0.50-1.71). In Period II, the O/E ratio showed a statistically significant decrease in the monthly rate of exposure to Brand 1 (O/E 0.48, 95% CI, 0.25-0.84).

**Conclusion:** The observed results suggest that LLDCs packaged in opaque containers reduces the risk of unintentional exposure.

### 135. Markers of oxidative stress and inflammation are more elevated in the exhaled breath condensate of workers exposed to nano-TiO<sub>2</sub> than to nano-Fe oxide particles

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**Objective:** Health-effects of engineered nanoparticles in the human are little understood. In experimental studies nanoparticles cause oxidative stress, alterations in genes expression, inflammation, apoptosis and cancers. However, very limited data are available in exposed humans.

**Methods:** Post-shift markers of oxidation of lipids (malondialdehyde, 4-hydroxy-trans-hexenal, 4-hydroxy-trans-nonanal, aldehydes C6-C12, 8-iso-prostaglandin F<sub>2α</sub>), nucleic acids (8-hydroxy-2-deoxyguanosine, 8-hydroxyguanosine, 5-hydroxymethyl uracil) and proteins (o-tyrosine, 3-chloro-tyrosine, and nitrotyrosine), in addition to leukotrienes were analysed by LC-ESI-MS/MS in the exhaled breath condensate (EBC) and urine of workers. Subjects were exposed either to nano-titanium dioxide (TiO<sub>2</sub>) (14 males, mean age 33.7 ± 10.0 years) or nano-Fe oxides (14 males, mean age 43.1 ± 7.5 years) in the pigment production industry, and compared to controls (14 males, mean age 33.7 ± 8.1 years and 25 males, mean age 38.5 ± 7.5 years, respectively). Aerosol



exposure in the workplace was measured by scanning mobility particle sizer (SMPS) and aerodynamic particle sizer (APS) spectrometers and monitors P-TRAK and DustTRAK DRX.

**Results:** In TiO<sub>2</sub> pigment production, the median number concentration was  $38 \times 10^4$  ( $1 \times 10^4$  to  $2 \times 10^5$ ) particles/cm<sup>3</sup> and median mass concentration 1.9 (0.1-30) mg/m<sup>3</sup>. In brown/red Fe oxide pigment production, the median number concentration was  $11.8 \times 10^3$  ( $10.2 \times 10^3$  to  $0.8 \times 10^3$ ) particles/cm<sup>3</sup> and median mass concentration 0.13 (0.1-0.32) mg/m<sup>3</sup>. In neither workplace did the concentration of aerosol exceed the maximum allowed limits; however 70-90% of particles of TiO<sub>2</sub> and 80-90% of particles of Fe oxides were smaller than 100 nm in diameter. The workers did not have respiratory symptoms and their lung functions were unimpaired compared to controls; however concentrations of all post-shift markers of oxidation of lipids, nucleic acids and proteins and leukotriene B4 were higher ( $p < 0.001$ ) in their EBC, but not in urine. In the TiO<sub>2</sub> exposure group, all markers were higher by 30-70% than in Fe oxides workers; cysteinyl leukotrienes were elevated in TiO<sub>2</sub> exposed workers only.

**Conclusion:** This study suggests adverse effects of exposure to aerosols containing a high proportion of nanoparticles of TiO<sub>2</sub> and Fe oxides with signs of inflammation and genotoxic/carcinogenic effect due to the oxidation of nucleic acids. As TiO<sub>2</sub> and Fe oxides are of low toxicity, the effects may be attributed to the nanoparticles. The diameter of inhaled particles seems more important than the chemical composition, because nano-sized particles are able to cross cell membranes, unlike chemically identical bulk TiO<sub>2</sub> and Fe oxides. As the non-soluble particles are removed from the lungs with a very long half-life, EBC appears a preferred biological fluid for the evaluation of their deleterious effect.

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### 136. Relationship between long-term exposure to ambient air pollution, blood pressure and inflammatory processes among young subjects

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**Objective:** Endothelial dysfunction and chronic inflammation are the first steps of the pathological pathway leading to atherosclerosis and cardiovascular diseases. It is known that air pollution promotes cardiovascular diseases.<sup>1,2,3</sup> We aimed to investigate the relationship between the particulate matter air concentration and the level of blood inflammatory markers among healthy people aged between 15-21 years old.

**Methods:** We recruited permanent residents of two Polish cities (Lublin and Krakow) with very similar urban structure characteristics, but significantly different mean 10-year ambient air pollution levels, PM<sub>2.5</sub> (22.4 versus 41.7 mcg/m<sup>3</sup>) and PM<sub>10</sub> (29.4 versus 56.9 mcg/m<sup>3</sup>) respectively. Data about body mass index (BMI), lifestyle, ethnicity and family history were collected. Measurements of blood pressure (BP) were performed. Blood tests, including inflammatory parameters, were performed.

**Results:** In total 621 subjects (423 females, 198 males) aged  $17.98 \pm 1.06$  were recruited, 312 in Lublin, 309 in Krakow. There were no differences between groups in BMI (median 20.82 kg/m<sup>2</sup>), age, ethnicity and lifestyle. We found no significant differences in blood pressure (BP) or pulse pressure (PP) between subjects differing in exposure to air pollution; Lublin versus Krakow, diastolic BP ( $71.3 \pm 8.5$  versus  $69.7 \pm 7.7$  mmHg), systolic BP ( $123.8 \pm 12.7$  versus  $121.7 \pm 11.4$  mmHg), pulse pressure ( $52 \pm 10.9$  versus  $51.3 \pm 10.5$  mmHg). Subsequently 524 subjects underwent blood tests, all 309 in Krakow and 215 in Lublin. We found significantly higher inflammatory parameters in subjects living in Krakow. Lublin versus Krakow C-reactive protein (CRP) ( $0.03 \pm 0.10$  versus  $0.77 \pm 2.71$  mg/mL,  $p < .0001$ ), high-sensitivity-CRP ( $0.31 \pm 1.00$  versus  $0.50 \pm 2.93$  mg/mL,  $p < .0001$ ; OR: 1.3, 95% CI 1.1-1.6) and homocysteine ( $9.01 \pm 2.94$  versus  $10.30 \pm 2.61$  microM,  $p < .0001$ ).

**Conclusion:** This study shows that exposure to outdoor air pollution and other factors associated with living in a city with high air pollution could result in an increase of inflammatory response in healthy young people. The level of inflammatory markers is higher in people living in regions with a higher concentration of atmospheric particulate matter. No significant differences in basic cardiovascular parameters were found in healthy young subjects.

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### 137. Rapid cooling via ice water submersion for severe drug-induced hyperthermia

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**Objective:** While management of drug-induced hyperthermia prioritizes aggressive cooling, the method of cooling is debated. In controlled experiments, conductive cooling via ice-water submersion is most effective, achieving cooling rates of 0.2°C/minute, however many continue to recommend and employ convective cooling via a mist and fan. We report two patients with drug-induced hyperthermia cooled with ice-water submersion, to demonstrate the rapid cooling rates achieved with this method.

**Case report:** Case 1: A 27-year-old man presented with altered mental status and a temperature of 41.1°C after ingesting 4-fluoramphetamine. Vital signs were pulse 156/min, oxygen saturation 90%, finger-stick glucose (FS),  $< 2.5$  mmol/L; blood pressure and respirations were not initially obtained. On examination, he was agitated, with non-sensible speech, dilated pupils, diaphoresis, and hyperreflexia without clonus. The patient was treated with IV dextrose, IV midazolam and was subsequently submerged in ice water. Within 18 minutes, his core temperature fell to 38°C, giving

a mean cooling rate of 0.18°C/min. His vital signs stabilized, his mental status improved, and he left the hospital on day 2. Case 2: A 32-year-old agitated man, who was transported in a body bag, arrived with a core temperature of 44.4°C. Additional vital signs were blood pressure, 216/142 mmHg, heart rate 176 bpm, respiratory rate 38/min and FS 183 mg/dL. The patient was intubated, sedated with IV benzodiazepines and submerged in ice water. After 20 minutes, his temperature fell to 38.8°C, achieving a cooling rate of 0.28°C/min. He was extubated the following day, admitted to cocaine use, and discharged on day 10.

**Conclusion:** Patients who present to the Emergency Department with severe hyperthermia require immediate identification and rapid cooling to prevent multi-organ system failure, disseminated intravascular coagulation (DIC) and death. Published data for convection cooling, utilizing specialized body cooling units or helicopter downdraft, document cooling rates between 0.046°C/min and 0.3°C/min, however the external validity of these findings are limited by the methods employed. Our case series describes cooling rates via ice-water submersion that are both consistent with published data on conductive cooling techniques and in excess of those reported with evaporative techniques. These findings suggest that ice water submersion is an efficient, cost-effective and clinically feasible method of achieving rapid cooling in the clinical environment. Given these findings (and for ethical reasons), we would not endorse a randomized trial of cooling techniques, but rather encourage other clinicians to systematically collect data on cooling rates given their preferred techniques for comparative reporting.

### 138. Toxic exposures in young children resulting in tracheal intubation

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**Objective:** To determine the toxic exposures most frequently resulting in tracheal intubation in children.

**Methods:** The Toxicology Investigators Consortium (Toxic) Registry contains case details on all clinical consults seen by medical toxicologists via an international network. A search of the Toxic Registry was performed for all cases 2010-2014 with a treatment recorded as 'intubation' and age categories of <2 and 2-6 years. The 5 most frequently reported exposures for both single and multiple substance cases were reported.

**Results:** In total 122 intubations in patients age 0-6 were identified (<2 years 60; 2-6 years 62). Of these 95 (78%) intubations were associated with single agent exposures. The 5 most common single agent exposures identified were alpha-2 agonists (n = 12), opioids (n = 12), detergents (n = 9), caustics (n = 8) and envenomations (n = 8). Most of the alpha-2 agonist single agent exposures (11/12) involved clonidine. The other was brimonidine. Laundry pods were involved in 8/9 detergent exposures. Caustics identified were sodium/potassium hydroxide (n = 3), lye (n = 1), ammonia (n = 1), hydrochloric (n = 1) and sulfuric (n = 1) acid, and an unspecified caustic (n = 1). Envenomations associated with intubation were *Centruroides* scorpion (n = 4), *Loxosceles* spider (n = 3), and crotalid snake (n = 1). Multiple agent exposures were associated with

14 (11%) of intubations. The 5 most common multiple agent exposures were alpha-2 agonists (n = 4, clonidine 2, guanfacine 1, tetrahydrozoline 1), sedative-hypnotics (n = 4, zolpidem 2, buspirone 1, diazepam 1), opioids (n = 4), antidepressants (n = 3, bupropion 1, trazodone 1, venlafaxine 1), and cardiovascular medications (n = 3, beta-blockers 2, digoxin 1). An unknown agent was associated with 13 (11%) intubations.

**Conclusion:** The agents most frequently associated with intubation in young children were alpha-2 agonists and opioids. This was seen in both single and multiple agent exposures. Given the widespread availability of prescription opioids and associated respiratory depression/central nervous system depression, the prominence of opioids is expected. However, the severity of alpha-2 agonist may not be well recognized. This data is consistent with an unpublished analysis of the US National Poison Data System (NPDS) from 2000-2013 which found that clonidine was the leading agent associated with intubation in children < 6 years in both single substance ingestions (856/5517; 15.5%) and polysubstance ingestions (1052/6491; 16.2%). An additional published analysis of NPDS data revealed a recent trend of an increasing number of symptomatic pediatric exposures to alpha-2 agonists.<sup>1</sup> This effect is presumably due to the increased use of alpha-2 agonists in the treatment of attention deficit (hyperactivity) disorder in young children.

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### 139. Too bad to be true? Osmol gap > 300 mOsm/L

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**Objective:** Evaluation of patients who may have ingested toxic alcohols is complex, in part because serum concentrations are not readily available in many institutions. Surrogate markers such as the osmol gap (OG), are used to predict serum concentrations. We report a case of a markedly elevated OG that incorrectly led to its interpretation as a laboratory error.

**Case report:** A 33-year-old man was brought to the emergency department (ED) after he was found obtunded. His family reported that he was in his usual state of health until the morning of admission. He had no known significant medical or psychiatric history, and took no medications. He drank alcohol occasionally and did not use illicit drugs. On arrival to the ED, his vital signs were blood pressure 170/100 mmHg and heart rate 96/min. His oxygen saturation was 100% while ventilated with a bag valve mask, and his Glasgow Coma Scale score was 3. The patient was immediately intubated for airway protection. The remainder of his physical examination was unremarkable. His laboratory tests showed pH 6.77, bicarbonate 7 mEq/L, anion gap 39 mEq/L, lactate 1.9 mmol/L, BUN 17 mg/dL, creatinine 1.5 mg/dL, calcium 10.5 mg/dL, ethanol 17 mg/dL and osmol gap 301 mOsm/L. The extremely

elevated osmol gap was initially interpreted as a laboratory error by the treating hospital, and the poison control center (PCC) was not contacted until 6 hours later. Fomepizole was initiated after contact with the PCC, and hemodialysis (HD) started 8 hours after arrival. Despite treatment with fomepizole and emergent HD, the patient remained severely acidemic with a persistently elevated anion gap. His repeat osmol gap was 196 mOsm/L. He developed seizures refractory to antiepileptic medications on hospital day 2, hemodynamic instability the following day, and died on hospital day 3. The patient's autopsy showed numerous calcium oxalate crystals in the kidneys, brain and heart on microscopy. His initial serum ethylene glycol (EG) concentration was 1,394.3 mg/dL (225 mmol/L).

**Conclusion:** An OG greater than 50 mOsm/L increases the predictive value for a toxic alcohol ingestion. There are only a few case reports in the medical literature of OG greater than 300 mOsm/L, but in this case it led to a medical error and delay in care.

#### 140. Severe hypertensive crisis and takotsubo cardiomyopathy after intrathecal clonidine pump failure

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**Objective:** Clonidine is a central alpha(2)-agonist antihypertensive used widely for indications such as opioid/alcohol withdrawal, Attention Deficit Hyperactivity Disorder and the management of chronic pain. In recent times, clonidine withdrawal has not been commonly reported. We describe an unusual case of clonidine withdrawal causing life-threatening sympathetic storm and takotsubo cardiomyopathy.

**Case report:** A 47-year-old man with chronic back pain, treated with clonidine for many years via intrathecal pump (550 mcg/24hours), presented to our emergency department following collapse and complaining of sudden worsening of back pain, severe headache, diaphoresis, malaise, nausea and vomiting. A few hours prior to presentation, his subcutaneous pump beeped, suggesting malfunction. On presentation his vital signs were pulse 100 bpm, BP 176/103, temperature 37.8°C and O<sub>2</sub> saturations 100% (room air). Acute clonidine withdrawal with hypertensive crisis was suspected. An intravenous clonidine loading-dose of 150 mcg was given, followed by 150 mcg/hour infusion. Despite this, 5 hours later, severe chest pain, dyspnoea, tachycardia (150 bpm), hypoxia (SpO<sub>2</sub> 82%), with BP 180/120 ensued. CXR showed pulmonary oedema. ECG showed sinus tachycardia with no ST elevation. The toxicology service was consulted and advised repeated boluses of clonidine 25 mcg every 5-10 minutes, with ongoing clonidine infusion to control his blood pressure with addition of glyceryl trinitrate (GTN) infusion, positive pressure ventilation and intravenous benzodiazepines. Bedside echocardiogram showed takotsubo-type stress-induced cardiomyopathy pattern. Serum troponin-I was markedly elevated. Subsequent in-patient coronary angiography showed minor irregularities in the major vessels. Over the next 3 days in ICU, GTN and clonidine infusions were weaned. Discharge was 12-days later on oral clonidine, metoprolol, perindopril, aspirin and oxycodone SR. Two months later an echocardiogram was normal. The intrathecal pump was removed.

**Conclusion:** Clonidine withdrawal syndrome results from sudden cessation of long-term oral therapy. It can cause phaeochromocytoma-like symptoms 8-24 hours after clonidine cessation. Features may include hypertensive crisis with end-organ dysfunction. Increased plasma catecholamine concentrations are reported in previous cases. Withdrawal is primarily managed with re-institution of clonidine and targeted organ-specific therapies. The dose-equivalence between intravenous and intrathecal clonidine is unknown making titration difficult. Consequently, titration of intravenous dosing to clinical effect is likely to be the best option. Direct-acting vasodilators may be needed to treat refractory hypertension. This is a unique case of severe clonidine withdrawal after intrathecal pump failure with hypertensive crisis and takotsubo cardiomyopathy. Clonidine use for non-hypertension indications is increasing. Withdrawal syndrome should be considered in hypertensive crisis after cessation of long-term clonidine therapy.

#### 141. Special populations: Pediatric propofol infusion syndrome treated with extracorporeal membrane oxygenation, hemodialysis and carnitine

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**Objective:** Propofol infusion syndrome (PRIS) is a complication with a high mortality rate. It is characterized by cardiac failure, metabolic acidosis, rhabdomyolysis, hyperlipidemia and fatty infiltration of the liver. The mechanism may involve the increase in free fatty acids due to impaired beta-oxidation. Propofol inhibits carnitine palmitoyl transferase (CPT) I and II which convert free fatty acids to acyl coenzyme A.<sup>1</sup> Carnitine is a substrate for CPT I and acquired carnitine deficiency could contribute to impaired fatty acid oxidation. PRIS is also associated with bradycardia and a right bundle branch block with convex ST segments in V1-V3 similar to Brugada Syndrome. PRIS typically occurs with propofol doses greater than 4 mg/kg/h for > 48 hours. Further predisposing factors include steroid and catecholamine administration. We describe a case of propofol infusion syndrome (PRIS) in a pediatric patient treated successfully with venoarterial extracorporeal membrane oxygenation (VA-ECMO), hemodialysis and L-carnitine.

**Case report:** A 16-year-old boy was transferred to our hospital for treatment of arteriovenous malformation rupture. He required high amounts of sedative medications and for 4 days he received propofol at a rate of 1.5-9 mg/kg/h including 9 mg/kg/h for 2 days prior to discontinuation. After the infusion was ceased, he developed wide-complex tachycardia and myocardial depression; VA-ECMO was initiated. His vital signs were temperature 38.4°C, heart rate 123 bpm, BP 57/32 mmHg, respiration rate 17 bpm, oxygenation saturation on 100% 0.6 FiO<sub>2</sub>. Significant laboratory values were sodium 171 mEq/L, potassium 5.32 mEq/L, CO<sub>2</sub> 17 mEq/L, creatinine 2.0 mg/dL, lactate 9.7 mmol/L and creatine kinase 5899 units/L. Urine output had decreased from approximately 1 mL/kg/hr to 0 over the 8 hours prior to assessment. His ECG showed a wide complex rhythm with ST changes resembling Brugada pattern. We recommended treatment with L-carnitine (6000 mg bolus, then 18 mg/kg 4 hourly for 10 days) on the theory that it could facilitate fatty acid beta-oxidation. His acidosis



improved approximately 9 hours after the initiation of ECMO and lactate decreased over the next week. He remained on ECMO for 6 days and hemodialysis continued for 30 days. He was discharged from the hospital after 2 months with some cognitive deficits.

**Conclusion:** PRIS is a serious complication of prolonged propofol therapy especially in children. There are only 2 case reports in the literature of hemodialysis and ECMO being used to treat PRIS. This case adds carnitine to the options to treat this dire complication.

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## 142. Air transport of a severe salicylate intoxicated patient: Unforeseen risks

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**Objective:** Helicopter transport of the agitated patient is an important safety issue. The primary concern is that an agitated patient could potentially interfere with aircraft integrity and stability. Many air medical units have protocols regarding the transport of agitated patients requiring pre-flight intubation, however none address the specific potential deleterious effects associated with intubation in the face of severe salicylism.

**Case report:** A 17-year-old male presented to the emergency department following a massive salicylate overdose. Initial findings were blood pressure 166/108 mmHg, heart rate 130 beats/minute (bpm); temperature 37°C, respiratory rate 30 breaths/minute and pulse oximetry 98%. Initial physical examination revealed altered mental status with confusion, tachypnea, tachycardia and vomiting. Laboratory findings revealed pH 7.42, PCO<sub>2</sub> 23.9 mmHg, bicarbonate 15.5 mmol/L and a serum salicylate concentration of 129 mg/dL. Emergent hemodialysis was recommended which required interhospital transfer. Helicopter transport was arranged. Prior to lift off, the patient was noted to be agitated and intravenous (IV) midazolam (2.5 mg) was administered. The patient was orotracheally intubated using rapid sequence intubation with vecuronium (20 mg IV), fentanyl (200 mcg IV) and midazolam (10 mg IV). On arrival at the accepting facility, vital signs were BP 147/55 mmHg, heart rate 200 bpm with a ventricular tachycardia per the cardiac monitor, temperature 42.9°C, respiratory rate 25 breaths/minute and pulse oximetry of 92% with end-tidal CO<sub>2</sub> of 75 mmHg. Repeat laboratory findings included pH 7.23, PCO<sub>2</sub> 65.1 mmHg, bicarbonate 27.3 mmol/L and salicylate concentration of 109 mg/dL. Attempts to hyperventilate the patient were unsuccessful. Medical interventions included a continuous sodium bicarbonate infusion, aggressive cooling measures and hemodialysis. After two hemodialysis sessions, the salicylate concentration was 31 mg/dL and the patient was extubated.

**Conclusion:** Intubation of the agitated salicylate patient may result in rapid clinical deterioration. This is caused by sudden worsening of acidosis associated with rapid distribution of salicylate into the central nervous system due to a lack of effective respiratory compensation following intubation. Air medical units have a low threshold for intubating agitated patients due to safety concerns

surrounding transporting agitated patients by air. The risks of intubating patients suffering from severe salicylate toxicity must be carefully considered prior to undertaking air transport as endotracheal intubation should be avoided if at all possible. For these patients ground transport, if feasible, is preferred.

## 143. Intoxicated ICU patients: Not only high long-term mortality but also high risk for a low quality of life

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**Objective:** The mortality of intoxicated ICU patients after hospital discharge is disproportionately high.<sup>1</sup> This finding indicates that an ICU admission could be seen as a warning sign for adverse outcome. However, little is known about the health-related quality of life (HRQOL) of the survivors. The aim of this study is to evaluate the HRQOL of intoxicated ICU patients, one year after discharge.

**Methods:** We performed a single center prospective cohort study. All intoxicated ICU patients of the University Medical Center in Utrecht, admitted between 1 January 2009 and 1 May 2013, were included. One year after their admission, patients received a survey containing the EuroQol EQ-5D-3LTM to analyze the QOL. If necessary they were reminded by sending another survey and they were also contacted by telephone. The HRQOL was compared to both the whole ICU population and the general population matched for gender/age.

**Results:** In total, 115 patients were admitted because of an intoxication (1.5% of all ICU admissions). The in-hospital mortality was 3.5% and the mortality one year after ICU admission was 9.6%. The response rate for completed questionnaires was 26.5% (n = 26). The overall reported median HRQOL one year after ICU discharge was 0.71 (IQR 0.37-0.84), the general population matched for gender/age scored 0.88 (IQR 0.84-0.89) and the general ICU population scored 0.86 (IQR 0.77-1.0). A large proportion of the intoxicated ICU patients reported a very poor HRQOL ( $\leq 0.4$ ) in comparison to the general ICU population (25.9% versus 9.0%). Most severe problems were documented in the category of anxiety/depression and pain.

**Conclusion:** The response rate of intoxicated ICU patients to our questionnaires was disappointingly low. We do not have an explanation for this. However, the responding patients report an alarmingly low HRQOL one year after discharge. The increased mortality rate of intoxicated patients after one year in combination with the very low HRQOL is an alarming sign. Clearly, more attention should be paid to the wellbeing of intoxicated ICU patients after hospital discharge. The next step should be to confirm our findings in another prospective but much larger cohort of intoxicated ICU patients. Finding the causes of the low HRQOL should have high priority.

## Reference

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#### 144. Critical limb ischemia after intra-arterial injection of dissolved clorazepate dipotassium tablets

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**Objective:** First report on a case of acute ischemia of the lower limb after intra-arterial (IA) injection of crushed and dissolved Tranxilium® tablets in the femoral artery. The Tranxilium® 5 mg formulation contains clorazepate dipotassium, potassium carbonate, talcum, gelatin, erythrosine and titanium dioxide.

**Case report:** A 42-year-old drug addict male was admitted to the surgical department 1 hour after an accidental IA-injection of a heated and filtered solution of 2 x 5 mg crushed Tranxilium® tablets in the right femoral artery. The clinical examination revealed a cold and very painful right leg, the foot was pale but arterial foot-pulses were still palpable. The skin of the leg from the groin to the toes was livid-mottled. After the patient was transferred to our ICU, a vasodilative therapy with alprostadil was started due to the disturbed microcirculation. Fentanyl and metamizole were administered intravenously to manage the severe pain and anticoagulation was initially performed with enoxaparin subcutaneously and acetylsalicylic acid (aspirin) orally. After 14 hours a fasciotomy had to be performed due to rhabdomyolysis and compartment syndrome of the lower leg. Due to oliguria and highly elevated creatine kinase (CK 79.803 U/L), hemodiafiltration was performed on day 2 and 3. Urine production normalized under falling CK-values with slightly increased creatinine not exceeding the upper normal value. Peri- and postoperative aspirin was stopped and enoxaparin was replaced by intravenous unfractionated heparin. Full anticoagulation therapy was hampered due to secondary bleeding with the need of red blood cell transfusion. An infected skin necrosis occurred in the wound region leading to secondary sepsis. Microbiologic analysis revealed no relevant bacterial pathogen. During the period of sepsis delirious symptoms were symptomatically treated with intravenous haloperidol and midazolam. The patient's condition improved after a wound debridement and treatment with broad-spectrum antibiotics. On day 12 he was transferred to the normal ward and on day 14 a skin graft was transplanted. The further course was uneventful and he was discharged on day 20.

**Conclusion:** IA-injection of crushed Tranxilium® tablets can lead to severe ischemia most likely due to inflammation of endothelium, arterial thrombosis and disturbance in microcirculation. It remains unclear whether clorazepate dipotassium or the excipients of Tranxilium® were responsible for the disturbed microcirculation. However, microembolism seems unlikely since the injected solution was filtered. Anticoagulation, antiplatelet drugs and vasodilative treatment with iloprost or alprostadil should be started immediately and the decision for fasciotomy should not be delayed.

#### 145. Pentobarbital coma with loss of pupillary light reflex

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**Table 1.** Blood pentobarbital concentration and clinical signs after intentional overdose.

Hospital day	Pentobarbital serum concentration (mg/L)	Neurological exam
1	–	Pupils slowly reactive to light
2	57 mg/L	All brain stem reflexes absent
3	–	All brain stem reflexes absent
4	32.75 mg/L	Pupils slowly reactive to light
5	–	Gag reflex present, squeezes hand on command
6	6.43 mg/L	Patient able to follow simple commands
7	0.26 mg/L	Patient able to write her name
8	–	Patient extubated and following all commands; neurologically intact

**Objective:** Drug toxicity mimicking brain death is well described in the literature. Coma and loss of brain stem reflexes are reported in barbiturate overdose, but typically with retention of the pupillary light reflex. We present a case of pentobarbital toxicity with complete loss of brain stem reflexes and an isoelectric electroencephalogram (EEG).

**Case report:** A 40-year-old female presented to the emergency department after being found unresponsive in her home with two empty bottles of veterinary pentobarbital at her side. She was intubated without sedation. Vital signs upon arrival were BP 79/50 mmHg, HR 112 bpm, RR 17 breaths/minute, temperature 38.3°C, and oxygen saturation 98% on 100% oxygen by mechanical ventilation. Her past medical history consisted of depression. Documented home medications were clonazepam, lorazepam and venlafaxine. Physical examination demonstrated pupils slowly reactive to light and absence of all other brain-stem reflexes. A urine drug immunoassay indicated presence of barbiturates and benzodiazepines. On hospital day (HD) two, physical examination revealed absence of all brain stem reflexes, including pupillary light reflex. An EEG showed no electrical activity. A serum pentobarbital concentration performed by gas chromatography-mass spectrometry (GC/MS) was 57 mg/L (therapeutic range 1-5 mg/L). A comprehensive serum drug assay performed demonstrated a nordiazepam concentration of 0.054 mg/L (therapeutic range 0.2-1 mg/L), and was negative for other co-ingestants. On HD 8 she was extubated without evidence of neurologic sequelae. Table 1 displays the timeline of the patient's physical examination findings and associated pentobarbital concentration.

**Conclusion:** Coma mimicking brain death has been associated with barbiturate toxicity. Our patient had loss of all brain-stem reflexes including pupillary light reflex at a serum pentobarbital concentration of 57 mg/L. This case illustrates the importance of correlating serum drug concentrations with the clinical and EEG findings in the comatose overdose patient prior to determination of brain death.

#### 146. Compartment syndrome secondary to neuroleptic malignant syndrome

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**Objective:** Neuroleptic malignant syndrome (NMS) is a drug-induced emergency most commonly associated with administration of antipsychotics. The primary manifestations of this syndrome are agitation, hyperthermia, autonomic dysfunction and muscle rigidity. We present a case of compartment syndrome due to NMS.

**Case report:** A 34-year-old male with a past medical history of depression presented to the emergency department following an ingestion of 20 tablets of 20 mg olanzapine. The patient did not have a prolonged down time as reported by emergency medical services (EMS). Initial vital signs were heart rate 114 beats per minute (bpm), blood pressure (BP) 131/84 mmHg, respiratory rate 16 breaths per minute, pulse oximetry 100% on room air and temperature 37.6°C. Physical examination revealed a minimally responsive male with bilateral pinpoint pupils. The musculoskeletal examination was unremarkable with no evidence of compartment syndrome. Initial serum laboratory values revealed a white blood cell count of  $11.2 \times 10^3/\mu\text{L}$ , bicarbonate 18 mmol/L, anion gap 17 mEq/L, creatinine 1.3 mg/dL, AST 190 U/L and lactate 3.7 mmol/L. A urine drug immunoassay was unremarkable. Computerized tomography of his head demonstrated no abnormalities. He was intubated by rapid sequence intubation for airway protection, and placed on a midazolam infusion at 10 mg/hour for sedation. Five hours after admission the patient's vitals were BP 220/110 mmHg, heart rate 150 bpm and rectal temperature 40.3°C. He was noted to have generalized muscle fasciculations. The patient was paralyzed with 10 mg IV vecuronium and his midazolam infusion was increased to 20 mg/hour. He was cooled with ice bags, chilled normal saline infusion and a cooling blanket. Examination of the paralyzed patient demonstrated a tense left calf. A Stryker Intra-Compartmental Pressure Monitor System was used to assess the left lower extremity for compartment syndrome. All four left lower extremity compartments had elevated pressures ranging from 70 to 130 mm Hg. Orthopedic surgery was consulted and a bedside fasciotomy was performed. On hospital day number two the patient was extubated and his vital signs had normalized. His creatine kinase peaked at 32,600 U/L. Follow up interview with patient confirmed his overdose. He denied other co-ingestions or leg pain or injury prior to his suicide attempt.

**Conclusion:** Rhabdomyolysis, a common manifestation of NMS, rarely leads to acute compartment syndrome in this setting. When evaluating patients with NMS, it is important to evaluate them for compartment syndrome in all four extremities, especially if they are paralyzed for agitation.

#### 147. Acute fulminant fat embolism syndrome following high-volume intramuscular and accidental intravascular injection of paraffin/oil-based steroid solution

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**Objective:** We present a rare case of fulminant acute fat embolism syndrome (FES) following intravascular injection of an oil-based

steroid solution with delayed diagnostics, acute onset pulmonary distress and progressive deterioration.

**Case report:** A 40-year-old male pedestrian was admitted to a trauma centre after being hit by a car. His primary complaint was anterior chest pain, aggravated by deep inspiration. Examinations revealed a sternum fracture and lung contusion. The patient was stable and discharged with oral analgesics. Seven days later he was referred to a thoracic surgery ward with coughing, haemoptysis, haemoglobin 8.3 mmol/L, elevated leucocyte count and increased C-reactive protein (CRP). Pulmonary X-rays revealed basal infiltrations. Suspecting pneumonia, the patient was discharged with antibiotics and referred for further evaluation at a pulmonary medicine ward. Parallel to the admissions the patient self-administered an oil-based (paraffin) steroid solution by intramuscular injections for cosmetic purposes. The patient had observed blood on aspiration, and then relocated the needle without attempting to aspirate before injecting 140 ml of the oil-steroid solution in each biceps muscle. Shortly after, he described near fainting and haemoptysis both indicating an accidental intravascular injection. The patient failed to inform the clinicians of this incident at the previous admission. Over the next 3 days he experienced increasing shortness of breath, fever and haemoptysis. He presented with acute hypoxic respiratory failure, tachypnoea (48 breaths/min), tachycardia (101 beats/min), fever (38.7°C) and anaemia (haemoglobin 5.2 mmol/L). Laboratory values revealed pH 7.46, PCO<sub>2</sub> 5.32 kPa, PO<sub>2</sub> 6.7 kPa, base excess 4.6 mmol/L, leucocytes (10.1 mmol/L) and CRP 46 nmol/L. Pulmonary X-ray showed bilateral symmetrical alveolar and interstitial infiltrates. He was transferred to the ICU due to respiratory distress and suspected chemical pneumonia, acute respiratory distress syndrome (ARDS) and FES. A high resolution CT revealed no paraclinical sign of pulmonary embolism but showed bilateral consolidations with ground-glass opacities. A broncho-alveolar lavage revealed diffuse bleeding from the ostia and submucosa. He was treated with tranexamic acid and prednisolone with improvement in symptomatology and was discharged 8 days post-admission. At follow up 3 months later he experienced no pulmonary symptoms and X-ray showed remission of the bilateral infiltrates.

**Conclusion:** Acute fulminant fat embolism syndrome can mimic pneumonia, post-traumatic lung injury and other more frequent causes of respiratory failure. Despite delayed diagnosis, a multidisciplinary approach with supportive care measures and specialized treatment contributed to a full recovery in this case.

#### 148. Multiple intensive care admissions associated with analytically confirmed recreational use of phenibut (β-phenyl-γ-amiobutyric acid) purchased over the Internet

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**Objective:** Phenibut (β-phenyl-γ-amiobutyric acid) is a GABA<sub>B</sub> agonist similar to baclofen, acting as a GABA mimetic, primarily



at GABA<sub>B</sub> and GABA<sub>A</sub> receptors. Phenibut was utilised as a hypnotic by Russian astronauts in the 1960s. Its use outside this setting is poorly described, although it is marketed via the Internet as an anxiolytic and nootropic agent. We describe toxicity following exposure to analytically confirmed phenibut, which was purchased over the Internet.

**Case report:** A 43-year-old male last seen well 4 hours previously, arrived in the Emergency Department (ED) via ambulance with marked episodes of agitation, interspersed with episodes of somnolence. He was administered 10 mg intramuscular midazolam for his agitation with minimal effect. Heart rate was 110 bpm, BP 160/60 mmHg and respiratory rate 20/minute. Temperature was normal. He had dilated pupils and was experiencing intermittent episodes of dystonia. There was no clonus or hyperreflexia. Given his ongoing fluctuating agitation and sedative state he was sedated, intubated and monitored in the intensive care unit (ICU). Full blood count, electrolytes and liver function tests were normal. He was extubated the following day with normal vital signs and admitted to taking 30 g of phenibut. He was assessed by the psychiatry team, deemed not to be a suicide risk and was discharged with community follow-up. Past history included depression and three similar ED presentations following exposure to phenibut. Two of these had resulted in ICU admission. He purchased the phenibut product over the Internet for anxiety and insomnia and had been taking 2 g every night for 6 weeks. A sample of the powder labeled phenibut was supplied by the patient and analysed using nuclear magnetic resonance spectroscopy (NMS) and gas chromatography-mass spectrometry (GCMS). The purity of the powder was 98% 4-phenyl-2-pyrrolidinone, the lactam of phenibut.

**Conclusion:** In this case exposure to phenibut lead to clinical toxicity characterised by significant fluctuation in conscious state, including severe agitation requiring general anesthetic sedation and care in a critical care environment. Regulatory agencies in Australia should review interventions that may limit further harm associated with exposure to phenibut.

#### 149. How to evaluate the severity of lithium-poisoned patients admitted to the intensive care unit?

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**Objective:** Lithium poisoning may be complicated by neurological and cardiovascular failure and management remains difficult in the absence of predictive factors of severity. The objectives of our study were to describe lithium-induced complications and to analyze the prognosticators on admission in a cohort of poisoned patients admitted to the ICU.

**Methods:** We conducted a retrospective study including all the patients admitted during 20 years in our ICU with plasma lithium concentrations > 1.5 mM. Poisoning severity was defined by the onset of seizures, requirement of catecholamine infusion or mechanical ventilation for > 48 hours. Demographic, clinical and toxicological data were obtained. Results were expressed as percentage or median [interquartile interval]. Parameters significantly

associated with severity were identified using a multivariate analysis by logistic regression ( $p < 0.05$ , SAS© software). Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

**Results:** In total 128 patients (M/F ratio, 0.66), aged 46 years [35; 55] were included. The Simplified Acute Physiology Score (SAPS II) for these patients was 30 [19; 44] with acute (A, 12%), acute-on-chronic (AC, 64%) and chronic lithium poisoning (C, 26%). The ingested dose was 8.0 g [1.2; 2.4] and the plasma lithium concentration on admission and at the peak was 2.8 mM [1.9; 4.1] and 3.2 mM [2.3; 5.4], respectively. About 40% of patients had ingested other drugs (ethanol and benzodiazepines mainly). Neurological complications were Glasgow Coma Scale (GCS) on admission (14 [11; 15]); the worst GCS during ICU stay (12 [7; 14]) and the onset of seizures (8%) were not different between the 3 groups. A significant alteration in consciousness (GCS < 7) was more frequently observed in A and AC groups ( $p = 0.002$ ) while patients in the C group more frequently developed confusion, myoclonus and hypertonia ( $p < 0.01$ ). Cardiovascular complications included shock (20%), sudden bradycardia (2%) and asystole (2%). Other observed complications were aspiration pneumonia (34%), rhabdomyolysis (9%) and nephrogenic diabetes (10%). Poisoning was severe in 38% of the cases. Using multivariate analysis, sustained release lithium (OR, 2.84; CI, [1.07; 8.50],  $p = 0.04$ ), plasma lithium (OR, 1.34; CI, [1.08; 1.74];  $p = 0.008$ ), GCS (OR, 0.75; CI, [0.65; 0.86],  $p < 2.10^{-5}$ ) and serum creatinine (OR, 1.003; CI, [1.001; 1.010];  $p = 0.1$ ) predicted the onset of severity (AUC, 0.82 CI, [0.73; 0.82]; sensitivity was 70%, specificity 87% and the positive predictive value 76% (negative predictive value 83%). Four patients died (only in the AC group). The ICU stay length was 5.0 days [2.5; 10.5] and was significantly longer in the C group ( $p = 0.004$ ). On ICU discharge, group C patients were more frequently confused ( $p = 0.003$ ) while A and AC group patients were more frequently asymptomatic.

**Conclusion:** Lithium poisoning may be life-threatening. Identification of prognosticators (sustained release, GCS, serum creatinine and lithium concentration) may allow an optimal management in the ICU by improving hemodialysis indications.

#### 150. Admission criteria in pediatric intensive care units in acute poisoning

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**Objective:** To assess the specific clinical aspects of acute poisoning cases admitted in the Pediatric Intensive Care Unit (PICU) and to establish the main admission criteria in these cases.

**Methods:** We performed a 5-year retrospective study (2010 to 2014) of children with acute poisoning admitted in the PICU, taking into consideration the following aspects, etiology, age, clinical manifestations and length of stay. For evaluation of the admission criteria in PICU, we used a control group consisting of all cases

with acute poisoning having the same etiology that were admitted in the Toxicology Department.

**Results:** Out of the total of 6,435 acute poisoning cases admitted in our hospital in the specified period, 102 children were treated in PICU. The children were aged between 28 days and 17 years, with a median age of  $9.06 \pm 6.05$  years and two peaks of incidence (2-5 years and 13-16 years). The main substances involved in these cases were cholinesterase inhibitor insecticides, carbamazepine, cardiovascular agents and nitrates. Mechanical ventilation was performed in 31 patients (30.4%). The main clinical manifestations were coma (60.8%,  $n = 62$ ), seizures in 16 cases (15.7%), acute respiratory failure and respiratory arrest 7 cases (6.9%), acute liver failure (4.90%,  $n = 5$ ), acute pulmonary edema (2.9%,  $n = 3$ ), acute renal failure (2.9%,  $n = 3$ ), cardiac disturbances (2.9%,  $n = 3$ ) and multiple system organ failure (1.0%,  $n = 1$ ). There were 11 deaths (10.8%) and the implicated agents in these cases were cholinesterase inhibitors insecticides ( $n = 7$ ), nitrates ( $n = 2$ ), hydrocarbons ( $n = 1$ ) and abuse substances ( $n = 1$ ). Comparing cases admitted in PICU within the control group consisting of 1,474 patients the main clinical signs leading to admission in PICU were coma, seizures, acute respiratory failure and respiratory arrest. The length of hospitalization in PICU was between 1 hour and 23 days with a median value of  $2.1 \pm 3.6$  days.

**Conclusion:** In poisoned children the rate of severe cases needing admission in PICU is low, about 1.6% in our study, nevertheless these are life-threatening situations with mortality of 10.8%. The main admission criteria in PICU for poisoned children are coma, seizures, acute respiratory failure and respiratory arrest.

### 151. Prolonged mixed metabolic and toxic encephalopathy in carbamazepine poisoning

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**Objective:** Carbamazepine, a carbamylated derivative of iminostilbene, structurally related to the cyclic antidepressants, is used as an antiepileptic and also in the treatment of bipolar disorder and neuropathic pain. The clinical manifestations of toxicity involve the central nervous, cardiovascular and respiratory systems.

**Case report:** A 48-year-old female, with no relevant medical history, was admitted 6 hours after ingestion of 40 tablets of her son's carbamazepine 200 mg in a suicidal attempt. On admission she had deep coma (Glasgow Coma scale [GCS] 3), intermediary pupils, BP 160 mmHg, heart rate 120 bpm with sinus rhythm and diuresis. She was intubated with no pulmonary rales. A cerebral CT scan was normal. The blood concentration of carbamazepine was 22.57 mg/L (therapeutic 6-12 mg/L) and carbamazepine and metabolites were present in urine. A complete blood count showed no abnormality except an ammonia concentration of 46  $\mu\text{mol/L}$  (normal 33), with normal hepatic enzymes and only a slightly elevated creatine kinase. She was given a gastric lavage, activated charcoal, ventilator support, fluid resuscitation and alkaliniza-

tion. Over the next 2 days she remained deeply comatose, with carbamazepine blood concentrations of 20.58 and 24.10 mg/L and ammonia concentration of 40 and 46  $\mu\text{mol/L}$ . On day 5 the carbamazepine concentration was 18.3 mg/L. The ammonia concentration increased to 57  $\mu\text{mol/L}$  and her neurological status remained unchanged. On day 7, at a carbamazepine concentration of 5.62 mg/L, the patient opened her eyes spontaneously, but was agitated and uncooperative. Her ammonia concentration was 83  $\mu\text{mol/L}$ . With slight sedation and at a carbamazepine concentration of 3.12 mg/L and ammonia concentration 38  $\mu\text{mol/L}$  she was weaned from ventilatory support (day 10) and had a favorable outcome. She was discharged after 15 days of hospitalization in good physical condition and referred to a psychiatric unit.

**Conclusion:** Prolonged encephalopathy in this case was due to the neurotoxicity of carbamazepine in addition to metabolic hyperammoninemia. The mechanism of carbamazepine-induced hyperammoninemia is not understood.

### 152. Acute lipoid pneumonia presenting as acute coronary syndrome in an amateur fire breather

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**Objective:** Lipoid pneumonia, injury and infection from the aspiration of hydrocarbons, initially described in the 1920s has decreased due to less common use of mineral oils as nasal drops and laxatives.<sup>1</sup> Cases continue to persist, now more commonly seen in as a professional hazard of fire-eaters. Patients presenting with pneumonia secondary to acute hydrocarbon pneumonitis present similar to other infectious pneumonias.<sup>2</sup> We present a novel case of a patient with hydrocarbon aspiration who presented with symptoms of acute coronary syndrome (ACS) without fever or shortness of breath and having electrocardiogram (ECG) abnormalities.

**Case report:** The patient had increasing left-sided chest pain with radiation to the left arm coupled with an ECG demonstrating inferior lead t-wave inversion. Evaluation for acute coronary pathology included a chest X-ray demonstrating consolidation in the left lung base, at which point the patient disclosed his history of fire breathing. Symptom progression led to concern for pulmonary embolism and chest CT demonstrating near collapse of the left lower lobe and atelectasis in the right middle and lower lobes. The case concludes with management via physical pulmonary interventions of chest physiotherapy and positive end expiratory pressure therapy rather than pharmacologic interventions.

**Conclusion:** Of the varied case reports of patients with acute exogenous lipoid pneumonia, typically patients present with symptoms of infectious pneumonia. This case demonstrates a novel presentation of isolated chest pain with ECG findings concerning for ACS in an amateur fire breather.

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### 153. Paroxysmal atrial fibrillation after cannabis smoking

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**Objective:** Cannabis is the most widely used illicit drug worldwide. In addition to central nervous system side effects cardiovascular adverse effects like vasovagal syncope, myocardial ischemia and different forms of arrhythmia have been described. We describe paroxysmal atrial fibrillation after cannabis use in a previously healthy male.

**Case report:** A previously healthy 18-year-old male, an occasional marijuana smoker, was found comatose with paroxysmal atrial fibrillation (AF) after a private party. On admission he was drowsy, with bilateral miosis, ventilator support, normal pulmonary sounds, BP 90/60 mmHg, irregular heart beat at a frequency of 120-180, no fever and normal diuresis. An ECG showed AF, narrow QRS complexes and no ST-T abnormalities. Toxicological screening on admission was negative for ethanol in blood and positive for tetrahydrocannabinol (THC) in urine. A cerebral CT scan was normal. Troponin and creatine kinase (CK-Mb) were within the normal range. Transthoracic echocardiography showed cavities with normal dimensions, no kinetic abnormalities, global systolic function 60% and diastolic function AF. A complete blood count, electrolytes, thyroid tests and acid-base equilibrium were normal. The treatment was supportive; in addition to antiplatelet drugs and anticoagulants, pharmacologic cardioversion was tried. The patient was weaned from ventilator support 7 hours after admission; he was conscious, with normal breathing and normal laboratory blood tests. A toxicological urine screening at 6 hours was positive for THC. The arrhythmia persisted at high frequency despite antiarrhythmic medications. Transesophageal echocardiography showed normal cavities, with no dilatation, no thrombosis, normal filling and emptying velocities and left ventricle normokinetics. It was decided to perform electric cardioversion under analgesedation; he was administered synchronised biphasic 100 J electric shock and reverted to sinus rhythm at 60 bpm. The outcome was favorable and the patient was discharged in good physical condition.

**Conclusion:** In this healthy young patient, no other aetiology except cannabis consumption was found for his paroxysmal atrial fibrillation. The arrhythmic cardiovascular effects of cannabis are rare. Some studies have shown that cannabinoids have an action on cardiovascular regulatory centers and on peripheral autonomic system through the CB<sub>1</sub> cannabinoid receptor.<sup>1</sup> Other studies have shown that cannabis might have a direct effect on autonomic activity or on Purkinje fibres, and on coronary microcirculation.<sup>2,3</sup>

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### 154. Atypical neuroimaging findings in a patient presenting with overdose: A case report

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**Objective:** The most frequent abnormalities found after hypoxic-anoxic injuries on CT scan are bilateral hypodensity of the globi pallidi.<sup>1,2</sup> We report a case of a patient presenting with isolated bilateral cerebellar infarcts whose diagnosis initially was a cerebrovascular accident rather than anoxia from drug overdose.

**Case report:** A 67-year-old female was transferred from an outside hospital after she was found unconscious. She was noted to be unarousable, and a CT scan of the head showed bilateral cerebellar infarcts on a non-contrast CT of the brain, concerning for ischemic stroke. Tissue plasminogen activator (tPA) was not administered as she was deemed to be outside the therapeutic window. On arrival to our facility, she was comatose and intubated with a National Institutes of Health Stroke Scale (NIHSS) of 25. CT angiogram of the head and neck showed patent vessels. Unenhanced MRI of the brain again revealed bilateral inferior cerebellar infarcts, restricted diffusion of supratentorial cortex and right lentiform nucleus suggestive of global hypoperfusion injury. A review of the patient's history revealed that she was depressed, and had several tablets on her chest when first found. A urine toxicology screen was positive for benzodiazepines and opiates. A comprehensive toxicologic analysis revealed flurazepam, oxycodone metabolite, ibuprofen, diphenhydramine, acetaminophen, caffeine, tramadol, buspirone and topiramate. The patient died 3 days later after the family made the decision for withdrawal of care.

**Conclusion:** Hypoxic-anoxic brain damage follows a typical pattern on the CT depending upon the selective vulnerability of different areas of brain. Severe global hypoxic-ischemic injury in this population primarily affects the gray matter structures: basal ganglia, thalami, cerebral cortex, cerebellum and hippocampi. It is important that toxicologists are aware that hypoxia-anoxia on CT scan can present as variable abnormalities. This will prevent delay in diagnosis as well as treatment.

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### 155. Clinical profile, management and outcomes of severely poisoned patients requiring critical care: Experience of a poison treatment centre in Hong Kong

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**Objective:** Poisoning is an important cause of organ dysfunction and metabolic derangements and patients who are severely



poisoned often require critical care. We report our experience of managing severely poisoned patients requiring critical care at the Prince of Wales Hospital Poison Treatment Centre (PWHPTC), a tertiary referral centre for poisoning management in Hong Kong.

**Methods:** We evaluated the clinical profile, management and outcomes of all patients requiring admission to the intensive care unit, high dependency unit and coronary care unit for poisoning at the PWHPTC.

**Results:** From January 2011 to October 2014, 1502 patients (male:female 557:944, median age 45 years, range 2 months to 98 years) with poisoning received treatment at the PWHPTC. Of these 75 patients (male:female 38:37, median age 49 years, range 6 months to 92 years) with poisoning were admitted to the intensive care unit (n = 68), coronary care unit (n = 2) or high dependency unit (n = 5) for management. A total of 122 agents were involved and 32 patients (43%) were poisoned with more than one agent. The most common agents involved were sedatives/hypnotics (n = 25), antipsychotics (n = 11), cardiovascular drugs (n = 8), herbal medicines (n = 8), antidepressants (n = 7) and household chemicals (n = 7). Most patients took the overdose as a suicidal attempt (n = 44, 58.7%) and accidental poisoning occurred in 11 patients (14.6%). Thirteen patients (17.3%) were diagnosed as having adverse events to drugs/herbs and the other 7 patients required critical care for substance abuse. The most common conditions requiring critical care were neurological conditions e.g. impaired conscious level, seizures (n = 39), cardiovascular complications e.g. arrhythmias, hypotension (n = 16) and airway problems/respiratory failure (n = 7). Forty-one patients (54.7%) received airway management with or without ventilation support and 17 patients (22.7%) required antiarrhythmic agents and/or inotropic drugs for hemodynamic support. Twenty patients (26.7%) received specific antidotes and hemodialysis was used in two cases to enhance elimination of toxins. All patients survived and the median duration of stay in the critical care units was 3 days (range 1-39 days).

**Conclusion:** Intensive care plays an important role in the management of poisoning. Most patients responded to intensive support care while specific treatment and antidotes were necessary for selected patients.

### 156. Analysis of clinical factors that predict diagnosis in suspected acute poisoning

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**Objective:** The diagnosis of acute poisoning depends on an accurate history. Concordance of a history of poisoning with laboratory diagnosis varies.<sup>1,2</sup> A history of paracetamol poisoning is moderately reliable whilst reliability of a history of illicit drug poisoning is low to moderate.<sup>3,4</sup> The objective of the study is to use regression analysis of significant clinical risk factors to develop a diagnostic prediction model.

**Methods:** A retrospective analysis of 677 patients with suspected acute poisoning was performed. Risk factors for the diagnosis of acute poisoning were identified by univariate analysis and a prediction model was developed using logistic regression and tested by receiver operating characteristic (ROC) curve analysis.

**Results:** A prediction model using logistic regression identified the following significant risk factors: age less than 50 years, a

history of poisoning, a negative history of trauma, a history of alcohol ingestion and a history of psychiatric treatment with an adjusted odds ratio of 2.37 (1.42-3.94, p = 0.001), 70.93 (25.02-201.06, p < 0.001), 6.74 (3.50-12.96, p < 0.001), 10.63 (5.08-22.24, p < 0.001) and 1.71 (1.04-2.81, p = 0.035) respectively. ROC curve analysis showed an AUROC of 0.866 (0.838-0.894, p < 0.001) for the prediction model compared to 0.788 (0.748-0.828, p < 0.001) for a history of poisoning alone.

**Conclusion:** Despite the high odds ratio for a positive history of poisoning, other risk factors still retained an independent influence in the prediction model. Using regression analysis, a multi-factorial prediction model accurately predicted the diagnosis of acute poisoning.

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### 157. Analysis of risk factors that predict severity of acute poisoning

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**Objective:** Risk factors correlating with poisoning severity include age, intentional poisoning, respiratory and circulatory failure, unresponsiveness and seizures.<sup>1-3</sup> The Glasgow Coma Scale (GCS) and the Poison Severity Score (PSS) have prognostic value and have been validated clinically.<sup>4,5</sup> The objective was to identify factors related to severity and compare the prognostic value of single and composite risk factors.

**Methods:** A retrospective study was carried out in a general hospital registering > 100,000 emergency patients/year, comparing clinical, electrocardiographic and biochemical parameters of 350 patients (aged ≥ 14 years), with a diagnosis of acute poisoning established from clinical findings and laboratory results. The PSS was computed automatically from inputted parameters using database queries. Single parameters and composite clinical scores in two groups of poison severity (PSS ≤ 1 and PSS > 1) were compared.

**Results:** GCS, pH and pCO<sub>2</sub> were significant continuous risk factors of severity of poisoning. The clinical scores modified Early Warning Score (MEWS) ≥ 1, alert, voice, pain, unresponsive (AVPU) > 1 and AVPU > 2 showed significant risk for severity with Odds Ratio of 4.91 (95% CI 2.96-8.14; p < 0.001), 14.05 (95% CI 7.02-28.13; p < 0.001) and 115.74 (95% CI 26.69-502.00; p < 0.001), respectively. Separate univariate regression analyses showed that all three clinical scores (MEWS, AVPU and GCS) had a significant prognostic risk with adjusted Odds Ratio 2.635, 8.234 and 3.344, respectively. Receiver operating characteristic (ROC) analysis showed similar AUC values: 0.805 (95% CI 0.710-0.899;

$p < 0.001$ ) for MEWS, 0.847 (95% CI 0.760-0.934;  $p < 0.001$ ) for AVPU and 0.843 (95% CI 0.754-0.932;  $p < 0.001$ ) for GCS.

**Conclusion:** Individual factors have limited utility as predictors of severity of poisoning, whereas composite clinical scores were more predictive. The AVPU scale may be a more practical clinical tool for risk stratification of acute poisoning to guide initial care in acute poisoning.

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## 158. Importance of abdomen CT scan and gastroscopic pharmacobezoar removal following massive acute drug overdose

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**Objective:** Pharmacobezoar formation following massive drug ingestion can have serious implications and it is important to consider the formation of bezoars in the treatment of acute drug overdose.<sup>1</sup>

**Case series:** We describe three cases of pharmacobezoar formation following massive drug ingestion and the importance of CT evaluation as a diagnostic tool and upper gastrointestinal (GI) endoscopy removal as a decontaminating technique. Three patients were admitted to the Emergency Department (ED) with life-threatening signs and symptoms for psychoactive drug overdose (valproic acid, mirtazapine and quetiapine) requiring advanced life support. All patients underwent gastric lavage with a large bore orogastric probe (42 French). Considering the high number of ingested tablets (mean of 109 tablets per patients), drug formulation (extended release drug) and serious clinical symptoms presented at the admission to ED, abdomen tomography was performed in order to determine if gastric drug bezoar formation had occurred. Abdomen CT-scan revealed the presence of gastric bezoars in each patient. Subsequently, upper GI endoscopy was performed and the

bezoar successfully removed thereby reducing drugs absorption. The average time for eyes opening and extubation in these patients was  $33 \pm 7$  hours (mean  $\pm$  SD) and the average length of stay was  $10 \pm 3$  days (mean  $\pm$  SD). No mechanical complications due to repeated upper GI endoscopy were reported.

**Conclusion:** After massive drug overdose involving extended release drug formulations pharmacobezoar formation should be suspected. Therefore, abdomen CT scan should be performed in order to allow adequate GI decontamination by upper GI endoscopy pharmacobezoar removal and to improve clinical outcome.

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## 159. Endoscopic retrieval of enteric-coated aspirin tablets in massive overdose

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**Objective:** Pharmacobezoar is a described complication of enteric-coated aspirin treatment and overdose.<sup>1</sup> However, endoscopic retrieval of retained pill fragments following potentially life-threatening aspirin ingestion to prevent continued absorption has not been previously described. We describe such a case.

**Case report:** A 35-year-old female presented to the Emergency Department (ED) after taking 474 x 325 mg enteric-coated aspirin tablets as a suicide attempt 7 hours prior to arrival. On arrival the patient was awake and alert with complaints of nausea, vomiting and abdominal pain but denied having tinnitus. The patient's vital signs on arrival were blood pressure 135/73, heart rate 113 beats/minute, respiratory rate 16, oxygen saturation 99% on room air, temperature 98.2°F. The patient's initial labs included a salicylate concentration of 60.2 mg/dL, blood gases pH 7.43 mmHg, pCO<sub>2</sub> 27 mmHg, pO<sub>2</sub> 109 mmHg, bicarbonate 17.5 mEq/L, anion gap 16.4. Whole bowel irrigation (WBI) using polyethylene glycol (PEG) via a nasogastric tube, and sodium bicarbonate infusion were initiated in the ED. Despite bicarbonate therapy and WBI the salicylate concentration rose to 76.5 mg/dL. She became more confused and agitated requiring intubation with repeat vital signs notable for temperature 102.1°F, heart rate 150 beats/minute, blood pressure 153/81 and a repeat salicylate concentration of 103.4 mg/dL (14 hours post-ingestion), then 151.6 mg/dL 2 hours later. The patient was noted to be hypotensive, requiring norepinephrine and neosynephrine for pressor support. Given concern for severe toxicity with possible retained aspirin tablets, we consulted with a gastroenterologist who performed an endoscopy 18 hours post-ingestion, removing multiple intact pills as well as concretions. Immediately after endoscopy, a repeat salicylate concentration was 104.6 mg/dL and continuous veno-venous hemodialysis (CVVHD) was initiated. The patient's salicylate concentration trended down: 113.2 mg/dL, then 94.4 mg/dL (6 hours post-endoscopy) at which time hemodialysis (HD) was initiated and the patient's subsequent salicylate concentration fell to 33.1 mg/dL after 4 hours of HD.

The patient required vasopressor support for 1 additional day, and was extubated on hospital day 4, with a normal mental status on hospital day 5. The patient continued to improve, but remained hospitalized for persistent renal failure.

**Conclusion:** Endoscopic removal of concretions and aspirin pill fragments, in addition to aggressive supportive care and enhanced elimination is a consideration in preventing further salicylate absorption and mortality in life-threatening salicylate overdose.

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## 160. Acute poisonings and rhabdomyolysis: A 10-year retrospective study in a medical university clinic

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**Objective:** Rhabdomyolysis is a well-known complication in poisoned patients, with acute kidney injury (AKI) as a serious complication. There are only a few larger studies on the subject and there are no recent and relevant studies from Europe. Therefore, we performed a 10-year retrospective study including all patients treated for rhabdomyolysis in a medical clinic, studying clinical characteristics, aetiologies, treatment, complications and mortality. Further, we studied correlations between creatine kinase (CK), myoglobin and creatinine (as a marker of renal function and thereby AKI), and whether CK/myoglobin ratio is a predictor of AKI in this patient group.

**Methods:** The study included all patients treated for rhabdomyolysis at the Department of Medicine, Oslo University Hospital, from 2003 and until the end of 2012. Rhabdomyolysis was defined as serum CK values greater than 5 times the upper limit of normal, and AKI was defined as an increase in serum creatinine above the upper limit of normal range.

**Results:** In total 341 patients met the inclusion criteria; 67% were males and median age was 54 years (range 17–99). AKI occurred among 51%, and 10% required dialysis. Mortality in the group as a whole was 4%. The most common cause for rhabdomyolysis in this non-surgical cohort was acute poisoning. This aetiology, however, was complex and based on the three major predisposing factors, immobilization (60%), prescription drugs (55%) and illicit drugs and/or alcohol (35%). The maximum serum CK and myoglobin correlated equally to creatinine values for the included patients. Logistic regression showed that the S-myoglobin value was better in predicting the development of AKI than the CK. The CK/myoglobin ratio was also a good predictor for AKI; values lower than 5.70 increased the likelihood of developing AKI, whereas higher values indicated that development of AKI was less likely.

**Conclusion:** Acute poisoning was the most common cause of rhabdomyolysis in this medical cohort, but it was difficult to assess whether the cause was the medication/toxic agent per se or the resulting immobilization from coma. S-myoglobin was a better predictor for AKI than CK, and the CK/myoglobin ratio could be useful to assess the likelihood of developing AKI.

## 161. Modern intermittent haemodialysis (IHD) is an effective method of removing salicylate in chronic topical salicylate toxicity

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**Objective:** To describe a case of modern IHD including extraction ratios and expected efficacy in a case of topical salicylate toxicity initially diagnosed as asthma. There is a paucity of literature on modern dialysis efficacy on salicylate removal.

**Case report:** A 54-year-old, 100 kg male presented with worsening dyspnea over one week and was diagnosed with asthma. He had a past history of type 2 diabetes mellitus and hypertension. He had applied a 100 g tube of Dencorub Extra Strength Heat Gel<sup>®</sup> (methyl salicylate 26%) daily for the previous week for aches and pains; equivalent to 260 mg/kg/day of methyl salicylate (360 mg/kg/day salicylate). The patient did not have a cough, fever, wheeze, infective symptoms or a past history of asthma. He complained of nausea and vertigo but no tinnitus. On examination he was afebrile, with a blood pressure of 144/72 mmHg, a respiratory rate of 33, heart rate 95 and an oxygen saturation of 98% on room air. His chest was clear with a soft abdomen and normal mental state. Laboratory analyses revealed blood gas pH 7.45 (7.35–7.45), HCO<sub>3</sub> 10 mmol/L (22–25), pCO<sub>2</sub> 14 mmHg (35–45), base excess 14, lactate 0.9 mmol/L (0.5–1.6) with a raised anion gap of 30. Renal function showed mild impairment (creatinine 122 micromol/L; reference 90–100). The blood salicylate concentration was 5.7 mmol/L (normal < 0.4 mmol/L). He was diagnosed with chronic salicylate toxicity and started on urinary alkalinisation. Given the elevated salicylate concentration and clinical state, he was also started on IHD and dialysed for 5 hours. Multiple salicylate concentrations were taken from the afferent and efferent limbs of the dialysis machine. Extraction ratios were calculated (0.44), clearance rates (78.5 mL/min) and expected efficacy (1.96) (Kt/V where K = instantaneous clearance, t = minutes, V = volume of distribution). Salicylate concentrations declined rapidly following initiation of haemodialysis with minimal rebound observed. His clinical state improved and he was discharged on day 3 after hospital presentation.

**Conclusion:** Modern IHD is an effective method of removing salicylates after chronic topical toxicity.

## 162. Massive carbamazepine overdose treated with continuous veno-venous hemodialysis

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**Objective:** Carbamazepine (CBZ) overdose can result in significant neurologic and cardiovascular toxicity and is compounded



by the presence of an active metabolite, carbamazepine-10,11-epoxide (CBZE).<sup>1</sup> Hemodialysis (HD) has previously been shown to be effective in removing CBZ with clearance ranges from 40-64 mL/min (mean 53.6 mL/min).<sup>2</sup> The efficacy of continuous venovenous hemodialysis (CVVH) in eliminating CBZ and CBZE has not been previously described. We report a fatal case of CBZ overdose in which CVVH was utilized. Using time-of-flight mass spectrometry, CBZ and CBZE concentrations were measured in both serial serum samples and in CVVH effluent in order to calculate extracorporeal clearances.

**Case report:** A 41-year-old woman was found unresponsive and asystolic after ingestion of an unknown quantity of CBZ and valproic acid. Advanced Cardiovascular Life Support (ACLS) was administered with successful return of spontaneous circulation. The patient required vasopressors and ventilator support in the intensive care unit. Initial CBZ serum concentrations were markedly elevated (70.6 mcg/mL) and continued to rise despite the administration of activated charcoal (74.1 mcg/mL at 6.5 hours). Due to the patient's continued hemodynamic instability, extracorporeal removal was initiated using CVVH (Prismaflex®). Over the first 30 hours, CVVH removed a total of 1,293 mg and 1,261 mg of CBZ and CBZE, respectively. The clearances achieved for CBZE (mean 25.2, range 17.7-42.6 mL/min) exceeded that for CBZ (mean 18.1, range 12.7-28.7 mL/min). The serum concentrations of CBZ only declined by 7.8 mcg/mL (mean 45.65, range 49.5-41.7), while CBZE increased by 15 mcg/mL (mean 30.84, range 21.7-37.6). The patient subsequently underwent further CVVH and intermittent HD with gradually declining CBZ and CBZE concentrations over 10 days. Unfortunately, she was declared brain dead and expired during weaning of supportive care.

**Conclusion:** CVVH effectively removed CBZ and CBZE with higher clearances for CBZE, probably attributable to its lower degree of protein binding. During CVVH, serum CBZ concentrations declined slightly while CBZE concentrations increased. This likely reflects continued and prolonged absorption of CBZ coupled with conversion to and accumulation of CBZE. Our sampling methodology allowed a pharmacokinetic assessment of an extracorporeal procedure in an overdose case of a drug with evidence of continued and prolonged gastrointestinal absorption.

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### 163. Accidental intrathecal administration of bleomycin: Favourable outcome after cerebrospinal fluid exchange

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**Objective:** Bleomycin is an antineoplastic agent used for the intravenous treatment of lymphomas. The inadvertent intrathecal injection of antineoplastics continues to occur despite the development of preventative strategies. We report a patient who mistakenly received intrathecal bleomycin for lymphoma. Prompt cerebrospinal fluid (CSF) exchange resulted in a positive outcome without major adverse effects.

**Case report:** A 55-year-old man with diffuse large B-cell lymphoma had been treated since 24 January 2014 according to the R-ACVBP protocol (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) every other week. Intrathecal methotrexate was administered simultaneously. After one cycle, the response was excellent and the chemotherapy seemingly well tolerated. During the fourth cycle of chemotherapy, bleomycin instead of methotrexate was mistakenly injected intrathecally. The error was identified approximately 1 hour post-injection. To limit potentially toxic effects of bleomycin, CSF was removed and replaced by normal saline solution. This procedure was repeated on 8 occasions over a period of 45 minutes with a total of 137 ml CSF removed and replaced by 80 ml normal saline. The patient only experienced moderate pain during the procedure. In addition 40 mg dexamethasone was given to prevent cerebral edema. Neurological monitoring at the end of the procedure and then every 4 hours was uneventful. The chemotherapy was postponed temporarily. On day 5 post-injection, the patient complained of rotary vertigo that improved after symptomatic treatment. A cerebral MRI showed no abnormalities except a small subdural hemorrhage. On day 24 post-injection, the patient experienced a new episode of vertigo associated with nausea, vomiting and nystagmus. Complementary investigations were performed and one month later a bilateral vestibular loss was diagnosed. These symptoms were not the consequence of accidental intrathecal administration of bleomycin. Six months post-injection, a disease remission was confirmed with the patient in good general condition.

**Conclusion:** Limited data are available for the management of inadvertent intrathecal injections. To our knowledge, this is only the second case reported with bleomycin and a favorable outcome after CSF exchange.<sup>1</sup> Successful CSF exchanges have also been reported after intrathecal methotrexate or cytarabine overdose. Unfortunately, even immediate CSF lavage after intrathecally administered vincristine generally leads to a fatal outcome probably because of irreversible central nervous toxicity. Our case suggests that CSF exchange is an adequate option to remove intrathecal bleomycin without major adverse effects probably because of the low neurotoxic potential of this drug.

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### 164. Complete spinal paralysis following a brachial plexus block treated with lipid infusion

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**Objective:** Interscalene (brachial plexus) anesthetic blocks are routinely employed for many surgical procedures, especially ones involving the shoulder. Complete spinal paralysis and spinal shock after this type of block is extremely rare. We present a case of severe bupivacaine toxicity involving this anesthetic block in which the patient had complete spinal paralysis and was treated with Intralipid® infusion.

**Case report:** A 56-year-old woman underwent uncomplicated left shoulder bone spur removal under general anesthesia (2 mg midazolam, 100 mcg fentanyl, 150 mg propofol and sevoflurane) in an outpatient surgery center. Afterwards, the anesthesiologist performed a brachial plexus block for post-operative pain control utilizing 30 mL of bupivacaine (0.25%). Shortly after completion of the block, the patient developed bilateral widely dilated pupils, respiratory arrest and hypotension. The patient was intubated, administered IV fluids, ephedrine (15 mg IV) and transferred to an emergency department (ED). On arrival her vital signs were: BP 108/56 mmHg, pulse 86/minute and respiratory rate 24/minute on a ventilator. Her pupils were 6 mm bilaterally with no response to light. She had no response to painful stimulation and had spontaneous respirations on a ventilator. Her initial blood tests were significant for a phosphorus of 1.7 mg/dL and lactate of 4 mmol/L. The remainder of the biochemical parameters were normal. In the ED she was administered a fluid bolus (1 L saline) and 20% intravenous lipid emulsion (85 ml IV). Over the next 4 hours the patient progressively regained motor and sensory functions followed by successful extubation in the ED. She was admitted to the hospital and discharged the next day without any neurologic sequelae.

**Conclusion:** We present a case of complete spinal paralysis and spinal shock following a brachial plexus block. The patient was treated with intravenous lipid emulsion, which was temporally associated with improvement. The role of Intralipid® is unclear for similar complications associated with local anesthetic use.

## 165. Hemodialysis in glycine toxicity

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**Objective:** Glycine is a widely used in irrigation fluid during gynecologic and urologic procedures due to its low electrical conductance. Massive absorption with toxicity has been associated with its use in these types of procedures. We report a case of severe glycine toxicity with profound hyponatremia, pulmonary edema and status epilepticus successfully treated with hemodialysis. We were unable to find any similar cases of glycine toxicity treated with this modality and believe that this is the first case reported.

**Case report:** A 43-year-old woman with a history of uterine fibroids underwent transvaginal uterine myomectomy in preparation for *in vitro* fertilization at an outpatient surgery center. During the procedure she was irrigated with 10 liters of 1.5% glycine with vaginal output of only 2 liters. The procedure was aborted when her pulse oximetry reading was noted to be abnormal and she had frothy pink sputum from her laryngeal mask airway. She was intubated and transported to the emergency department (ED) for further evaluation. Upon arrival in the ED, her serum sodium was 102 mmol/L and her ammonia 727 mcmol/L. Shortly after ED

arrival she had witnessed tonic-clonic seizure activity. In addition, she had pulmonary edema on chest X-ray. She was initially treated with 3% saline with rapid normalization of serum sodium to 112 mmol/L within 60 minutes and her seizure activity resolved. The hypertonic saline infusion was discontinued and 0.9% saline infusion was initiated. At 3 hours, her serum sodium was 118 mmol/L. For her pulmonary edema, she was treated with furosemide resulting in urine output of 3 L within the first 2 hours. A video EEG revealed ongoing subclinical seizure activity despite propofol and midazolam infusions and hemodialysis was initiated for glycine toxicity. Her subclinical seizure activity resolved during a 4 hour course of intermittent hemodialysis which was then followed by continuous venovenous hemofiltration. At 24 hours her serum sodium had risen to 130 mmol/L. At 48 hours she was extubated and she recovered without neurologic sequelae.

**Conclusion:** We present a case of severe glycine toxicity associated with hyponatremia and status epilepticus. Hemodialysis, used in this case, may be helpful when aggressive management with sodium infusion and supportive care are inadequate.

## 166. Safety and efficacy of phenobarbital for benzodiazepine detoxification

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**Objective:** Benzodiazepine use can result in clinical issues such as memory impairment, dependence and abuse.<sup>1</sup> Withdrawal symptoms can vary from simple rebound anxiety to life-threatening seizures. Severity is associated with short-acting benzodiazepines, prolonged or high-dose use.<sup>2</sup> Although multiple clinical approaches are used, limited data are currently available on the safety and effectiveness of benzodiazepine detoxification protocols. A fixed-dose phenobarbital taper, a long-acting cross-tolerant medication, has been used by our Clinical Toxicology Unit for 30 years. We undertook this study to formally investigate its safety and effectiveness.

**Methods:** Using our database, a retrospective study was carried out in order to evaluate all patients treated with fixed-dose phenobarbital taper for benzodiazepine detoxification from January 2006 to December 2012. The primary outcomes, assessed during hospital stay and at the 1st and 12th month after discharge, were safety, tolerability and efficacy of protocol.

**Results:** Over the 6-year study period 213 patients were treated, median age 41 years, 60% male (n = 129). Of these 46% (n = 98) of patients were solely addicted to benzodiazepine, while 54% (n = 115) had concomitant abuse with alcohol, opioids or both. Overall, 12 different benzodiazepines were abused, with lorazepam the most commonly used (n = 84, 32%). Psychiatric comorbidity was found in 76% of patients (n = 162), with anxiety and depression disorders as the most prevalent. No major adverse phenobarbital side effects were observed and no patients showed any severe benzodiazepine-related withdrawal syndrome. Average hospital length of stay was 8.5 days. All patients were treated initially with 50-100 mg phenobarbital every 8 hours, on the basis

of referred abuse and adjusted on account of symptoms. Phenobarbital was progressively tapered during hospitalization and rehabilitation. The tolerability of the protocol was confirmed by the low drop-out rate (10%,  $n = 22$ ). At time of discharge, 70% ( $n = 132$ ) of patients were completely benzodiazepine-free. Phenobarbital was completely tapered off over in a 3 month period. Analyzing the relapse rate of the treated patients during the years 2011-2012, 70% ( $n = 32$ ) maintained a benzodiazepine-free status at 12 month follow up.

**Conclusion:** Our study suggests that phenobarbital detoxification is a good choice for patients with benzodiazepine dependence on the basis of the efficacy (low relapse rate), safety (no major adverse effect) and tolerability (low drop-out).

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## 167. Treatment of hospitalized acute poisonings in Estonia (EstTox 2009)

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**Objective:** To describe the treatment of hospitalized acute poisonings in adults in Estonia during one year.

**Methods:** All acute poisonings in adults (> 16 years) presenting to a hospital in Estonia from 1 May 2009 until 30 April 2010 were included.

**Results:** The incidence of hospitalized acute poisoning was 0.6 per 1,000. There were 622 cases during the study year. The median age was 35 years (range 16-90) and 47% were males. Ethanol ( $n = 78$ ; 27%) and benzodiazepines ( $n = 62$ ; 19%) were the main toxic agents taken by males and females, respectively. Complications were present in 298 (48%) cases. The most frequent complications were neurological symptoms (18%) and respiratory depression (14%). In 93% of them the complications were already present on admission. Treatment was given in 97% of the cases, mainly intravenous fluids (95%), gastric lavage (28%) and intubation (13%). An antidote was given in 7% of the cases, mainly naloxone (3%), flumazenil (1.6%) and N-acetylcysteine (1.4%). Treatment in an Intensive Care Unit (ICU) was required in 28% of cases. The main indications were coma (OR 7, CI 4-13) and complications (OR 4, CI 3-6). ICU treatment was required in 48% and 41% of the poisonings with tricyclic antidepressants and neuroleptics, respectively. Seventeen patients died, resulting in an in-hospital mortality of 2.7%. Most patients (60%) were discharged with follow-up, mainly psychiatric (40%) or to a general practitioner (16%). The median hospital stay was 1 day (range 0-34 days).

**Conclusion:** The high rate of complications and intubation may reflect that most acute poisonings are treated at a pre-hospital level, whereas only the most severe ones are hospitalized. The frequent

use of gastric lavage may reflect a tradition of gastric lavage as first line decontamination and overuse of this procedure. The low number of patients treated with N-acetylcysteine compared to other European countries<sup>1</sup> corresponds well to the lower frequency of paracetamol overdoses in Estonia.

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## 168. Ventricular tachycardia in mixed drug overdose treated successfully with lidocaine and magnesium sulfate

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**Objective:** Ventricular tachycardia (VT) is life threatening in drug overdose patients. The treatment of VT in mixed drug overdose is rarely discussed. We present a patient with mixed drug overdose that presented with pulseless VT refractory to defibrillations that was treated successfully with intravenous lidocaine and magnesium sulfate.

**Case report:** A 45-year-old female with a history of major depression presented to hospital with a history of unconsciousness of unknown duration. Empty drug packs equating to quetiapine 16800 mg, hydroxyzine 700 mg, mirtazapine 1680 mg, lorazepam 84 mg, sulpiride 11200 mg, flurazepam 1680 mg and zaleplon 560 mg were found next to her. On arrival her vital signs were temperature 36.1°C, pulse 114 beats/min, and blood pressure 97/57 mmHg. On physical examination, her Glasgow Coma Scale (GCS) was 3, and she had isocoric pupils 4 mm in diameter with normal light reflex, clear respiratory sounds and a regular heartbeat. The blood sodium, potassium, calcium, magnesium, arterial blood gas and troponin-I concentrations were all normal. The urine benzodiazepine concentration was > 1000 ng/mL. An electrocardiogram showed sinus tachycardia with a QTc of 408 ms. There was no structural lesions on brain computed tomography. Mixed drug intoxication was diagnosed. Six hours after admission, her GCS improved to E2 V3 M5. Frequent ventricular premature complexes were noted on monitoring and a repeat electrocardiogram showed short runs of VT with a QTc of 761 ms. She had an episode of pulseless VT and biphasic 200 J defibrillation was delivered. The cardiac rhythm temporarily returned to sinus rhythm but pulseless VT recurred twice more with recovery after biphasic 200 J defibrillation. A loading dose of intravenous lidocaine 200 mg, magnesium sulfate 2 g and a maintenance dose of lidocaine 2 mg/min were prescribed. No more VT episodes occurred after lidocaine and magnesium sulfate treatment. She was transferred to ITU for close observation. One day after admission, the electrocardiogram disclosed normal sinus rhythm with a QTc of 539 ms. She recovered uneventfully and was discharged after 3 days.

**Conclusion:** Four of the medications (quetiapine, hydroxyzine, mirtazapine, sulpiride) this patient ingested have been reported to induced QT prolongation and torsades de pointes. This case illustrates that lidocaine and magnesium sulfate can effectively



terminate VT refractory to defibrillations in patients with QT prolongation after a mixed drug overdose.

### 169. Isoniazid poisoning: Pharmacokinetics and effect of dialysis after massive ingestion

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**Objective:** Isoniazid is a rare overdose that causes seizures; there is limited evidence, mainly case reports, to guide treatment. We describe ingestion of a massive dose of isoniazid in a patient who was dialysed.

**Case report:** We report a 20-year-old female migrant who presented with recurrent seizures after ingesting 25 g isoniazid. She was treated with activated charcoal, repeated doses of midazolam for the seizures and given multiple doses of pyridoxine (14 mg), limited by availability. She was admitted to intensive care 5.5 hours post-ingestion and commenced on continuous veno-venous haemodiafiltration (CVVHDF). She had further seizures which were treated with parenteral benzodiazepines and pyridoxine. Dialysis was continued until 30 hours post-overdose and then ceased. She gradually recovered, was extubated on day 3 and had no long-term sequelae. Five serum samples from the patient were available and isoniazid was quantified using a liquid chromatography-mass spectrometry (LC-MS/MS) method. A two compartment model with first order input (with fixed absorption co-efficient  $K_a$ ) adequately described the timed concentration data. The effect of CVVHDF was modelled as a time-dependent covariate, best described by an exponential decay in clearance due to CVVHDF. Pharmacokinetic analysis suggests that there was initially good clearance with CVVHDF (four times endogenous clearance) which rapidly declined within hours.

**Conclusion:** In patients with isoniazid poisoning early presentation, good supportive care and high dose benzodiazepines are likely to be sufficient treatment, including pyridoxine, if available. Dialysis did appear to increase isoniazid clearance for a few hours after commencement, and the earlier it is used the more effective it will be.

### 170. Intravenous lipid emulsion for treatment of local anesthetic systemic toxicity

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**Objective:** Intravenous lipid emulsion is considered a first line treatment for local anesthetic systemic toxicity.<sup>1,2</sup> We present a

case of lidocaine cardiotoxicity in a newborn in order to show the efficacy of intravenous lipid emulsion in newborns.

**Case report:** A newborn at term with streptococcal meningoen- cephalitis developed seizures soon after birth. A pharmacological coma was induced and on the fourth day of life lidocaine was administered because seizures were resistant to other therapies. Lidocaine was administered as a bolus, at a dose of 6 mg/kg, then in continuous infusion, at a dose of 6 mg/kg/h for 18 hours, then 4 mg/kg/h for 12 hours. Lidocaine caused widening of the QRS complex and bradycardia but these cardiac alterations were successfully treated with intravenous lipid emulsion (as bolus at a dose of 2 mL/kg).

**Conclusion:** Intravenous lipid emulsion is effective in the treatment of local anesthetic systemic toxicity in newborns.

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### 171. Acute renal failure and neurological damage after topical application of brake fluid containing diethylene glycol

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**Objective:** Diethylene glycol (DEG) has been used for pharmaceutical preparations in place of glycols, resulting in cases of poisoning. Metabolic acidosis, acute renal failure, neurologic impairment and delayed neurotoxicity are typical clinical effects.<sup>1</sup> We describe a case of severe intoxication due to topical application of brake fluids containing DEG.

**Case report:** A 29-year-old Nigerian man was admitted to the Emergency Department for abdominal pain, nausea and weakness. For two months he had treated an exfoliative dermatitis with topical applications of a brake fluids containing 50-70% of DEG (on the advice of a friend). He presented with acute renal failure (creatinine 15.5 mg/dL, BUN 40 mmol/L) and anuria at admission. Arterial blood gas analysis showed pH 7.25, bicarbonate 16.4 mmol/L and lactate 0.6 mEq/L. Arterial blood pressure was high and treated with nitroprusside. He was transferred to the nephrology ward and renal biopsy showed severe proximal tubular damage with vacuolation, without calcium oxalate crystals. He underwent hemodialysis and was intubated on day 5 for development of lethargy and respiratory failure. Brain CT scan and magnetic resonance imaging (MRI) were negative. On day 10 he developed a severe peripheral neuropathy and tetraplegia. MRI of the brain showed cerebrospinal radiculoneuritis at cranial nerves and impregnation of cauda equina roots with electroencephalogram (EEG) signs of diffuse cerebral damage. Evoked potential studies showed deafness. From the 17th day, he presented a progressive neurological improvement

and recovery of diuresis. One month after hospital admission he was awake, with absent photomotor reflex bilaterally and corneal reflex, marked loss of strength in the upper limbs, paraplegia and normal renal function. After transfer to a rehabilitation ward, he was discharged 3 months later able to walk. On samples collected 7 days after hospitalization, DEG was absent in serum but present in a trace amount in the urine (< 2 mg/dL).

**Conclusion:** Although DEG is poorly absorbed through intact skin, it is hypothesized that systemic toxicity may occur because of the combination of damaged skin, large areas being treated and repeated applications of the product,<sup>2</sup> as in our patient.

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### 172. How common are exposures to soluble film automatic dishwashing products in the UK? A retrospective UK National Poisons Information Service (NPIS) study conducted from January 2008 to October 2014

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**Objective:** Concerns have been raised about the potential dangers of soluble film automatic dishwashing tablets. These products, marketed for their ease of use, require no removal from an outer wrapper. Some consist only of a powder while others also contain a liquid or gel component. The tablets most commonly contain a source of hydrogen peroxide, sodium carbonate, sodium tripolyphosphate, non-ionic surfactants and enzymes, and typically have a pH of 9–11. The contents are contained within a water-soluble polyvinyl alcohol film. This study was undertaken to determine the number of enquiries and exposures referred to the UK NPIS between January 2008 and October 2014.

**Methods:** Enquiries to the UK NPIS relating to soluble film automatic dishwasher tablets from doctors and other health care workers based in the UK were analysed retrospectively for the period January 2008 to October 2014.

**Results:** There were 380 enquiries concerning exposure to soluble film coated tablets. These enquiries were received predominantly from NHS 111/NHS Direct/NHS 24 (52.9%) which provide advice by telephone to the general public on health matters including toxic exposures, general practitioners including out-of-hours services (30.0%) and hospitals (10.0%). The calls related to 377 patients, of which the majority were children aged 5 years or less (93.1%). The vast majority were accidental exposures occurring in the home (98.4%). Exposure to water-soluble film tablets occurred mainly as a result of ingestion (96.6%); eye contact (1.6%), skin contact (0.5%) and exposures involving multiple routes of exposure (1.3%) made up the remaining cases. The WHO/IPCS/EC/EAPCCT

Poisoning Severity Score was known in 371 of 377 cases: 247 of 371 (66.6%) cases were asymptomatic (PSS 0), 123 had a PSS 1 and one had a PSS of 2. Although the majority of patients remained asymptomatic following ingestion alone (65.7%), of those developing symptoms, vomiting was reported most commonly, occurring in around a quarter of cases (n = 96). Nausea (n = 7) and coughing (n = 6) were also present and three patients developed a rash.

**Conclusion:** Exposure to soluble film automatic dishwashing tablets rarely resulted in clinically significant symptoms, which is surprising given the potential hazard of the material, though vomiting occurred in 26%. Hence, it is probable that the amount ingested was very small. When children bite into a tablet they tend to spit it out, though some material may cling to the wet surfaces of the mouth, due to the hygroscopic nature of the powder.

### 173. Has the International Association for Soaps, Detergents and Maintenance Products (AISE) product stewardship programme had an impact on the number of liquid laundry detergent capsule exposures reported to the UK National Poisons Information Service (NPIS)?

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**Objective:** In 2001, the cleaning products industry in Europe launched liquid laundry detergent capsules; the products were first marketed in North America in 2011. The capsules are a pouch of concentrated liquid laundry detergent in a water-soluble polyvinyl alcohol membrane that can be placed directly in washing machines. In Europe, these liquid detergents most commonly contain anionic surfactants (20–35% per capsule), non-ionic surfactants (10–20%), propylene glycol (8–20%) and ethanol (2–5%) and have a pH of 7–9. Currently, more than 1 billion liquid laundry detergent capsules are sold each year in the UK. These capsules can release their contents prematurely when they come into contact with moisture, which can cause local irritant damage, especially to the eyes and, in addition, central nervous system depression. In December 2012 AISE established a voluntary programme requiring that safety measures be implemented to reduce visibility of, and restrict access to, liquid detergent capsules by small children. The large majority of the market signed up to this programme, and implementation occurred in the UK over several months in 2013. This study was undertaken to determine if the AISE programme has had an impact on the number of exposures from liquid laundry detergent capsules reported to the UK NPIS.

**Methods:** Enquiries to the UK NPIS relating to liquid detergent capsules from doctors and other health care workers based in the UK were analysed for the period January 2012 to September 2014.

**Results:** There was no significant difference between the number of enquiries (n = 433) or exposures (n = 422) in 2012 and in the number of enquiries or exposures (413 and 407, respectively) reported between October 2013 and September 2014. However,

taking into account sales volumes, there were 0.36 exposures per million units sold in the 12 months from October 2013 to September 2014, which is significantly lower ( $p = 0.0335$ ) than the number of exposures per million units sold (0.47 per million) in 2012.

**Conclusion:** The AISE recommendations appear to have significantly reduced the number of exposures per million units sold (though not the number of enquiries or exposures) and reported by doctors and other health care workers to the NPIS. However, when a product becomes established in the market there are usually fewer enquiries to NPIS over time regarding its toxicity, and this may also have been a factor in the apparent reduction in exposures per million units sold.

#### 174. Incidence of carbon monoxide intoxication in Belgium

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**Objective:** To describe the number of incidents, victims and deaths caused by carbon monoxide (CO) intoxication in Belgium and to evaluate the effect of preventive measures.

**Methods:** Data on CO poisoning were collected from hospital emergency services, centers for hyperbaric medicine and coroner's offices. Belgian hospitals with emergency services and centers for hyperbaric medicine collaborate voluntarily and fill in a registration form for every patient admitted for carbon monoxide intoxication. Information is collected on place and type of treatment, type of intoxication, evolution, place and cause of the incident. Data are also received from coroner's offices. A press clipping service was used as a complementary source of data.

**Results:** Over the 1995-2013 registration period 13,144 CO incidents were reported. These incidents included 26,411 victims of whom 713 (2.7%) died. The overall incidence in Belgium dropped from 16.6/100,000 in 1995 to 11.3 in 2013. This decrease is mainly due to a diminishing number of accidents with gas-powered tankless water heaters and heating appliances using gas, coal, wood or oil. Incidents caused by fire or by exhaust fumes from cars or machines have remained at the same level throughout the registration period. Over the 19 year registration period the number of deaths dropped from 61 to 26 per year. The crude mortality rate dropped from 0.60 to 0.23/100,000. The global mortality rate during the registration period was 0.36/100,000. In total, 580 fatal incidents causing 713 deaths were registered. The major causes were hot water appliances (31.4%), followed by coal stoves (12.2%) and fire (12.2%). Successful suicide attempts with the exhaust fumes from a car accounted for 9.8%. For 12,835 incidents (involving 25,710 victims) the date of the accident was known and 78% accidents occurred during the winter from 1 October to 31 March.

**Conclusion:** During this 19 year period of registration we noted an important decline in the number of incidents, victims and deaths by carbon monoxide intoxication. Legislation passed in 1989 and 1995 imposing intrinsic safety devices for gas-powered water heaters probably contributed to this decline, as well as public awareness campaigns carried out each year at the beginning of the winter season. As incidents due to preventable causes continue to happen, efforts must be maintained to inform the public of the dangers of CO intoxication.

#### 175. Acute pulmonary injuries from chlorine-based swimming pool disinfectants in northern Germany

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**Objective:** Swimming pools have to be disinfected on a regular basis to maintain water quality and reduce the risk of infections to users. The majority of the chemicals used for disinfection are chlorine-based. The main ingredients are trichloroisocyanuric acid (symclosen) and dichloroisocyanuric acid (trocclosen). Moderate and severe injuries by inhalation are common accidents even under normal conditions of use.

**Methods:** For the period 2000-2014 all cases with accidental, inhalational exposure of chlorine-based swimming pool disinfectants reported to the GIZ-Nord Poisons Centre were identified. Conditions of exposure, severity of symptoms, ToxIndex, age distribution and annual and seasonal distributions were analysed.

**Results:** During the analysis period GIZ-Nord Poisons Centre observed an increasing number of incidents with chlorine-based pool chemicals. In total 139 cases were identified that met the inclusion criteria. In more than 60% the exposure occurred while inhaling from a just opened container of the product. The rest occurred from inhalation of the product dissolved in water or were not well documented. According to the Poisoning Severity Score 12% had no, 66% minor, 13% moderate, 1% severe symptoms and 8% were not well documented. No fatalities occurred. The Tox-Index is defined as the sum of all cases classified as lethal, severe or moderate in relation to the number of all exposure cases. This index for pool products was quite high with 14%. The ToxIndex for individuals < 18 years was 13% and for adults 16% are astonishingly similar.

**Conclusion:** GIZ-Nord Poisons Centre observed an increasing number of lung injuries caused by chlorine-based pool chemicals in northern Germany. Interestingly these intoxications occurred during use as intended. The analysis of our data showed that these chemicals carry an unacceptably high risk for consumers. The national surveillance authorities in Germany were informed. European Poisons Control Centres play a key role in toxicovigilance with their numerous connections to both the public and to health professionals. All these centres should analyse their cases with chlorine-based pool chemicals and in case of similar results establish an EU-wide initiative to make these products safer. In our opinion very simple measures such as single packaging for each chlorine tablet could significantly reduce the risks.

#### 176. MAGAM II: Prospective observational multicentre poisons centre study on eye exposures caused by cleaning products

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**Objective:** Local toxic effects on the eye are frequently reported following cleaning product exposures. New EU Chemicals Legislation (Regulation (EC) No 1272/2008) is intended to prevent, among others effects, irreversible eye damage by labeling hazardous products (mixtures) with Hazard Phrase 318: 'Causes serious eye damage'. The objective of this study is to identify cleaning products with potential for irreversible eye damage by collecting and following up human exposure data from poisons centres (PC).

**Methods:** A multicentre binational prospective observational PC study. All human eye exposures to detergents or maintenance products reported to nine PCs taking calls from public and professionals during an 18-month period were included. Follow-up was performed for all cases by structured telephone interview. In cases involving medical treatment a written medical report was requested and collected. Severity of eye effects was rated according to Poisoning Severity Score.<sup>1</sup>

**Results:** In total 586 cases were included; 369 children, 210 adults, and 7 seniors were exposed. Occupational exposure occurred in 24 cases. In 528 cases follow-up was successful. Of these 200 of 528 patients (38%) consulted a physician (mainly an ophthalmologist) and 55 medical reports confirmed the severity of ocular lesions. Severity of injury (according to PSS) was asymptomatic (n = 47), mild (n = 446) or moderate (n = 35). Symptoms most frequently reported were redness (62%), burning (38%) and lacrimation (15%). Cases with prolonged symptoms (that is > 24 hours) were minor (n = 54) or moderate (n = 18). In terms of treatment, irrigation was performed in 94% of cases. Healing was reported in all cases. Duration of eye symptoms was < 12 hours (n = 340), 12-23 hours (n = 62), 1-6 days (n = 67) or 7-20 days (n = 5) and < 21 days (n = 8).

**Conclusion:** Healing within 20 days was reported in all cases with follow up information. No patient developed severe eye injury; 6% suffered from moderate and 84% from mild eye injury. Duration of symptoms was  $\geq$  12 hours in 25% of all cases with follow-up. That is in contrast to the results of a prospective study on oral exposures by detergents, where gastrointestinal symptoms developed in 43%, seldom with prolonged duration (> 8 hours in 7% only).<sup>2</sup> Thus PC data can be important for regulatory risk assessment of detergent and cleaning products.

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## 177. Trends in cyanide exposures reported to the UK National Poisons Information Service (NPIS) from 2008 to 2012

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**Objective:** Cyanide is highly toxic; several antidotes are available but there is no rapid diagnostic test for cyanide toxicity to aid the emergency management of patients. Understanding the types of cyanide exposure and the severity of resulting features may guide management of such patients.

**Method:** A retrospective observational study of telephone enquiries to the UK National Poisons Information Service (NPIS) concerning cyanide was performed for the period 2008-2012. Calls were analyzed for cyanide compound, symptoms, poisons severity score (PSS) and antidote use. Death data from the Office National Statistics (ONS) were also obtained for the same time period.

**Results:** There were 458 enquiries between 1 January 2008 and 31 December 2012 involving 442 exposures to cyanide. The source of exposure was reported as a plant product in 172 enquiries (38%), 98% of which were due to accidental exposure. Of plant exposures, 69% were asymptomatic. There were 134 (29%) enquiries regarding exposure to products of combustion (POC), of which 40% were classified as severe and a further 25% as moderate. Enquiries concerning cyanide salts and hydrogen cyanide generated 90 enquiries (20%). Of these, 67% concerned adults and 49% occurred in the workplace; 17% were classed as intentional exposures. The majority of patients reported only mild symptoms, commonly dizziness and headache. The remaining 13% of enquiries concerned cases in which cyanide exposure was discussed as part of the differential diagnosis in patients with unexplained toxicity or reduced level of consciousness. In nine cases an antidote was given prior to contacting with NPIS: hydroxocobalamin was administered in four cases, sodium thiosulphate in three and dicobalt edetate in two. An antidote was advised in 21 cases (5%), 20 of which involved POC exposure. Sodium thiosulphate was recommended in 11 cases, hydroxocobalamin in eight and dicobalt edetate in two. The ONS reported 22 deaths from cyanide over the same time period: five in 2008, five in 2009, four in 2010, six in 2011 and two in 2012; none of these had been reported to the NPIS.

**Conclusion:** Exposure to cyanide-containing plants was the most common source of cyanide exposure reported to the NPIS. Exposure to the multiple toxins in POC resulted in the most severe PSS. Most cases of cyanide exposure not related to POC were asymptomatic and minimal medical care was required. The majority of cases were managed without the use of an antidote. Twenty-two fatalities occurred during the study period.

## 178. Epidemiology and clinical characteristics of hydrofluoric acid (HF) exposures: 6-years' experience of the Pavia Poison Control Centre

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**Objective:** To evaluate the epidemiology and clinical characteristics of hydrofluoric acid (HF) exposures.

**Methods:** Retrospective case review of HF exposures from January 2007 to September 2013. Cases were assessed for demographic and clinical data, modality of exposure, time to Emergency Department (ED) presentation (for domestic exposure), treatment and outcome.

**Results:** In total 164 cases were evaluated (84% with age > 18 years) and divided into group A (domestic exposure n = 135) and group B (occupational n = 29). Group A: Twenty-six (19%) accidental exposures involved patients < 18 years (n = 20 < 3 years; n = 3 3-6 years; n = 3 10-18 years). In patients younger than 6 years (14%) the modality of accidental-exposures were ingestion/oral mucosa (57%) and dermal/ocular contact (43%). In adults (n = 109) accidental and intentional exposure were registered in 94 and 15 cases, respectively. Accidental exposure involved mainly dermal/ocular (84/94; 89%), ingestion (n = 9) and inhalation (n = 1). In dermal/eyes accidental exposure (n = 84) ED evaluation was performed within 12 hours in 49 cases (58%), 12-24 hours in 13 cases (16%) and > 24 hours in 22 cases (26%). Selected cases of this group were hospitalized for at least 24 hours to rule out systemic hypocalcemia and (after hospital discharge) followed up for weeks until healing. No systemic effects and sequelae occurred. Intentional exposures were characterized mainly by ingestion (14/15) and by dermal/intramuscular injection in 1 case. Two lethal cases were registered and involved intentional ingestion. All exposures regarded domestic products (HF < 15%). Group B: These included dermal/ocular (n = 23) or inhalation (n = 6) exposures involving products with HF < 15% (n = 8), 15-30% (n = 2) and > 30% (n = 16). In 4 cases nitric acid and sulphuric acid were also involved. Inhalation exposure resulted in respiratory symptoms requiring nebulized calcium gluconate treatment. Dermal effects were more severe (versus domestic exposure) and related to incorrect use of individual protection devices. Two cases required hand plastic surgery referral. There were no fatal cases. In both groups patients were treated with prolonged topical antidotal treatment (calcium gluconate gel) with plastic surgery and onychectomy in selected cases.

**Conclusion:** HF is a highly toxic weak acid with protoplasmic activity. Clinical presentation may be complex and confusing with delayed local and systemic effects. Serious morbidity and death can occur. Main factors influencing clinical manifestations are (i) concentration, (ii) modality of exposure/contact/time/volume, (iii) percentage of body surface area involved and (iv) association with other caustics. Antidotal treatment exists and prolonged topical calcium gluconate is effective and permits ambulatory management of patients. HF is also a health risk in non-professional exposure.

### 179. A rare complication of ethyl acetate poisoning

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**Objective:** Ethyl acetate poisoning is rarely reported and is of low toxicity. Mucosal irritation and central nervous system (CNS) depression in high concentration is most commonly described. We present a case of ethyl acetate poisoning in a patient who required surgery due to foreign body formation.

**Case report:** A 57-year-old female presented to the emergency department (ED) after a suicide attempt with ethyl acetate ingestion

(about 200 mL) thirty minutes earlier. The initial vital signs were all within normal ranges and the initial symptom was vomiting. No nasogastric (NG) tube irrigation or activated charcoal were given due to low toxicity. The initial laboratory data including complete blood count, differential count, creatinine, sodium, potassium, and alanine transaminase were all within normal range. However, the patient became drowsy with respiratory distress due to stridor one hour after arrival. Emergency intubation was then performed for airway protection and desaturation followed by NG insertion for decompression. She was then admitted to intensive care unit. She was extubated 4 days later in a stable condition but during attempted removal it became clear that her NG tube was stuck in the stomach. Panendoscopy (PES) was then performed and showed a gastric foreign body attached to NG tube with hard content. The foreign body could not be removed via PES. Surgical intervention for foreign body removal was performed the next day. The patient recovered well after surgery and was discharged after 14 days in hospital. We then did a small experiment and put both a polyvinylchloride (PVC) NG tube and a silicon NG tube in ethyl acetate solution. Six hours later, the PVC NG tube was dissolved and the silicon NG was intact. When we mixed ethyl acetate with hydrochloric acid to mimic the gastric environment, some suspended solid materials formed and attached to NG tube.

**Conclusion:** Ethyl acetate is of low toxicity with few cases reported; however, it can lead to formation of a hard solid foreign body in the stomach and cause obstruction. In addition, PVC NG tubing can dissolve in ethyl acetate solution. Hence, we recommend using silicon NG tubing for ethyl acetate ingestion if necessary.

### 180. Caustic exposures reported to the Belgian Poison Centre

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**Objective:** The Belgian Poison Centre is commonly consulted for exposures to caustic substances, potentially causing important injuries and a heavy psychological and economic burden. Nevertheless, no systematic study has so far been published to estimate their incidence. In this preliminary study, we aim to identify the main products involved and the relevant variables to organise a surveying system.

**Methods:** Call files recorded between 1 January and 30 June 2014 were screened. Only actual exposures were included. Agents were limited to household, industrial and plant protection products and to biocides. Veterinary and voluntary exposures were excluded. Only one call was counted for a single event. All cases were analysed manually to identify any potential caustic exposure, based upon the product composition as present in our database and upon the detailed case record. For the period up to 10 March 2014 an exploratory follow-up was performed by telephone if judged useful and if technically possible.

**Results:** Of the 6,296 exposures selected in the first phase, 628 were retained as potentially caustic. A successful follow-up by telephone was performed in 96 cases. We collected 121 (19.3%) professional and 507 (80.7%) domestic cases. The main injury causing chemicals were acids (180/628, 28.7%) and bases (238/628, 37.9%), especially inorganic bases (181/628, 28.8%). For the household exposures only, there was a clear preponderance

of bases (194/507, 38.3%) over acids (136/507, 26.8%). We found 127 children in our domestic series (25.0%). The most frequently involved products were drain cleaners (103/628, 16.4%). There was an obvious dominance of dermal exposures in the professional group (96/121, 79.3%), with the remaining mainly ocular (39/121, 32.2%). We observed a more equal distribution of exposure routes in domestic cases with 209 dermal (41.2%), 148 oral (29.2%) and 139 (27.4%) ocular exposures. The remaining cases involved multiple routes. The most striking symptoms were dermal burns with 8 third degree burns, 50 second degree burns and 110 burns of first or unspecified degree. There were 46 cases with eye pain, 22 with vision defects or corneal lesions and 5 with eyelid oedema. Additionally, there were 32 cases with oral burns.

**Conclusion:** We received 628 calls about accidental caustic exposures over one semester with often significant consequences, confirming that caustic burns are a real public health problem because of their frequency and severity. Acids and bases (alkalis), especially inorganic bases, were the main causative substances. Drain cleaners were most frequently involved. These data illustrate the need for preventive and regulatory action.

### 181. Serious magic-nano-like lung oedemas caused by a liquid stain protection product: Using two new tests as a combined screening tool for aerosol products

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**Objective:** In 2006 in Germany, cases of severe pulmonary health impairment were observed after normal use of “Magic Nano” sealing sprays. The rapid and complete documentation of more than 150 cases, initiated by the BfR Committee of Poisonings, together with the German Poison Centers, led to different research projects including chemical analysis of the aerosols, particle distribution, targeting cell culture systems, animal studies and isolated perfused lung (IPL) experiments. It could be shown, that the “nano” case series pattern of signs and symptoms have close similarities to the “waterproofing spray syndrome”. There are strong indications, that the main effect is the “carrier effect” of “aerosol-born” solid nano-like particles which carry, via their surface, the product’s surface-active substances deep into the lung. After a small case series of serious “magic nano-like” lung oedemas caused by a liquid stain protection product, the BfR Committee of Poisonings intended an additional study based on two promising testing methods of the recent research: The relative mass fraction index (Eta-test) and the isolated perfused lung (IPL-test).

**Methods:** For testing the original liquid stain protection product was obtained in a German do-it-yourself store. Test 1: This test is carried out by spraying defined quantities of the product into a control volume and measuring the concentration of health-related size fractions. This procedure takes into account spray ageing, especially size reduction of the droplets due to solvent evaporation. Test 2: The IPL is proposed as a model for testing acute toxicity. Ventilated rat lungs are exposed to aged aerosols with proper

particle size of approximately 1 µm generated from the liquid spray formulation. Lung compliance and lung resistance are continuously monitored during exposure. Dose-dependent deviations from the controls are used as read-out parameters.

**Results:** Altogether the results and in particular the comparison of the two tests have shown, that the Eta-test with its elevated relative mass relation and the rapid, severe lung impairment in the IPL-test proved the acute toxic pulmonary potential, which was detected in the small BfR case series. Both tests showed definitely, in particular the IPL, that spraying of the liquid stain protection product is connected with a severe risk of lung impairment for the user.

**Conclusion:** This promising test battery needs to be evaluated further with aerosol products to investigate and prevent human toxicity. IPL as a screening method may help avoid acute animal inhalation studies in the future in line with the 3R-principle.

### 182. Delayed life-threatening airway edema after caustic ingestion in a child

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**Objective:** The purpose of this report is to describe a case of life-threatening airway edema in a child presenting the day after an asymptomatic caustic ingestion.

**Case report:** A 2-year-old male ingested 28 ml of HTH Super Algae Guard™ (28-32% benzyl/alkyl quaternary ammonium compounds) and immediately experienced a choking episode and spat out the liquid. He was asymptomatic on presentation to the emergency department 2 hours after ingestion and was observed for 4 hours. He experienced no dysphagia, dyspnea, vomiting, drooling, stridor, or intolerance to oral feeding during his course. He was discharged home 6 hours after ingestion. Twenty-four hours after ingestion, the patient began experiencing difficulty breathing and drooling. He presented to the emergency department a second time and was found to have tachypnea, stridor, wheezing, nasal flaring and subcostal retractions. Mild peri-oral cyanosis was also noted. He was taken to the operating room immediately and intubated by an otolaryngologist with direct laryngoscopy. Significant supraglottic airway edema with a normal trachea down to the carina was noted on bronchoscopy. Esophagoscopy revealed esophagitis in the middle and distal thirds of the esophagus. All chest X-rays taken during his stay were normal. The patient was extubated 48 hours after intubation and significant improvement of supraglottic airway edema was noted. His stridor resolved in less than 24 hours. The patient experienced no further respiratory issues during his stay. He was discharged with a nasogastric tube in place for one week of nasogastric feeds. A barium swallow study of his esophagus performed 30 days after ingestion revealed no abnormality. He had no pulmonary symptoms or exam abnormalities 30 days after ingestion.

**Conclusion:** The difficulty correlating symptoms on presentation and esophageal injury after unintentional caustic ingestion is well described in multiple studies.<sup>1-3</sup> This case is notable for the development of severe, life-threatening supraglottic airway edema 24 hours after unintentional caustic ingestion. Further study is warranted to determine the incidence and identifiable risk factors of airway injury in asymptomatic patients presenting after unintentional caustic ingestion.



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### 183. Kettle descalers: A brewing issue

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**Objective:** Household products used to remove limescale from domestic kettles contain strong acids (e.g. formic, phosphoric and hydrochloric acids) and are present as gels, liquids or tablets. Accidental exposure may occur when a kettle is descaled and subsequently the contaminated water is used to prepare food or beverages (including infant feeds) without removal of the descaler liquid. We wished to see whether enquires concerning these products were increasing.

**Methods:** A retrospective review of telephone enquiries to UK National Poisons Information Service (NPIS) from 1 January 2009 to 31 December 2013 concerning accidental ingestion of kettle descalers. Total accesses to TOXBASE<sup>®</sup> (the clinical toxicology database of the National Poisons Information Service) for the same period were also examined.

**Results:** The NPIS received a total of 1,324 enquiries relating to 1,360 accidental ingestions of kettle descalers during the 5 year period. Most of these exposures (n = 881, 65%) concerned adult patients who had used the water to prepare hot beverages or cook foods such as vegetables, pasta, rice and noodles. Two hundred and thirty exposures (17%) involved infants under the age of 2 years who had been given a contaminated bottle feed. Of 1,360 exposures, 361 (26.5%) reported symptoms. Amongst these patients the most frequently reported symptoms were buccal irritation (n = 108), abdominal pain (n = 84), vomiting (n = 45) and nausea (n = 42). Over the study period the number of enquiries regarding exposure has increased from 227 in 2009 (0.4% of the total number of enquiries received by NPIS) to 327 in 2013 (0.6% of the total NPIS enquiries). During the same period there was an increase in the total number of accesses to information about kettle descalers on TOXBASE<sup>®</sup> from 889 in 2009 to 1166 in 2013, although these accesses involve deliberate exposure and general information enquiries.

**Conclusion:** The number of telephone enquiries to the UK NPIS regarding accidental exposure to household kettle descalers is increasing. Ingestion is associated with toxicity among all ages, including babies. These exposures might be avoided by addition of a non-toxic visual deterrent which would alert the user that the kettle water was still contaminated with descaler.

### 184. Update: Cases of aerotoxic syndrome reported to BfR

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**Objective:** German physicians have to report cases of poisoning (§ 16e Chemicals Law) to the Federal Institute for Risk Assessment (BfR). This obligation also applies to cases of “aerotoxic syndrome”, a non-official term used to describe certain health impairments occasionally seen in aviation medicine after so called smell events. After a first analysis in 2013, BfR has received an increasing number of case reports with symptoms attributed to the aerotoxic syndrome.

**Methods:** Cases of aerotoxic syndrome reported so far under § 16e were evaluated and recorded in the form of standardised case reports. Data were assessed regarding possible risks posed by smell events, also with a view to a potential tricresyl phosphate (TCP) contamination of cabin air. Categorisation of the health impairment followed the poisoning severity score (PSS), and causality (exposure versus symptoms/signs) was assessed by the BfR standard three-level model.

**Results:** Between 2009 and 2013 BfR documented 295 cases of smell events. All persons concerned were adults and members of flying personnel. Most of them complained about odours which were often described as similar to the smell of oil or burned material. The severity ranged from “none” (31%) to “moderate” (5%). The symptoms most frequently experienced were headache, dizziness, nausea and disturbances of the nervous system such as drowsiness, prickling and numbness. In all cases reported to BfR, if samples were tested for TCP, blood concentrations were below the limit of detection, which is in good accordance with the comprehensive study of the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance.<sup>1</sup>

**Conclusion:** In the majority of cases reported by flying personnel, no cause for the reported smells or symptoms could be found. Multifactorial events must be assumed. These include the influence of potential pollutants such as carbon monoxide, ozone and residues of de-icing fluid. The reported clinical signs could also be related to or aggravated by jetlag, unfavourable working hours, varying pressure conditions, turbulences and dehydration, combined with an increased sensitivity of the crew members for this issue. BfR has not received any report on cases of health impairment among passengers.

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### 185. Drinking strep test reagents: A case of nitrite poisoning

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**Objective:** Nitrite poisoning may cause methemoglobinemia. We describe a case of methemoglobinemia after drinking a small bottle of rapid strep test reagent containing sodium nitrite.

**Case report:** A woman in her twenties was brought to the casualty clinic by ambulance after behaving strangely and having jumped into the water in the harbour. On presentation she was alert, but agitated, and expressed ideas with psychotic content. She denied any suicidal intention. She had previously been treated at a psychiatric outpatient clinic, did not use any medication, and had no history of psychosis. She reported smoking cannabis the previous night. Physical examination was unremarkable, with pulse 76, oxygen saturation 100%, temperature 36.4°C, normal pupil size, and blood glucose 6.2 mmol/L. She was assessed as psychotic and in need of admission to a psychiatric ward. While waiting for transfer, she drank two bottles of a rapid strep test reagent she found in the examination room. The 10 mL bottles were part of a rapid antigen detection test kit for group A streptococci, one containing a 2 molar solution of sodium nitrite, the other a 0.2 molar solution of acetic acid. The Norwegian Poisons Centre was consulted and advised transfer to hospital. On arrival at her local hospital she had cyanotic lips and facial oedema. On 4 L/min of oxygen her respiratory rate was 18, oxygen saturation 95% and pulse 90. Further physical examination was unremarkable. Hemoglobin was 12.3 g/dL. She was given olanzapine 10 mg and ibuprofen 400 mg. During observation in the intensive care unit (ICU) she became somnolent. Her blood was brown when obtaining arterial blood gases; pH was 7.41, PCO<sub>2</sub> 5.8 kPa, PO<sub>2</sub> 10.0 kPa, lactate 1.3 mmol/L, and methemoglobin 22%. Methemoglobinemia was diagnosed, and she was transferred to the university hospital to be assessed for antidote treatment. She was alert on arrival. On 15 L/min of oxygen her respiratory rate was 16, oxygen saturation 94% and pulse 56. She was admitted to the ICU and treated with oxygen only. Repeated arterial blood gases showed decreasing concentrations of methemoglobin; 18% on admission, and 7% three hours later. She recovered uneventfully, and next morning the methemoglobin concentration was normal. She was still showing symptoms of psychosis, and after examination by the liaison psychiatrist she was admitted to the psychiatric ward.

**Conclusion:** Reagents for rapid strep test kits can contain nitrites in concentrations high enough to produce clinically significant methemoglobinemia if ingested.

## 186. Carbon monoxide poisoning: Comparison between French and German monitoring systems

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**Objective:** Carbon monoxide (CO) intoxication is still a public health issue. Each country has its own system of notification and

here we compare the French and German systems. The Poison Centres (PC) of Strasbourg and Freiburg are only 60 km apart. The population served by PC Strasbourg is one-third of that served by PC Freiburg.

**Methods:** We retrospectively analyzed human exposures to carbon monoxide (CO) reported to the Poison Center (PC) Strasbourg (France) and Freiburg (Germany). Each person exposed to CO, with or without symptoms, was defined as a case.

**Results:** From January 2011 to September 2014, 1,102 CO intoxications were reported to the PC Strasbourg and the most frequent sources were boilers, water heaters or use of an engine at home (CO gas), and 598 intoxications by other sources such as smoke or exhaust gases (CO smoke) (respectively 247/199 in 2011, 322/172 in 2012, 387/157 in 2013 and 146/70 until September 2014). For CO gas, symptoms occurred in 525 cases; only 9 cases were severe and 7 resulted in death. For the 598 others exposures (CO smoke) 3 cases were severe and 4 patients died. Fire brigades or emergency physicians report exposures to carbon monoxide (CO gas) 24 hours a day to the French Poisons Centers or to the Regional Agency of Health (ARS). The data are recorded in a national database, developed by the French Institute for Public Health Surveillance (INVS). To the PC Freiburg, 487 cases were reported (118 in 2011, 148 in 2012, 136 in 2013, 85 until September 2014). Symptoms occurred in 349 cases; 19 cases were severe and 3 patients died. There was no distinction between CO produced by boilers, water heaters and engines and CO produced by smoke. The percentage of deaths was the same for the two centers (0.6%) but severe cases were more common in Germany than in France (3.9% versus 0.7%).

**Conclusion:** CO poisoning in France was 3.5 times more frequent than in Germany but this was probably the result of the reporting system. The national French system of CO poisoning notification, is useful for epidemiological analysis and the risk management. Many more cases are reported to the French PC compared to the German PC, because in France CO intoxication is a reportable disease.

## 187. Liquid laundry pods on either side of the Rhine

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**Objective:** Over the past few years, exposures to liquid laundry pods (LLP) have been a real problem in France and other European countries. LLPs are responsible for more severe pediatric intoxications than other laundry detergents. The Poison Centres (PC) of Strasbourg and Freiburg are 60 km part and the population served by PC Strasbourg is one-third of that served by PC Freiburg. We compared enquiries about LLPs in the two PCs.

**Methods:** We retrospectively analyzed human exposures to liquid laundry pods reported to the Poison Center (PC) Strasbourg (France) and Freiburg (Germany). Any person exposed to a pod, with or without symptoms, was defined as a case.

**Results:** From January 2010 to June 2014, 553 cases were reported to the PC Strasbourg (51 in 2010, 87 in 2011, 122 in 2012, 195

in 2013, 98 between January and June 2014). The age groups involved were infants 82, toddlers 444, school children 8, adults 6 and unknown 13. The route of exposure was oral (81%), ocular (9%) or dermal (8%). Symptomatic cases accounted for 412 (74%); 3.8% (n = 16) of the symptomatic cases were rated moderate (drowsiness, hypotonia, keratitis), but with no sequelae. In PC Freiburg 50 exposures have been reported (none in 2010-11, 9 in 2012, 22 in 2013, 19 in 2014, January-July). The age groups involved were infants 4, toddlers 46 and school child 1. No adult or senior were exposed. The routes of exposures were oral (n = 48), ocular (n = 1) or oral and ocular (n = 1). Symptomatic cases were rated moderate (n = 8) or mild (n = 39) according to the PSS. Two cases with French LLPs were recorded.

**Conclusion:** As reported before<sup>1</sup>, the proportion of symptomatic cases is high (76%), young children are most commonly involved (96%) and ingestion is predominant (82%). The number of recorded cases in PC Freiburg was less than a tenth, compared to the cases recorded in PC Strasbourg during the whole study period. One reason may be a lower availability of LLP in Germany (they were not marketed in Germany before 2012), and there are currently only six different LLPs recorded by PC Freiburg, but 78 by PC Strasbourg. Although many Germans living near the border shop in France, only two cases with French LLPs were reported in Freiburg.

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## 188. Current status of carbon monoxide poisoning in Belgium

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**Objective:** To describe the number of incidents, victims and deaths caused by carbon monoxide (CO) intoxication in Belgium in 2013.

**Methods:** Data on CO poisoning were collected from hospital emergency services, centers for hyperbaric medicine and coroner's offices. A press clipping service was used as a complementary source of data.

**Results:** In 2013, 538 incidents were registered. These incidents included 1,251 victims of whom 26 died (2.1%). The incidence of CO poisoning in Belgium in 2013 was 11.3/100,000. The crude mortality rate was 0.23/100,000. The majority of incidents were accidental (93%). Occupational intoxications represented 4% and suicide 1%. Of the 48 occupational intoxications 44% were caused by exhaust fumes, 25% by fire at the workplace, 17% by heating systems at work and 10% were workers of the emergency services intoxicated at an intervention site (6% unknown). The majority of incidents (n = 358) were caused by a combustion appliance at home; 103 incidents were caused by fire, 26 by exhaust fumes and for 51 the cause was unknown. In decreasing order of importance combustion appliances causing CO intoxication were water heaters (34%), space heating appliance connected to a chimney (23%), central heating boiler (17%), indoor barbecue, charcoal fire or heating appliance not connected to a chimney (9%), unknown (9%) and

heating appliance not specified (8%). Incidents mostly happened in the living room (26%) and the bathroom (24%). There were 25 fatal incidents resulting in 26 deaths. Seven of these incidents occurred in the bathroom and were caused by a water or space heater on gas; 5 were caused by fire, 5 by space heaters in the living room, 3 were suicides with car exhaust fumes, 2 by a central heating boiler and 2 by an open indoor charcoal burner. For one incident the cause was unknown. There were 2 mass intoxications. Both happened in a hall for parties. In the first one the evacuation pipe of the central heating boiler had come off. There were 23 victims. The second included 17 victims and was caused by butane terrace heaters that had been put inside.

**Conclusion:** The majority of CO incidents are accidental and caused by home water and space heaters. In order to lower the incidence, prevention should focus on the replacement of old water heaters without safety devices and on the correct installation and maintenance of space heaters.

## 189. Pediatric exposures to laundry detergent capsules

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**Objective:** Laundry detergent capsule (LDC) pediatric exposures have been an emerging public health event. Each LDC contains 15-32 mL of highly concentrated surfactants in easy dissolvable polymer membranes. LDCs look like bonbons or toys, so they are very attractive to children who explore them with their mouths and squeeze with their hands. The risk of corneal damage and severe respiratory and esophageal effects due to accidental exposure to LDCs has been documented.

**Methods:** We analyzed our laundry detergent capsule exposures from 2010-2014 by child identification, call site, route of exposure, LDC (by type, colour and accessibility), circumstances of exposure, presented symptoms, management site and medical outcome.<sup>1</sup> Every case was followed by one or more recalls depending on the severity of clinical signs and the healing time.

**Results:** Between 29 July 2010 and 30 September 2014 the National Poison Control Center in Milan handled 1,717 accidental exposures to LDC. A variety of sixty types of LDC divided into approximately 13 colours, belonging to different brands was identified. Overall, the majority of exposures (n = 1,686; 98.2%) concerned children: < 1 year (n = 39; 2.3%), 1 year (n = 386; 22.9%), 2 years (n = 572; 34.3%), 3 years (n = 314; 18.6%), 4 years (n = 189; 11.2%), 5-9 years (n = 174; 10.3%), 10-16 years (n = 12; 0.7%). Most incidents (n = 1,678) occurred at home, 6 at the supermarket, 1 at school and 1 at a community center. Exposure to LDCs occurred mainly as a result of ingestion alone (n = 1,145; 67.9%), oral mucosa exposure alone (n = 222; 13.2%), with eye contact alone (n = 91; 5.4%) and skin contact alone (n = 17; 1.0%). Multiple routes of exposure were involved in 12.5% of cases (n = 211). The medical outcome was known in 1,590 exposures out of 1,686. No symptoms were present in 351 cases (20.8%), the symptoms were minor in 1,099 cases (65.2%), moderate in 125 cases (7.4%) and major in 15 cases (0.9%).



**Conclusion:** This study showed that exposures to LDC represent a risk of poisoning especially for children. The risk is represented by the high concentration of surfactants that probably has a dehydrating action on tissues. Due to the characteristics of LDC, the quantity of liquid in contact with the mouth, skin and eyes is bigger in comparison with the other laundry detergents. LDC exposures required hospital evaluation more often than other laundry detergent products due to more severe clinical effects.

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## 190. Inquiries to the New Zealand Poisons Centre concerning exposures to aerosol oven cleaners

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**Objective:** To describe the characteristics of aerosol oven cleaner exposures using data reported to the New Zealand Poisons Information Centre.

**Methods:** Telephone inquiries involving human exposures to aerosol oven cleaners from August 2007 to July 2014 were retrospectively reviewed. Data on patient age, gender, routes and circumstances of exposure, and recorded signs and symptoms were collated and analysed.

**Results:** In total 148,774 human exposure inquiries were received over the study period. Of these inquiries, 698 cases (0.5%) involved oven cleaners including 527 adults, 131 children and 40 adolescents; 461 in females, 228 in males with 36 unknown. Ninety-five percent of exposures occurred in the home. Exposures involved the skin (n = 280), ingestion (n = 165), inhalation (n = 142) and eyes (n = 111). Skin exposures occurred mainly in adults (232/280 cases), commonly on the arms (44%) and hands (27%), less commonly the face (9%) and legs (5%). Dermal symptoms developed in more than 90% of adults, including irritation (n = 29 cases), redness (n = 78), pain (n = 51), swelling (n = 10), blistering (n = 22) and unclassified burns (n = 35). Ingestions were reported in 73 adults, 73 children and 19 adolescents. In adults 54/73 cases were via contaminated food and 17/73 were via direct contact. Children were more commonly exposed directly (42/73 via direct contact, 22/73 via contact with aerosol deposited in the oven and 9/73 via contaminated food). Following ingestion patients reported no symptoms (n = 86), irritation or minor burns to the lips and mouth (n = 37), an unpleasant taste to the food (n = 20), throat irritation or soreness (n = 6), and gastrointestinal disturbances (n = 16). The majority of inhalational exposures occurred in adults (135/142 cases). Following inhalation, throat irritation or soreness (n = 51) and cough (n = 30) were common; dyspnoea (n = 5), chest discomfort (n = 9), breathing difficulty (n = 5), nausea (n = 5) and dizziness (n = 6) were less common. Most eye exposures also occurred in adults (87/111 cases). In the 40 cases where effects were recorded, symptoms included irritation (n = 6), pain (n = 12), redness (n = 17), burning (n = 5) and stinging (n = 4).

**Conclusion:** Exposures to oven cleaner aerosols are rarely reported, but may result in chemical burns to the skin, eyes, lips and mouth. Secure product storage is essential in preventing child exploratory

exposures and the use of gloves, protection of the upper arms, safety glasses and a face mask are important proactive measures to eliminate harmful exposure in adults using these products.

## 191. The European Chemical Emergency Network (ECHEMNET): An EU-level network of experts to respond to cross-border chemical incidents

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**Objective:** To discuss the outputs of the ECHEMNET project in the assessment of serious cross-border threats to public health from chemicals.

**Methods:** The principal aim of ECHEMNET is to support the European Commission and EU Member States in the implementation of the EU Decision on serious cross border threats to health (1082/EU/2013) and the WHO International Health Regulations. This is being achieved by: developing and testing a well-defined and robust mechanism to provide a rapid risk assessment for emerging chemical threats; improving intersectoral preparedness; further developing a network of toxicological and public health experts to aid with the acute phase response to incidents and; supporting the roll-out of the RASCHEM risk assessment platform by engaging end-users and providing guidance documents on national risk assessment for chemicals. Project outputs were tested in the 2014 CELESTE Quicksilver Exercises and subsequent ECHEMNET command post exercises are planned in 2015. Throughout the project, engagement with stakeholders, end users and relevant competent authorities will be undertaken. The network will also respond in “pilot mode” to emerging EU chemical threats during the lifespan of the project.

**Results:** The EU Decision on serious cross border threats to health identifies a need to provide authoritative, transparent and independent risk assessments for the European Commission and EU Member States to ensure a coordinated response to serious health threats. ECHEMNET has developed a chemical focussed rapid risk assessment (RRA) which has been tested and commented on by end-users. Exercising and engaging with future end-users and stakeholders has been undertaken to ensure that the guidance documents and working mechanisms are developed to be robust and fit for purpose. A framework of required skills has also been developed enabling recruitment of appropriate independent experts to the network that can provide support in the acute phase of an emerging threat.

**Conclusion:** The network and guidance documents developed in ECHEMNET will contribute to an efficient and coherent EU-level

response to potentially devastating cross-border chemical events. The project will try to enable incorporation of the experience of, and best practices adopted by, one Member State following an incident to benefit other Member States and ensure that the response to such incidents is complementary to that of other sectors and actors (e.g. the EU Civil Protection Mechanism [CPM]; World Health Organization [WHO] and the European Centre for Disease Control [ECDC]).

## 192. Reports on cases of poisoning from eye exposure, in particular, detergents and cleaning agents

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**Objective:** In Germany, attending physicians are obliged to report cases of poisoning to the Federal Institute of Risk Assessment (BfR), based on the German Chemicals Act. Such reporting also includes cases of accidental eye exposure to chemical substances or products both from the private household and occupational environment. The cases of poisoning reported are evaluated with regard to the causal relationship and the degree of severity of the health impairment<sup>1</sup> experienced. Subsequently, they are documented in a standardized way and thus, made available for corresponding analyses.

**Methods:** The study referred to all cases of accidental eye exposure reported in the period from 1 February 2013 to 31 July 2014. It included all age groups and both sexes. Cases of exposure where no causal relationship existed were excluded from the study.

**Results:** During the study period, BfR received a total of 6,457 reports on cases of poisoning in humans. Of these, 4,024 cases referred to eye exposure. In 3 of these cases, no causal relationship could be established between the toxic agent and the manifestations observed so that 4,021 cases were available for further analysis. Of these 96% (n = 3,856) were workplace accidents. Only 165 cases occurred in the private sphere. Detergents or cleaning agents were involved in 980 cases of eye exposure, thus ranking first in frequency among the product groups<sup>2</sup> involved. Next in frequency were disinfectants (n = 471) and construction products (n = 270). Altogether, 4 cases of severe eye health impairment were reported, all had been caused by workplace accidents. There were no reports of severe eye damage from detergents and cleaning agents from the consumer sector within the study period.

**Conclusion:** The majority of cases reported to BfR referred to occupational poisoning. Among these, cases of eye exposure accounted for a high proportion (65%). Detergents and cleaning agents are the agents involved most frequently in cases of eye exposure. Cases of severe health impairment affecting the eyes were reported from the occupational sphere only, i.e. not from the sector of consumer products. There was no report on any severe chemical eye burns from exposure to detergents or cleaning agents from the consumer sector during this period.

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## 193. Spurious serum chloride measurement in severe metabolic disturbance associated with 2-butoxyethanol ingestion

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**Objective:** Glycol ethers are an uncommonly implicated agent in poisoning cases. We report a case of 2-butoxyethanol (ethylene glycol monobutyl ether) ingestion causing significant metabolic disturbance treated with continuous renal replacement therapy.

**Case report:** A 38-year-old female was transferred to a metropolitan hospital having presented to a rural facility 6 hours after ingestion of a window cleaner containing 2-butoxyethanol. On admission she had tachypnoea and a venous blood gas showing a combined respiratory alkalosis and metabolic acidosis. The anion gap as calculated from a point of care blood gas machine was marginally elevated at 19 mmol/L but when calculated on a formal laboratory sample was significantly higher at 32 mmol/L. The difference in values was accounted for by a serum chloride value of 113 mmol/L on the blood gas machine compared to 100 mmol/L on laboratory sample. This discrepancy persisted during further biochemical sampling with the maximum difference between chloride values reaching 18 mmol/L, approximately 13 hours post-ingestion. The biochemical analysis in both cases was done by potentiometry using an ion-selective electrode. However the blood gas machine utilised an undiluted, direct technique whilst the laboratory machine used a diluted, indirect technique. Management involved orogastric alcohol infusion to inhibit alcohol dehydrogenase (ADH) and potentially limit the formation of toxic metabolites, as well as continuous renal replacement therapy to reverse the profound metabolic disturbance. Over the next 24 hours the metabolic abnormalities returned to normal and the discrepancy between lab and blood gas chloride values disappeared.

**Conclusion:** Previous reports of butoxyethanol ingestion have reported coma, hypotension and metabolic acidosis. Our case was unusual in that the primary acid-base disturbance was a respiratory alkalosis, although a concurrent metabolic acidosis was also present. In a previous case a hyperchloraemic metabolic acidosis in the context of butoxyethanol ingestion occurred, however it would appear that only one source of sampling was used.<sup>1</sup> Salicylates have been shown to produce a falsely elevated chloride concentration at toxic concentrations and hence potentially normalising the anion gap in circumstances where an elevated anion gap might be important diagnostically.<sup>2</sup> Clinicians dealing with cases such as this need to be aware of such potential caveats in biochemical testing.

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## 194. Retrospective analysis of oral exposure to vinegar essence in Austria, 2002–2013

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**Objective:** Vinegar essence is acetic acid diluted with water. Vinegar on the market contains up to 25 g acetic acid/100 g (25%). For industrial use the water-free part may contain up to 80%. Legally regulated, in Austria this type of vinegar essence had been available in supermarkets until recently, although there were restrictive regulations. Austria is the only German speaking country in which 80% vinegar essence was available and popular as a descaling and cleaning agent in households and heavily diluted as a salad dressing. The Poisons Information Centre (PIC) in Vienna, Austria, performed a retrospective analysis of calls to the centre regarding oral intake of vinegar essence accidentally or in suicidal attempt.

**Methods:** Data from the PIC database involving vinegar essence oral exposures were evaluated for the period of 2002–2013. Acute exposures were analysed for age and intent of exposure (accidental or suicidal).

**Results:** In 12 years we documented 64 cases of oral exposure of vinegar essence (Table 1) and 21 (33%) of them had chemical burns to the gastrointestinal tract. In total 3 (5%) patients died due to the systemic effects. The high percentage of children with no symptoms can be explained by the fact that their milk or food was mixed with diluted vinegar essence in water from the kettle during its use as a descaler.

**Conclusion:** Highly concentrated acetic acid including vinegar essence represents a serious health hazard in Austrian households. Stronger legal regulations and/or more controls are required to prevent accidental and intentional exposure.

**Table 1.** Accidental and suicidal oral intake of vinegar essence in adults and children.

Symptoms	Adult		Child	
	Accidental n = 27	Suicidal n = 13	Accidental n = 23	Suicidal n = 1
None	6 (22%)	0	10 (43%)	0
Nausea, vomiting	3 (11%)	1 (8%)	3 (13%)	0
Gastrointestinal irritation	7 (26%)	1 (8%)	3 (13%)	0
Gastrointestinal burns	7 (26%)	8 (61%)	5 (22%)	1 (100%)
Death	1 (4%)	2 (15%)	0	0
Unknown	3 (11%)	1 (8%)	2 (9%)	0

## 195. Fear of secondary exposure of healthcare personnel can lead to disproportionate measures

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**Objective:** Increased risk of terrorist attacks has motivated hospitals to prepare for the admission of patients contaminated with chemical agents. This is apparent from the development of protocols and exercises with large-scale incident scenarios. It has been observed by the Dutch Poisons Information Center (DPIC) that increased concern about secondary exposure when treating contaminated patients, sometimes results in disproportionate precautions. This is illustrated by three incidents in 2014.

**Case report:** Case 1. A patient who ingested paraquat was washed before transportation to the emergency department (ED) because of contamination with vomitus and faeces. A paramedic and the patient's wife reported feeling unwell at that point. Although the DPIC and local health authority informed the ED that the risk to healthcare personnel was negligible, the patient was treated using personal protective equipment (PPE) including airway protection. Several healthcare workers felt unwell after treating the patient who died 16 hours post-ingestion. A morgue employee also reported health complaints although the deceased had already been placed in an airtight body bag. Relatives were not allowed to see the deceased due to safety concerns and an emergency cremation was performed. Case 2. The DPIC was consulted after dermal exposure in a patient to hydrofluoric and hydrochloric acid. He had already showered himself. Although unremarkable from a toxicological perspective, media later reported that the ED was evacuated for several hours after the attending physician reported minor respiratory distress. Firefighters entered the ED with airway protection to take air samples which were negative. Persons that had been in contact with the patient underwent a health check. 3. Two persons (one deceased, one unconscious) were found in a domestic setting where a chlorine smell was noticed. Emergency responders at the incident and personnel at the ED who treated the unconscious patient complained about mucous membrane irritation. Thereafter, the ED was closed and the fire service installed decontamination units outside the hospital as a precaution. Attending personnel showered and changed clothing. Household bleach was later identified as cause of the chlorine smell.

**Conclusion:** In the presented cases, relatively minor symptoms experienced by healthcare personnel led to disproportionate measures. Unnecessary precautions can delay treatment of possibly critically ill patients. Although precautions to minimize secondary exposure of healthcare personnel are useful, it is important to raise awareness about the relatively low risk of treating a seriously intoxicated patient without use of extra PPE. Reducing irrational "fear of chemicals" is an important step in this process.

## 196. Dichloroethane as a cause of Parkinsonism: A case report

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**Objective:** Parkinsonism is a syndrome defined by the presence of tremor at rest, bradykinesia and rigidity. The leading cause of neurodegenerative Parkinsonism is Parkinson's disease, but chronic exposure to chlorinated pesticides is among other causes of Parkinsonism.<sup>1,2</sup> 1,2-Dichloroethane is a chlorinated hydrocarbon



solvent which is well absorbed through the lungs and the skin. Little information is available on the effects of dichloroethane in humans. The target organs after ingestion are the liver and kidney but damage of neurones and respiratory distress can also occur.

**Case report:** A 55-year-old man was investigated and treated in our Neurological Out-patient Department for asymmetrical rest tremor, sleeping disorders and visual disturbances. During the investigation pathological changes of the substantia nigra were found in transcranial sonography and single-photon emission computed tomography, with cortical atrophy detected by computed tomography and magnetic resonance imaging. Changes typical of other diseases were not found. The absence of treatment effect with levodopa suggested it was unlikely to be Parkinson's disease. After detailed history taking, it was discovered that the patient had suffered acute inhalational and percutaneous poisoning by dichloroethane in 1999. Depression of the central nervous system and respiratory insufficiency were dominant in the clinical picture at that time. He recovered one month after poisoning, but the recovery was partial. He had visual disturbances immediately after this incident and these may have been deteriorating. Three years later he developed sleeping disorders. Tremor at rest, postural tremor and bradykinesia started approximately 5 years ago. In the last 2 years he has been treated with levodopa and propranolol, but treatment is ineffective.

**Conclusion:** This case demonstrates the possibility of developing Parkinsonism after acute poisoning by 1,2-dichloroethane.

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## 197. Ethylene glycol poisonings associated with acute kidney injury in the Slovak Republic

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**Objective:** The ingestion of antifreeze products containing toxic ethylene glycol can trigger a serious medical problem. The aim of this retrospective analysis was to study poisoning with ethylene glycol leading to acute kidney injury (AKI) in patients hospitalized across Slovakia. This analysis involved medical reports of hospitalized patients after consultation with the National Toxicological Information Centre (NTIC).

**Methods:** Details of exposures to products containing ethylene glycol reported to the NTIC were collected from January 2005 to November 2014. A detailed analysis of all the survivors who suffered from AKI was performed.

**Results:** Over a 10 year period there were 263 enquiries about ethylene glycol exposure, involving 113 hospitalized individuals of whom 12 (10.6%) died. There were 21 survivors (20.8%) who suffered from AKI. The mean age was 46 years, with males dominating (62%). In some individuals biochemical analysis showed

severe metabolic acidosis with extreme pathological values of a minimum pH 6.68, serum bicarbonate 1.4 mmol/L, maximum creatinine 1126 micromol/L, anion gap (calculated with potassium) 45.2 mmol/L and serum potassium 7.4 mmol/L. According to the Poison Severity Score (PSS), 19 of the 21 cases with AKI (90.5%) resulted in severe poisoning. Ethanol therapy and haemodialysis were used in 76% and 95% of the cases, respectively. Fomepizole was used only once in a severely poisoned 16-year-old boy.

**Conclusion:** Even very serious poisoning with ethylene glycol can usually be successfully managed with ethanol, haemodialysis and supportive treatment.

## 198. Complicated diagnosis of ethylene glycol poisoning: A case report

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**Objective:** Ethylene glycol poisoning usually results in typical clinical and laboratory findings in early hospital presentation.<sup>1</sup> Sometimes the diagnosis may be complicated and delayed if patients are admitted late, with inadequate history and renal insufficiency is already apparent.

**Case report:** A 77-year-old male presented at the regional hospital after 3 days of illness with headache, nausea, vomiting, left-sided back pain and decreased diuresis. He had become unwell after ingestion of a soft drink. On physical examination he was cardiovascularly stable with symptoms of dehydration, mild hypoxemia, mild painful left-side abdominal palpation and a superficial trophic ulcer on the left shin. Laboratory testing revealed elevated inflammatory markers and leucocyturia and uremia. Hepatic and pancreatic markers were normal; blood gases analysis was also normal (pH 7.4). Urinary infection was suspected and antibacterial treatment was started. Despite intensive antibiotic and rehydration treatment lasting 3 days the patient's condition worsened and renal failure progressed. He was transferred to the University hospital to start hemodialysis and to differentiate causes of renal insufficiency. Ultrasound examination showed normal kidney size with thickened renal parenchyma. It was differentiated from acute post-infection glomerulonephritis, sepsis, anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis. A renal biopsy revealed unexpected calcium oxalate crystals in the renal canaliculi with diffuse necrosis. The causes of renal oxalosis were discussed and the case history was revised. The patient and a friend had drunk antifreeze 3 days before admission to the regional hospital. His friend survived without sequel because he had also consumed ethanol.

**Conclusion:** Late presentation to the hospital after ethylene glycol poisoning can complicate and delay diagnosis. Prolonged vomiting with hypochloremic alkalosis can mask metabolic acidosis, a typical sign of such poisoning.

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## 199. Dishwasher tablets: Corrosive or irritant following accidental exposure?

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**Objective:** Automatic dishwasher tablets are a common household product which can be potentially corrosive. Newer products may contain disilicates rather than metasilicates and therefore cause fewer corrosive effects. This study was performed to characterise enquiries to the National Poison Information Centre of Ireland (NPIC) regarding exposures to dishwasher tablets and to assess their corrosive risk.

**Methods:** Enquiries to the NPIC between 1 January 2011 and 31 December 2013 about exposure to dishwasher tablets were retrospectively identified on the enquiry database. Data was extracted on patient demographic, route of exposure, symptoms and Poison Severity Score (PSS).

**Results:** A total of 208 patients were identified during the study period. There were 62 enquiries in 2011, 66 enquiries in 2012 and 80 enquiries in 2013, a 21.2% increase on the previous year. Ingestion was the commonest route of exposure ( $n = 206$ ; 99.0%). The majority of patients were children less than 5 years of age ( $n = 193$ ; 92.8%) and 144 (69.2%) were  $\leq 1$ . In total 46 (22.1%) patients were symptomatic and all developed minor symptoms only, with vomiting ( $n = 30$ ; 65.2%) being the most common symptom reported. Other symptoms included nausea ( $n = 3$ ; 6.5%), coughing ( $n = 3$ ; 6.5%) and diarrhoea ( $n = 1$ ; 2.2%). No patients developed moderate/severe symptoms.

**Conclusion:** Most patients exposed to dishwasher tablets were children less than 5 years of age, who had ingested the product. Exposure via this route did not result in symptoms in the majority of case ( $n = 159$ ; 76.4%). Symptomatic cases developed minor effects only. No corrosive effects from this household product were seen in the cases reported to the NPIC. Accidental ingestion of small amounts of this product results in irritant effects at most.

## 200. Extensive rhabdomyolysis enhanced acute renal failure in a severe delayed ethylene glycol poisoning

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**Objective:** Acute ethylene glycol intoxication is life-threatening emergency that, if not diagnosed correctly and treated aggressively, has a high risk of persistent end-organ damage. The toxicity is due to a combination of severe metabolic acidosis caused by glycolic acid and precipitation of calcium oxalate crystals resulting in impaired organ function, especially in the kidneys. Rhabdomyolysis is characterized by the breakdown of skeletal muscle resulting in the subsequent release of intracellular contents into the circulatory system, resulting in myoglobinuria and acute renal failure.

**Case report:** A 24-year-old male was admitted 24 hours after ingestion of 200 ml ethylene glycol in a suicidal attempt. The

patient was a former athlete, 110 kg body weight and 1.90 m tall, with a large muscular mass. On presentation he had dizziness, restlessness, agitation, hyperventilation, tachycardia, emesis and diuresis; soon after he became comatose and was intubated and put on ventilator support. He had hemodynamic instability and vasopressor support was initiated. Laboratory tests revealed severe metabolic acidosis with increased anion and an osmolar gap. In addition, he had elevated CK 969 U/L and myoglobinemia of 603 mcg/L, BUN 48.5 mg/dL and creatinine 2.75 mg/L. We rapidly started continuous-venovenous haemodiafiltration in an attempt to reverse the toxic damage, along with ethanol infusion, volemic repletion, alkalization and supportive measures. We maintained the patient on ventilator and renal support. On day 2 he became oliguric, but was hemodynamically stable. The acidosis corrected after 24 hours but the CK, myoglobinemia, BUN and creatinine increased. The CK peaked on day 9 (6800 U/L), myoglobinemia on day 10 (2235 mcg/L), BUN (257 mg/dL) and creatinine (5.40 mg/dL) on days 14-15. An MRI highlighted diffuse edematous and hemorrhagic modification at the level of the gluteal and adductor muscles. The patient was extubated on day 11 and became polyuric on day 12 with the slow resolution of altered parameters and renal support was stopped. On day 22 the renal parameters returned to normal and diuresis was within the normal range. The patient was discharged on day 24 with normal renal function and no sequelae.

**Conclusion:** In this case, acute renal failure was due to direct ethylene glycol toxicity and a concomitant myoglobinuric state. Rhabdomyolysis developed in an agitated and then comatose patient, with large muscular mass and prolonged immobilisation, with acidosis and decreased blood flow. A direct myotoxic effect of ethylene glycol may be involved.

## 201. Hydrogen sulfide poisonings in Denmark 2004–2014

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**Objective:** Hydrogen sulfide is a potentially lethal gas that occurs naturally i.e. in volcanic fumes, when organic material degrades, and as a by-product of industrial processing.<sup>1</sup> Due to an increasing number of enquiries regarding hydrogen sulfide to the Danish Poison Information Centre, a rise in poisoning cases and possibly new exposure methods were suspected and investigated. Previously, Denmark has only seen case-reports.

**Methods:** An analysis of data from the Danish Poison Information Centre indicates a slight increase in the number of more or less validated poisoning cases, when excluding registrations of more than one enquiry regarding the same case, and cases with no data available.

**Results:** The poisoning cases primarily occurred in places/industries where hydrogen sulfide is known to occur. Of 46 cases the distribution was as follows: sewer 6, farming industry 12, ships 3, laboratories 3 and wells 3. Six cases had unknown source of exposure, and 13 cases had other agents involved, including one suicide. There have been fatal outcomes of hydrogen sulfide poisoning in the past 3 consecutive years in Denmark.

**Conclusion:** An analysis of available data indicates a slight increase in the number of cases of hydrogen sulfide poisoning. One case of suicide and three accidental laboratory exposures are the most unexpected cases in this series. This is remarkable as poisoning is relatively easily prevented with the use of detectors. Perhaps there is the need to raise awareness of the risks of hydrogen sulfide poisoning.

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## 202. The dangers of chlorinated pools: A case of severe keratitis and episcleritis

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**Objective:** The toxic effects of chlorine from swimming pools are well known and are characterized mainly by irritant/asthmatic symptoms affecting the respiratory system. We report a pediatric case of severe acute ocular damage due to the high-chlorine concentration in a domestic swimming pool.

**Case report:** A 10-year-old boy was evaluated to the pediatric Emergency Department (ED) because of acute onset of bilateral periorbital swelling associated with a marked pain to eye movements. Physical examination was normal except for a severe bilateral palpebral edema associated with conjunctival hyperemia and a progressive fluffy white growth over both corneas. Furthermore, the sclera appeared thickened and hung over the iris which appeared depressed. All eye movements were limited and the child had great difficulty in keeping his eyes open. He also reported intense pain on acupressure. The history was positive for chronic allergies; no recent trauma no contacts with potentially irritating substances or animals were signaled. No respiratory symptoms were registered. Blood count and serum electrolytes concentration were normal while there was a mild increase in inflammatory markers values. Ophthalmologic evaluation described linear epithelial erosions of the cornea and clinical signs consistent with keratitis and episcleritis requiring eye irrigation with physiological salt solution, local corticosteroid and antibiotic therapy (dexamethasone and tobramycin). An accurate history revealed that the child had spent some time (1 hour) with a friend in a domestic swimming pool. After swimming, the patient reported seeing halos and rainbows around lights, typical symptoms of corneal edema and then photophobia, tenderness in eye movements and conjunctival hyperemia. Investigation revealed the father of patient's friend had applied (erroneously) chlorine-derived tablets (90% chlorine per tablet) to the pool water, that afternoon. The patient's clinical condition gradually improved with a progressive reduction in edema. The

boy was discharged after 48 hours with the indication to continue local therapy (dexamethasone and tobramycin for 10 days). The clinical follow-up (at 7 and 20 days) revealed a complete resolution of edema and conjunctival hyperemia.

**Conclusion:** Ocular toxic effect may be present in the absence of irritant/asthmatic symptoms affecting the respiratory system. The ocular effects, although severe at ED-presentation, completely resolved in 2 weeks. The use of chlorine in domestic pools may represent a health risk including the risk of local toxic effects and it is important that a specific warning for correct use should be stressed.

## 203. Use of a polyamphoteric solution in the event of ocular and cutaneous chemical accidents: 12 cases

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**Objective:** Polyamphoteric washing solutions have been used for several years, mainly in industrial settings for initial management of accidental ocular or cutaneous chemical splashes. We report 12 cases of chemical exposure treated with a polyamphoteric washing solution.

**Methods:** Multicentric study and retrospective collection of 12 cases of the use of polyamphoteric washing solution in the management of ocular and cutaneous chemical splashes. The product used is a proprietary blend and the ingredients are unknown to some authors. The criteria studied included the circumstances (work, assault, domestic), nature of the chemical and pH, type of exposure, clinical signs initially and after washing, initial and final evaluation of pain as assessed by a visual analog scale (VAS) and conclusion of the specialized advice.

**Results:** Among the 12 cases, there were 8 occupational exposures, 1 assault, 2 domestic exposures and 1 exposure at school. The chemicals involved were alkalis (n = 5), acids (n = 3) and chemicals of unknown pH (n = 4). There were 7 ocular, 2 cutaneous and 3 cases involving both routes of exposure. One cutaneous exposure was immediately classified as deep injury and 3 were superficial. Cutaneous application of the washing solution was delayed (90 minutes) in the patient with the deep injury (case number 4). In the case of bilateral ocular exposure by a plant latex (case number 1), the polyamphoteric solution washing was performed after two ocular washes with water and oral morphine which may have helped to reduce pain. The mean initial VAS was  $8.0 \pm 2.62$ ; the final VAS after ocular or cutaneous washing was  $1.75 \pm 1.48$ .

**Conclusion:** Preliminary results show that early application of a polyamphoteric washing solution relieves ocular and cutaneous signs after chemical splashes. The osmolar and chemical action of these solutions appear to limit penetration of chemicals into the deep layers of ocular epithelium, dermis and hypodermis. Other clinical studies are necessary to validate this hypothesis.



**Table 1.** The use of a polyamphoteric solution in 12 cases of ocular and/or dermal chemical exposure.

Case	Chemical agent	pH	Type of exposure	Time before washing	Initial clinical signs	Initial VAS	Clinical signs after washing	Final VAS	Specialised diagnosis (ophthalmologist or dermatologist)
1	<i>Euphorbia lathyris</i> latex	9	Ocular bilateral	310 min	Blepharospasm, ocular pain	10	Disappearance of pain and blepharospasm	3	Moderate corneal damage
2	Lacrimatory agent		Ocular bilateral	30 min	Ocular hyperaemia, pain	10	Disappearance of hyperaemia	0	Normal ophthalmic exam
3	Acrylic lacquer		Ocular unilateral	20 min	Ocular hyperaemia and pain	6	Disappearance of hyperaemia	0	Normal ophthalmic exam
4	AGS 60® Anti-etching product	14	Cutaneous	90 min	Pain, deep injury	8	Disappearance of pain, persistence of deep injury	0	Deep injury, debridement, cutaneous grafting
5			Ocular bilateral and cutaneous	20 min	Ocular pain, blepharospasm, phlyctens	10	Conjunctival irritation	4	Normal ophthalmic exam
6	98% Sulfuric Acid (Oleum)	1	Ocular bilateral and cutaneous	5 min	Ocular pain, facial erythema	9	Disappearance of facial erythema and pain	2	Normal ophthalmic exam
7	25% Caustic soda	12	Ocular bilateral and cutaneous	30 min	Ocular pain, facial erythema	8	Disappearance of facial erythema	2	Normal ophthalmic exam
8	98% Sulfuric Acid (Oleum)	1	Cutaneous	1 min	Blemishing of neck and thorax	9	Persistence of blemishing areas, later spontaneous healing	3	Normal ophthalmic exam
9	Calcium hydroxide Ca(OH) <sub>2</sub>		Ocular bilateral	89 min	Ocular hyperaemia pain, palpebral oedema	10	Diminution of pain	3	Minimized conjunctival injury
10	Mewa Bio-Circle® grease remover	8.5	Ocular unilateral	110 min	Blurred vision, feeling of veiled left eye	1	Diminution of visual disturbances	0	Normal ophthalmic exam
11	Indal Proclean® Detergent	1.5	Ocular unilateral	Not known	Ocular hyperaemia, visual disturbances	9	Diminution of visual disturbances and disappearance of hyperaemia	3	Normal ophthalmic exam
12	Bactifoam® alkaline antibacterial agent	13	Ocular unilateral	171 min	Ocular hyperaemia, blepharospasm	6	Disappearance of hyperaemia and blepharospasm	1	Normal ophthalmic exam

## 204. The effectiveness of patient-tailored treatment for acute organophosphate poisoning

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**Objective:** To determine a new pralidoxime (PAM) treatment guideline based on the severity of acute organophosphate (OP) intoxication patients. Severity was based on the Acute Physiology and Chronic Health Evaluation (APACHE) II score (if  $\geq 26$  or not) and dynamic changes in serum butyrylcholinesterase (BuChE) activity. **Methods:** The enrolled patients were randomized into experimental group and control group. All patients received supportive care

measurements and atropinization. Each enrolled patient was treated with 2 g PAM intravenously as the loading dose. The control group was treated according to the World Health Organization's recommended PAM Regimen<sup>1</sup>, and the experimental group was treated according to their APACHE II scores<sup>2</sup> and dynamic changes in BuChE activity. If a patient's APACHE II score was  $\geq 26$  or there was no elevation in BuChE activity at the 12th hour compared to the 6th, a double dose of the WHO's recommended PAM was given. Pralidoxime was discontinued when the patient was free of OP poisoning symptoms and signs. The activities of serum butyrylcholinesterase and red blood cells (RBC) acetylcholinesterase and the serum pralidoxime concentrations were also measured for further analysis.

**Results:** Forty-six organophosphate poisoning patients were included with 24 in the control group and 22 in the experimental group. The hazard ratio of death in the control group to that of the experimental group was 97.51 (95% CI 1.167-8146.933,  $p = 0.0425$ ). The RBC acetylcholinesterase activity was elevated in the experimental group but was not elevated in the control group.

The experimental group did not exhibit a higher pralidoxime blood concentration than the control group.

**Conclusion:** The use of pralidoxime can be guided by patient severity. This may help to improve the outcome in OP-poisoned patients.

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## 205. Acute human toxicity of emamectin

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**Objective:** Emamectin, a macrocyclic lactone, is increasingly used in Asia as an insecticide, but few cases of toxicity in humans have been reported. Our objective was to analyse cases of emamectin toxicity reported to the Taiwan National Poison Center (PCC-Taiwan) to better understand the toxicity profile of emamectin in humans. In Taiwan emamectin is available as a 2.5% liquid also containing 2% abamectin.

**Methods:** We conducted a retrospective analysis of all emamectin exposures reported to the PCC-Taiwan from 1986 to 2012. Their demographic and clinical data were then analyzed to identify potential predictors of severe effects and clinical presentation following acute emamectin poisoning.

**Results:** In total 77 patients were reported with emamectin toxicity, including 69 with oral and 8 with non-oral exposures. Symptoms reported were gastrointestinal, neurological, cardiovascular and/or respiratory manifestations. Among patients with oral exposure, 23 were asymptomatic or had only mild poisoning. Three patients (4.3%) died following deliberate emamectin ingestion. The median dose of emamectin ingestion was 161.5 ml in the moderate/severe/fatal groups compared to 57.1 ml in the mild poisoning group. Conscious disturbance in the moderate/severe/fatal groups occurred in 22 (47.8%) cases, but in only 4 (12.9%) patients with mild poisoning. The development of moderate to severe toxicity was positively associated with conscious disturbance (including agitation, coma, drowsiness) and a larger dose of emamectin ingested.

**Conclusion:** Although emamectin is thought to be of low toxicity to humans, severe effects can occur and may be associated with conscious disturbance and respiratory problems. The effects are similar to those seen with ivermectin and milbemycins. The exact mechanism of toxicity remains unclear but emamectin is believed to cause effects via the activation of glutamate-gate chloride channel in nerve and muscle cell to affect the gamma-aminobutyric acid (GABA) receptors. There is no specific treatment for emamectin intoxication. Most victims of emamectin intoxication treated with supportive care have a good prognosis, but severe complications occur in some cases.

## 206. PiCCO interpretation for acute glyphosate intoxication with shock: Favors cardiogenic origin

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**Objective:** Glyphosate, a commonly used herbicide worldwide, is thought to be of low toxicity to humans. However, severe intoxication with mortality and morbidity has been reported including unconsciousness, pulmonary edema, shock, metabolic acidosis, arrhythmia, respiratory failure, acute renal injury and death. We report a case of cardiogenic shock after glyphosate ingestion.

**Case report:** A patient drank about 100 ml glyphosate in a suicide attempt 3 hours before visiting our emergency department. The initial presentation was shock, reduced consciousness and respiratory failure. The initial vital signs were temperature 36°C, heart rate 129 bpm, respiratory rate 30/min, BP 90/59 mmHg and Glasgow Coma Scale (GCS) 9 (E4V1M4). We performed emergency intubation and resuscitation. Hemogram and biochemistry showed leukocytosis with left shift (WBC 22300/mcL, Hb 14.0 g/dL, segment 89.5%, band 1.5%), normal renal, liver function and electrolytes. The urine paraquat concentration was <5 ppm and blood cholinesterase activity was normal (8.64 U/ml). After intubation, blood gases were normal. The blood lactate was 73.2 mg/dL (5.7–22) indicating tissue hypoperfusion and shock. In ICU, we used PiCCO (Pulse indicator Continuous Cardiac Output) for shock status monitoring. On the first day of ICU admission, PiCCO data showed CI (Cardiac Index) 2.78 (normal range 3.0–5.0 L/min/m<sup>2</sup>), ITBVI (Intrathoracic Blood Volume Index) 1063 mL/m<sup>2</sup> (normal > 850), EVLWI (Extravascular Lung Water Index) 12.0 mL/kg (normal < 10). PiCCO data interpretation indicated cardiogenic shock due to low CI, adequate ITBVI and increased EVLWI. After supportive care and dopamine infusion, the cardiogenic shock and critical condition improved. On the 3rd day of ICU admission, the PiCCO data showed the low cardiac index had improved (CI 4.23 L/min/m<sup>2</sup>) with ITBVI 1316 mL/m<sup>2</sup> and EVLWI 7.8 mL/kg. Cardiac echo showed an ejection fraction of 65% with adequate left ventricular systolic function and normal wall motion.

**Conclusion:** There are some reports of severe glyphosate intoxication causing shock. Our case is the first case of glyphosate intoxication with shock analysed by PiCCO and indicated the shock is cardiogenic in origin. The mechanism and correlation of glyphosate intoxication and cardiogenic shock need more toxicokinetic research. Furthermore, other differentials of shock should be considered such as septic shock and hypovolemic shock but these were less likely. Septic shock would not progress within 3 hours, and there was no obvious blood or fluid loss in our patient. In addition the ITBVI was adequate. More cases with PiCCO evaluation and prospective studies are necessary.

## 207. Glyphosate intoxication resulting in ventricular dysrhythmias and cardiogenic shock

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**Objective:** A rare case of glyphosate intoxication presented with ventricular dysrhythmias and cardiogenic shock treated successfully by extracorporeal membrane oxygenation (ECMO).

**Case report:** A 46-year-old male who has no underlying disease was sent to our emergency department (ED). He had ingested 100 ml of glyphosate 50 minutes earlier in a suicidal attempt. He was fully conscious and the vital signs at triage were blood pressure (BP) 143/91 mmHg, heart rate 72 beats/minute, respiratory rate 20 times/minute and body temperature 36°C. Nausea and vomiting were the main presentations when he arrived at ED. Physical examination revealed no specific abnormalities. He was given gastric irrigation using a nasogastric tube and normal saline immediately on arrival. Serial blood tests including arterial blood gas analysis (ABG), chest X-ray (CXR) and 12-lead electrocardiography (ECG) were also arranged. The ECG showed sinus rhythm with 90 beats/minute, QRS 134 ms and QTc 550 ms. The profound shock (BP 75/45 mmHg) 50 minutes later and received 1 L of saline and norepinephrine 21 µg/min by intravenous infusion. CXR revealed mild cardiomegaly. Laboratory studies showed white blood cell count 13100/µL, sodium 141.6 mEq/L, potassium 4.16 mEq/L, blood urine nitrogen 10 mEq/dL, creatinine 0.98 mEq/dL and troponin-I < 0.02 ng/mL. He had dyspnea and the pulse oximetry showed SpO<sub>2</sub> 77% about 90 minutes after his arrival and he was intubated. At that time, ECG showed non-specific intraventricular conduction block with 54 beats/min, QRS 176 ms and QTc 521 ms. Dopamine 16 µg/kg/min intravenous infusion was prescribed for symptomatic bradycardia with shock (BP 53/18 mmHg). Two hours after his arrival, he had sudden onset of pulseless ventricular tachycardia; defibrillation (200 joules) and cardiopulmonary resuscitation resulted in return of spontaneous circulation. The lactate and ABG showed lactic acidosis (lactate 37.3 mg/dL and because of refractory cardiogenic shock (BP 71/19 mmHg) induced by non-specific intraventricular conduction block, the cardiovascular surgeon was consulted for extracorporeal membrane oxygenation (ECMO). He was admitted to ICU for veno-arterial ECMO support for 36 hours. He no further episodes of arrhythmia or shock and ECMO was stopped; he was extubated 4 days later.

**Conclusion:** Cardiogenic shock and ventricular arrhythmia are rarely seen in glyphosate intoxication.<sup>1</sup> Since there is no antidote, supportive care is the main treatment option. If supportive care fails then ECMO should be considered as one of the treatment of choices in severe cases.

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## 208. Acute poisoning with the neonicotinoid insecticide imidacloprid misdiagnosed as organophosphate intoxication

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**Objective:** Imidacloprid is a relatively new insecticide. Animal studies indicate relatively low toxicity to mammals but

information on human poisoning is limited.<sup>1-3</sup> Imidacloprid acts on the central nervous system as an agonist at the nicotinic acetylcholine receptor. However, few articles state that imidacloprid can decrease the cholinesterase activity in humans. Here, we present a case of attempted suicide with unknown substance, with an initial decrease in cholinesterase activity, mistreated with pralidoxime (PAM).

**Case report:** An 87-year-old male with prostate cancer drank an unknown amount of unknown insecticide due to depressive mood 5 hours before arrival to our emergency department (ED). He received a gastric lavage with charcoal at a local hospital and was transferred. He complained of dry mouth and mild miosis was found, but no fever, dyspnea, chest pain or abdominal pain. Organophosphate intoxication was suspected due to a low cholinesterase activity (5.83 kU/L) and PAM was given. He was admitted to ICU for further care. After admission, conscious level remained good but bilateral lung field crackles was noticed even after atropine. He was intubated and further doses of PAM given. He had no fever. Other signs of organophosphate poisoning such as salivation, lacrimation or diarrhoea were not noted. His conscious level was E2VeM4-5 after intubation. We stopped PAM on day 2, as he became progressively flaccid without signs of organophosphate intoxication, although the cholinesterase activity had dropped a little. Muscle weakness was suspected to be due to PAM. He was extubated on day 3 with full recovery in muscle power and conscious level. The cholinesterase activity was 6.43 kU/L on Day 2 and 5.69 kU/L on day 3. He was transferred to an ordinary ward on day 4 and discharged on day 8. Ten days later, imidacloprid (4 ppm) was detected in a urine sample.

**Conclusion:** Imidacloprid may decrease cholinesterase activity in humans, which may result in the misdiagnosis of organophosphate intoxication. PAM may cause patient deterioration as it interferes with the transmission of neuronal impulses power.

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## 209. Successful treatment with hemodialysis for acute renal failure after glyphosate poisoning: A case report

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**Objective:** Glyphosate is a herbicide which is commonly used in Taiwan. Intentional ingestion is the most common reason for acute glyphosate intoxication. Acute renal failure, followed by electrolyte imbalance and metabolic acidosis occurred in a patient with severe intoxication, and is highly predictive of mortality. Hemodialysis has been successfully used in the treatment of severe glyphosate intoxication, but the case numbers are small, and its use



is still controversial. We report a case of severe glyphosate intoxication with acute renal failure who was successfully treated with hemodialysis.

**Case report:** A 37-year-old man, with a history of depressive disorder, was sent to the Emergency Department (ED) after ingestion of 3 “gulps” of glyphosate in a suicide attempt. Gastric lavage was performed, and activated charcoal given immediately after arrival. Initial laboratory data revealed acute renal failure (serum creatinine 2.05 mg/dL) and mild metabolic acidosis (pH 7.32, pCO<sub>2</sub> 31.8 mmHg, bicarbonate 16.1 mmol/L). Serum cholinesterase activity and urine paraquat were determined and found to be within the normal range and negative, respectively. Serum creatinine continued to rise and was 5.22 mg/dL on day 2, and 9.14 mg/dL on day 3, despite adequate urine output. Respiratory distress developed, but chest X-ray showed no increased infiltration. Intubation was performed due to respiratory failure. A nephrologist was consulted and hemodialysis arranged. The patient was admitted to intensive care unit and given 3 courses of hemodialysis. The serum glyphosate concentration dropped from 1980 ppm to 356 ppm after hemodialysis, and the urine glyphosate concentration also decreased from 11300 ppm to 9350 ppm. Meanwhile, the serum concentration of aminomethylphosphonic acid (AMPA), the metabolite of glyphosate, increased from 1.6 to 1.7 ppm, and urine concentration increased from 82.1 to 82.6 ppm. His renal function recovered well after hemodialysis (serum creatinine 1.0 mg/dL on day 12), and he was discharged on day 14 without any sequelae.

**Conclusion:** Hemodialysis is an effective treatment for patients with severe glyphosate poisoning and acute renal failure. Both the physical condition and laboratory data from this patient support its use. Hemodialysis should be considered early in patients with glyphosate intoxication and renal failure to improve the prognosis.

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## 210. Chlorfenapyr intoxication: A fatal case with acute pancreatitis

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**Objective:** Chlorfenapyr is a new pesticide. It is a pro-insecticide that interferes with mitochondrial oxidative phosphorylation resulting in disruption of production of ATP and cellular death.<sup>1</sup> Chlorfenapyr intoxication has rarely been reported in human. We present a case of chlorfenapyr poisoning with profound sweating, acute pancreatitis and death.

**Case report:** An 80-year-old male presented to our emergency department because of abdominal pain and profound diaphoresis lasting for five days. Eight days earlier, he had attempted to commit suicide by ingesting about 200 mL of 10% chlorfenapyr. The

laboratory result showed elevated lipase (2163 IU/L) and acute pancreatitis was diagnosed. He died 11 days after ingestion of the chlorfenapyr.

**Conclusion:** To the best of our knowledge, this is the first case of chlorfenapyr-induced acute pancreatitis. Another feature of our case is that our patient had a 3-day latent period before development of symptoms and died 11 days after ingestion. This is not commonly seen in the patients with chlorfenapyr intoxication in the literature.<sup>2,3</sup> Our patient experienced profound diaphoresis which is a specific feature in patients with chlorfenapyr intoxication.

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## 211. Cardiovascular findings in a prospective case series of fatal diazinon poisoning in children

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**Objective:** Diazinon (dimpylate) is a contact organophosphate compound with a broad range of insecticidal activity. This insecticide is widely and easily available in Romania, being used especially in rural areas for controlling ectoparasites in animals. The aim of this study was to evaluate the cardiovascular findings in fatal diazinon poisoning in children.

**Methods:** In the Toxicology Department of our hospital we performed a 2-year prospective study in children admitted for acute poisoning with organophosphate compounds who developed cardiovascular manifestations at admission or during hospitalization. We studied the cardiotoxic effects by clinical examination corroborated with cardiac monitoring, electrocardiographic record and echocardiographic examination.

**Results:** Between October 2011 and September 2013, 12 children (aged 2–14 years) with acute organophosphate poisoning who developed cardiovascular manifestations were admitted in our department. Of these, 4 children (aged 2, 3, 7 and 14 years) with diazinon ingestion had a fatal outcome. All these deaths were due to ingestion of a concentrated solution of diazinon 60%. One case was a suicidal attempt, while the other 3 were unintentional exposures. In only one case (a 2-year-old), was the dose specified by the caregivers and was reported to be a teaspoon (5 ml). In other cases, the dose ingested was not established. In all 4 cases the time between exposure and presentation in our hospital was between 2 and 4 hours. At admission, all 4 patients presented a brief period of tachycardia ± hypertension, followed by the development of classic cholinergic syndrome with bradycardia ± hypotension. Bradycardia and hypotension were quickly corrected by administration of atropine. In 3 cases bradycardia and/or hypotension

reappeared in evolution, and in one case these were the terminal event. Wide complex tachycardia was the final event in the other 3 cases. All patients who died developed signs of vasoplegic or cardiogenic shock and 3 patients had signs of congestive heart failure. Electrocardiographic abnormalities were seen in all fatal cases including ST-T abnormalities (n = 4), premature ventricular beats (n = 3), premature atrial beats (n = 2), intraventricular conduction defects (n = 2) and prolonged QTc interval (n = 2). Laboratory tests showed significant electrolyte disturbances (hyponatremia, hypokalemia) in all fatal cases.

**Conclusion:** Diazinon poisoning in children is a major health problem associated with cardiovascular complications and fatal outcome in many cases. It becomes imperative for national authorities to take a decision regarding the prohibition of these products.

## 212. Acute pancreatitis in carbofuran poisoning: A case report

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**Objective:** Carbofuran is a carbamate insecticide that causes transient acetylcholinesterase inhibition at nicotinic and muscarinic receptors. The occurrence of excess cholinergic stimulation can lead to pancreatic ductal hypertension, increasing of pancreatic secretion resulting in acute pancreatitis.

**Case report:** A 22-year-old male, an occasional marijuana and ethanol consumer, was admitted after a pesticide ingestion in a suicidal attempt. On admission he was sedated with pinpoint pupils, hypersalivation, abdominal tenderness, diaphoresis, fasciculations, no fever, on ventilator support with bronchorrhea and crepitations on lung auscultation, BP 145/73 mmHg and heart rate 107 bpm with sinus rhythm. The plasma cholinesterase activity was below normal. Toxicological urine analysis was positive for carbofuran and hydroxycarbofuran and the blood was negative for ethanol. A complete blood count showed leucocytosis; he had elevated concentrations of amylase and lipase, but normal LDH, AST, ALT and bilirubin. After atropinisation, volume replacement and antiseptors his status improved; he was weaned from ventilator support 24 hours after admission. An abdominal CT scan revealed pancreatic and peripancreatic oedema, duodeno-hepatic fluid collections with confluence trends and duodenal wall oedema, and he was diagnosed with acute pancreatitis; there was no evidence of gallstones. After 3 days, the cholinesterase activity and pancreatic enzymes returned to normal values. A second CT scan showed a well delimited homogeneous pancreas with slight infiltration of peripancreatic fat in the cephalic region. The patient was discharged after 7 days with normal organ and system function, and normal laboratory tests. A follow up CT scan after 1 month was normal.

**Conclusion:** Acute pancreatitis is a severe and rare adverse effect following carbamate poisoning; it is seen more often after organophosphate poisoning (12%) and in carbofuran poisoning has been described in only a few cases.

## 213. A dangerous sip: Acute copper nitrate accidental poisoning in a child

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**Objective:** Copper compounds are mainly found in insecticides, fungicides and algicides or used as wood and paint preservatives. Inorganic sulphate or nitrate salts are available as dust, wettable powders or fluid concentrates, and may be involved in human poisoning. Cases of acute poisoning are generally voluntary with suicidal intent, and rarely described for accidental ingestion of nitrate salts in children.<sup>1</sup> We report a pediatric case of severe acute accidental copper nitrate poisoning.

**Case report:** A 13-year-old male presented to the emergency department (ED) 30 minutes after accidental ingestion (50 mL) of Oligal blue<sup>®</sup> pesticide, which contains copper nitrate 12-17% (estimated dose 6-8 grams). At admission the patient had greenish vomiting and initial glycosuria (200 mg/dL); proteinuria presented 4 hours after ingestion. The plasma copper concentration at admission was 954 mcg/dL (normal 50-130). Twenty-four hours later, intravascular hemolysis occurred and hemoglobin (Hb) decreased to 11.8 g/dL. Intravenous hydration (100 mL/h) and high dose N-acetylcysteine (150 mg/kg/90 min bolus; 300 mg/kg/24 hours) were immediately administered. During the second day the clinical picture worsened with black urine discoloration, Hb 10.7 g/dL and serum creatinine 1.86 mg/dL. Chelation with oral penicillamine 300 mg/kg/6 hours was started and continued for 5 days. The patient underwent blood transfusion due to a progressive Hb decrease (Hb 7.8 g/dL) on day 4, and a gastroscopy showed multiple ulcerative gastric lesions on day 6. Seven days after admission urine discoloration resolved, the copper plasma concentration normalized (122 mcg/dL) and the patient was discharged in good clinical condition with normal renal and liver function. Methemoglobin was tested and was normal. At 15 days follow-up the patient referred good general condition and was asymptomatic with normal laboratory tests.

**Conclusion:** Acute ingestion of copper nitrate salts can cause gastric lesions and bleeding, hemolysis, methemoglobinemia, hypotension, hepatic damage and acute tubular necrosis. Ingestion of 10-20 g of soluble copper salts and a plasma copper concentration greater than 500 mcg/dL are reported to be potentially lethal. In this child an estimated ingestion of 6 g of copper nitrate was associated with elevated copper plasma concentrations, acute gastrointestinal manifestations, hemolysis and urine discoloration. Oral penicillamine effectively reduced plasma copper concentrations. Supportive therapy and blood transfusions were administered to treat hemolysis and high dose N-acetylcysteine to prevent toxic liver effects.

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## 214. Sodium monofluoroacetate-induced coma reversed by acetamide administration

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**Objective:** To describe the clinical features of sodium monofluoroacetate (SMFA) poisoning, and to discuss the use of acetamide as antidote.

**Case report:** A 28-year-old female with a history of metamphetamine and ketamine abuse was brought to the Emergency Department (ED) for impaired conscious level. She had attempted suicide by ingestion of an unknown amount of unfamiliar red-coloured rodenticide solution brought from China and 200 mL of a cosmetic solution. Her initial vital signs were normal in the ED. At 2 hours after ingestion, she developed a brief convulsion and became severely agitated which was controlled by haloperidol and midazolam bolus injection. She then remained semi-comatose (Glasgow Coma Scale [GCS] E1 V3 M5) for the next 60 hours. Physical examination did not reveal any focal neurological deficit or toxidrome. Her initial investigations were normal except mildly elevated plasma creatine kinase concentration (peaked at 3633 IU/L). Urine myoglobin was undetectable. A brain CT scan and lumbar puncture showed no abnormality. By 18 hours post-ingestion, she developed acute anuric renal failure despite her normal haemodynamic state. Her urine output re-established with supportive fluid and electrolyte management by 48 hours post-ingestion when the plasma creatinine concentrations peaked at 365 µmol/L. Her adjusted plasma calcium concentration dropped from 2.26 to 1.91 mmol/L, and was corrected by intravenous calcium gluconate administration. In view of her clinical signs, a diagnosis of SMFA poisoning was suspected. Acetamide (2.5 gram every 12 hours intramuscularly for 14 days) was administered as an antidote starting 56 hours post-ingestion. Her consciousness began to improve 12 hours after administration of acetamide. When she became fully conscious by day 4, she was found to have severe bilateral cerebellar truncal and peripheral ataxia. A brain magnetic resonance imaging (MRI), performed on day 22, showed hyperdense signals on T2-weighted images in the splenium of corpus callosum. Biochemical analyses confirmed the presence of SMFA in the patient's urine and the rodenticide samples by gas chromatography-mass spectrometry (GC-MS). Specific analysis for tetramine, warfarin and superwarfarin were negative.

**Conclusion:** SMFA, or compound 1080, is highly toxic. It has been banned in China, but is still a common adulterant in rodenticides. Management is mainly supportive, including correction of hypocalcaemia, hypotension, metabolic acidosis, and control of convulsions. Ethanol, acetate, sodium succinate, monoacetin and acetamide have been tested in animals for antidotal activity.<sup>1</sup> Here we presented the use of acetamide in a human case and it was well tolerated.

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## 215. Epidemiology of acute pesticide poisoning in Greece: A 2-year analysis

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**Objective:** To present a descriptive retrospective analysis of patients acutely intoxicated by pesticides in Greece during the years 2012 and 2013. All intoxication cases that reach any health unit of the country are reported to the Greek Poison Control Center. This epidemiological research is based on the records of the Greek Poison Control Center of Greece.

**Methods:** The records of all the events involving pesticide poisoning that occurred in 2012 and 2013 were reviewed. The data collected included the age and sex of the patient, the date and the area of Greece where it happened, the pesticide involved, the etiology of the intoxication (occupational exposure, accidental exposure and suicide attempt) and the route of exposure (inhalation, ingestion or through skin contact). The pesticides were classified according to their chemical substance in eight groups: organophosphates, carbamate insecticides, carbamate herbicides and fungicides, chlorinated hydrocarbon insecticides, pyrethrins, paraquat, glyphosate and others (neonicotinoids, triazines, copper, sulfur, etc). Deaths attributed to pesticide poisoning were also recorded. A statistical analysis was performed.

**Results:** During the study period a total of 922 cases were referred to the Poison Control Center. Of these 62.4% were male and 37.5% were female with a mean age of 52.5 years. In 100 cases the patients were children with a mean age of 4 years. There was a higher incidence of poisoning from April until August directly linked to the period of application of pesticides in agriculture. The majority of these incidences happened at rural areas of the country, and only 6% occurred in the capital, Athens. In 37.7% of the cases the poisoning was accidental, in 15.6% due to suicide attempts whereas the rest were occupational exposures (46.6%). The main pesticides involved were pyrethrins (28.1%), glyphosate (20.8%) and organophosphates (18%). There were 14 fatal cases, all in individuals who intentionally ingested pesticides.

**Conclusion:** This review reveals for the first time the epidemiologic features of the pesticide poisoning in the Greek population. The number of cases during these two years indicates that in Greece pesticide intoxication remains an important public health issue. The high percentage of occupational and accidental exposure suggests that there is a need for public health policies and training programs for the correct and safe use of these agents by agricultural workers.

## 216. Severe amitraz poisoning in a teenager

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**Objective:** There are few published reports of amitraz poisoning which is a triazapentadiene pesticide, an alfa-2 adrenergic agonist in the amidine chemical family used to control ectoparasites in



animals. In overdose amitraz may produce central nervous system depression with cardiovascular and respiratory symptoms.<sup>1,2,3</sup>

**Case report:** A 17-year-old male was admitted in our hospital after having been found in a coma in his room by his parents. Twelve hours previously he had attempted suicide with ingestion of amitraz and several drugs (amoxicillin, cefuroxime and ketoprofen). When found he had coma, mydriasis, bradycardia, superficial respiration and corneal lesions. Clinical features on admission were Glasgow Coma Scale (GCS) 6, nonreactive mydriasis, heart rate 55 beats/min, BP 65/35 mmHg, respiration 12/min. He was also noted to have diuresis and self-inflicted lesions on the left forearm. He was admitted to ICU and received supportive care with intravenous fluids and mechanical ventilation for 7 hours. The heart rate in the first 7 hours after admission varied between 43 to 60 beats/min; blood pressure values remained low (65/9 mmHg to 70/40 mmHg) and then returned to normal (90/55 mmHg). The blood count and glucose concentrations remained normal and blood pH values varied from 7.34–7.36. A urine toxicology screen was positive for amitraz and metabolites. There were no ECG changes and a heart ultrasound was normal. By 19 hours after ingestion of amitraz the patient regained consciousness; pupil size and reactivity became normal and heart rate and blood pressure returned to normal values. Neurological examination was normal and the patient was referred to the psychiatric ward.

**Conclusion:** There is no specific antidote for amitraz poisoning but this patient recovered fully after only symptomatic and supportive care. The misuse of amitraz for deliberate self-harm emphasizes the necessity for continued toxicovigilance.

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## 217. Severe but reversible toxicity with aldicarb ingestion

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**Objective:** Aldicarb is the most potent of the carbamate pesticides. There is limited information on its effects in deliberate self-poisoning. We aimed to describe the clinical effects and laboratory investigations in a large aldicarb overdose.

**Case report:** A 57-year-old female was found unconscious and incontinent of urine with a bottle of aldicarb pesticide. She was intubated and ventilated. En route to hospital she became bradycardic and hypotensive; 600 mcg atropine was administered and

these resolved. In the emergency department she was again bradycardic and hypotensive, hypersalivating, cold, clammy and had small pupils. She was given another 600 mcg atropine and her heart rate and blood pressure improved for 1 hour. She was observed to have generalised weakness. Over the next 4 hours she continued to be bradycardic and hypotensive despite large boluses of atropine (doubling doses up to 50 mg) and commencement of an atropine infusion at 20 mg/h. She had multiple seizures and was treated with a midazolam infusion. She was transferred to intensive care and a noradrenaline infusion was commenced. She remained comatose with ongoing seizure activity for 24 hours and was loaded with phenytoin. From 24 hours post-ingestion the noradrenaline and then atropine infusions were decreased and ceased. Sedation was ceased and 48 hours post-overdose she was Glasgow Coma Scale (GCS) 5, hyperreflexic with upgoing plantar responses. A cerebral CT scan was done because of concerns about hypoxic brain injury but was normal. Over the next 24 hours her level of consciousness improved and she was extubated. She was discharged to mental health with no sequelae and admitted to taking 2 teaspoons of aldicarb mixed with water. On admission her plasma cholinesterase was 0.3 kU/L (reference 4.3–10.6 kU/L) and her red cell acetylcholinesterase was 10 U/gHb (reference 38–66 U/gHb). The plasma cholinesterase was 0.6 kU/L at 24 hours and within the normal range (5.6 kU/L) at 48 hours. The red cell cholinesterase recovered more rapidly to 37 U/gHb at 24 hours and 58 U/gHb at 48 hours. High concentrations of aldicarb were detected in her blood on admission.

**Conclusion:** Aldicarb poisoning causes rapid onset severe toxicity with muscarinic and nicotinic excess, seizures and decreased level of consciousness. This patient responded to large doses of atropine, vasoconstrictors and supportive care. Despite the severity and concerns about hypoxic brain injury the patient made a full recovery. Cholinesterase activities were low on admission consistent with severe toxicity but recovered to normal within 24 to 48 hours confirming the reversible effect of carbamate pesticides.

## 218. Two cases of severe methomyl pesticide intoxication

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**Objective:** Methomyl is a carbamate pesticide. We report two cases of methomyl intoxication, one involving methomyl powder and the other a suspension concentrate also containing methanol.

**Case series:** A 43-year-old woman was brought to the emergency department (ED) in a stuporous state after ingestion of 100 ml solution of liquor and methomyl powder. She showed cholinergic symptoms and metabolic acidosis with an anion gap of 20.7 mEq/L and osmolar gap of 9.8 mOsm/kg. Atropinization was initiated. On the 2nd hospital day the systolic blood pressure fell despite a continuous infusion of vasopressors. On echocardiography, akinesia of the mid to apical wall of left ventricle with 39.8% of ejection fraction was observed. On the 5th hospital day, cyanosis on 4 distal extremities was observed and IV heparin was started. On the 11th hospital day the patient's mental status recovered. On the 23rd hospital day a double below-knee amputation and double wrist disarticulation amputation were performed due to distal extremity

necrosis. The initial pseudocholinesterase activity was 2173 IU/L. In the second case a 53-year-old woman was brought to the ED in an unresponsive state after ingestion of 200 ml methomyl in suspension. She had collapsed 1 minute after ingestion. After successful resuscitation, IV atropine, vasopressor, ethanol, mechanical ventilation, continuous renal replacement therapy (CRRT) and extracorporeal membranous oxygenation (ECMO) were initiated. She had metabolic acidosis with an anion gap of 28.1 mEq/L and an osmolar gap of 12.4 mOsm/kg. On the 4th hospital day, asystole cardiac arrest occurred and after 20 minutes resuscitation was suspended. The initial serum ethanol concentration was 161 mg/dL and pseudocholinesterase 391 IU/L; the urinary methanol concentration 569 mg/L.

**Conclusion:** Severe shock which does not respond to vasopressors can occur in methomyl intoxication. Severe toxic symptoms including sudden collapse can occur very quickly after ingestion because of synergistic toxicity of methomyl and methanol.<sup>1</sup>

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## 219. Massive parenteral manganese overdose: Minimal role for hemodialysis

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**Objective:** Manganese-associated Parkinsonism with associated brain MRI findings is well described in occupational exposure, among chronic methcathinone users, and in patients receiving chronic total parenteral nutrition (TPN). We present the first reported case of poisoning by parenteral manganese administration with a systematic evaluation of hemodialysis efficacy.

**Case report:** A 52-year-old, 50 kg woman with history of Hashimoto's thyroiditis underwent elective outpatient parenteral chelation with adjunctive vitamin and mineral therapy for perceived metal toxicity. Instead of receiving 800 mg magnesium chloride, she was administered 800 mg of compounded manganese chloride (MnCl<sub>2</sub>, 4 mL of 200 mg/mL) through errors in prescribing, compounding, dispensing and administration. For comparison, MnCl<sub>2</sub> for TPN is formulated as 0.1 mg/mL. During administration, the patient described flushing. In the emergency department she was asymptomatic with normal vital signs. Her physical examination was unrevealing without neurological abnormalities. In an attempt to minimize CNS Mn deposition and in the face of limited human pharmacokinetic data following acute parenteral Mn exposure<sup>1</sup>, the patient underwent two hemodialysis sessions (blood flow rate of 360 mL/min and dialysate flow rate of 700 mL/min) at 7 and 21 hours following manganese exposure. She received 5 days of sodium calcium edetate (1 g/m<sup>2</sup> over eight hours). Her initial serum manganese concentration obtained 6 hours after exposure was 120 mcg/L (2.19 μmol/L; normal < 5 mcg/L, 0.09 μmol/L). Following hemodialysis her serum manganese concentration had

decreased to 20 mcg/L (0.36 μmol/L). The extraction ratio at hemodialysis onset was 0.28 and decreased to 0.10 at hemodialysis conclusion. Despite the aggressive fall in the patient's serum manganese concentration, analysis of dialysate from the first hemodialysis session revealed a total elimination of only 604 mcg (11 μmol) manganese (1.4% of manganese burden). A magnetic resonance imaging (MRI) scan on hospital day 2 revealed T1 hyperintensities within the bilateral globi pallidi, consistent with manganese poisoning. On day 5, she was discharged with a repeat serum manganese concentration of 2.2 mcg/L (0.04 μmol/L). One month following her exposure, her MRI was unchanged and she remained asymptomatic.

**Conclusion:** Manganese poisoning is known to be associated with irreversible neurologic toxicity. Hemodialysis did not appear to offer significant elimination benefit in the treatment of this case of acute parenteral manganese toxicity, beyond standard care with sodium calcium edetate.

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## 220. Pregnancy outcome after metal-on metal hip arthroplasty: A case report

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**Objective:** Metal-on-metal hip prostheses are frequently used in young patients, including women of childbearing age. Patients bearing these devices can develop elevated chromium and cobalt blood concentrations. High-doses of these metals during pregnancy can result in reproductive adverse effects in experimental animals. Only a few cases have been reported but they do not suggest an increased risk of malformation in babies born to mothers with elevated chromium and cobalt concentrations.<sup>1</sup> We describe the outcome in a pregnant woman with elevated metal concentrations due to a metal-on-metal hip prosthesis.

**Case report:** A 36-year-old woman had an unilateral metal-on-metal hip arthroplasty performed 13 years earlier for an avascular necrosis of the femoral head. Radiological tests were performed annually. At age 31 the X-ray showed an initial implant wear with metal debris in the periprosthetic tissue. In 2013 she became pregnant and blood cobalt and chromium concentrations were determined for the first time at gestational week 31. High metal concentrations were detected in blood and urine, with chromium 43 mcg/L (normal 0.05–1 mcg/L) and 138 mcg/L (normal 0.1–1.5 mcg/L) and cobalt 55 mcg/L (normal 0.1–0.5 mcg/L) and 304 mcg/L (normal 0.05–0.35 mcg/L). No systemic symptoms were present, therefore chelating therapy was not indicated. At gestation week

39, a healthy female infant was delivered by caesarean section. Chromium and cobalt concentration were 34 mcg/L and 48 mcg/L in the mother and 5.3 mcg/L and 26 mcg/L in the baby.

**Conclusion:** Although the Expert Advisory Group of the British Committee on the Safety of the Devices recommends that women should be advised to postpone pregnancy at least two years after metal-on-metal hip implantation, in the case here reported, high chromium and cobalt concentrations were detected far beyond that period. Our case is in agreement with the previously cases that maternal high chromium and cobalt concentrations does not increase the reproductive risk in women with hip replacement;<sup>2</sup> however, further investigations are required in order to evaluate offspring physical and mental development. This observation allows women of childbearing age to plan their pregnancies or to avoid an unnecessary elective termination.

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## 221. BfR case series of elevated metal levels caused by metal-on-metal implants

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**Objective:** Figures published by German health insurance providers, show that a total of about 200,000 artificial hip joints were implanted in Germany in 2011. Metal-on-metal (MoM) implants have been applied for about 15 years; their construction provokes extreme minimization of the joint line. To reduce wear, special materials such as chromium (Cr), cobalt (Co), nickel (Ni) and molybdenum (Mo) are used. The MoM toxicological problem is the formation of very fine metal debris, depending on the geometry of and strain on joint surfaces. This may sometimes lead to extremely elevated blood concentrations of Co, Cr, Ni or Mo. In some cases, such concentrations may exceed the blood concentrations recorded for example in occupational medicine as well as the respective substantiated limit values. We describe eight cases reported to the BfR-DocCenter (2006–2012).

**Case series:** The individual reports as well as an analysis of cases reported so far under the Chemicals Act §16e were performed, evaluated and recorded in the form of standardised case reports. The existing data were evaluated and assessed regarding possible risks to elevated metal concentrations. The Poison Severity Score (PSS) was used to categorise the health impairment. The causality (exposure versus symptoms/signs) was assessed by the BfR-standard “Three-Level-Model”. All were adult males between 52 and 69 years of age. All had highly elevated concentrations of Co, Cr and Mo above occupational exposure limits. In two cases the MoM-implants were replaced by ceramic implants followed by a successive decrease of the Co, Cr and Mo blood and urine concentrations. The general state of mental health of the patients improved; in one case the lost creative power of a performing artist fully returned.

**Conclusion:** The BfR case series show weak evidence for a negative health impact due to elevated metal concentrations in blood and urine caused by MoM implants based on the BfR “Three-Level-Model”. However, the findings should raise awareness that the source of contamination is located within the body, and it is in direct contact with tissues, blood and lymphatic vessels. Further assessment and investigations should consider that MoM-derived debris may have particle size ranges of fine or even ultrafine (nano) particulate matter.

## 222. Evaluation of human cases with elemental and inorganic mercury exposure compared to German human biomonitoring (HBM) values

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**Objective:** German physicians have to report cases of poisoning to the BfR-DocCenter. The data are condensed into data files for analysis. Since current research shows the complex effects of elementary mercury (Hg) on human health, in particular regarding the relationship between the dose and clinical signs, the BfR-Committee on Poisonings initiated an investigation of well documented cases of poisonings on elemental and inorganic Hg. The task was to re-evaluate existing German Human biomonitoring (HBM) values for mercury, based on additional well-documented human cases. HBM values (in body fluids) support assessment of intoxication where if the HBM1 is exceeded, exposure is indicated and if the HBM2 is exceeded then intervention is required to reduce exposure and/or treat.

**Methods:** In total 41 cases of elemental and inorganic Hg poisoning, mainly from the BfR-case database, were analysed. The age, sex, aetiology, time course, amount, active ingredient, route, category, symptoms, latency, diagnosis and therapy, outcome, Poison Severity Score (PSS), causality, toxin detection and general comments were recorded and contrasted with each other in tables. Clinical data were evaluated in terms of the different dose-response relationships between the various age groups and gender.

**Results:** The comparison of the measured mercury concentrations in the blood with the PSS revealed that 4 cases with Hg-concentrations below the HBM1 value had minor and moderate PSS; an additional 4 cases with concentrations between the HBM1 and HBM2 values had moderate and severe PSS. Half the cases in which all grades of PSS (but not fatal) are represented, had Hg blood concentrations between 15–40 µg/L, which is only slightly above the HBM2 value. Particularly striking is that 10 cases in this group had severe PSS. For urine concentrations below the HBM1 value the analysis shows, that there are PSS levels between “no”, “minor” and “severe”. Among the cases with values between HBM1 and HBM2, there were cases with “minor”, “moderate” and “severe” PSS. A fifth of the cases with relevant Hg urine concentrations (two with “severe” PSS) out of 30 proven mercury poisonings would have fallen below the HBM2 value. For the remaining cases, no clear relationship was provided by the mapping.

**Conclusion:** This comparative assessment shows that more than 10 of the Hg-poisoned patients had concentrations that did not correspond well to the German HBM values system. This analysis



comparing the HBM-values against a case series of patients with mercury poisoning should start a discussion about a re-evaluation of the HBM Hg reference values.

### 223. Assassination with arsenic: A special case

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**Objective:** To show the involvement of a Poisons Information Center in establishing the time frame of arsenic poisoning in the assassination of an Indonesian activist.

**Case report:** In September 2004, a political activist travelled from Jakarta (Indonesia) to the Netherlands to complete his studies. His flight included an airplane transit in Singapore. Shortly after leaving Singapore he became seriously ill with symptoms of vomiting, severe stomach ache and watery diarrhoea. Because of severe pain he received sedative medications and about two hours before arrival he was found dead in his chair. Since the cause of death was not clear autopsy was performed and the Dutch Forensic Institute (DFI) took blood and stomach samples. Due to the political implications of this death, report of the results was delayed. In November 2004 the DFI reported high doses of arsenic in the samples of blood (3 mg/L) and stomach (465 mg). When these results became known the Dutch Poisons Information Center (DPIC) was contacted and asked to assess the time frame in which the poison could have been administered. The main question was if the victim could have been poisoned before he left home or during his voyage and before or after the airplane transfer.

**Conclusion:** Inorganic arsenic, which is tasteless and odorless, is well absorbed by the gastrointestinal route. After a high dose, as indicated by the amount found in his stomach and blood, symptoms will arise between 10 minutes and an hour after ingestion. There is no good correlation between intake and blood concentration but a blood concentration higher than 1 mg/L is considered lethal. At lower doses death may be postponed for several days. Considering the time of onset, the severity of the symptoms and death within 10-12 hours, the duration of the flight from Singapore to Amsterdam, we concluded the administration of this dose had to be either during the transit (in which case most likely shortly before boarding) or in the second airplane (soon after take-off). This information (along with other details) was used in the search for a possible culprit, which concentrated on the Indonesian airline. In 2007 one of the pilots was sentenced to 14 years imprisonment. To the present day, the Indonesian government is still investigating this case and its broader political context.

### 224. Risk of lead poisoning in patients with retained lead fragments in the body

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**Objective:** Few papers have been published on the risk of lead poisoning from lead foreign bodies retained in the body, the majority of them being case reports.

**Method:** A retrospective descriptive analysis of patients with retained lead in the body hospitalized in a secure hospital unit between 2008 and 2013 whatever the reason of admission. Data were collected on time since injury, nearest position of intracorporeal lead relative to a joint, blood lead concentration and hemoglobin.

**Results:** Of the 2,647 patients admitted in the unit between 2008 and 2013, nine of them had retained lead foreign bodies. Except for one patient who was injured before the age of one, and 3 patients who were shot a few weeks before admission to our unit, the median age of the 5 patients with chronic lead exposure was  $37.9 \pm 5$  years when the injury occurred, and the median delay between injury and the first lead blood concentration was 4,123 days (11.3 years, range 1,871-24,424 days). When X-rays were performed ( $n = 7$ ), the location of the retained lead was: less 2 cm from a joint ( $n = 3$ ), in the abdomen ( $n = 3$ ) and in the limb far from a joint ( $n = 1$ ). The lead pieces were single ( $n = 1$ ) or multiple ( $n = 6$ ) and no bullet or fragment show any deterioration on X-ray. No patient showed symptoms of lead poisoning. The results of blood sampling showed a median blood lead concentration of  $92 \pm 27$  mcg/L (NR < 200), and a hemoglobin concentration of  $14.2 \pm 0.9$  g/L (NR: 12-16) without any sign of red blood cell immaturity.

**Conclusion:** Case reports of lead poisoning from retained bullet fragments in the body show a clear deterioration of lead when situated close to a joint or in a cavity, as lead is dissolved by synovial fluid and can be disseminated in blood; in addition there may be a delay of > 10 years between the injury and onset of toxicity.<sup>1</sup> In our cases the lead fragments had not deteriorated even when close to a joint or in a cavity, and no signs or symptoms of poisoning occurred.

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### 225. Cobalt cardiotoxicity in a patient with bilateral metal-on-metal (MoM) arthroplasty

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**Objective:** Metal-on-metal (MoM) hip replacement can result in high blood cobalt concentrations. Cobalt systemic toxicity is well known for thyroid and cardiac effects. Hearing loss, ocular toxicity and peripheral neuropathy are also reported. Only single case reports of cobalt systemic toxicity following metal arthroplasty are available. This concern is still under recognized and long-term epidemiological studies are required in addition to appropriate time-dependence and cut-off concentrations for cobalt systemic toxicity. We report one more case of severe acute cardiac dysfunction in a patient with an elevated blood cobalt concentration.

**Case report:** A healthy 38-year-old man had undergone staged bilateral MoM total hip replacement 10 and 9 years ago. Within a year following the first hip replacement, he experienced symptoms

(squeaking and pain from the hip joint) which indicated incorrect functioning of the device. On April 2013, he was referred to a cardiac intensive care unit for cardiogenic shock. A non-ischemic dilated cardiomyopathy from an unspecified origin was diagnosed. He admitted an excessive alcohol intake due to a festive lifestyle. Thyroid function was unaffected. Eight months later, cardiac function dramatically improved (LVEF about 50%) whilst alcohol intake was stopped but beta-blocker, angiotensin converting enzyme (ACE) inhibitor and diuretic therapies were still needed. The cobalt blood concentration was 267.2 µg/L (normal < 0.91 µg/L). A CT scan showed massive osteolysis and granulomatous tissue reactions. A revision arthroplasty was performed and blood cobalt concentration decreased to 54.21 µg/L.

**Conclusion:** A recent review of published case reports of systemic toxicity related to metal hip prosthesis<sup>1</sup> evidences cardiotoxicity in 11 patients; the blood cobalt concentration exceeded 350 µg/L in most patients. As for heavy beer drinkers in the 1960s, alcohol intake reported in our case could have been a co-factor for cobalt-induced cardiomyopathy but improvement required ongoing cardiac medications despite alcohol withdrawal.

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## 226. Clinical management of foodborne botulism poisoning in emergency setting: An Italian case series

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**Objective:** To evaluate the clinical presentation characteristics of foodborne botulism (FBo) poisoned patients admitted to Emergency Departments (EDs) to obtain clinical data useful for emergency physicians with suspect cases to help with diagnosis and early antidotal treatment.

**Methods:** A retrospective analysis of cases of FBo registered at Pavia Poison Control Centre (PCC) was performed during the study period (2007–2013). Implicated food, clinical presentation, latency between symptoms/ED admission/treatment, clinical course, response to the antidote administration and laboratory analysis data were analyzed.

**Results:** In total 98 cases were studied (mean age 55.14 ± 17.9; 53/98 male) and 17 outbreaks (involving more than 2 people) were registered. History was positive for consumption of vegetables (77%) and fish (16%) in water or oil, or meat conserve in 88.7% of cases. In 81 cases (93.2%) the causative food was home-made, in 4 cases it was industrial and in 2 cases the food was ingested at a restaurant. The most common symptoms reported in the ED were dysphagia (55.1%) followed by ocular manifestations including diplopia (40%), difficulty accommodating (32%), mydriasis (26%) and ptosis (18%), and xerostomia (35%). In three cases dys-

phagia was the unique neurological manifestation of the poisoning. Twenty-four patients (24%) required mechanical ventilation. Antitoxin was administered in 59 patients (60.2%), with an average of 63 hours after neurological symptoms onset; 26% were treated within 24 hours. In this group, 7 patients (26%) required mechanical ventilation (mean duration 13.6 ± 5.6 days) (versus 53.8% in treated group after 24 hours; mean duration 21 ± 15.5 days). Five adverse reactions were registered. Laboratory analysis confirmed the poisoning in 66.4% of cases; toxin type B was the most common identified (83.6%). Serotype A was isolated in 6 cases (12.2%); among these 83% required mechanical ventilation (p = 0.004). Permanent neurological sequelae occurred in 1 case. There was one death in this case series.

**Conclusion:** Botulism is a rare disease in which early correct diagnosis is difficult and may require a toxicological consultation. In Italy, more than 50% of FBo cases (average 29 cases/year) are managed by our PCC. This intoxication represents a medical challenge for emergency physicians. Clinical presentation in the ED can be undefined, diagnostic procedures problematic and patients must be monitored because of dramatic respiratory failure. So PCC support is essential for the diagnosis and the management of poisoned patients (e.g. specific laboratory tests, antidote treatment), and in the identification and surveillance of possible outbreaks.

## 227. Botulism caused by vacuum packed whitefish (*Corregonus lavaretus*)

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**Objective:** Botulism poisoning is rare and caused by toxins produced under anaerobic conditions by the bacterium *Clostridium botulinum*. There are 7 varieties (A-G) of the toxin. In the Nordic countries serotype E is the most common. It is prevalent in seabed vegetation ingested by various species of fish. The toxin binds irreversibly to presynaptic nerve terminals at the motor endplate inhibiting the release of acetylcholine. Autonomic cholinergic nerve terminals are also affected. Recovery is traditionally thought to be entirely dependent on the formation of new nerve terminals. Antitoxins can be given to halt progression of symptoms.

**Case report:** A 54-year-old woman was admitted to the emergency department (ED) after waking up in the morning feeling extremely tired, weak and dyspneic. The symptoms progressed, and she experienced difficulties focusing her eyes and complained of double vision. The mydriatic pupils did not respond to light and extremity reflexes were very weak, but she had full tactile sense. She was intubated and put on a ventilator because of descending paralysis and rapidly declining breathing. A head CT scan and a CF-examination showed no abnormalities. Blood samples were all within the normal range. It was revealed that the patient had eaten vacuum packed whitefish approximately 36 hours before admission. The first symptoms appeared 12 hours after ingestion. A suspicion of botulism arose and the Swedish Poisons Information Centre was contacted for advice. Antitoxin was sent to the hospital and the patient received two vials (a minimum of 10,200 units of type E) of a heptavalent antitoxin. The presence of toxin type E was confirmed in samples from blood, gastric fluid and remaining pieces of the whitefish. The patient improved significantly and was extubated after 7 days. Although weak, she was able to walk.

She was rehabilitated in hospital for 3 weeks. During that time the dominating symptoms were orthostatism, fatigue and constipation. At follow-up 2 months later, she was still weary and had some pain, mainly in larger muscle groups. Pupil reactions and eye movements had returned to normal. Four months after the incident she felt almost recovered and was able to go back to work.

**Conclusion:** Since it is common knowledge that the botulinum toxin damages the nerve terminals irreversibly and the formation of new nerve cells takes months, her quick initial recovery after being given antitoxin was remarkable. Several weeks of dependence on a respirator would otherwise have been expected.

## 228. Dangerous palytoxin exposure after boiling coral

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**Objective:** Reports regarding human exposure to palytoxin (PLTX) and palytoxin-like compounds have increased in recent years. The main routes of intoxication include oral intake of contaminated seafood or inhalation after direct contact with aerosolized water during *Ostreopsis* species algal blooms.<sup>1,2</sup> We describe two unusual cases of inhalation exposure to PLTX, involving a father and daughter, after boiling a pot of water containing a rock polluted by the cnidarian zoanthids *Palythoa* species.

**Case report:** At the end of January 2014, a marine aquarium hobbyist was attempting to remove a colony of zoanthids from a rock by boiling it. During this procedure, the patient (together with his daughter of 18 months) inhaled steam for 10 minutes. After 3 hours both patients developed symptoms of fever, cough, headache, dyspnoea, respiratory effects and gastrointestinal discomfort. Within 2 hours, they were admitted to a local emergency department (ED). During the clinical observation the father suffered from vomiting (treated with fluids) and the child from high fever (treated with paracetamol). Biochemical investigations revealed a moderate leukocytosis ( $15.96 \times 10^3/\mu\text{L}$ ) in the father. Symptoms resolved after 12 hours and the patients were discharged 48 hours later. At 6-month follow-up there was complete resolution of clinical features and the absence of late respiratory manifestations (such as asthma-like symptoms or bronchial inflammation and bronchoconstriction). Biological samples, corals and some aquarium water were collected for specific analysis. Initial analysis on the coral confirmed the clinical suspicion and underlined massive concentrations of PLTXs.

**Conclusion:** Clinical history, symptoms and lab confirmation for PLTX allowed us to make the diagnosis of poisoning from the boiling coral in both patients. The child particularly experienced fever and upper respiratory tract irritation. In our experience, the clinical manifestations resolved completely without late complications. In the literature, asthma-like symptoms or bronchial inflammation lasting 1 to 3 months and requiring prolonged corticosteroid treatment are reported.<sup>2,3</sup> Considering the definite risk of intoxication, aquarists working with zoanthids should be

warned about the potential danger of PLTX inhalation/dermal/ocular exposure.

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## 229. LSD poisoning after ingestion of contaminated beef in a family of four

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**Objective:** We report the adulteration of beef with lysergic acid diethylamide (LSD) and the subsequent poisoning of a family of four.

**Case report:** The regional poison center was contacted by a hospital to report a possible food poisoning of a family of four that became ill within an hour after eating a meal. The adult male fell ill first, but within an hour, all four family members became symptomatic including a 38-week pregnant female, and siblings aged five and seven. Complaints of dizziness, progressing to hallucinations, and tingling extremities were reported by all. Both children were electively intubated. The pregnant female underwent an emergent delivery via cesarean. All patients experienced resolution of their symptoms within 18 hours and were ultimately discharged from the hospital within two days. The family had recently moved into the house. The adult male had prepared a meal with bottom round beef, vegetables and cheese. The ingredients had been purchased immediately prior to preparation. One child ate beef only. Scraps of meat and packaging were collected for evidence and forwarded to the County Forensic Toxicology Laboratory for analysis. Several pieces of the meat were homogenized and extracted using a routine liquid/liquid alkaline procedure followed by analysis by gas chromatography mass spectrometry (GC/MS). LSD was identified on the meat by GC/MS comparison to a standard of LSD. Targeted analysis for LSD by liquid chromatography tandem mass spectrometry (LC-MS/MS) confirmed the presence of LSD in the victims' urine specimens.<sup>1</sup>

**Conclusion:** Contamination of food with hallucinogens is an extremely rare event. The adult male denied involvement in adulterating the meal and passed a polygraph. No other victims or other samples from the same vendor have been identified. The source of LSD has not been determined and the police investigation is ongoing.

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### 230. Deadly threat in the preserving jar

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**Objective:** Botulism is a rare cause of foodborne poisoning. In Germany, almost 20 cases of botulism are registered by the Robert Koch Institute every year. Most of them are caused by the consumption of home-canned vegetables.

**Case report:** A 47-year-old woman presented to a hospital at the end of April 2014. She had suffered from diplopia and dizziness during the preceding night. Brain stem insult was excluded by cranial computed tomography. Within one day, however, the patient's condition dramatically worsened with bilateral ptosis, progressive dysphagia, dysarthria, and respiratory insufficiency requiring intubation and artificial respiration. A few hours after this patient was admitted, her husband developed similar but less pronounced symptoms and presented to hospital. He reported that two days previously he and his wife had eaten salad containing self-canned wax beans. In consideration of this anamnesis and the observed symptoms, botulism was suspected. Eight days after admission, botulinum toxin A was identified in the patients' serum by an *in vivo* animal test model. Although the wife was treated with neostigmine a paralytic ileus occurred. Gut motility was successfully restored by the buccal application of pilocarpine and prucalopride. After treatment at an intensive care unit for 19 days, the patients were transferred to a rehabilitation unit. From there, the husband and wife were discharged at the beginning and in the middle of October 2014, respectively.

**Conclusion:** The reported cases demonstrate the classic symptoms and the typical course of foodborne botulism. In addition to respiratory insufficiency requiring artificial respiration over a long time period the inhibition of gut motility became life-threatening in one case. The paralytic ileus caused by botulinum toxin A was successfully treated by the combined administration of a muscarinic and a 5-HT<sub>4</sub> receptor agonist.

### 231. Accidental *Panaeolus foenicicii* exposures: No clinically relevant effects in children

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**Objective:** Accidental exposure to little brown mushrooms is a matter of concern, especially in children. In case of *Panaeolus foenicicii* historic and current literature offers little help to poison

information centres regarding correct risk assessment. The objective of the study was to assess possible toxic effects of *Panaeolus foenicicii* in cases of accidental exposure.

**Methods:** The basis for this analysis is a prospectively designed, observational database (Propi) powered by a working group of the Society for Clinical Toxicology (Gesellschaft für Klinische Toxikologie, GfKT) especially dedicated to elucidate toxicity of mushrooms of uncertain toxicity. Inclusion criteria for this study were accidental ingestion of at least 1 cm<sup>3</sup> of a single mushroom species. Follow up of at least 4 hours and identification of the mushroom by a certified mycologist was mandatory.

**Results:** In total 19 cases of exposure to *Panaeolus foenicicii* met all inclusion criteria. Only children were involved, 10 girls and 9 boys, aged between 1 and 10 years (median 3.25 years). The circumstance of exposure was accidental in all cases. The quantity ingested was reported as 1-2 mushrooms in 14 cases and 3-5 mushrooms in 5 cases. Three patients received a single dose of activated charcoal. Of the 19 patients 16 cases did not develop any symptoms, 2 complained of minor abdominal discomfort, one child was temporarily slightly more active according to the mother. This episode lasted one hour. Outcome was favourable in all cases.

**Conclusion:** Our prospective case series with mushrooms identified by a mycologist demonstrates that the typically small amounts of *Panaeolus foenicicii* ingested by children probably do not lead to clinically relevant symptoms.

### 232. Lights and shadows of urinary amanitin concentration in clinical practice

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**Objective:** The urinary concentration of amatoxin has been shown to be a useful diagnostic tool to confirm *Amanita phalloides* intoxication. The threshold of the analytical sensitivity is 0.22 ng/mL, with a functional sensitivity of 1.5 ng/mL.<sup>1</sup> Nevertheless, the predictive and diagnostic value of the concentration of amanitin detected remains uncertain.<sup>2,3</sup>

**Methods:** We studied the reliability of urinary amanitin analysis in 45 patients diagnosed with amatoxin poisoning reported to the National Milan Poison Control Centre in 2010. Diagnosis was based on the history of mushroom ingestion, severe gastroenteritis and mycological identification of *Amanita* species. Urine samples were collected in order to perform the amanitin ELISA test.

**Results:** Urinary amanitin concentrations ranged from 3 to 243 ng/mL. Of these, 28 patients (62%) developed a severe hepatitis, while 11 showed signs of mild to moderate hepatic involvement. The remaining 6 patients were positive for amanitin (4 to 25 ng/mL), but did not show hepatic alterations. The analysis of receiver operating characteristic (ROC) curve, related to the accuracy of urinary amanitin in amatoxin-induced hepatitis diagnosis, was performed; specificity and sensitivity was calculated for each measured value.<sup>4</sup> In our population the best diagnostic performance was achieved by using 5 ng/mL as a cut-off value.

**Conclusion:** The urinary concentration of amanitin is a useful tool for the diagnosis of intoxication by amatoxin. Our results suggest  $>5$  ng/mL as the value of urinary amanitin positivity. The 6 patients showing an amanitin urinary concentration  $>10$  ng/mL in the absence of any signs of liver impairment raise questions over the specificity of the test. Therefore, test results must always be interpreted as part of an entire diagnostic work-up and the clinical history of the patient, supported by consultation with a toxicologist.

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### 233. Mushrooms poisoning in Italy: A 2-year case series (2012-2013) from the Pavia National Poison Centre

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**Objective:** Mushroom poisoning is a major health risk in many countries.<sup>1</sup> At present, the exact incidence of mushroom poisonings in Italy cannot be precisely estimated. The aim of this study is to describe mushrooms poisoning in Italy managed by the Pavia Poison Centre, with particular regards to the mushroom species involved, the patients' clinical course and outcome, and the critical issues in the diagnosis and treatment of these poisonings.

**Methods:** A retrospective review of all cases of mushroom poisoning referred to Pavia Poison Centre over a 2-year period (2012-2013) was conducted. The included cases were assessed for age, sex, circumstances of exposure, mushroom species involved, clinical picture, latency of symptoms, hospital stay, urine alpha-amanitin detection and outcome. Wild mushrooms not subject to mycological control before ingestion are considered in this study “not controlled”, whereas those purchased in a shop or consumed at restaurant are referred as “controlled”.

**Results:** During the study period, 1,881 cases distributed all over Italy were included (males 48%; average age  $45 \pm 20.6$  years). “Not controlled” mushrooms were ingested in 85% of cases (1,599/1,881). *Boletus edulis*, genus *Agaricus* and *Armillaria mellea* have been the most frequent species referred by patients. *Armillaria mellea*, *Entoloma lividum*, *Omphalotus olearius* and the

genera *Amanita*, *Boletus* and *Clitocybe* were the most frequently identified by mycologists at hospital admission. The most common symptoms described among all patients were gastrointestinal. Ninety-six patients (6%) developed liver damage, all after ingestion of “not controlled” mushrooms. Most of these patients (82%) manifested gastrointestinal symptoms at least 6 hours after ingestion of the mushroom. Six patients (0.31%) required liver transplantation. The mortality rate was 0.26%. Alpha-amanitin in urine was positive in all fatal cases, in 62.5% of cases who developed liver damage and in 25.6% of cases with long latency over 6 hours from the meal.

**Conclusion:** Mushroom poisoning may represent a real life-threatening clinical condition that may require early and specific approach. A latency period of over 6 hours after mushroom ingestion may represent a predicting factor for severe poisoning. Mycological identification and urine alpha-amanitin are crucial for mushroom poisoning management but present some limitations. The interaction of multiple professional figures (emergency physician, clinical toxicologist, mycologist) is needed to properly evaluate every single case of mushrooms poisoning.

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### 234. Mushroom poisoning: A proposed new clinical classification

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**Objective:** The classification of mushroom poisoning is arguably useful for clinicians managing cases as it may assist in the diagnostic process. Existing schemes do not account for newly identified types of mushroom poisoning. In attempting to rectify this problem we have developed a new classification scheme and used this to inform development of a diagnostic algorithm based on clinical presentation, for cases where the identity of the consumed mushrooms is uncertain.

**Methods:** We undertook a literature review using the term “mushroom poisoning” and then targeted searches based on particular identified mushroom genera/species. Papers defining newer syndromes of mushroom poisoning, not covered in earlier classifications, were selected for more detailed review. Poisoning syndromes were included where there was clear delineation of distinctive clinical features, usually with additional data on culprit species. A matrix of principal clinical effects for each syndrome was created, tabulating common and unique features and this was used to construct a diagnostic algorithm.

**Results:** Over 1,600 papers were identified, from which a core set of 75 were considered. This yielded 21 distinct mushroom poisoning syndromes which were the basis for the new classification and diagnostic algorithm. We propose 6 broad groups, most with sub-groups. Group 1 - Cytotoxic mushroom poisoning; specific major internal organ pathology, causing either primary hepatotoxicity or primary nephrotoxicity. 1A, primary hepatotoxicity (amatoxins); 1B, early primary nephrotoxicity (amino hexadienoic acid; AHDA); 1C, delayed primary nephrotoxicity (orellanines). Group 2 - Neurotoxic mushroom poisoning; poisoning causing primary neurotoxicity. 2A, hallucinogenic mushrooms (psilocybins and related toxins); 2B, autonomic-toxicity mushrooms (muscarines); 2C, CNS-toxicity mushrooms (ibotenic acid/muscimol); 2D, morel neurologic syndrome (*Morchella* spp.). Group 3 - Myotoxic mushroom poisoning. 3A, rapid onset (*Russula* spp.); 3B, delayed onset (*Tricholoma* spp.). Group 4 - Metabolic-toxicity mushroom poisoning; includes a wide variety of poisoning syndromes and clinical presentations. 4A, GABA-blocking mushroom poisoning (gyromitrins); 4B, disulfiram-like (coprines); 4C, polyporic mushroom poisoning (polyporic acid); 4D, trichothecene mushroom poisoning (*Podostroma* spp.); 4E, hypoglycaemic mushroom poisoning (*Trogia venenata*); 4F, hyperprolactinemia mushroom poisoning (*Boletus satanas*); 4G, pancytopenic mushroom poisoning (*Ganoderma neojaponicum*). Group 5 - Gastrointestinal irritant mushroom poisoning. Group 6 - Miscellaneous adverse reactions to mushrooms. 6A, Shiitake mushroom dermatitis; 6B, erythromelalgic mushrooms (*Clitocybe acromelalgia*); 6C, *Paxillus* syndrome (*Paxillus involutus*); 6D, encephalopathy syndrome (*Pleurocybella porrigens*). The diagnostic algorithm consists of 6 linked sections covering all 5 groups and 21 poisoning syndromes.

**Conclusion:** The proposed classification and diagnostic algorithm may need adjustment as new poisoning syndromes emerge.

### 235. How can we reduce the number of mushroom poisonings among immigrants and tourists?

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**Objective:** An example of preventive work at the Swedish Poisons Information Centre with the intention of reducing the incidence of mushroom poisonings among immigrants and tourists.

**Case report:** In August 2014 the Swedish Poisons Information Centre was contacted about a family of six Syrians living in a refugee camp who had eaten a meal of soup made from *Amanita virosa* and onions. Five were adults, including a pregnant woman in gestational week 28, and one a six boy. Symptoms of nausea, vomiting and diarrhoea developed the following morning in all patients. Based on their history and clinical presentation, silibinin and N-acetylcysteine were started immediately after arrival at the hospital. All had positive urinary amatoxin. Two family members, including the boy, developed severe liver impairment and two others, moderate impairment. Although the pregnant woman had no liver impairment, she had the highest urinary amatoxin value. All recovered without sequelae, and the pregnant woman, now in gestational week 37, continued the pregnancy without complications.

**Conclusion:** Every year a number of foreigners suffer from mushroom poisoning. The main cause of intoxication is misidentification of mushrooms that look like the edible ones they have picked

in their home countries. During the autumn of 2014 the Poisons Centre had a large number of calls regarding this group of people, resulting in a substantial number of hospital visits. A few years ago the Poisons Centre produced a brochure about poisonous mushrooms in 26 different languages. The purpose of this brochure was to prevent mushroom poisonings among immigrants and tourists. It is available for free download on our website. As in the above described incident, we wanted the information to reach the target group as soon as possible, but the challenge was how to reach a group that does not read Swedish newspapers, watch Swedish television and with no social network. The Poisons Centre contacted the Migration Board who, in less than 24 hours, spread the information about the brochure to all refugee camps and to all local administration boards in Sweden. We also wrote a press release for the TT News Agency that was published in at least 22 newspapers and got the attention of radio news. This is an example of how Poisons Centers can react to events such as this and act pre-emptively to hopefully reduce the number of mushroom poisonings among foreigners in the future.

### 236. A rare case of acute renal failure related to *Amanita proxima* ingestion

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**Objective:** The first cases of acute renal tubulopathy related to *Amanita proxima* poisoning were described in 1994.<sup>1</sup> The mushroom contains a toxin responsible for the allenic-norleucine syndrome, characterised by kidney damage that occurs earlier than in *Cortinarius orellanus* poisoning and generally improves with complete resolution within ten days.<sup>2,3</sup>

**Case report:** A 45-year-old female was admitted to hospital because of nausea, vomiting and heartburn which started the day before. Symptoms occurred 8 hours after eating a single large wild mushroom. Three friends who had the same meal were all asymptomatic. Twelve hours after the admission the woman became anuric and blood tests showed an impaired renal function with creatinine 13 mg/dL, urea 240 mg/dL, AST 240 U/L and ALT 350 U/L. The patient was transferred to the nephrology department of the Hospital Di Venere of Bari and the PCC of Milan was consulted. The toxicologist supposed a nephrotoxic syndrome caused by the consumption of *Amanita proxima* and sent a picture of the mushroom ingested to a mycologist who identified the species as *Amanita proxima* Dumée, Bull (typical volva reddish-orange, ivory white hat, scaly stalk) sometimes mistaken for *Amanita ovoidea*. Haemodialysis was performed for 5 days with supportive care. Her urine output gradually increased, the serum creatinine decreased and AST and ALT normalized.

**Conclusion:** *Amanita proxima* contains an allenic-norleucine toxin (different from orellanine for the absence of inhibition of alkaline phosphatase), responsible for reversible kidney damage, characterised by tubulointerstitial nephritis with acute tubular necrosis and



renal failure. Occurrence and seriousness of symptoms seem to be variable and dependent on the amount ingested.

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### 237. From delightful mushroom to poisoning: A Danish mushroom syndromes survey

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**Objective:** Exploring nature and collecting plants and mushrooms as food items for the new Nordic kitchen has evolved in recent years. This behaviour has led to several cases of improper intake of fresh mushrooms resulting in poisonings requiring advanced treatment. Based on clinical symptoms mushrooms intake can be divided in toxic syndromes. We evaluated the representation of nine mushroom syndromes in the Danish mushroom poisoning profile from January 2006 to October 2014.

**Methods:** Enquiries about mushroom poisoning to the Danish Poisons Information Centre (DPIC) were collected, reviewed and divided in the nine mushroom syndromes based on the xenobiotic content of the mushrooms and symptomatology: amatoxin, gyromitrin, muscarine, disulfiram-like, anticholinergic, psilocybin, gastrointestinal, orellanin and haemolytic syndromes.<sup>1</sup> Unidentified but non-symptomatic exposures and other, identified but non-toxic exposures were additional groups.

**Results:** Mushroom exposures represented approximately 2% of all calls to DPIC in 2006–2013, with a slight increasing tendency in the last 4 years. Mushroom exposure syndromes are seasonal in the autumn peaking in September, except psilocybin which is represented evenly throughout the entire year. Mushroom syndrome distributions in 2006–2014 are shown in Table 1. Mushrooms

causing gastrointestinal symptoms were most frequent. In 68 cases, cytotoxic mushroom ingestion (amatoxin, gyromitrin and orellanin) caused severe and potentially life-threatening poisoning, with the amatoxin syndrome as most dominant. The unidentified mushrooms mainly involved mushrooms partly identified by process of elimination (i.e. not cytotoxic species). The non-toxic mushrooms mainly involving accidental ingestion in children.

**Conclusion:** Collecting mushrooms for food without comprehensive knowledge of edible species and their toxic counterparts caused several severe poisonings, primarily within the amatoxin and gastrointestinal syndromes. Preventive measures in terms of information and education are needed, combined with online guidance for mushroom collectors.

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### 238. Evaluation of the benefit of a mushroom identification service for the National Poisons Information Centre, Norway in 2013–2014

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**Objective:** Exposures to mushrooms are common enquiries to the National Poisons Information Centre (NPIC) in Norway. The identification of mushrooms is difficult, but essential in the assessment of poisoning severity and determining suitable treatment. The NPIC use the service of a mycologist company, who act as on call consultants. The aim of the study was to evaluate the benefit of this service.

**Methods:** All inquiries of mushroom exposures requiring identification by our mycologists between 2013 and November 2014 were included. Before sending the identification request, the staff on call assessed what their advice would be without the identification and how much time they would have spent trying to identify the mushroom. The mycologists received photographs of the mushroom from the caller by Multimedia Messaging Service (MMS) together with a description of the habitat and the geographic area. The mycologist communicated the identification back to the caller and NPIC by MMS. After the identification was made, the identity of the mushroom was noted together with the NPIC's final advice to the caller.

**Table 1.** Mushroom syndrome distributions in 2006–2014 in Denmark, number of cases (Abstract 237).

Year (total no. of DPIC cases)	2006 (6,026)	2007 (10,464)	2008 (13,241)	2009 (17,434)	2010 (18,127)	2011 (19,584)	2012 (20,851)	2013 (23,171)	2014 (> 23,000)
Amatoxin	4	5	8	8	7	3	2	7	15
Gyromitrin	0	0	0	0	0	0	1	0	0
Muscarine	3	2	0	1	1	0	2	0	4
Disulfiram like	1	1	0	1	3	2	0	1	6
Anticholinergic	11	6	7	8	10	9	5	29	5
Psilocybin	9	15	5	13	8	21	15	23	9
Gastrointestinal	11	3	13	5	10	7	8	11	38
Orellanin	4	0	2	0	0	0	1	1	0
Haemolytic	0	0	0	0	0	0	0	0	0
Non-toxic	15	17	27	77	53	61	55	68	127
Unidentified	114	85	104	95	185	172	160	190	180

**Results:** A total of 366 cases were referred to mushroom experts for identification; 31 cases were excluded from the study because the NPIC did not receive an identification. This could be due to the caller not sending the MMS-photograph, despite our advice, or contacting the experts directly by telephone. In 307 cases the mycologists were able to identify the mushroom. In 25 cases identification was not possible, but seriously poisonous mushrooms were ruled out. In 3 cases the mushroom could not be identified or ruled out. In 192 cases NPIC advice would have been observation at home with administration of activated charcoal without the identification service. With identification, activated charcoal was recommended in 17 cases. Medical assistance or hospital admission would have been recommended in 41 cases without the aid of the mycologists, but only 4 cases was referred after identification. The extra time the NPIC would have used to identify the mushrooms without this service, was estimated to be 10-20 minutes in 44% of the inquiries, and 0-10 minutes in 35% of the inquiries. The identity of the mushroom would still have been uncertain in most cases.

**Conclusion:** Mycologists are a valuable resource in the identification of mushrooms. The NPIC gives more correct and efficient advice with the benefit of this service. It also prevents unnecessary medical treatment and hospital admissions.

### 239. Pediatric mushrooms poisoning: A fairy tale to warn children and adults

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**Objective:** The National Poison Control Center of Milan (NPCCM) handles each year about 1,000 enquiries concerning suspected mushrooms poisoning. During the last 4 years the NPCCM detected an increase in pediatric exposures. It is fundamental to keep an eye on the actions of the child, who can ingest the mushrooms found in play areas outdoors. The necessity of consulting an expert mycologist to identify the fungi before cooking is paramount. The parents' role is crucial to stem the problem. The NPCCM has therefore developed a fairy tale for the education of children and their parents.

**Methods:** A brief and illustrated fairy tale showing four paradigmatic characters each representing specific attitudes that the public may have regarding mushroom consumption was devised. We also produced an English version<sup>1</sup> to obtain greater diffusion for the next World EXPO that will take place in Milan. The story was tested on children aged between 5 and 12 years, admitted to our hospital's pediatric department. Children have chosen to recite their favorite character. During this special day, national media was present and interviewed the child actors and authors. The resulting news report was broadcast on TV news regional networks.

**Results:** During the fairy tale presentation, children and their parents were enthusiastic. Children and adults easily learned the dangers of mushrooms. The original fairy tale created and illustrated by NPCCM specialists, was approved by the Ministry of Health, and was published on its website at the institutional level. Mycological groups are making efforts to distribute the story to the public.

**Conclusion:** We observed that children can teach adults to live in a safer world. Our intention is to distribute the fairy tale in primary schools in order to educate them from an early age to have a respect for nature. We suggest that a fairy tale is a tool to prevent mushrooms poisoning.

### Reference

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### 240. Mushroom poisoning: A descriptive study of 19 cases

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**Objective:** To describe the clinical, analytical and toxicological characteristics of patients attending the emergency department for mushroom poisoning.

**Methods:** We studied mushroom poisonings identified and treated in the emergency department of our hospital between 1 August and 5 November 2014. Hepatotoxicity was defined as analytical determinations of AST and ALT > 1000 U/L. Nephrotoxicity was defined as creatinine > 5 mg/dL. Amatoxins in urine were determined using a competitive immunoassay technique where levels > 3 ng/mL were considered positive.

**Results:** Nineteen patients with mushroom poisoning were included. Thirteen (68.4%) were male, and the mean age was 53 years (range 22-84 years). Eight patients belonged to an epidemic outbreak ( $\geq 2$  patients affected by the same ingestion of mushrooms) and 11 cases (58%) were isolated. The botanical identity of the species responsible for the poisoning was established in 8 patients: *Hygrocybe punicea* (n=4), *Macrolepiota rhachodes* (n=1), *Lepiota brunneoincarnata* (n=1), *Amanita phalloides* (n=1) and *Cortinarius orellanus* (n=1). The time between ingestion and the onset of symptoms was < 6 hours in 9 patients and > 6 hours in 10 patients. In the first group (< 6 hours), all patients had gastrointestinal symptoms and none had hepatotoxicity. In the second group, two patients had hepatotoxicity (*Lepiota brunneoincarnata* in one case and an unidentified mushroom in the other) and one patient developed nephrotoxicity (*Cortinarius orellanus*). Amatoxins in urine were investigated in 5 patients, but were positive (9 ng/mL) in only one case (unidentified species). The ingestion of mushrooms considered hepatotoxic was treated with activated charcoal, silybinin, penicillin and forced neutral diuresis. The remaining cases received symptomatic treatment, including haemodialysis in the patient who developed nephrotoxicity. Eight patients required hospitalization (stay > 24 hours), of which three required ICU admission. All patients evolved favourably without sequelae except for the patient with nephrotoxicity due to *Cortinarius orellanus* in whom renal failure (creatinine 7 mg/dL) persists three months after ingestion.

**Conclusion:** Mushroom poisonings are common in our region. Pure gastrointestinal syndrome is the most common manifestation, but some patients develop hepatotoxicity or nephrotoxicity. Hepatic

recovery is usual but renal failure may persist as a consequence of ingestion of *Cortinarius orellanus*.

## 241. Intensive support therapy and mortality in *Colchicum autumnale* poisoning

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**Objective:** *Colchicum autumnale* (autumn crocus) contains the alkaloid colchicine which has antimetabolic properties. Poisoning with colchicine results in acute gastroenterocolitis, multiple organ failure and bone marrow suppression. The aim of this study was to evaluate intensive support therapy and mortality in *Colchicum autumnale* poisoning.

**Methods:** This was a retrospective study of all *Colchicum autumnale* poisoned patients admitted at the University Medical Centre Ljubljana between 2000 and 2014. The inclusion criterion was serum colchicine confirmation by gas chromatography-mass spectrometry (GC-MS). The medical files of enrolled patients were reviewed and comparisons were made using the chi-square test.

**Results:** A total of 13 *Colchicum autumnale* poisoned patients (mean age 58 years, 43% men) were included. All patients mistakenly ingested *Colchicum autumnale* instead of wild garlic (*Allium ursinum*) and developed acute gastroenterocolitis on average 5 hours after ingestion. In total 20% (3/13) of patients were admitted to the intensive care unit for intensive support therapy was acute respiratory failure and cardiogenic shock (3/3) that caused death in two patients on the third day after ingestion. They were all treated with assisted mechanical ventilation and vasopressors, but only the patient who survived developed leukopenia with sepsis that was treated with a granulocyte colony-stimulating factor and antibiotics. This patient also received haemodialysis due to acute kidney failure in the second week. Leukopenia also developed in two additional patients who were not treated in the intensive care unit. They received prompt granulocyte colony-stimulating factor therapy and did not develop infection. Red blood cell and platelet transfusions were given to two patients in the intensive care unit (2/3). Platelet transfusion was also indicated in two additional patients (2/10) not treated in the intensive care unit. The patients requiring intensive support therapy had increased serum troponin ( $p = 0.01$ ) and decreased cardiac output detected by echocardiography ( $p = 0.01$ ) compared to the other colchicine poisoned patients.

**Conclusion:** The mortality in *Colchicum autumnale* poisoning was 15%. Intensive support therapy is indicated in acute respiratory failure and cardiogenic shock that can be predicted by a positive serum troponin concentration. Bone marrow suppression, requiring granulocyte colony-stimulating factor therapy and transfusion, may develop in patients without multi-organ failure.

## 242. Poisoning with *Cicuta virosa* in Sweden

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**Objective:** Cowbane (ciguë aquatique [fr], Wasserschieferling [de], *Cicuta virosa* L., Apiaceae) is duly regarded as a poisonous plant

as it contains cicutoxin, a powerful central nervous system (CNS) stimulant, that acts by blocking gamma-aminobutyric acid A (GABA<sub>A</sub>) receptors causing neuronal depolarisation resulting in rapid onset seizures. Lack of knowledge of how to recognize its roots can lead to confusion with edible plants. Here we report a case where a meal was prepared from cowbane mistaken for roots of the common reed.

**Case report:** Three families on vacation during late spring in central Sweden decided to cook and try porridge made from the roots of common reed, after finding information on the Internet regarding its use as a famine food. Collected roots from a nearby lake were boiled and mashed together with butter and spices and many of the group members tasted small amounts of the apparently delicious dish. Several of the individuals who had ingested small amounts reported nausea, and after approximately 30 minutes the three young women (16-20 years of age) who had eaten more (2-3 tablespoons each) developed tremor, vomiting and, in two cases, seizures. All involved were treated with activated charcoal, and the seizures resolved after 5 and 15 mg of diazepam, respectively. Two of the three young women were observed at hospital overnight, and the third was treated for signs of a mild rhabdomyolysis and not discharged until five days later. Pictures and roots of the plant were sent to the Poison Information Centre where our examination concluded that the plant material originated from cowbane and not common reed. Samples of the porridge and roots were analysed with high performance liquid chromatography and mass spectrometry confirming the presence of cicutoxin and other tremorgenic hydroxylated polyacetylenes. Comparison of toxin content in roots collected at the same site and in the porridge indicated a 10-fold higher concentration of toxins in the cooked porridge.

**Conclusion:** Lack of botanical knowledge is an apparent risk of poisoning when foraging and using wild collected food resources, such as mistaking cowbane roots for common reed rhizomes. The findings in this case report indicate that cooking actually increases the toxicity as the concentrations of the toxins were considerably higher in the prepared porridge than in the roots.

## 243. *Nerium oleander* ingestions are relatively benign

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**Objective:** *Nerium oleander* (common name oleander) is an ornamental and opportunistic plant that flourishes in temperate climates. The cardiac glycosides that are present in *Nerium oleander* have been used therapeutically to treat congestive heart failure, are active ingredients in some skin care products and are being investigated for the management of cancer. As an ornamental, *Nerium oleander* is an attractive flowering plant that is cultivated easily in residential and public gardens; therefore, its ubiquitous presence creates opportunities for unintentional exposures by children. Additionally, it has legendary status in folklore as being a very poisonous plant. The objective of this project was to profile ingestion exposures by humans to *Nerium oleander*, as reported to US poison information centers, to determine the morbidity and mortality of those exposures.

**Methods:** Ten consecutive years of human plant exposure ingestions from the American Association of Poison Control Centers National Poison Data System (AAPCC NPDS) were queried to identify all *Nerium oleander* exposures. The data were analyzed



to identify all symptomatic exposures and to profile them by outcome and reason for exposure. Descriptive statistics were used to characterize the data.

**Results:** There were 668,111 plant ingestion exposures reported to the AAPCC NPDS over the 10-year period. *Nerium oleander* accounted for 4,327 (0.6%) exposures. Symptoms that were reported as related to *Nerium oleander* ingestion occurred in 354 (8.2%) patients. Within the symptomatic group gastrointestinal symptoms predominated: vomiting was reported in 123 (34.7%), nausea in 59 (16.7%), abdominal pain in 24 (6.8%) and diarrhoea in 14 (4.0%). Tachycardia was reported in 16 (4.5%) and bradycardia in 23 (6.5%). The other common symptoms were oral irritation in 40 (11.3%) and drowsiness/lethargy in 24 (6.8%). No fatalities or major effect outcomes (life-threatening) were reported. Moderate effects (prolonged or bothersome) were reported in 52 (14.7%) of the symptomatic patients. Only seven occurred in children less than 6 years of age and 35 moderate outcomes were reported in adults  $\geq$  20 years of age. Suicide attempts or misuse of *Nerium oleander* were responsible for 75% of all moderate effect outcomes.

**Conclusion:** *Nerium oleander* ingestion exposures were relatively benign, with the exception of those who ingested it intentionally for the purpose of self-harm or misuse. Gastrointestinal symptoms were reported most commonly.

#### 244. Attempted suicide by ingestion of ricin soup

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**Objective:** Ricin, a lectin from the beans of the castor oil plant *Ricinus communis*, is known to be very toxic. Nevertheless, ingestion of whole castor beans rarely results in severe toxicity. We describe a case of attempted suicide with ingestion of soup prepared from castor beans.

**Case report:** A 55-year-old man was hospitalized because of sudden vomiting in the evening of day 0, followed by paroxysmal upper abdominal pain. Physical examination showed pulse 64/min, BP 130/85 mmHg, oxygen saturation 96% and temperature 36.9°C. Laboratory results showed leucocytosis (11.7/nL) and lactate hydrogenase (LDH) 419 U/L. On day 1 the C-reactive protein (CRP) increased to 44 mg/L. He developed watery diarrhoea. Abdominal X-ray showed fecal impaction. He was treated with intravenous fluids. The patient explained that he had tried to commit suicide by ingesting soup made from the pulp of castor beans. He prepared the soup from 16 bags of castor beans using a recipe from the Internet. On day 3 the CRP peaked at 113 mg/L and he developed a fever ( $>39^{\circ}\text{C}$ ). On day 4 he had haematuria and rectal blood loss. Leukocytes peaked at 23/nL. Renal function deteriorated acutely (creatinine 204 micromol/L, urea 13.1 mmol/L) and albumin decreased to 27 g/L. On day 6 he developed melena. Treatment with fluconazole was initiated for oropharyngeal candida. On day 8 albumin reached its lowest value (24 g/L) and

on the following day the LDH peaked at 619 U/L. Renal function improved (creatinine 111 micromol/L, urea 6.2 mmol/L); however, liver enzymes increased, with ALP 197 U/L, gamma-GT 427 U/L, AST 100 U/L and ALT 128 U/L. Abdominal pain increased and he developed ileus. On day 10 amylase was slightly elevated (131 U/L) but ultrasound showed no pancreatitis or liver abnormalities and a normal biliary system. Nausea and vomiting disappeared and abdominal pain decreased on day 11 and oral feeding was initiated. Abdominal CT showed terminal ileitis. On day 12 leucocytosis resolved; fluconazole treatment was stopped because of increased liver enzymes. From day 14 he showed strong improvement; liver enzymes decreased and bowel movements normalized. He was discharged on day 16 in good health.

**Conclusion:** Ingestion of soup prepared from crushed castor beans can result in a serious intoxication. The number of castor beans ingested in this case (probably 80-160) was far above the estimated lethal dose in humans but it seems likely that the patient survived this exposure because ricin was partly deactivated during soup preparation.

#### 245. Poisoning due to wisteria seed ingestion: The Pavia Poison Centre case series

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**Objective:** Ornamental plants belonging to *Wisteria* species are known to cause a severe gastrointestinal syndrome associated with neurological manifestation, fever and weakness after the ingestion of seeds or leaves. Some toxic compounds, among which a double-chain lectin, called wistarina (that acts like a ricin, binding to galactose-containing structures of the gut and inhibiting protein synthesis) were isolated from these plants.<sup>1</sup> Nowadays very few cases are reported in literature.<sup>2</sup> We described a case series of human ingestion of wisteria seeds.

**Methods:** A retrospective study of all cases of human ingestion of wisteria seeds referred to Pavia Poison Centre (PPC) from January 2007 to November 2014 was performed. Patients were assessed for demographic data, modality of exposure, clinical manifestations, treatment and outcome.

**Results:** Fifty-one cases were studied (mean age  $16.8 \pm 16.0$  years; range 1-57). Thirty-five (68.6%) were pediatric patients (range 0-14 years), among which only three were younger than 3 years old. All the ingestions were accidental. In two cases the ingestion was due to the belief in beneficial properties of these seeds. Time of presentation at emergency department ranged between 30 minutes to 10 hours (mean time  $4.2 \pm 2.2$  hours). With regard to clinical manifestations, 8/51 (15.7%) patients, asymptomatic at hospital admission, were lost to follow-up. Among the other 43 patients, only one (2.3%) presented with oropharyngeal irritation and developed mild epigastric discomfort. Vomiting was present in 37/43 (86%) patients, severe diarrhoea was present in 5/43 (11.6%) patients and 3/43 (7%) patients manifested fever. No patients showed central nervous system involvement. All patients were treated symptomatically and completely recovered within 48 hours.

**Conclusion:** In our case series gastrointestinal symptoms were the most frequently described, according with the published cases.<sup>2</sup> However, none of our patients developed neurological manifestations.

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### 246. Culinary mistakes involving daffodils: Do you know your onions?

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**Objective:** To study the pattern of enquiries concerning daffodil ingestion to the National Poisons Information Service in the UK.

**Method:** Telephone enquiries concerning daffodils and narcissi (excluding other Amaryllidaceae species) received by the NPIS between 1 January 2007 and 31 December 2013 were analysed retrospectively and reviewed for any reference that could indicate a culinary mistake.

**Results:** A total of 233 enquiries were received during the specified time period. Most exposures (n = 231, 99%) were ingestions, of which 217 (94%) were accidental. In fourteen cases (6%) daffodils were ingested in a deliberate self-harm attempt. Forty-eight exposures (21%) were the result of culinary error. Thirty one patients (65%) consumed the bulb alone, nine (19%) the stem or leaf, three (6%) the flower and one (2%) the bulb and the stem. In three exposures (6%) the plant part was unrecorded and in one case (2%) the whole plant was ingested. All culinary ingestions of leaf, flower or stem occurred between December and May whilst 78% of bulb ingestions occurred between July and November. No exposures resulted in severe toxicity, although 28% resulted in minor gastrointestinal features including nausea, vomiting and diarrhoea, the majority of which settled within a few hours of exposure. Less than 1% resulted in moderate toxicity with symptoms lasting up to 24 hours.

**Table 1.** Exposure to *Hydrangea* species, *Aquilegia* species and *Wisteria* species.

Plant	Type of plant	Parts	Number of patients	Enquiries where patients asymptomatic n (%)	Gastrointestinal features (n)	Other signs	More than 1 enquiry/patient
<i>Aquilegia</i>	Perennial	Seeds, leaves, flowers	46	41 (89%)	4	NK (1)	21%
<i>Hydrangea</i>	Shrub	Leaves, flowers	75	66 (88%)	8	Coughing (1), salivation (1), dyspnoea* (1)	6.7%
<i>Wisteria</i>	Climber	Seeds, leaves, flowers	61 + 4 groups	50 (77%)	10	Dizziness (2) Skin features (2) Mouth oedema (1) NK (2)	13.6%

\*May relate to underlying bronchiectasis.

**Conclusion:** When in bud, daffodils present as thin, green stems which could be confused with spring onions. The bulb can be mistaken for traditional onions.<sup>1</sup> Enquiries concerning culinary ingestion of daffodils and other *Narcissus* species are uncommon but are associated with unpleasant and potentially avoidable features. Consideration should be given by retailers to avoid marketing these species in the vicinity of vegetables as an avoidable potential exists to confuse decorative household plants with food plants.

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### 247. Three “toxic” plants

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**Objective:** The UK National Poisons Information Service (NPIS) maintains TOXBASE©, an international poisons database. In order to ensure that it is kept up-to-date telephone enquiries to NPIS are regularly reviewed. Items without an entry on TOXBASE© but that are searched for more than twice are considered for addition.

**Methods:** Information was extracted from the UK Poisons Information Database UKPID, and reviewed using Excel. Three flowering plants which are listed as toxic in the literature and on the Internet but which do not feature on TOXBASE® were identified. Because little recent information on exposure was found from the standard searches, telephone enquiries from 1 September 2007 to 31 August 2014 were reviewed.

**Results:** The plants identified were *Aquilegia* spp, *Hydrangea* spp and *Wisteria* spp (Table 1). For *Aquilegia* there were 57 enquiries involving 46 patients, with more than one enquiry made about 21% of patients, and 3 enquiries for one case. All enquiries involved children (< 8 years) and none had more than minor toxicity. The apparent toxicity of *Aquilegia* spp may result from an 1893 French

book<sup>1</sup> linking its toxicity to aconitine. Of the accidental exposures to the shrub *Hydrangea* (80 enquiries, 75 patients; all but 5 aged 10 years or less), no patient had more than minor toxicity. Exposure to the climber *Wisteria* (75 enquiries, 61 patients + 4 groups; all but 5 aged 10 years or less; mainly accidental [2 unknown]) resulted in a higher proportion of patients with minor symptoms (20.0%, cf. *Aquilegia* 8.7%; *Hydrangea* 14.7%) One child was reported to have moderate toxicity after exposure to *Wisteria* but features were likely unrelated to the exposure and are not included in the table.

**Conclusion:** Accidental exposure to these plants did not result in serious toxicity but lack of reliable information means that it is difficult to know how to manage these patients, with multiple calls being common.

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## 248. Abstract withdrawn

## 249. Acute liver injury after ingestion of rhubarb leaves: A case report

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**Objective:** Rhubarb is a common edible plant, all parts of which are known to contain oxalates and anthraquinones.<sup>1</sup> Usually only young rhubarb stems are used for food and leaves are not recommended, but there is a rising trend to use any kind of green plants in raw salads or smoothies without thinking about safety. Acute rhubarb toxicity is usually described as nephrotoxic poisoning due to oxalates.<sup>2</sup> More rarely yellowness of the skin, liver enlargement, elevated liver enzymes and cholestasis have been described in rhubarb intoxication. Also there are case reports of hepatotoxicity with other anthraquinone-containing plants.<sup>1</sup> The authors of this paper did not find cases of acute liver injury caused by rhubarb, without oxalate injury of kidneys. We describe a case of hepatotoxic poisoning after ingestion of raw rhubarb leaves.

**Case report:** A previously healthy 47-year-old female prepared and drank a smoothie of pear, cucumber and fresh rhubarb leaves. Two hours later she felt thickness of mouth and had difficulty swallowing. Six hours later diarrhoea developed and the following day she complained of stomach pain and severe nausea. On day 3 she contacted the Estonian Poisons Information Centre and was recommended to present to hospital. She presented at the Emergency Medicine Department of the North Estonia Medical Centre at day 4. On admission the main complaints were nausea, dry mouth, diarrhoea, weakness and mild epigastrium pain. Liver enzymes were strongly elevated (ALT 6000 U/L, AST 5000 U/L). Renal markers were normal. Tests for hepatitis and autoimmune diseases were negative. She was initially admitted to the nephrology department for expected kidney damage but was transferred to gastroenterology on the next day. Her condition started to improve on day 8 and she was discharged from hospital on day

11, although the ALT and AST serum concentrations were still elevated.

**Conclusion:** Rhubarb leaves are not recommended for consumption and may cause serious poisoning resulting in kidney damage due to oxalate poisoning. Reports of acute liver toxicity of rhubarb are rare, but it may occur when raw rhubarb leaves are eaten.

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## 250. Plants: Analysis of exposures reported to the National Milan Poison Control Center (2010–2013)

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**Objective:** The main objective of our study was to perform a statistical analysis of exposures to plants reported to the National Milan Poison Control Center (NMPCC) from 2010 to 2013.

**Methods:** A retrospective analysis on requests for toxicological consultation to the NMPCC concerning plant poisonings. The requests originated from all Italian regions. The characteristics of the patients and plants involved, circumstances of exposure and the severity of the symptoms were evaluated.

**Results:** During the study period, the NMPCC registered 3,671 consultation requests due to plant exposure involving 4,060 patients. Most of the enquiries came from Lombardy (n = 1,182; 29.1%). A significant increase in exposures was noted between May and August, followed by an unsurprising decrease during winter. Children aged 0-14 years account for most cases (n = 2,847, 70.0%). Adults were involved in only 20.1% of cases (n = 817); 9.7% of patients (n = 396) were of unknown age. Males were involved in 1,896 cases (46.7%) and females in 1,758 cases (43.3%); the gender was unknown in 202 cases (5.0%). Enquiries also involved pets and accounted for 5.02% of cases (n = 204). Intentional exposure was reported in 102 subjects (2.5%), compared to 3,907 (96.2%) accidental cases. In 51 cases (1.3%) the circumstance was not identified. In 85.9% (n = 3,489) of cases the exposure or poisoning occurred at home and the majority of patients involved were asymptomatic (n = 2659; 65.5%). In total there were 1,401 (34.5%) symptomatic patients and the most common clinical symptoms were vomiting, diarrhoea and oropharyngeal disorders, and in severe cases mydriasis, tachycardia and hallucinations. Cases followed over time were 1,466 (36.1%) and the Poison Severity Scores of these cases were: 377 minor, 167 moderate, 48 severe, 811 no intoxication, 7 symptoms unrelated, 5 allergic reactions and 51 unavailable.

**Conclusion:** Children and pets are curious by nature and this puts them into contact with toxic plants more easily.<sup>1</sup> Even if the number of intoxicated subjects is relatively low in comparison to the total people exposed, it is important to recognize that plant exposure can



lead to serious complications. This is paramount in order to prevent severe intoxications.<sup>2</sup>

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## 251. Opioids may bind protein targets associated with the serotonin syndrome

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**Objective:** With the introduction of antidepressants with serotonin activities, serotonin syndrome (SS) has become increasingly recognized as an adverse event. Multiple mechanisms/pathways have been recognized that precipitate SS. The Mayo clinic reported<sup>1</sup> that opioids were a common association with SS precipitated in the hospital critical care setting, notably fentanyl (19/33 cases). Tramadol labeled for SS was noted in three cases while meperidine was noted in another two. Cheminformatics tools may identify targets that may explain this physiology.

**Methods:** A software tool that predicts small molecule binding to protein ligands was used. This tool primarily uses ChEMBL reports (a chemical database of bioactive molecules with drug-like properties) of drug target binding for comparisons. The tool performs a similarity analysis of a drug to these known binders to predict if a drug in question may also bind the ligands of the target protein. The analysis was performed for opioids to see if off-target binding to serotonergic proteins might be predicted to explain a potential association with some class members and SS.

**Results:** The software tool predicts opioid binding to a number of serotonin target proteins that may precipitate SS. A number of opioids similar to tramadol may bind the serotonin transporter; dextromethorphan, fentanyl, meperidine and tilidine. Fentanyl and oxycodone are predicted to bind the synaptic vesicular amine transporter 2 (VMAT2). Fentanyl is predicted to bind monoamine oxidase (MAO) A and B, while methadone may bind MAO B. 5-Hydroxytryptamine 2a (5-HT<sub>2a</sub>) receptor binding is predicted for alfentanil and fentanyl, while 5-HT<sub>1a</sub> activity is predicted for fentanyl, hydrocodone and methadone. Medline reports confirm some predictions. For fentanyl, 5-HT<sub>1a</sub><sup>2</sup> and transporter<sup>3</sup> activity is noted. Serotonin re-uptake inhibitor activity was documented for dextromethorphan, methadone and meperidine.<sup>3</sup>

**Conclusion:** A cheminformatics approach can rapidly provide a biological plausibility assessment for a clinical observation. The tool predicted target binding sites with literature documentation, but predicted additional opioid binding relevant to SS. Further research and binding studies for some opioids appear warranted.

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## 252. In vitro inhibition of aldehyde-dehydrogenase by mushroom extracts

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**Objective:** Aldehyde hydrogenases (ALDH) catalyse the NAD-dependent oxidation of aldehydes and are crucial metabolic (aldehyde-detoxification) and regulatory (retinol pathway) enzymes. A cysteine molecule is involved in the catalytic oxidation at the active centre of ALDH. The ALDH inhibitor disulfiram is an established antidipsotropic pharmaceutical. Additionally, ALDH inhibitors are under exploration as anticraving agents in cocaine-addiction and as sensitising medications in cancer chemotherapy.<sup>1</sup> A natural ALDH-inhibitor is coprine, isolated from the mushroom *Coprinus atramentarius*, which causes the well-known coprine-syndrome when eaten together with alcohol. Other mushrooms which allegedly cause the same syndrome, as reported in partially contradicting sporadic case reports and in field-guides, are *Clitocybe clavipes* and *Boletus luridus*. Recently we reported a case series with coprine-like syndrome after consumption of the mushroom *Echinoderma asperum* together with alcohol. In an *in vitro* assay we demonstrated the inhibition of ALDH (from yeast) by *E. asperum*.<sup>2</sup> Here we investigated extracts of the other potentially ALDH-inhibiting mushrooms mentioned above using the same assay. In addition, we tested the hypothesis that the inhibiting principle of *E. asperum* interacts with cysteine in the catalytic-centre of ALDH by adding mercaptoethanol to the assay.

**Method:** Freshly collected specimens of the above mentioned mushrooms and of *B. edulis*, *Pleurotus ostreatus*, *Agaricus bisporus*, *B. rhodopurpureus*, *B. rhodoxanthus*, *Lycoperdon umbrinum* and *E. asperum* were stored at -20°C until extraction. Extraction procedure and NADH-dependent ALDH assay were performed as described previously.<sup>2</sup> In the ALDH assay, NADH formation by oxidation of acetaldehyde by NAD<sup>+</sup> was measured at 340 nm on a multiplate UV-photometer.

**Results:** 1) Extracts of *B. luridus*, *B. rhodopurpureus*, *B. rhodoxanthus*, *B. edulis*, *Lycoperdon umbrinum* and *C. clavipes* inhibit the ALDH catalysed and NADH-dependent oxidation of acetaldehyde. 2) Extracts of *P. ostreatus* and *A. bisporus* do not cause inhibition. 3) The inhibition of ALDH by extract from *E. asperum* is prevented by mercaptoethanol.

**Conclusion:** *B. luridus*, *B. rhodopurpureus*, *B. rhodoxanthus*, *B. edulis*, *Lycoperdon umbrinum* and *C. clavipes* have ALDH inhibiting properties *in vitro*. No reports describing a coprine syndrome are known with *Lycoperdon umbrinum*, *B. rhodopurpureus*, *B. rhodoxanthus* or *B. edulis*. Thus, the clinical relevance of this observation has to be assessed. Mechanistically, the active cysteine in ALDH seems to be involved in the inhibition of ALDH by *E. asperum*.

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### 253. Abstract withdrawn

### 254. Abstract withdrawn

### 255. A novel screening method to detect *in vitro* neurotoxicity: Effects of illicit drugs on neuronal activity

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**Objective:** The demand to develop fast and cost-effective *in vitro* methods to investigate the ability of substances to affect the central nervous system is increasing. A recently developed technique is the multi-electrode array (MEA). This is a physiological approach to measure activity in neuronal networks that can originate from a variety of neuronal preparations. In this study, we functionally characterized the neuronal networks, determined the optimal analysis strategy and investigated the effects of several illicit drugs on neuronal activity.

**Methods:** MEAs were used to determine neuronal activity in primary rat cortical neurons. Mean spike rate was determined during baseline and exposure recordings per active electrode after which electrodes in the same well were averaged. In addition, different time windows were analysed. We investigated the effect of acute exposure (30 minutes) to several neurotransmitters (GABA, glutamate, dopamine, serotonin, acetylcholine, nicotine) and several drugs (MDMA, mCPP, amphetamine).

**Results:** Exposure to glutamate, dopamine and serotonin increased neuronal activity 200% (30  $\mu$ M), 60% (0.03  $\mu$ M) and 40% (10  $\mu$ M), respectively. In contrast, neuronal activity was completely inhibited at higher concentrations. Acetylcholine increased neuronal activity 200% at 1 mM, whereas GABA and nicotine inhibited neuronal activity completely at 3  $\mu$ M and 1 mM, respectively. The effect following exposure to most substances was time-dependent. For example, the maximal increase in activity induced by 1 mM acetylcholine was approximately 200% during the first 5 minutes of exposure, whereas the increase was no longer present at later time points. MDMA, amphetamine and mCPP decreased neuronal activity completely, with EC<sub>50</sub> values of 106, 113 and 33  $\mu$ M, respectively.

**Conclusion:** To prevent false negatives, effects on neuronal activity should be determined in different time windows and not

only within the total exposure time. A variety of receptors was present in our cultures, as indicated by the change in activity following exposure to many neurotransmitters. Also, effects on neuronal activity due to drug exposure can be detected. In conclusion, MEAs combined with neuronal networks can be applied as a novel *in vitro* screening tool to rapidly determine effects of substances on the central nervous system.

### 256. Mitochondrial toxicity of valproic acid and its reversion using L-carnitine: First results from an experimental model

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**Objective:** Valproic acid (VPA) may be responsible for liver toxicity following massive ingestion or prolonged treatment, but its exact mechanisms are still debated, although liver mitochondrial toxicity has been suggested. L-carnitine is used to prevent or reverse VPA toxicity. Our objectives were three-fold. To build a model of acute intoxication (IP injection of VPA at 80% of its LD<sub>50</sub>, i.e. 775 mg/kg) and subacute poisoning (IP injection of 500 mg/kg/day VPA for 7 or 14 days) in the Sprague-Dawley rat, to evaluate the resulting liver toxicity using routine plasma and mitochondrial function markers and to investigate its reversion using L-carnitine (200 mg/kg/day IP for 3 days).

**Methods:** To investigate VPA acute toxicity, venous and liver samplings were obtained at Day 1 (D1), D4 and D7 under general anesthesia. To investigate VPA subacute toxicity, catheterized rats were used, blood sampled at D1 and the day after the last VPA injection (D8 or D15) with liver sampling at D8/D15. To study its reversion using L-carnitine (versus solvent), blood samples were obtained at D1 (before VPA), then D8 (before antidote) and D11 (after 5-day antidote administration) with liver sampling at D11. Plasma markers (AST, ALT, bilirubin, gamma-glutamyltransferases, LDH, glucose) and several mitochondrial and cytosolic enzyme activities (mitochondrial complex-1, citrate synthase, catalase, glucose-6-phosphate dehydrogenase, superoxide dismutase, glutathione peroxidase, xanthine oxidase) and markers of oxidative stress (reduced/oxidized glutathione, ATP/AMP and malonaldehyde) were measured in the peripheral leucocytes and liver cells. Comparisons were performed using the adequate statistics (multiple comparison tests with Tukey correction and Student t-tests for non-paired variables).

**Results:** Two rat models of VPA poisoning were set-up. Significant increase in plasma lactate was obtained on D4 of the acute poisoning as well as D7 and D14 of the subacute poisoning. Significant decrease in ALT was observed on D7 and D14 of the subacute poisoning. None of these parameters was significantly modified by L-carnitine in comparison to the solvent. Analysis of the different biomarkers and enzyme activities in the leukocytes and hepatocytes supported the onset of significant mitochondrial cytotoxicity; however, no significant reversion with L-carnitine was obtained in comparison to the solvent.

**Conclusion:** Two models of acute and subacute VPA intoxication were set-up in the rat. Increase in lactate and decrease in ALT

support the onset of hepatotoxicity. Similarly, biomarker modifications suggest the onset of mitochondrial cytopathy. In our rat model, L-carnitine does not seem more efficient than the solvent to reverse the overlooked markers of plasma and hepatocyte impairment.

## 257. Characteristics of occupational fatalities from inhalation injury in confined versus non-confined spaces (2003 to 2010)

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**Objective:** Toxicity from an inhalational exposure is an important cause of occupational fatalities. Characteristics associated with inhalational occupational deaths are not well-described. Our objective is to compare the characteristics of occupational fatalities from inhalation injury in confined versus non-confined spaces.

**Methods:** We analyzed the 2003 to 2010 restricted data from the U.S. Bureau of Labor Statistics Census of Fatal Occupational Injuries (CFOI) database. The CFOI database records workplace deaths by collecting data from state and federal administrative sources. Chi-square analysis was performed to determine if significant associations exist between the location of injury and specific variables of interest.

**Results:** Over the 8-year study period, 510 inhalation-related deaths were identified. In total 482 cases were analyzed following exclusion of cases that were not classified by space and deaths deemed to be not work-related due to acute reaction to illicit drug use while working. Of the remaining 482, 211 (43.8%) occurred in confined spaces and 271 (56.2%) occurred in non-confined spaces. The majority of fatalities due to inhalation injury in confined and non-confined spaces were found to be in Caucasian males. Table 1 compares characteristics for inhalational deaths in confined and non-confined spaces. Carbon monoxide was responsible for

**Table 1.** Characteristics of occupational fatalities by occupation and toxicant.

Occupation	Confined	Non-Confined
Professional (managers)	31 (44%)	40 (56%)
Protective Service & Military (security guards, first-responders)	8 (36%)	14 (64%)
Service (cleaners, food preparation)	*	33 (92%)
Agriculture (farmworker)	22 (92%)	*
Industry (construction, automotive service, painters)	111 (43%)	145 (57%)
Transportation (tractor-trailer or truck driver, movers)	36 (49%)	37 (51%)
Toxicant		
Carbon monoxide	32 (19%)	134 (81%)
Halogens and halogen compounds	*	28 (90%)
Chemical products, including cleaning agents, paint, lacquer and varnishes	9 (28%)	23 (72%)
Coal, natural gas, and petroleum fuels	8 (57%)	6 (43%)

Fatal injury data were calculated by Drexel Division of Medical Toxicology with restricted access to BLS CFOI microdata. \*No data or data that do not meet BLS publication criteria.

most of the inhalation-related deaths and more of those deaths occurred in non-confined spaces. Younger workers were far more likely to die in confined spaces while older workers were more likely to die in non-confined spaces ( $p < 0.001$ ). There was a significant difference between confined space deaths and non-confined space deaths with respect to toxicants, month of incident, time of incident, and occupation categories (all  $p < 0.001$ ).

**Conclusion:** The data analyzed demonstrates statistically significant differences in the characteristics associated with work-related inhalational fatalities in confined versus non-confined spaces.

## 258. Evaluation of clinical effects after high pressure injection injuries of the hand using 20 years' experience of Pavia Poison Centre: A toxicological and surgical emergency

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**Objective:** To describe clinical manifestations of cases of high-pressure injection (HPI) injuries referred to the Pavia Poison Centre (PPC), in order to identify toxic effects and treatments. HPI injury of the hand represents one of the most serious surgical emergencies of the upper extremities.

**Methods:** A 20-year retrospective analysis (1995-2014) assessed all cases for sex, age, nature of the injected fluid, site of HPI, clinical manifestations, treatment and outcome. The factors influencing the seriousness, the extensiveness of subcutaneous damage and the functional outcomes of patients were assessed.<sup>1</sup>

**Results:** Forty-two cases were studied (37 M; mean aged  $40.9 \pm 10.5$  years). The mechanism of injury was described in 24 (57%) cases with 20 injections by pressure guns and 4 due to blast pipe pressure. The most common injury was to the non-dominant hand. More than 36% of injections occurred to the index finger. The second most affected region was the palm (19%) whereas the thumb was only involved in 17% of cases. The fluids involved were oily substances (38%), solvent-based paints (17%), water-based paints (14%), organic solvents (12%), fats (10%), solid materials (5%), gas (2%) and unknown (2%). The most serious injuries occurred with solvent paints and oils. The clinical course was characterized by edema (69%), pain (63%), punctiform skin lesions (44%), necrosis (16%), local hyperemia (12.5%) and reduced function (9.5%). Digit ischemia (9%) and necrosis (6%) were also involved. Fifty-one per cent of patients were admitted to the emergency department (ED) within 6 hours of the incident. Outcomes are available for 10 cases that underwent urgent immediate surgical exploration/decompression; 4 had a finger amputation (3 solvent-based, 1 water-based paint), 2 reported permanent sensory deficits (1 paint solvent, 1 hydraulic oil), 1 developed decreased function of the hand and 3 patients recovered without sequelae. The amputation rate of these injuries is up to 10% without adequate treatment and on average, the time between injection and presentation in ED was 24 hours.

**Conclusion:** The real gravity of HPI injuries is often missed by the emergency room physician who, due to the apparent lack of initial injury, ignores the potential morbidity of the injury itself.



All patients with HPI injuries should be considered at risk for amputation and be referred for immediate surgical assessment.

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## 259. Unintentional needlestick injuries in livestock production

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**Objective:** To characterise the pattern of needlestick injury in livestock producers, their employees or relatives while vaccinating or injecting medications into animals.

**Methods:** A retrospective study was conducted of calls to the New Zealand National Poisons Centre during the two year period between 1 January 2012 and 31 December 2013, regarding accidental needlestick injuries suffered as a result of treating livestock with injectable preparations. Information on patient age, sex, type of agent involved, and site of the unintentional injection was collated.

**Results:** During the two year period there were 175 calls regarding 150 incidents. Victims ranged in age from 25 months to 74 years. Males predominated, with an overall male-to-female ratio of 2.1 to 1. The most common site of injection was the “hand”, followed by the finger, thumb, leg and thigh, and forearm. The most common agents involved were animal vaccines (~71%), followed by anthelmintics and antibiotics (10.7%). Nutritional supplements, including selenium (sometimes included in vaccines) and copper (6%) also featured. The nine incidents involving copper were all referred for urgent medical attention as both local tissue injury and systemic toxicity are described effects of copper self-injection, and there is no very effective antidote.<sup>1</sup> There were two cases involving a prostaglandin F2 alpha analogue, inadvertent self-injection of which has been linked to miscarriage in a female veterinarian.<sup>2</sup> There were no cases implicating anaesthetics or euthanasia agents.

**Conclusion:** These data suggest a significant incidence of needlestick injuries in this industry, with resultant risks including tissue damage, acquired infection, and systemic toxicity. Tissue injury can be particularly severe from vaccines containing oil adjuvant.<sup>3</sup> The injuries can be debilitating, costly, and may lead to loss of productivity. Farmers and their employees who inject livestock need to be aware of the risks of this activity and should utilise measures to decrease unintentional needlestick injury. Special attention is required for systemically toxic compounds including copper and prostaglandins. Education needs to be undertaken initially and repeated regularly for workers performing injection procedures.

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## 260. Tympanic membrane perforation and cranial nerve VII and VIII injury due to a hot metal injury: A case report

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**Objective:** We describe a novel case regarding work-related cranial nerve VII and labyrinthine injury due to molten slag.

**Case report:** A 43-year-old male mechanic presented with a recent history of cutting metal with a blowtorch underneath a car. A piece of molten metal, commonly known as slag, fell into his right ear while fixing the vehicle. The patient experienced immediate right sided facial droop and vertigo. Upon examination in the emergency department, he was noted to have a small blister on the anterior aspect of his right external auditory canal, a 70% perforation of his right tympanic membrane with charring of the edges, and a complete cranial nerve VII paralysis. Both conductive and sensorineural hearing loss was evident on examination as the patient subjectively reported complete loss of hearing from his right ear and had no bone or air conduction to his right ear with Rinne and Weber hearing tests. Complete conductive and sensorineural hearing loss was later confirmed by a formal audiogram. A non-contrasted maxillofacial CT revealed a 4 mm metallic foreign body imbedded in the medial portion of the right middle ear cavity. The patient was subsequently admitted to the trauma service for further observation. The otolaryngology service removed the metal fragment the following day using a binocular microscope. No further penetration by the slag into the inner ear canal was noted on direct visualization. One month later a gold weight was placed in the patient’s upper eyelid by otolaryngology for eye protection as he was still unable to spontaneously close his eye. Four months after the initial injury his vertigo had improved greatly. By month 8 he had spontaneously regained some return of function of his facial nerve, however his hearing had not improved.

**Conclusion:** Isolated cranial nerve and labyrinthine injuries remain infrequently reported sequelae of maxillofacial traumatic injuries. This case represents the only known reported isolated cranial nerve VII and labyrinthine injuries due to a hot metal fragment penetrating the tympanic membrane. This case is a caution to workers to wear protective equipment while working with hot metal.

## 261. Indian Krait (*Bungarus caeruleus*) envenoming: A clinical and neurophysiological investigation of neuromuscular dysfunction

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**Objective:** To investigate the time course, severity and the treatment response of neuromuscular dysfunction in definite Indian Krait envenoming with neurophysiological testing and clinical observations.

**Methods:** Definite Indian Krait bite cases were recruited from the Teaching Hospital Anuradhapura, Sri Lanka from April to October 2014. Cases were confirmed with venom specific immunoassays in patient serum or by expertly identified snakes. All patients had serial neurological examinations and had stimulated concentric needle single-fibre electromyography (sfEMG) of the orbicularis oculi on two to six occasions. Patients were reviewed at 6 weeks.

**Results:** There were 33 krait bite patients with a median age 35 (interquartile range [IQR]: 22 to 55) and 24 were males. Patients reached the study hospital a median of 3.3 hours post-bite (1.5 to 7 hours). Eight patients were non-envenomed, eight had partial ptosis, and 17 had clinically significant neurotoxicity including extra-ocular, facial, bulbar and neck flexor paralysis on admission (median: 3.2 hours post-bite), with three having tidal volume < 250 mL. The eight non-envenomed patients had no neurotoxicity, normal sfEMG and none were given antivenom. Eight patients with partial ptosis had normal sfEMG, six received antivenom and all recovered within 20 to 32 hours. In 17 patients, clinical features rapidly progressed from ptosis to divergent strabismus, complete ophthalmoplegia, facial muscle, neck flexion and bulbar weakness, in descending order. Within 4 hours post-bite, sfEMG showed high mean jitter (64.0-99.4  $\mu$ s; median 86.2  $\mu$ s) with 32-61% fibres having blocks. All 17 patients received 20 vials of Indian polyvalent snake antivenom a median of 3.5 hours post-bite (IQR: 2.8-4.8). However, the paralysis worsened and the tidal volume declined below 250 mL in 13 patients within 4-6 hours post-bite requiring mechanical ventilation. Five patients developed complete limb paralysis. From 6-12 hours, sfEMG showed very high mean jitter (139.3-341.5  $\mu$ s; median 161.0  $\mu$ s) with blocks in 71-100% of fibres. Neuromuscular activity improved in ascending order over 22-54 hours, with associated reduction in jitter and blocks on the sfEMG. When patients were extubated a median of 96 hours post-bite (54-216 hours), none had any features of neurotoxicity. All survived. In five severely envenomed patients, sfEMG showed a high number of fibres with jitter > 30  $\mu$ s with blocks in < 10% on discharge (10-12 days post-bite). At 6 weeks, sfEMG was normal in all except two patients.

**Conclusion:** Despite early antivenom therapy, neuromuscular dysfunction progressed in Indian Krait envenoming. The descending paralysis resolved in reverse order and sfEMG correlated with, and better defined, the neuromuscular dysfunction.

## 262. External validation of the paracetamol-aminotransferase multiplication product to predict hepatotoxicity from paracetamol overdose

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**Objective:** Risk prediction in paracetamol poisoning treated with N-acetylcysteine helps guide initial patient management and disposition, including early transfer to a liver unit. The paracetamol-aminotransferase multiplication product may be a useful and less time-sensitive risk predictor. The aim of this study was to validate this multiplication product in an independent cohort of patients with paracetamol overdose.

**Methods:** Using a prospective toxicology dataset of poisoned patients presenting to a large inner-city UK teaching hospital, we identified by electronic search all paracetamol overdoses from February 2005 to March 2013. We assessed the diagnostic accuracy of the multiplication product (using first measured serum aminotransferase concentration and the simultaneous paracetamol concentration) for the outcome of hepatotoxicity (any ALT > 1000 IU/L), especially at the pre-specified cut-off points of 1,500 mg/L x IU/L (10,000 mcmol/L x IU/L) and 10,000 mg/L x IU/L (66,000 mcmol/L x IU/L).

**Results:** Of 3823 total paracetamol overdose presentations, there were 2743 acute single (40 missing ALT), 452 delayed single (> 24 hours post overdose), 426 staggered (ingestion over > 1 hour) and 202 supratherapeutic ingestions. Altogether, 34 patients developed hepatotoxicity: 10 acute single, 10 delayed single, 13 staggered and 1 supratherapeutic ingestion. Among the acute single ingestion patients, a multiplication product > 10,000 mg/L x IU/L had a sensitivity of 80% [95% CI 44%, 96%] and specificity of 99.6% [99.3%, 99.8%], and > 1,500 mg/L x IU/L had a sensitivity of 100% [66%, 100%] and specificity of 92% [91%, 93%]. Overall, 16 patients with a multiplication product > 10,000 mg/L x IU/L developed hepatotoxicity (likelihood ratio 247, 95% CI 128, 478), and 4 patients with a multiplication product between 1,500 and 10,000 (likelihood ratio 2.5, 95% CI 1.0, 6.0). No patient with a product < 1,500 mg/L x IU/L who received N-acetylcysteine developed hepatotoxicity.

**Conclusion:** In acute paracetamol overdose presenting within 24 hours of a single ingestion, the multiplication product has an extremely high diagnostic accuracy for predicting hepatotoxicity in patients treated with N-acetylcysteine. Regardless of ingestion type, a product > 10,000 mg/L x IU/L was associated with a very high likelihood, and < 1,500 mg/L x IU/L with a very low likelihood, of developing hepatotoxicity. The multiplication product should be considered more widely in risk-assessment of paracetamol-poisoned patients, particularly acute single ingestions presenting within 24 hours of exposure.

## 263. Do benzodiazepines worsen tramadol toxicity? An experimental study in the rat

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**Objective:** Since dextropropoxyphene withdrawal from the market in 2011, tramadol poisonings have significantly increased. Presentation of tramadol intoxication includes seizures, serotonin syndrome and respiratory depression. Benzodiazepine coingestion has been suggested to worsen tramadol toxic-

ity; however, its exact role is not established. Our objectives were to describe tramadol-related neurorespiratory effects in Sprague-Dawley rats, focusing at the dose-effect relationships and the consequences of its association to diazepam, suggesting possible mechanisms of interaction.

**Methods:** To study the dose/effect relationships, three tramadol doses (45, 75 and 120 mg/kg; LD<sub>50</sub> 150 mg/kg) were studied in comparison to the control. Body temperature (using telemetry), respiratory effects (using plethysmography) and neurological effects (using clinical scales and EEG) were studied. Concentrations of tramadol, diazepam, and their respective metabolites (M1, M2, M5, nordiazepam, oxazepam and temazepam) were measured using liquid chromatography coupled to mass spectrometry of high resolution. Peripheral (plasma and platelet) and brain (frontal and parietal lobes) serotonin and other monoamines were measured using HPLC coupled to fluorimetry. For each animal and each time, we calculated the difference between the parameter value at that time and baseline and the area under the curve of its time course. Comparisons were performed using two-way ANOVA followed by post-tests using the Bonferroni correction.

**Results:** Tramadol induced dose-dependent sedation, hypothermia, early seizures and respiratory depression characterized by significant increase in inspiratory and expiratory times. Diazepam co-administration significantly increased respiratory depression (by the addition of physiological effects) but suppressed convulsions. Serotonin reuptake inhibition in the brain, of early onset after tramadol administration, was not altered by diazepam, suggesting an additional GABA to the serotonin component of seizures. Our study highlighted the predominant role of tramadol in seizures but its metabolite M1 in the onset of respiratory depression.

**Conclusion:** Tramadol neurorespiratory toxicity is dose-dependent with resulting increased depression, but reduced seizures in combination to diazepam. Drug-drug interactions are mainly pharmacodynamic, however, an additional contribution of the observed alterations in both M1 and M5 concentrations cannot be ruled out.

## 264. The myth of the half RR rule and QT prolongation

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**Objective:** QT interval measurement on an electrocardiogram (ECG) is integral to risk assessment of torsade de pointes (TdP), particularly in drug overdose. There remains controversy regarding the definition of an abnormal QT. The '½ RR Rule' where a QT interval is abnormal if it is greater than half the R-R interval, is often used, with little evidence to support it. The QT nomogram defines a QT interval abnormal if the QT-heart rate (HR) pair from an ECG is above the abnormal line on the nomogram.<sup>1</sup> This study aimed to investigate the diagnostic accuracy of the 1/2 RR Rule as a risk assessment tool for TdP and compare it to the QT nomogram.<sup>1</sup>

**Methods:** The sensitivity and specificity of the 1/2 RR Rule was calculated using a previously published dataset, including 129 cases of drug-induced TdP and 316 controls (non-cardiotoxic

**Table 1.** The half RR Rule sensitivity and specificity compared to the QT nomogram for each drug cohort.

Drug	No. of cases	PPA (95% CI)	NPA (95% CI)	Overall agreement (95% CI)
Amisulpride	89	100% (93–100%)	36% (18–59%)	84% (75–91%)
Thioridazine	57	100% (76–100%)	17% (8–33%)	40% (28–54%)
Citalopram	311	97% (82–100%)	33% (27–39%)	39% (34–45%)
Quetiapine	202	100% (66–100%)	19% (14–25%)	23% (17–29%)
Venlafaxine	369	95% (75–100%)	29% (24–34%)	33% (28–38%)
Mirtazapine	81	–	37% (27–49%)	37% (27–49%)
Oxycodone	50	100% (46–100%)	40% (26–56%)	46% (32–61%)
Risperidone	41	100% (46–100%)	19% (9–37%)	29% (17–46%)

overdoses), compared to the QT nomogram, QTcB > 500 ms and QTcF > 500 ms.<sup>1</sup> In addition, QT-HR pairs were extracted from 8 different cohorts of drug overdose admissions recruited to the Hunter Area Toxicology Service where the QT-HR had been manually measured on an ECG. The RR was calculated from the HR. The overall, positive and negative percent agreement (PPA and NPA) of the 1/2 RR Rule compared to the QT nomogram as an imperfect gold standard for determining an abnormal QT interval for each drug, was calculated to determine the value of the rule as a risk assessment tool.

**Results:** The sensitivity and specificity of the 1/2 RR rule was 87.6% (95% CI 80.4–92.5%) and 52.87% (95% CI 47.2–58.4%), respectively compared to the QT nomogram which was 96.9% (95% CI 91.8–99%) and 98.7% (96.6–99.6%). It was also less sensitive than QTcB > 500 ms and had a lower specificity than QTcB > 500 ms and QTcF > 500 ms. In the cohorts of drug overdose the ½ RR Rule had poor NPA (Table 1). This translates into more than half of the patients being monitored unnecessarily for each drug.

**Conclusion:** The 1/2 RR Rule was not as sensitive as the QT nomogram for drug-induced TdP. It had very poor NPA in overdose patients resulting in patients receiving unnecessary cardiac monitoring and repeat ECGs.

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## 265. Influence of naltrexone induction regime on the concentrations of stress hormones during rapid opioid detoxification

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**Objective:** Stress response induced by rapid opioid detoxification can be decreased with a novel scheme of opioid antagonist naltrexone induction. Stress hormones, cortisol and adrenocorticotropic hormone (ACTH), have been used in few studies as direct markers of the stress response during opioid detoxification. Statistically significant increases of both markers have been



**Table 1.** The serum concentrations of stress hormones before naltrexone and after induction in controls (single 12.5 mg) and the intervention group (gradually increasing dose from 50 µg to a total of 12.5 mg).

Hormones	Time	Group	Value	p value
Mean ACTH (pg/L)	1 h before induction	Control	33.72	0.266
		Analyzed	41.72	
	1 h post induction	Control	55.00	0.031
		Analyzed	29.32	
	5 h post induction	Control	32.58	0.643
		Analyzed	27.12	
23 h post induction	Control	28.77	0.157	
	Analyzed	39.16		
Mean cortisol (nmol/L)	1 h before induction	Control	818.46	0.85
		Analyzed	807.16	
	1 h post induction	Control	948.27	<0.001
		Analyzed	677.72	
	5 h post induction	Control	842.04	0.19
		Analyzed	730.52	
23 h post induction	Control	825.04	0.913	
	Analyzed			

reported during detoxification under general anaesthesia and conscious sedation. We present the results of randomised double-blind study comparing stress response to different opioid antagonist naltrexone induction regimes during rapid opioid detoxification under conscious sedation.

**Methods:** In a randomised double-blind study the control group (n = 30) received a single 12.5 mg dose of naltrexone and the intervention group (n = 30) received a gradually increasing dose from 50 µg to a total of 12.5 mg according to a predefined protocol. The serum concentrations of stress hormones were measured before naltrexone induction and at 1, 5 and 23 hours after the induction and compared in both control and intervention groups.

**Results:** Following naltrexone induction, concentrations of cortisol and adrenocorticotrophic hormone increased significantly (p = 0.031 for adrenocorticotrophic hormone and p < 0.001 for cortisol, respectively) in the control group and decreased in interventional group (Table 1).

**Conclusion:** Gradually increasing doses of naltrexone reduces the stress response during a rapid opioid detoxification procedure under conscious sedation.

## 266. Validation of two different screening ELISA assays for synthetic cathinones (mephedrone/methcathinone and MDPV) with confirmatory LC-MS in intoxicated patients

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**Objective:** Due to their amphetamine/cocaine like effects, synthetic cathinones are a new trend in the recreational drug market and the paucity of human toxicological data combined with numerous drug-related cases of abuse, dependence, intoxica-

tion and deaths has generated great concern in the international scientific community. Within the National Early Warning System (NEWS) we compared screening analysis in urine samples (using specific mephedrone/methcathinone and MDPV kits) with liquid chromatography-mass spectrometry (LC-MS) data on urine samples from poisoned patients admitted to emergency departments (EDs).

**Methods:** The study was conducted on 202 clinical urine specimens collected from severely intoxicated patients admitted to Italian EDs, from April 2011 to January 2013, for a clinically suspected abuse of any kind of novel psychoactive substance. Screening data obtained by ELISA assays (Randox<sup>®</sup> Laboratories Ltd, limit of detection (LOD) 0.40 and 20.0 ng/mL for mephedrone/methcathinone and MDPV, respectively) were compared to determinations gained by LC-MS (including detection of 13 parent cathinones, LOD 10 ng/mL, based on the availability of certified reference standards).

**Results:** Mephedrone/methcathinone: 195/202 samples gave values < 7 ng/mL by screening ELISA assay and tested negative by LC-MS. Seven specimens showed concentrations > 16 ng/mL (above the upper limit of the standard curve) by screening immunoassay, and only 4 of them resulted positive by LC-MS (2 for butylone, 1 for MDPV, and 1 for 4-MEC, mephedrone and pentadrone). MDPV: 168/174 samples gave values ≤ 200 ng/mL by screening ELISA and tested negative by LC-MS. Five samples showed concentrations above the upper limit of the standard curve (> 850 ng/mL), while 1 specimen gave a value of 300 ng/mL. Among these, 3/6 samples were confirmed positive by LC-MS analysis (1 for butylone, 1 for pentadrone and 1 each for butylone and MDPV).

**Conclusion:** These data highlight a good global correspondence (positive + negative results) between the two analytical methods, showing disagreement in few cases concerning positive results. This discrepancy may be due to interference/cross-reactivities of ELISA assay, or the presence of substance/metabolites not yet included in LC-MS standards. Furthermore, no false negatives were detected by ELISA screening, thus supporting the promising usefulness of this rapid and reliable tool as first approach in the emergency setting, followed by confirmatory LC-MS analyses even though the current availability of reference standards is limited due to the continuous turnover of new synthetic substances in the drug market.

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## 267. The cathinones are the most commonly reported Novel Psychoactive Substances (NPS) associated with Emergency Department presentations with acute drug toxicity reported to the European Drug Emergencies Network (Euro-DEN)

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**Objective:** There is limited information on the novel psychoactive substances (NPS) involved in presentations to the Emergency Department (ED) with acute recreational drug toxicity. The European Drug Emergencies Network (Euro-DEN) project involves longitudinal collection of data from 14 sentinel centres in 10 countries on ED presentations with acute drug toxicity across Europe; one aim of this project is to provide more detailed information on the harms associated with the use of NPS.<sup>1</sup>

**Methods:** The Euro-DEN project database was searched to identify cases between 1 October 2013 and 30 June 2014 where an NPS had been used prior to presentation to the ED. Data was extracted on the self-reported NPS involved, other recreational drug(s) involved and the reporting centre.

**Results:** There were 3,573 cases reported to Euro-DEN, 318 (8.9%) of these involved one or more NPS. The distribution of cases from the individual Euro-DEN centres were: Barcelona 1, Basel 2, Copenhagen 1, Dublin 24, Gdansk 38, London 197, Mallorca 3, Munich, 23, Oslo 8 and York, 21; there were no NPS cases reported from the Drogheda, Paris, Parnu or Tallinn Euro-DEN centres. Of the reported cases 190 (59.7%) related to use of one or more NPS only and 128 (40.3%) related to the co-use of one or more NPS with one or more classical recreational drug(s). The cathinone class of NPS were the most commonly reported NPS to have been used, and was involved in 249 (78.3%) of cases. Of these, 39 cases related to “branded” NPS, where the specific compound/NPS involved was not known/reported. The frequency of NPS reported to the Euro-DEN project were 25I-NBOMe n = 1, 2/3-C drugs n = 7, 4,4'-DMAR n = 1, amphetamine type stimulants n = 3, cathinones n = 249 (mephedrone n = 156, methedrone n = 63, MDPV n = 16, other cathinones n = 14), methoxetamine n = 2, synthetic cannabinoid receptor agonists n = 18, tryptamines n = 4 and other NPS n = 7.

**Conclusion:** Mephedrone is the most common NPS associated with recreational drug presentations to the ED in Europe, despite the European Union Council recommendation for its control under national legislation following the EMCDDA risk assessment in May 2010. Data from the Euro-DEN project on the NPS associated with ED presentations can enable clinical toxicologists to provide more tailored management advice to clinicians working in the ED and inform legislative authorities on the patterns of harm associated with these products across Europe.

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## 268. Monoamine transporter and receptor interaction profiles of psychoactive benzofurans

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**Objective:** The aim of this study was to investigate the pharmacology of a series of newly abused psychoactive benzofurans *in vitro*.

**Methods:** We assessed monoamine reuptake transporter (NET, norepinephrine transporter; DAT, dopamine transporter; SERT, serotonin transporter) inhibition, benzofuran-induced monoamine release, and binding to monoamine transporters and receptors. Human embryonic kidney (HEK) 293 cells stably expressing the human NET, DAT, and SERT were used to test transporter inhibition and monoamine release. Binding affinities to monoamine transporters and receptors and functional 5-hydroxytryptamine 2A (5-HT<sub>2A</sub>) and 5-HT<sub>2B</sub> receptor activation were also assessed.<sup>1</sup>

**Results:** All benzofurans (5-APB, 5-APDB, 6-APB, 6-APDB, 4-APB, 7-APB, 5-EAPB and 5-MAPDB) predominantly inhibited the NET and SERT and only weakly the DAT. All benzofurans were more potent SERT than DAT inhibitors, similar to MDMA. The benzofurans also released monoamines through the transporter as known for classic amphetamines. However, some benzofurans also directly interacted with the 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptors and exhibited binding to adrenergic  $\alpha_1$  receptors. The benzodifuran 2C-B-FLY inhibited monoamine uptake only at very high concentrations but exhibited high affinity to the serotonin 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, and 5-HT<sub>2C</sub> receptors with strongest binding to the 5-HT<sub>2A</sub> receptor.

**Conclusion:** Benzofurans mainly inhibited the SERT and NET and released monoamines overall, similar to MDMA and suggesting similar empathogenic and psychotropic effects. However, the benzofurans also bound to  $\alpha_1$  and activated 5-HT<sub>2</sub> receptors. These direct effects on adrenergic receptors are distinct from those of classic amphetamines such as MDMA and methamphetamine. 5-HT<sub>2A</sub> receptor stimulation may result in more hallucinogen-like psychoactive properties and increased risk for serotonin syndrome and hyperthermia. Alpha-1 receptor stimulation has been associated with vasoconstriction, hypertension and hyperthermia. Serotonin 5-HT<sub>2B</sub> receptor activation has been associated with increased risk for heart valve fibrosis.

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## 269. Clinical toxicity of synthetic cannabinoid receptor agonist use

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**Objective:** Synthetic cannabinoid receptor agonists (SCRAs) are heterogeneous compounds developed as probes of the endogenous cannabinoid system or potential therapeutic agents, which clandestine laboratories subsequently synthesize and market as abusive designer drugs.<sup>1</sup> We assessed clinical toxicity associated with recent SCRA use in a large cohort of drug overdose patients. Based on prior literature, we hypothesized significant associations with agitation<sup>2</sup> and cardiotoxicity<sup>3</sup> when compared to marijuana.

**Methods:** This subgroup analysis of a large drug overdose cohort study involved consecutive Emergency Department (ED) patients

at two large urban teaching hospitals collected between 2009 and 2013. Clinical characteristics of patients with exposure to SCRA (SRCA subgroup) were compared with patients who smoked regular marijuana (MJ subgroup). Data included demographics, exposure details, vital signs, mental status and basic chemistries gathered as part of routine clinical care. Study outcomes included altered mental status (agitation, Glasgow Coma Scale [GCS]), and cardiotoxicity (myocardial injury, dysrhythmia). Dysrhythmia was defined as ventricular tachycardia or fibrillation. Assuming 30% prevalence of the predictor and outcome, we calculated the need to enrol 84 patients to show 3.5-fold relative risk with 80% power and 5% alpha.

**Results:** In total 89 patients reported exposure to any cannabinoid, of whom 17 reported SCRA (17 cases, 72 controls, mean age 38.7, 78% males, 34% Hispanic). There were no significant differences between SRCA and MJ with respect to demographics (age, gender, ethnicity), exposure history (suicidality, misuse, intent) or vital signs. Laboratory variables associated with SCRA overdose were lower mean bicarbonate ( $p < 0.05$ ) and elevated serum glucose ( $p < 0.05$ ). Mental status varied between SRCA and MJ, with agitation significantly more likely in SCRA subgroup (OR 3.3, CI 1.1-9.6). Cardiotoxicity was more pronounced in the SCRA subgroup with dysrhythmia significantly more likely (OR 9.8, CI 1.0-116).

**Conclusion:** SCRA overdose was significantly associated with more severe clinical toxicity than marijuana, including metabolic abnormalities, neurotoxicity and cardiotoxicity. Future studies should assess optimal treatment modalities to prevent adverse clinical outcomes following SCRA overdoses.

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### 270. Acute neuro-respiratory toxicity of 3, 4-methylenedioxypyrovalerone: An experimental study in the rat

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**Objective:** The use of the new psychoactive substances including cathinones has exponentially spread in France and Europe. 3,4-Methylenedioxypyrovalerone (MDPV) is one of the most commonly used and dangerous cathinones. Life-threatening poisonings and fatalities have been attributed to MDPV. Its neurotoxicity, investigated *in vitro*, may be more important

than cocaine with the inhibition of norepinephrine, dopamine and serotonin reuptake. However, experimental data are lacking *in vivo*. Our objective was to characterize MDPV-related acute toxicity on respiration, metabolism and locomotor activity in the rat.

**Methods:** A study in the Sprague-Dawley rats of ventilatory (using plethysmography), neurological (using clinical scales + EEG), body temperature (telemetry), metabolic (lactate measurement) and behavioral effects (open field to investigate locomotor activity, spatial exploration, abnormal movements and stereotypies; Dellu tests to investigate memory; labyrinth tests to study orientation); study of the dose-effect relationships (1, 3, 10 and 30 mg/kg, IP) in comparison with cocaine (10 mg/kg) and solvent; measurement of the concentrations of MDPV and its two main metabolites using tandem spectrometry. For each animal and each time, we calculated the difference between the parameter value at that time and baseline and the area under the curve of its time course. Comparisons were performed using two-way ANOVA followed by post-tests using Bonferroni correction.

**Results:** MDPV administration was responsible for a dose-dependent increase in temperature. With 30 mg/kg, hyperstimulation of ventilation with significant reduction in the inspiratory and expiratory times and significant increase in minute volume were observed, in comparison to the controls. EEG activity showed neither seizures nor significant variations in the spectral distribution. A significant increase in locomotor activity and spatial exploration were observed at 3 mg/kg, but decreased at the highest dose with the increase of stereotyped movements (retropulsion, head shaking, circling and weaving, leaking and biting). At 3 mg/kg, significant alteration in short-term memory appeared. All these modifications were correlated to the time-course of concentrations of MDPV and its metabolites.

**Conclusion:** MDPV is responsible for locomotor hyperactivity, hyperthermia, hypermetabolism and respiratory stimulation at low doses. By increasing MDPV doses, stereotypies occur without epileptic activity and locomotor activity decreases. Although rare in humans, the observed impairments in our experimental model suggest the possible facilitation of the onset of organ failure in the MDPV user.

### 271. Do users of new psychoactive substances take what they think they take? An overview of drug product contents analysed within the Swedish STRIDA project

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**Objective:** The new psychoactive substance (NPS) market is highly unregulated and new products are continuously launched. The STRIDA project monitors trends in acute NPS poisonings in Sweden and collects data on associated clinical signs and harms. Occasionally, intoxicated patients bring NPS items or products to the emergency room and these are analysed at the Swedish



Medical Products Agency. The objective was to determine whether the suspected or stated contents agreed with the results of urine/blood drug testing.

**Methods:** Patients from all of Sweden with suspected NPS intoxications are recruited to the STRIDA project when the Swedish Poisons Information Centre is consulted by caregivers. Drug items included in the STRIDA project were analysed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and nuclear magnetic resonance (NMR) spectroscopy. Urine and blood samples were collected and analysed for new and traditional psychoactive substances by LC-MS/MS. The method is updated as new psychoactives appear and reference material become available.

**Results:** Since the start of the STRIDA project in 2010, 83 suspected drug items (tablets, powder, liquids, herbal blends) have been analysed. Four items contained no drugs. In 27 items only pharmaceuticals ( $n = 17$ ), traditional psychoactives ( $n = 7$ ), doping agents ( $n = 2$ ) and dietary supplements ( $n = 1$ ) were detected. None of these cases included a patient history or product labelling suggesting NPS intoxication. The remaining 52 items contained at least one NPS and 9 contained more than one psychoactive substance. A subgroup of 42 items was suspected to contain a specific NPS, through self-report or product labelling, and for 39 items (93%) the analysis proved a correct suspicion. Three of these items contained additional substances; nicotine ( $n = 1$ ), caffeine ( $n = 1$ ) and one herbal blend with three synthetic cannabinoids. In 28 cases of the subgroup a relevant laboratory reference material was available and 25 urine/blood samples contained the same substance as was detected in the drug material. Polysubstance intoxication was present in 15 of these 28 cases.

**Conclusion:** There was a high degree of consistency between presumed and actual content in drug item analysis (93%). The NPS-positive items included in the STRIDA project were mostly pure (83% contained only one substance). Urine/blood analysis demonstrates that patients tested positive for the specific NPS found in the correct self-reported use of or labelled NPS item to a high degree (89%), but that polysubstance intoxication was common (54%), indicating simultaneous consumption of drugs from different items. Limitations of our findings include delayed patient sampling and insufficiently updated reference materials for analysis of body fluids.

## 272. Increased use of new psychoactive substances (NPS) in the Netherlands

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**Objective:** In recent years, the number of new psychoactive substances (NPS) appearing on the illicit drug market has strongly increased. In Europe, the number of newly detected substances is increasing every year, from 15 NPS in 2007 to 81 in 2013.<sup>1,2</sup> However, knowledge on the pharmacology and

toxicological risks of most NPS is lacking. Compared to other countries, NPS use in the Netherlands is low; however, recent data indicates that their popularity is increasing. We therefore investigated the appearance of NPS on the Dutch drug market over time.

**Methods:** Data from the Drugs Information and Monitoring System (DIMS) and the Dutch Poisons Information Center (DPIC) was collected. In addition, data on the clinical effects following NPS exposure was sampled.

**Results:** The number of NPS-containing drug samples submitted to DIMS increased from 22 in 2007 to 431 in 2013. From 2012 onwards, the number of NPS bought as a drug of choice exceeded those NPS appearing as adulterants in established drugs. The most frequently detected NPS in 2013 included 4-bromo-2,5-dimethoxyphenethylamine (2C-B), 4-fluoroamphetamine (4-FA), methoxetamine (MXE) and 5-(2-aminopropyl)benzofuran or 6-(2-aminopropyl)benzofuran (5-APB/6-APB). The number of NPS exposures reported to the DPIC increased from 3 exposures in 2007 to 35 in 2013. In 2013, most exposures involved 4-FA, mephedrone, MXE, 2C-B and 5-APB/6-APB. The clinical signs most frequently reported to the DPIC following NPS exposure, were neurological and psychological followed by cardiovascular symptoms.

**Conclusion:** The availability and use of NPS in the Netherlands is increasing. In addition to the presence of NPS in established drugs (as adulterants), NPS are now being bought as the drug of choice. Although little is known about the health risks of NPS, clinical effects may be severe. Therefore, monitoring trends in NPS availability and use should continue. Analytical confirmation of NPS exposure in intoxicated patients is important to evaluate the clinical effects following NPS exposure.

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## 273. Nopaine No Gain: A case of recreational ethylphenidate toxicity

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**Objective:** Ethylphenidate (EPH) is a psychostimulant which acts as a dopamine and noradrenaline reuptake inhibitor.<sup>1</sup> It is an analogue of methylphenidate that is available as a novel psychoactive substance (NPS), often sold under the street name "Nopaine".<sup>2</sup> We present a case of analytically confirmed acute toxicity associated with recreational use of ethylphenidate.

**Case report:** A 21-year-old male presented to the Emergency Department (ED) with anxiety, paranoia, agitation and visual hallucinations. He also described an episode of left-sided, retrosternal chest

pain lasting seconds and associated with palpitations and “tingling” in both hands. His symptoms started 3 hours after nasal insufflation of ethylphenidate, purchased from a UK-based Internet supplier. He reported using incremental doses over several hours to a total of 500 mg. Due to the onset of his symptoms, he self-medicated with 3 mg of etizolam, also purchased from an Internet supplier. On arrival in the ED he was restless and he had some features of stimulant drug toxicity (tachycardia 114 bpm, hypertension 184/98 mmHg and dilated (4 mm) pupils). He had a normal temperature and there was no evidence of hypertonia or clonus. ECG demonstrated sinus tachycardia with normal QT/QRS durations. A venous blood gas, full blood count and renal profile were normal; creatine kinase was slightly elevated at 290 IU/L. He was treated with three oral 5 mg doses of diazepam and admitted for observation. His symptoms settled and he was discharged 10 hours after his presentation. Paired serum and urine samples were collected with informed consent 20 hours after use. Samples were prepared by liquid/liquid extraction prior to analysis by high resolution accurate mass liquid chromatography-mass spectrometry (LC/MS). The acquired data files were then processed against in-house databases to identify the major components of the extracts. Ethylphenidate was detected in both the blood (0.24 mcg/mL) and urine (0.98 mcg/mL); the only other substances detected were diazepam (administered in ED) and etizolam (self-administered by the patient).

**Conclusion:** Ethylphenidate is not currently controlled in the UK. This is the first report with analytical confirmation of lone ethylphenidate acute toxicity. This suggests that its use is associated with stimulant-like features similar to those seen with other amphetamine type stimulants.

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## 274. Acute autonomic and psychotropic effects of LSD in healthy subjects in a placebo-controlled study

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**Objective:** Lysergic acid diethylamide (LSD) is the prototypic hallucinogen and continues to be widely used recreationally. However, no modern studies on the acute effects of LSD are available. The aim of this study was to assess the autonomic, adverse, and subjective effects of a single representative dose of LSD in healthy subjects.

**Methods:** After ethics approval, LSD (200 µg) and placebo were administered to 16 healthy subjects using a double-blind, randomized, placebo-controlled cross-over design. Outcome measures included blood pressure, heart rate, core body temperature, pupil size, adverse effects and subjective drug effects assessed up to 24 hours.

**Results:** LSD significantly increased blood pressure, heart rate, and body temperature for up to 5 hours. Pupil size was increased for up to 11 hours. LSD produced adverse effects including dry mouth, lack of appetite, dizziness and headache, which completely subsided within 72 hours. There were pronounced alterations in

waking consciousness including visual hallucinations, audio-visual synesthesia and derealization and depersonalization phenomena that lasted 12 hours. Additionally, LSD enhanced subjective well-being, happiness, closeness to others and openness. Maximal plasma concentrations of LSD (mean ± SD: 4.5 ± 1.4 ng/mL) were reached 1.7 ± 1 hours after administration and declined to 0.6 ± 0.4 and 0.2 ± 0.2 ng/mL by 12 and 24 hours, respectively. A close relationship between the plasma concentrations of LSD and the autonomic or psychotropic response of LSD over time was observed.

**Conclusion:** LSD produces marked hallucinogenic effects but also MDMA-like empathogenic mood effects. LSD also produces significant sympathomimetic stimulation. The subjective and sympathomimetic response to LSD lasts up to 12 hours and is closely associated with the LSD concentrations in plasma.

## 275. MDPV in Sweden: Checked-in, never left. Differences in market cycles of Novel Psychoactive Substances

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**Objective:** In Sweden, increasing consumption of new psychoactive substances (NPS) is a matter of concern. New substances appear rapidly, replacing NPS that have become restricted by law, forming a market cycle of “legal highs”. However MDPV, a stimulant cathinone, has continued to be a common source of enquiries to the Swedish Poisons Information Centre (SPIC), even after classification as a narcotic by the Swedish government in February 2010.<sup>1</sup> In this study we compare the incidence and temporal distribution of SPIC cases of suspected MDPV to other NPS that have undergone legal classification.

**Methods:** SPIC call data January 2010 to October 2014 was analyzed retrospectively. Cases of suspected MDPV poisoning and the five most prevalent NPS were identified. Only NPS that had undergone substance-specific narcotic classification by Swedish law by October 2014 were included.

**Results:** In total 7,049 calls were drug-related during the study period with 597 cases (8%) relating to MDPV. The next most frequent NPS were methoxetamine (n = 97), ethylphenidate (n = 91), 4-HO-Met (n = 60), 3-MMC (n = 59) and etizolam (n = 45) but these virtually disappeared shortly after their classification as narcotics. MDPV was outlawed in 2010 but most cases (> 85%) date from 2012 or later.

**Conclusion:** MDPV does not conform to the market cycle of “legal highs” seen for other NPS in our dataset. Instead of disappearing after narcotic classification, MDPV has established itself on the illegal drug market in Sweden. Its dopaminergic re-uptake inhibition may explain its high abuse liability and the high incidence of hospital admissions.<sup>2</sup> A steep rise in MDPV prevalence in this dataset is temporally associated with a Swedish Supreme Court appeal case in late 2011 that deemed all cathinones equipotent to amphetamine from a legal standpoint.<sup>3</sup> However, recreational doses of MDPV are typically many times lower than recreational doses of amphetamine.<sup>4</sup> Thus the legal precedent created incentives that may have contributed to MDPV’s persistence as an illegal substance in Sweden.

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### 276. Acute intoxications by synthetic cannabinoids in the emergency system: An Italian cases series

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**Objective:** Synthetic cannabinoids (SC) represents approximately 30% of novel psychoactive substances (NPS) signalled in recent years. This study examines the clinical manifestations of SC intoxicated patients seen in Emergency Departments (EDs) in Italy.

**Methods:** All cases evaluated by EDs network and followed by Pavia Poison Control Centre during a 2-year period (2010 to 2012) are included. Symptomatic patients with referred/suspected abuse of SC were included. Demographic data, clinical course and laboratory results (biological sample/consumed substance) were collected and evaluated.

**Results:** In total 40 patients (14-55 years) with acute SC intoxications were analyzed. Cases were collected from all over Italy. SC were mainly consumed (90%) by smoking and product(s) were bought online in 45% of cases. Advanced laboratory analysis (in order to detect the specific SC) were performed in 80% of cases (n = 32). The clinical considerations and the correlation between clinical manifestations and specific SC were performed in the subgroup of patients (21/32) positive for a SC in serum. The main clinical manifestations were tachycardia > 100 bpm (62%, n = 13), mydriasis (57%, n = 12), anxiousness/agitation (43%, n = 9), gastrointestinal symptoms (24%, n = 5), hypertension (19%, n = 4) and hallucinations (14%, n = 3); seizures were observed in 5% of cases. No lethal cases were registered. The SCs identified in serums sample were JWH-122 (n = 10), JWH-018 (n = 4), JWH-250/JWH-122 (n = 3), JWH-073 (n = 1), MAM-2201 (1 case), JWH-018/JWH-122 (n = 1) and JWH-018/JWH-122/JWH-073 (n = 1).

**Conclusion:** SC acute intoxications are an important and confirmed problem in the Italian emergency setting.<sup>1</sup> Clinical diagnosis is difficult and routine screening for tetrahydrocannabinol (THC) will be negative.<sup>2</sup> The emergency physician plays a key role in detection of acute SC intoxication in order to proceed with second level

analysis necessary to confirm the abuse.<sup>3,4</sup> According to emerging medical reports, close monitoring for functional and toxic damage is necessary.

**Acknowledgement:** Study supported by the Department for Antidrug Policies, Presidency of the Italian Council of Ministers.

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### 277. Bad trip due to 25I-NBOMe: A case report from the EU Project SPICE II Plus

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**Objective:** A new group of novel psychoactive substance, the N-(2-methoxybenzyl) derivatives of substituted phenethylamines of the “2C series” (Alexander Shulgin, PiHKAL), also called “NBOMes”, has recently emerged on the drug market. Among this group, 25I-NBOMe, the N-(2-methoxybenzyl) derivative of 2C-I, has previously been implicated in clinical intoxications and fatalities. 25I-NBOMe is an extremely potent drug with stimulant and hallucinogenic properties. We present a case with analytically confirmed 25I-NBOMe intoxication from the prospective study within the EU project SPICE II Plus.

**Case report:** A 42-year-old man took one sip of a pediatric analgesic syrup stored in the family’s refrigerator because he had a severe headache. Thirty minutes later he complained of restlessness. On arrival in the emergency department vital signs were unremarkable (blood pressure 120/80 mmHg, heart rate 96/min). Examination revealed excessively dilated pupils, strong sweating, disorientation to time and to person, and agitation. At that time the patient’s son reported that he had refilled the pediatric analgesic liquid with a self-made ethanolic solution of 25I-NBOMe (supposed 25I-NBOMe concentration 320 µg/ml). When the patient’s condition severely deteriorated within a short time, he was transferred to the intensive care unit. There he presented with severe agitation, auditory and somatic hallucinations, and complex visual hallucinations (particularly hallucinating serious road crashes). The patient was shouting and crying. 25I-NBOMe (2.56 ng/mL) and 2C-I (289 ng/mL) were found (LC-ESI-MS/MS) in blood serum samples obtained 1 hour after ingestion. The blood ethanol concentration was 0.04 g/L. The presumed analgesic liquid contained an unexpected



high concentration of 2,800 µg/ml 25I-NBOMe. Therapy consisted of supportive care, administration of intravenous fluids and benzodiazepines. After 6 hours the symptoms resolved, and the patient was discharged the next day without further complications.

**Conclusion:** This is a unique case of an analytically confirmed, accidental ingestion of 25I-NBOMe in a drug naïve adult. The pronounced symptoms resolved within 6 hours in accordance with former reports.<sup>1</sup> The relatively high concentration of 2C-I as compared to the concentration of 25I-NBOMe in the sample taken shortly after drug intake indicates a fast metabolic breakdown of 25I-NBOMe, probably due to enzymatic N-desalkylation. The clinical effects might be caused not only by 25I-NBOMe, but also, at least in part, by 2C-I. The case report will help to better understand clinical effects and toxicokinetics of 25I-NBOMe.

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## 278. Emergency department admissions due to disulfiram-ethanol interaction

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**Objective:** Disulfiram is used in the treatment of alcohol addiction. Concomitant intake of ethanol results in a disulfiram-ethanol reaction (DER) with symptoms including flushing, hypotension, nausea, tachycardia, headache, vomiting and cardiovascular collapse besides many other symptoms described in the literature. These may lead to hospital admission and the aim of our study was to characterize cases admitted to our department.

**Methods:** We retrospectively retrieved the electronic clinical files containing the key word disulfiram of all patients admitted from 4 November 2011 to 9 September 2014. Patients were included when they displayed symptoms possibly related to a DER and tested positive for ethanol.

**Case series:** Thirty one patients fulfilled the criteria and the diagnosis of DER was made by the attending physician in 26 patients albeit with some delay in 3 patients. In the 5 remaining patients a DER as defined by the presence of at least one symptom described in the literature may with hindsight have been overlooked. The median age of all 31 patients was 48 years (IQR 41–54) and 19 were male and 12 female. Median plasma ethanol concentration was 1.50 g/L (IQR 0.90–2.35). Hypotension defined as a systolic blood pressure lower than 90 mmHg or a diastolic blood pressure lower than 60 mmHg was most often reported and occurred in 90% of the cases. Median minimum systolic and diastolic blood pressures on admission were 86 mmHg (IQR 75–95) and 52 mmHg, respectively (IQR 41–59). Other clinical symptoms reported were flushing (61%), tachycardia (58%), confusion (39%), loss of consciousness (32%), nausea (32%), vomiting (16%), palpitations (16%), dyspnea (16%), chest pain (10%), headache (10%) and

tremor (10%). The median maximum heart rate during the stay in the emergency department was 105 bpm (IQR 87–118). Plasma lactate was available for 10 out of the 31 patients and varied between 12.4 and 82.0 mg/dL (normal range < 11.3 mg/dL).

**Conclusion:** Admission to the emergency department because of a DER is not rare and the incidence may be underestimated in our study because disulfiram use may not have been mentioned in some cases. DER is frequently accompanied by hypotension which may be a serious side effect. Furthermore our study illustrates that the diagnosis of possible DER symptoms is sometimes initially overlooked and suggests that in some cases it may even be missed. Therefore emergency physicians should keep a DER in mind to ensure proper recognition and treatment.

## 279. Abstract withdrawn

## 280. Laboratory confirmation of recreational drugs in Oslo, Norway

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**Objective:** The number of recreational drug overdoses is high, and novel psychoactive substance availability is steadily increasing. However, there are limited data with verified analyses from patients presenting in a clinical setting. In order to evaluate the impact of novel psychoactive substances (NPS) on recreational drug overdoses in Oslo, we analysed a selection of samples from overdose patients treated at the Oslo Accident and Emergency Outpatient Clinic (OAEOC) and Oslo University Hospital (OUH).

**Methods:** All data were collected from the OAEOC (saliva) or OUH (blood samples) from patients diagnosed with recreational drug overdoses. All samples were collected during 2014. Whole blood was screened using ultrahigh performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) for classical drugs of abuse<sup>1</sup>, modified to include designer benzodiazepines. Synthetic cannabinoids and a wide range of other novel psychoactive substances (cathinones, tryptamines, phenethylamines, designer opiates) were screened using the same technique. The saliva drug screening covered the same compounds using published methods for drugs of abuse and synthetic cannabinoids<sup>2</sup> and a similar method for NPS as for whole blood.

**Results:** A total of 37 blood samples (hospitalized patients) and 55 saliva samples (outpatients) were collected. Among the hospitalized patients, the most commonly found substances were amphetamine (17/37; 46%), clonazepam (17/37; 46%), methamphetamine (12/37; 32%), and tetrahydrocannabinol (THC) (8/37; 22%). No NPS was found in these blood samples. Among the

outpatients, the most commonly found substances were morphine (41/55; 75%), amphetamine (40/55; 73%), clonazepam (39/55; 71%) and its metabolite 7-aminoclonazepam (40/55; 73%), codeine (32/55; 58%) and methamphetamine (31/55; 56%). The following NPS were detected: 4-methylamphetamine (3/55; 6%), dimethyl-tryptamine (DMT) (2/55; 4%), methylone (1/55; 2%) and NN-dimethyl-MDA (1/55; 2%).

**Conclusion:** Although the availability of NPS is increasing and the number of case reports involving NPS is on the rise, the vast majority of the patients being treated at the OAEOC, or admitted to the hospital have taken classic drugs of abuse. Although the present material is limited in size and in time of collection, our data shows a dominance of amphetamine and methamphetamine among the stimulants, and opiates and benzodiazepines (especially clonazepam) among the sedatives.

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### 281. Acute poisoning by DOC (2,5-dimethoxy-4-chloroamphetamine): Report of 6 cases presenting together at the Emergency Department

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**Objective:** To report a cluster of 6 cases of DOC abuse that attended simultaneously at the Emergency Department (ED) and describe the characteristics of their clinical picture, treatment and evolution. This designer drug is rare in Spain and the presented cases show the special features of its effects, which are much more severe than those produced by the more common forms of amphetamines. This designer drug had its first alert in December 2007<sup>1</sup>, and lately a lethal case has been reported.<sup>2</sup>

**Case series:** Six Caucasian males, aged between 23 and 27 years, habitual drugs abusers on the weekends, arrived together in their own vehicle to the Emergency Department 2 hours after consuming a different substance to their usual abused drug. They decided to seek medical advice due to the fact that one of them had abnormal symptoms, including delirium, hallucinations and psychomotor agitation. Some minutes after arrival all of them developed similar and more severe symptoms with severe agitation and extreme aggressive behavior (n = 6), delirium (n = 6), hallucinations (n = 6), mydriasis (n = 6), tachycardia (n = 6) with a heart rate between 120 and 160 bpm and fever (n = 4) with a temperature between 38 and 39°C. They required mechanical restraint and high intravenous diazepam doses. Four of them developed rhabdomyolysis (CK 4,100-14,174) in the following hours and two had to be

admitted to the ICU to administer more intensive sedative drugs. No renal or other organ failure followed and all of them were discharged after 12 to 72 hours. EMIT urine screening showed the presence of amphetamine (n = 6), cannabis (n = 3) and opioids (n = 1). Urine analysis by gas chromatography/mass spectrometry detected amphetamine and 2,5-dimethoxy-4-chloroamphetamine in all cases.

**Conclusion:** These cases show the risk of abuse of the so called smart drugs, whose exact chemical composition is unknown by users and even by dealers and whose clinical effects cannot be foreseen.

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### 282. Acute health problems due to recreational drug use in patients presenting to an urban emergency department in Switzerland

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**Objective:** The frequency and clinical features associated with novel psychoactive substances are unclear. We describe acute medical problems due to recreational drug use in patients presenting to an emergency department in Switzerland.

**Methods:** The study was conducted at the University Hospital of Basel, Switzerland, between October 2013 and September 2014 and within the Euro-DEN project. All cases presenting with acute toxicity due to self-reported acute recreational drug use or with symptoms/signs consistent with acute toxicity were included. Cases of isolated ethanol intoxication were excluded. Drug tests were performed using immunoassays and liquid chromatography-tandem mass spectrometry (LC-MS/MS) to detect also novel substances.

**Results:** During one year there were 47,767 emergency department attendances of which 216 were directly related to acute toxicity with drugs of abuse. The mean patient age was 31 years and 69% were male. Importantly, analytical drug confirmation was available in most (n = 180) cases. Alcohol co-use was reported in 48% of the cases. Use of more than one recreational drug was reported in 28% of the cases and in 44% more than one substance was analytically confirmed. Most presentations were related to cocaine (36%), cannabis (31%), MDMA (9%), other amphetamines (7%), benzodiazepines (7%), heroin (7%), and LSD (5%). The most common analytically detected substances were cannabis (37%), cocaine (33%), benzodiazepines (21%), opioids excluding methadone and heroin (15%), amphetamines including MDMA (13%), and methadone (11%). There were only two cases of novel substances (one self-reported 2C-B, one analytically-detected pentylone). The most

frequent symptoms were tachycardia (31%), anxiety (27%), nausea or vomiting (23%) and agitation (22%). Severe complications included one fatality due to endocarditis, two acute myocardial infarctions, psychosis (n = 10) and seizures (n = 10). Most patients (68%) were discharged home, 8% were admitted to intensive care, and 9% were referred to psychiatric care.

**Conclusion:** Most medical problems related to illicit drugs concerned cocaine and cannabis and mainly included sympathomimetic toxicity and/or psychiatric disorders. Cases with acute toxicity linked to novel psychoactive substances appear to be uncommon in Switzerland.

### 283. Novel psychoactive substances: Findings in a regional toxicology center in 2014

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**Objective:** Many novel psychoactive substances (NPS) are easily available today. Product names and active components seem to change rapidly. Declaration of ingredients is often missing or misleading, e.g. some labels indicate the product does not contain cannabinoids although artwork and marketing routes suggests it does. For poisons centers and emergency medicine services it is important to know what drugs are in use in the area of their activity.

**Methods:** Drug samples were requested in all cases for suspected NPS poisoning reported to two poisons centers in Northern and Eastern Germany between January and October 2014. Untargeted chromatographic analysis (GC/MS) was performed for all samples.

**Results:** In total 17 samples were collected containing 26 active substances including cannabinoids, stimulants, medical drugs, others active substances, impurities and precursors. Adulterated herbal and cannabis products, approved pharmaceuticals, not approved pharmaceuticals with limited toxicity dataset and recently synthesised substances without any toxicological dataset as well as chemical precursors and impurities were identified (Table 1). In 16 products no or wrong ingredients were indicated on the label. The purity levels of constituents varied considerably.

**Conclusion:** Standard chromatographic toxicological analysis was able to identify active components in almost all products.

An unexpected wide variety of NPS are available for drug users in Germany, including agents reported only very recently in the literature. Product labels are often misleading. The legal status of the agents often remains unclear.

### 284. Diffuse alveolar hemorrhage following synthetic cannabinoid abuse

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**Objective:** Toxicity from synthetic cannabinoid use is increasing, but pulmonary toxicity is rare. We report a case of diffuse alveolar hemorrhage following abuse of the synthetic cannabinoid, K2.

**Case report:** A 32-year-old male with a history of asthma presented to the hospital complaining of cough and dyspnea for 5 days, with myalgias, fever, and blood-tinged sputum. He used K2, a synthetic cannabinoid, one day prior. Vital signs were pulse 98/min, BP 94/48 mmHg, respirations 20/min, temperature 37.7°C; and oxygen saturation 92% on room air. Exam revealed an ill-appearing male in respiratory distress with bilateral lung crackles. Chest radiography showed diffuse fluffy infiltrates. His respiratory status rapidly declined requiring emergency intubation. During intubation, the physician noted markedly bloody sputum. Bronchoscopy confirmed diffuse alveolar hemorrhage. The patient had a protracted intensive care course, and extensive testing failed to reveal any infectious, autoimmune or malignant causes. All cultures from peripheral blood and bronchoalveolar lavage were negative. The patient tested negative for HIV, Hepatitis B or C. Rheumatologic and hematologic workup was unremarkable including a negative GBM Ab IgG, ANCA, Anti-Smith, SSA, SSB, ANA, dsDNA Ab IgG, and Von Willebrand factor deficiency.

**Conclusion:** Synthetic cannabinoids have become increasingly popular drugs of abuse. Although they are agonists at cannabinoid receptors, they are structurally dissimilar to  $\Delta$ -tetrahydrocannabinol and produce more sympathomimetic effects.<sup>1</sup> Reports of severe toxicity from synthetic cannabinoids include cerebral ischemia, seizures, and psychosis.<sup>2</sup> There have only been two reported cases of pulmonary hemorrhage with chronic abuse.<sup>3</sup> As severe toxicity from synthetic cannabinoid use becomes more common, physicians should be aware of the varied adverse effects, including pulmonary toxicity.

**Table 1.** New drugs detected in drug samples (cannabis, amphetamines, cocaine and therapeutic opiates are not listed).

Cannabinoids	Stimulants	Therapeutic drugs	Other drugs
AB-001, AB-CHMINACA, AB-FUBINACA, AB-PINACA, XLR-11, 5F-PB22, AM-2201, QUCHIC (BB-22)	1-phenyl-2-(1-pyrrolidinyl)-1-pentanone ( $\alpha$ -PVP) Methylenedioxypropylvalerone (MDPV), 3',4'-Methylenedioxy- $\alpha$ -pyrrolidinobutylphenone (MD-PBP), 3',4'-Methylenedioxy- $\alpha$ -pyrrolidinopropylphenone (MDPPP), $\alpha$ -Pyrrolidinopropylphenone ( $\alpha$ -PPP)	Benzodiazepines (flubromazepam, diclazepam) Anaesthetics (diphenidine) (1-(1,2-diphenylethyl)piperidine), 2-MeO-Diphenidine (MXP), 1-(1-phenylcyclohexyl)piperidine (Phencyclidine), PVP), Opioids (AH-7921) Others (sildenafil, phenacetam)	Brolamfetamine, Ethylone, 4-Brom-2,5-dimethoxyphenylethylamine (2C-B), Impurities/degradation products/chemical precursors (8-Hydroxyquinoline, 2,5-Dimethoxy-4-bromacetophenone), 38 further ingredients



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### 285. Psychosis associated with acute poisoning by recreational drugs and novel psychoactive substances: A European case series from the Euro-DEN project

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**Objective:** Acute recreational drug and novel psychoactive substance (NPS) toxicity can be associated with psychosis. However, there are limited data available on how common this is and which drugs are most frequently implicated. We describe a case series of acute recreational drug toxicity associated with psychosis, and estimate the case psychosis rate for different recreational drugs.

**Methods:** The European Drug Emergencies Network (Euro-DEN) collects data on presentations to Emergency Departments with acute recreational drug and NPS toxicity at 14 centres in 10 countries.<sup>1</sup> Euro-DEN data from October 2013 to June 2014 was searched, and cases with psychosis were included. Additional data extracted included: age and gender, the drugs used, associated clinical features (hallucinations, agitation, anxiety) and outcome (hospital admission/discharge from ED). The case psychosis rate for a drug was calculated as the proportion of cases with psychosis amongst all cases in the Euro-DEN dataset where the drug was taken.

**Results:** Psychosis was present in 231 (6%) of the 3,573 cases collected within the study period; the median age of these cases was 27 years (range 17–78) and 188 (81%) were male. The most frequent recreational drugs reported in those with psychosis were amphetamine in 62 (27%) cases, cannabis in 56 (24%), cocaine in 40 (17%), heroin in 18 (8%), GHB/GBL in 17 (7%), MDMA in 14 (6%), LSD in 12 (5%), methamphetamine in 11 (5%) and mephedrone in 8 (3%). More than one drug was taken in 119 (52%) cases, including 65 (28%) cases in which ethanol was co-ingested. Additional clinical features were: agitation in 150 (65%), hallucinations in 99 (43%) and anxiety in 92 (40%) cases. Six (3%) cases were admitted to critical care, 76 (33%) were admitted to a psychiatric ward, 92 (40%) were medically discharged from the ED, and 31 (13%) self-discharged; one patient died in hospital. The overall case psychosis rate for the 3,573 cases was 6%. The

highest case psychosis rates were found for mushrooms 31%, LSD 20%, MDPV 19%, methylphenidate 18%, synthetic cannabinoids 17%, amphetamine 15%, methamphetamine 10%, cannabis 10%, dextromethorphan 10%, Z drug hypnotics 7%, cocaine 6%, mephedrone 5% and MDMA 5%. None of the 63 cases involving methedrone were psychotic.

**Conclusion:** Psychosis is a relatively uncommon feature of acute recreational drug and NPS toxicity overall, but the case psychosis rate varies considerably between drugs.

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### 286. When a law for terrorism risk provides help in the discovery of new psychoactive substances (NPS)

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**Objective:** To study if a law intended for the fight against terrorism can provide information on new psychoactive substances (NPS).

**Methods:** In 2001, letters containing white powder with anthrax were sent to American authorities resulting in 22 victims and 7 casualties. In France, several thousand suspect packages were tested with no toxicological substances found. A French task force against terrorism was created, which included Poison Centers. If a suspect letter or packet is discovered the fire brigade, CBRN (chemical, biological, radioactive, nuclear) Team, Securite Civile and Police Department, are initially involved. Information including the sender and receiver, aspect, smell and color are immediately sent to the French Security Authority (the Cellule Nationale Gestion, CNC) under the law (Circulaire 750-2011 February 18) for a risk evaluation. CNC can also request Poison Centers (PC) to undertake a risk evaluation, if required. The duty of the PC is to collect clinical symptoms, and to give advice on decontamination, use of antidotes and more, if actual exposure in people is suspected.

**Results:** In 2010, an alert in our Toxicovigilance Center occurred after a white powder was found in a local post office following accidental opening of packet; a Drugwipe test identified it as amphetamine and 2C-E (a psychedelic phenethylamine). In the same week, a clinical case of 2C-E was reported with a blood concentration of 9.1 mcg/L and 771 mcg/L in urine.<sup>1</sup> The sending of illegal chemical products in the post is occurring despite the risks of breaking the law.<sup>2</sup> In 2013 we reported seven NPS sent by post, and reported a case.<sup>2</sup> The drugs involved were 5F-P22, diclazepam, MTTA (MTA), MEOP (MEXP), 5 IAI, AMT (MPA) and 3,4-CTMP. They were reported to Office Français Drogues Toxicomanies (OFDT) and the EMCDDA. In 2013, 3,4-CTMP was unknown in France and Europe. In 2013, EMCDDA collected 81 NPS and found 651 European websites discussing them. Ethnological work with I-TREND (Internet Tools Research New Drugs)

has provided information from Deep-Web and The Onion Ring (TOR).

**Conclusion:** Discovery of unidentified powders sent by post, in the application of this law, can provide information on NPS.

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### 287. Severe poisoning after nasally administered mixture of NBOME compounds: A case report

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**Objective:** Novel psychoactive substances (NPS) recently appeared on the recreational drug market; they are used in various forms and are still poorly evaluated in humans. Among them, NBOME compounds are usually presented as small blotters impregnated for sublingual or buccal administration.<sup>1</sup> We describe a case of severe intoxication by a liquid mixture containing three NBOME compounds consumed nasally.

**Case report:** A 29-year-old patient, with a history of schizophrenia (treatment voluntarily interrupted) and addiction to cannabis (occasional) and LSD (weaned), experienced acute unconsciousness about one hour after a witnessed instillation of a drop of pink liquid in the nose. Other clinical findings were partial seizure with secondary extended generalization, bilateral and reactive mydriasis, tachycardia (120 bpm), hypertension (225/70 mmHg), hyperthermia (39°C) and profuse sweating, suggestive of serotonin syndrome. In the intensive care unit, this neurological failure, quiet coma interspersed with tonic movements, required invasive ventilation for 24 hours. Biological examination evidenced elevated creatine kinase (CK 25800 U/L) without renal impairment and hyperlactatemia (7.9 mmol/L). Urine drug analysis was negative with only LSD at the limit of quantification. Additionally, magnetic resonance imaging (MRI) showed bilateral and symmetrical lesions in the basal ganglia. A month later, the patient still had persistent memory impairment and significant abnormalities in executive functions, and an encephalopathy most likely of toxic origin. A sample of the fluid he had taken, advertised as a product related to mescaline or LSD, was recovered for analysis by high resolution mass spectrometry and revealed a mixture of three compounds, 25I-NBOME, 25C-NBOME and 25H-NBOME.

**Conclusion:** NPS are constantly evolving, both in their nature and appearance. Taking a drug similar to a known and familiar product by an alternative route can lead to severe and unexpected

clinical findings. In addition, high quality analytical techniques are required to ensure detection of the causal substances. This case reminds us how acute poisoning with NBOME derivatives (active from sub-milligram doses) may be dangerous and carry the risk of long-term sequelae.

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### 288. Severe agitation due to novel synthetic cannabinoid abuse treated with prehospital ketamine

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**Objective:** In July 2013, our paramedic system instituted a protocol for prehospital ketamine (5 mg/kg IM) for treatment of excited delirium syndrome and severe agitation resistant to verbal de-escalation or other sedative agents.<sup>1,2,3</sup> Shortly after this, a novel synthetic cannabinoid known as "black mamba" resulted in a large number of cases of severe agitation. ADB-PINACA was identified by spectrophotometry in products seized from affected patients.<sup>4</sup> We report the clinical course of a unique series of patients with ADB-PINACA exposure treated with prehospital ketamine for severe agitation.

**Case series:** Prehospital documentation, emergency department records, and inpatient hospital records were reviewed for all patients receiving prehospital ketamine from July 2013 to November 2013 within a single urban emergency medical services system. Case inclusion criteria were all patients receiving prehospital ketamine per protocol with use of synthetic cannabinoids documented in the paramedic trip report or hospital records. During the study period, 22 patients received prehospital ketamine. Eight patients (36%) had documented exposure to synthetic cannabinoids. Patients using synthetic cannabinoids had a median age of 26 years (range 21-31), and all were male. All were tachycardic (mean heart rate 157) and hypertensive (mean systolic blood pressure 180) prior to hospital arrival. Five were hyperthermic, and five were acidotic. Five later developed hypotension, although only one required vasopressor support. Three patients required intubation, however all patients were discharged within 24 hours of admission. There were no cases of laryngospasm, emergence phenomena or death.

**Conclusion:** Severe agitation due to ADB-PINACA exposure requiring treatment with prehospital ketamine was associated with hyperthermia, tachycardia, and hypertension. Delayed hypotension was seen in several cases. While several patients

required intubation, all patients did well with supportive care. Ketamine safely and effectively provided sedation allowing transportation from the field to the hospital where patients received definitive care in a resource-rich environment.

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### 289. Therapeutic difficulties with a symptom-triggered regimen for alcohol withdrawal syndrome

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**Objective:** Alcohol-related hospital admissions are common and these admissions are often complicated by Alcohol Withdrawal Syndrome (AWS). The aim of this study was to determine compliance with local guidelines for AWS management using a symptom-triggered regime and therapeutic difficulties encountered.

**Methods:** Data were collected on adherence to local guidelines for AWS management on medical patients admitted over 8 weeks. The guideline involves administration of chlordiazepoxide (25-50 mg) every 2 hours, if required, for the first 24 hours based on CIWA-Ar (Clinical Institute Withdrawal Assessment of Alcohol Scale-Revised) scoring. Total dose of chlordiazepoxide required in the first 24 hours is used to determine a reducing Fixed-Dose Programme (FDP) over the next 5-7 days. Data collected were number of CIWA-Ar scores recorded and mean time between scores taken in the first 24 hours, chlordiazepoxide dose required in the first 24 hours and time to FDP.

**Results:** There were 62 admissions in 58 patients; 86% were male and the mean  $\pm$  SD age was  $51 \pm 12$  years. Of these 34 (54%) were admitted primarily for AWS; AWS was a secondary diagnosis in 28 (46%). The mean time between CIWA-Ar score during the first 24 hours was  $5.2 \pm 2.8$  (range: 2-16; gold-standard 2) hours. The mean number of CIWA-Ar scores carried out in the first 24 hours (gold-standard 12) was  $7.7 \pm 3.6$  (range 0-16). The median (IQR, range) chlordiazepoxide dose given in the first 24 hours (maximum dose recommended 300 mg) was 75 (0-175, 0-500) mg. Three (5%) patients required  $> 300$  mg chlordiazepoxide, there were time delays between CIW-Ar in the first 24 hours in all of these patients (3, 3.5 and 12 hours). Overall, 40 (65%) patients required chlordiazepoxide in the first 24 hours and should have converted to the FDP, but it was only prescribed to 27 (44%); 6 (10%) self-

discharged before conversion, 2 (3.2%) were discharged 24 hours after admission and 5 (8%) were discharged  $> 24$  hours later but had required  $\leq 100$  mg. The mean  $\pm$  SD (range) time to initiation of FDP in these 27 cases was  $32.5 \pm 12$  (17-72) hours.

**Conclusion:** Symptom-triggered AWS regimens initiate treatment based on clinical severity and are tailored to individual need. However this relies on accurate, timely assessment of patients. In this study erratic dosing and early treatment delays with CIWA-Ar were observed which risk clinical deterioration. The variability in successfully following a symptom-triggered regimen may outweigh its benefits compared to fixed-dose programmes alone; however more robust clinical data are required to investigate this.

### 290. Respiratory depression and ventilatory support in synthetic cannabinoid exposures: Report from the ToxIC Registry

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**Objective:** Synthetic cannabinoid (SC) exposures often present to the Emergency Department (ED) with clinical effects which differ significantly from marijuana. These include seizures, psychosis and myocardial ischemia. In our experience we have seen cases of patients with CNS and respiratory depression requiring ventilator support after isolated SC exposure. We sought to examine the prevalence of this phenomenon in patients with SC exposure reported to the ToxIC registry.

**Methods:** All cases entered into ToxIC from 2011 to October 2014 which were selected as "Bath Salt, Synthetic Cannabinoid, other Designer Drug, or Agent referred to by a Street Name" were reviewed to identify SC exposures only. Other "designer drugs" were excluded unless co-exposures with SC; unknown exposures were excluded. Data was reviewed to evaluate the number of cases with "respiratory depression" as clinical effect and "Intubated/ventilatory support" as treatment.

**Results:** In total there were 108 cases, average age 27.1 years (SD 11.6, range 14-59), 86% male. Of these, 6 patients (5%) had respiratory depression, and 10 (9%) underwent intubation and ventilatory support. However, 8/10 of these had delirium, toxic psychosis or seizure reported as a clinical effect; only 2 had respiratory/CNS depression listed as the sole clinical effect which might require intubation.

**Conclusion:** Respiratory depression requiring intubation was uncommon in this cohort with isolated SC exposures. However, these data suggest that this effect, while not typical of traditional marijuana, can be seen after SC use. Presumably due to the long turnaround time and limited availability of testing for these compounds, the cases in this database are not confirmed SC exposures. However, the ToxIC registry includes only cases seen by a medical toxicologist, which should increase accuracy of reporting to a considerable extent. In this cohort, respiratory depression was an uncommon but reported effect after synthetic cannabinoid exposure. Intubation with ventilator support was also performed in several patients, although the majority of these were not for respiratory



depression. Clinicians evaluating these patients should be aware of this possibility.

## 291. Spice or marijuana: What's the difference?

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**Objective:** Synthetic cannabinoid receptor agonists (SCRAs), also known colloquially as K2 or Spice, are abusable designer drugs marketed as alternatives to marijuana.<sup>1</sup> Although these drugs are perceived as clinically similar, direct comparisons of toxicity are uncommon. We compared demographic, clinical and outcome case data of SCRAs and marijuana from a single poison control center (PCC) to determine if there are significant differences in clinical effects between SCRAs and marijuana.

**Methods:** We performed a retrospective analysis of all PCC cases coded as "synthetic cannabinoids" and "marijuana" from 2010 to 2014 at a single center. We chose this time frame because SCRA cases were first reported in 2010. All clinical effects were extracted from the electronic database and compared using Fisher's Exact Test.

**Results:** During the study period, there were 372 reported exposures to SCRAs and 915 marijuana exposures. There were no significant differences between SCRAs and marijuana with respect to tachycardia, hypertension, hypotension, agitation, hallucinations and drowsiness. However, when comparing SCRAs and marijuana, there were significant differences in the proportion of patients with chest pain, nausea, seizures, dyspnea and diaphoresis, all of which were all higher in SCRA patients ( $p < 0.05$  using Fisher Exact Test).

**Conclusion:** Despite theoretical similarities based on cannabinoid receptor binding, significant clinical differences appear to exist between SCRAs and marijuana based on PCC data. Limitations of the data include potential reporting bias and lack of positive identification of the implicated toxins in most cases. Further research to determine etiologies for these clinical disparities is necessary.

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## 292. Calls to the Finnish Poison Information Centre concerning drugs of abuse 2010–2013

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**Objective:** To investigate patterns of drugs abused in overdoses leading to calls to the Finnish Poison Information Centre (FPIC).

**Methods:** Calls related to acute poisoning of a drug of abuse were retrieved from the FPIC database and analysed.

**Results:** FPIC receives approximately 40,000 calls/year from health care professionals and the public. The total number of calls concerning drugs of abuse and poisonings for 2010–2013 was 633.

The number of calls related to drugs of abuse was 169 (0.5%) out of 31,098 calls concerning acute poisonings in 2010, 144 (0.45%) out of 31,682 in 2011, 147 (0.39%) out of 38,136 in 2012, and 174 (0.58%) out of 29,855 in 2013. Median age of the patients was 24 years (range 4 months to 85 years; age known in 64.5%), 55.6% were 20–29 years old. Symptoms occurred in 89% of the cases and 76% were advised to see a doctor. Amphetamine ( $n = 139$ ) and hallucinogenic amphetamines ( $n = 76$ ) accounted for 33.9% of the calls, gamma hydroxybutyric acid (GHB) and related agents for 11.8% ( $n = 75$ ), MDPV (3, 4-methylenedioxypropylone) for 9.7% ( $n = 62$ ), cannabis for 9% ( $n = 57$ ), LSD for 4.1% ( $n = 26$ ) and opiates (excluding medicinal products) for 1.2% ( $n = 8$ ). A proportion (17.3%,  $n = 110$ ) consisted of 53 different substances mentioned maximally 8 times/year. In 12.6% ( $n = 80$ ) the drug was unknown. The amphetamines were relatively constant over the years (40–64/year). MDPV peaked during the first months of 2010 but the number of calls dropped considerably after MDPV was nationally defined as a drug in June 2010.

**Conclusion:** Amphetamines have traditionally been the leading group of drugs abused in Finland. Opioid abuse is almost totally of medicinal products, and calls related to opioid abuse could not be differentiated from other calls related to these. Amphetamines still dominate in Finland. Designer drug "epidemics", such as that observed with MDPV, occur occasionally. Also of note is that enquiries related to a great variety of substances, most likely predominantly bought from Internet.

## 293. Presenting symptoms in GHB poisoned patients are independent of concomitant drugs

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**Objective:** Gamma hydroxybutyrate (GHB) causes reduced consciousness and is a frequent reason for Emergency Department (ED) admission. Concomitant drug use is concerning, since it was shown that symptoms are more severe in patients who have taken GHB in combination with other drugs.<sup>1</sup> Only agitation was shown to be more frequent in patients who co-ingested alcohol and unexpectedly, more pronounced coma was induced by GHB and cocaine/amphetamines in combination.<sup>2</sup> The aim of this study was to evaluate presenting symptoms in patients admitted due to GHB ingestion in combination with the other drugs.

**Methods:** A retrospective study of all GHB-poisoned patients admitted at the ED of the University Medical Centre Ljubljana. GHB poisoning was defined as reported GHB use and/or GHB confirmation by liquid chromatography-mass spectrometry (LC-MS). Age, sex, consciousness level, temperature, blood pressure, heart rate, respiratory rate, laboratory data and urine toxicology findings were recorded. GHB-poisoned patients were divided into six groups: GHB, GHB plus ethanol, GHB plus cocaine/amphetamine, GHB plus opioids, GHB plus cannabinoids and GHB plus multiple drugs. Comparison was made using the chi-square test.

**Results:** A total of 73 GHB-poisoned patients (mean age 27 years, 82% men) were included. Of these 37% of patients consumed only GHB; 27% concomitantly consumed ethanol, 8% amphetamines/cocaine, 6% cannabinoids, 3% opioids and 19% consumed multiple concomitant drugs. The cause of admission to the ED was reduced

consciousness in 93% of patients and aggression in 6% of patients. In addition 18% of patients had respiratory insufficiency on admission. Consciousness level ( $p = 0.48$ ), hypothermia ( $p = 0.29$ ), hypotension ( $p = 0.29$ ), bradycardia ( $p = 0.40$ ), respiratory insufficiency ( $p = 0.51$ ), vomiting ( $p = 0.76$ ), seizures ( $p = 0.10$ ) and agitation ( $p = 0.88$ ) did not differ between observed groups regarding concomitant drug consumption.

**Conclusion:** GHB-poisoned patients are admitted due to reduced consciousness level. The presenting symptoms in GHB-poisoned patients do not depend on concomitantly consumed drugs. It seems that symptoms of GHB overdose prevail over the other drugs. The other reason could be that these drugs are generally not taken at the same time as GHB and urine toxicology tests might be positive long after the physiological effects of these drugs subside.

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### 294. Stress-induced cardiomyopathy and delayed fatal dysrhythmia after huffing 1,1-difluoroethane

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**Objective:** We report a case of stress-induced cardiomyopathy and delayed fatal dysrhythmia after huffing 1,1-difluoroethane (DFE) from compressed air dusters. Halogenated hydrocarbons abuse (HHA) is associated with sudden cardiac death, which characteristically occurs after physical activity or a stressful event during or immediately after exposure. In such cases, death is attributed to acute cardiac dysrhythmia.

**Case report:** A 25-year-old woman with a history of HHA presented to a healthcare facility after being found unresponsive surrounded by several cans of compressed air duster. Upon paramedic arrival, she was asymptomatic. Initial laboratory studies were notable for a troponin of 21.33 ng/mL and potassium of 3.0 mEq/L. Initial electrocardiogram (ECG) showed no ectopy or ischemia and a normal QT interval. On hospital day two, the troponin was 23.62 ng/mL and echocardiogram demonstrated apical and anterior wall hypokinesis with an ejection fraction (EF) of 35-40%. Cardiac catheterization was performed 24 hours after presentation due to the elevated troponin and abnormal echocardiogram. Coronary angiography was normal. During left ventriculogram, the patient developed monomorphic ventricular tachycardia followed by ventricular fibrillation (VF). She received four defibrillations and 150 mg of amiodarone. She was admitted to the ICU with a normal neurologic exam. Repeat echocardiogram

after catheterization revealed an ejection fraction (EF) of 20-25% and abnormalities consistent with stress-induced cardiomyopathy. Repeat ECG revealed a QTc of 662 ms and anterolateral T-wave inversions. Thirty-two hours after presentation she spontaneously developed ventricular fibrillation and was pronounced dead after 45 minutes of failed resuscitation. She did not receive beta-adrenergic blockade during hospitalization. Pre-mortem blood confirmed the presence of DFE.

**Conclusion:** HHA is associated with sudden cardiac death. Our patient presented with stress-induced cardiomyopathy in the absence of atherosclerosis and died, in a delayed fashion, due to fatal cardiac dysrhythmia 32 hours after presentation. Death from HHA is thought to be due to myocardial sensitization. Dysrhythmia and death most commonly occur acutely. This case is unique as it illustrates delayed cardiac death with associated stress-induced cardiomyopathy in the setting of HHA. Cardiac instrumentation may predispose patients to cardiac dysrhythmia; this should be considered if cardiac catheterization is undertaken in patients with recent HHA and low risk of coronary artery disease. Clinicians evaluating HHA individuals should perform a screening ECG and serial troponins; any abnormality warrants admission with empiric beta-blockade.

### 295. Levamisole: A high-risk cocaine adulterant

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**Objective:** Levamisole is an antiparasitic which has been marketed since 1966; its use in humans was banned in the 1980s due to the risk of agranulocytosis and necrotizing vasculitis. It is still used in veterinary medicine, primarily as a nematicide. Since 2008, cocaine adulterated with levamisole began to be detected. The organoleptic characteristics of levamisole are similar to those of cocaine; it is cheap, widely available due to veterinary use, and has psychostimulant properties. The aim of this study was to describe the characteristics of consumers of cocaine adulterated with levamisole treated in the emergency department of our hospital.

**Case series:** Between May 2013 and July 2014, six patients were treated in the emergency department for acute adverse reactions after the consumption of, among other substances, cocaine adulterated with levamisole. Cocaine or its metabolites and levamisole were identified using gas chromatography-mass spectrometry (GC-MS). The six patients were all male aged between 26 and 41 years. In the first case, the patient presented with leukopenia and painful purpuric plaques located on the skin of the abdomen, arms and thighs with a retiform pattern (retiform purpura) with areas of central necrosis. Skin biopsy showed small vessel vasculitis with thrombotic phenomena. In cases 2, 3 and 4, there was a reduced level of consciousness and psychomotor agitation, which could also be attributed to the simultaneous use of other drugs (MDMA, GHB, ethanol). In cases 5 and 6, the patients presented with asystole, which, in one patient (who had also used heroin) was irreversible.

**Conclusion:** Levamisole is detected in cocaine users in Barcelona. In the cases presented here, the most severe outcomes were

retiform purpura with leukopenia and a possible association with irreversible asystole.

## 296. Mixed benzodiazepine-heroin acute toxicity is associated with more severe toxicity than heroin toxicity not associated with benzodiazepine use

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**Objective:** There has been a shortage of heroin in Europe in recent years, which has led to concerns that heroin users may switch to and/or use other drugs together with heroin, including benzodiazepines, resulting in unexpected consequences.<sup>1</sup> There is limited data available to be able to determine the characteristics of those who co-use benzodiazepines and heroin and/or whether this results in more severe toxicity.

**Methods:** The European Drug Emergencies Network (Euro-DEN) project involves longitudinal collection of data from 14 sentinel centres in 10 European countries on ED presentations with acute drug toxicity.<sup>2</sup> The Euro-DEN database was searched to identify cases from 1 October 2013 to 30 June 2014 where heroin had been used prior to presentation. Data extracted was: basic demographics, co-use of benzodiazepines, presentation level of consciousness, admission rates to critical care and length of hospital stay.

**Results:** There were 3,573 cases reported to Euro-DEN over this 9-month period; 872 (23.2%) involved self-reported use of heroin. Of these, 221 (25.3%) had also used one or more benzodiazepines (196 (88.7%) involved one benzodiazepine, 21 (9.5%) involved two benzodiazepines and 3 (1.8%) involved three benzodiazepines). There was significant variation across the Euro-DEN centres ranging from no heroin presentations involving a benzodiazepine in Barcelona, Copenhagen and Paris to 35.6% of heroin presentations in Oslo involving a benzodiazepine. There was no significant difference in the age or gender of the benzodiazepine-heroin and heroin cases not involving a benzodiazepine (mean age  $35.4 \pm 9.6$  versus  $36.7 \pm 9.6$ ,  $p = 0.1$ ; 79.2% versus 82.0% males,  $p = 0.1$ ) and there was no difference in the proportions with coma (GCS  $\leq 8/15$  and/or coded as coma; 8.1% versus 8.6%,  $p = 0.2$ ). However, the heroin-benzodiazepine group had a longer length of hospital stay (5 hours 46 minutes versus 4 hours 45 minutes,  $p = 0.03$ ) and were more likely to be admitted to critical care (10.4% versus 5.8%,  $p = 0.01$ ).

**Conclusion:** Co-use of benzodiazepines with heroin was seen in a significant minority of this large cohort of heroin toxicity Emergency Department presentations, although there was significant variation across Europe, and was associated with poorer outcomes. It is therefore important that those working with heroin users discuss the potential risks of co-use of heroin and benzodiazepines.

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## 297. Perception of prescription drug safety in an online national survey in the UK

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**Objective:** To investigate perception of prescription drug safety compared to illicit drug safety in an online national survey in the UK.

**Methods:** The survey was undertaken in July 2014 using an online market research company. Data analysed for this study was: perception of relative safety of prescription and illicit drugs (“Do you believe prescription drugs are safer than illicit drugs?”), prevalence of illicit drug use and prevalence of prescription drug misuse. Fisher’s exact test was used to determine statistical significance ( $\alpha$  level  $\leq 0.05$ ).

**Results:** In total 2,499 respondents completed the survey; the mean  $\pm$  SD age was  $48.0 \pm 15.6$  years, 49.9% were male. In total 693 (30.8%) reported lifetime use of an illicit drug and 984 (39.4%) reported lifetime misuse of a prescription drug. Overall, 1,836 (73.5%) reported they thought that prescription drugs were safer than illicit drugs. The relationship between perception of the relative safety of prescription/illicit drugs and lifetime use of illicit and prescription drugs is shown in Table 1. Those reporting that prescription drugs are safer than illicit drugs were less likely

**Table 1.** Relationship between perception of drug safety and prevalence of lifetime use for illicit and prescription drugs.

	“Do you believe prescription drugs are safer than illicit drugs?”		P-value
	Yes N (%)	No N (%)	
Lifetime use of illicit drugs			
Yes	466 (25.4)	227 (34.2)	<0.0001
No	1370 (74.6)	436 (65.8)	
Lifetime non-medical use of any prescription drug			
Yes	737 (40.1)	247 (37.3)	0.1946
No	1099 (59.9)	416 (62.7)	
Lifetime use of opioids			
Yes	729 (39.7)	239 (36.0)	0.1036
No	1107 (60.3)	424 (64.0)	
Lifetime use of benzodiazepines			
Yes	38 (2.1)	19 (2.9)	0.2872
No	1798 (97.9)	644 (97.1)	



to report use of illicit drugs ( $p < 0.0001$ ) and less likely to report non-medical use of prescription drugs, although not statistically significant ( $p = 0.1946$ ). There were no differences in reported non-medical use of prescription drugs overall, opioids or benzodiazepines amongst those reporting that prescription drugs are safer than illicit drugs.

**Conclusion:** Data on the perception of relative drug safety is important in understanding motivations for drug use. It is likely that the reasons for this are heterogeneous and further work is required to explore whether they may be based on previous experiences of drug use or whether in some individuals they directly impact the likelihood of an individual using different drugs.

## 298. Review of the European-Drug Emergencies Network (Euro-DEN) training package for non-specialist workers to assess acute recreational drug and novel psychoactive substance (NPS) toxicity in night-time economy environments

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**Objective:** The initial management of acute recreational drug and novel psychoactive substance (NPS) toxicity is often by non-specialist individuals working in the night-time economy. The European Drug Emergencies Network (Euro-DEN) project is developing a uniform guideline and an associated training package for the assessment and initial management of acute recreational drug/NPS toxicity for use by non-specialist night-time economy workers in Europe.<sup>1</sup>

**Methods:** Night-time economy workers in London, UK, Parnu/Tallinn, Estonia and Oslo, Norway were invited to attend a 1-2 hour interactive case-based discussion training session based around the Euro-DEN pre-hospital assessment guidelines. Participants self-assessed their competence on a scale of 0-10 in assessing acute drug toxicity before and after a training session. In addition, they rated the session length and overall quality and provided comments on further adaptations.

**Results:** In total 81 individuals (London 42, Oslo 39, Parnu/Tallinn 17) completed the questionnaire. The overall rating of the training session (out of 10) was  $8.3 \pm 1.4$ . Participants felt less confident in managing acute toxicity related to NPS ( $4.7 \pm 2.6$ ) compared to classical recreational drugs ( $6.2 \pm 2.5$ ,  $p < 0.001$ ); there was a significant improvement in their confidence after the training session (Table 1). In total 90 participants thought the training session was an appropriate length, 4 too short and 2 too long. Qualitative review of the comments identified two themes: i) increased information on different drugs and ii) more interactive/practical training.

**Table 1.** Confidence (as rated by questionnaire) in non-specialist workers in managing acute recreational drug and NPS toxicity attending a training session.

	Pre-training session	Post-training session	
Overall confidence in managing drug toxicity	$7.1 \pm 1.9$	$8.3 \pm 1.2$	$p < 0.001$
Confidence with classical drug toxicity	$6.2 \pm 2.5$	$8.0 \pm 1.5$	$p < 0.001$
Confidence with NPS toxicity	$4.7 \pm 2.6$	$7.1 \pm 1.9$	$p < 0.001$

**Conclusion:** The Euro-DEN night-time economy guidelines were well received and improved confidence in managing acute classical drug/NPS toxicity. Those working in the pre-hospital environment had less confidence in managing acute toxicity related to NPS. Qualitative feedback suggests that more practical, potentially with simulation-based, training would further improve the confidence of non-specialist workers in the pre-hospital environment in assessing drug toxicity.

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## 299. Deaths involving recreational drugs and novel psychoactive substances reported to the European Drug Emergencies Network (Euro-DEN): A review of the first 9 months

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**Objective:** Data on drug-related deaths is collected as a key indicator of the harms associated with recreational drug use, although there is often limited information available on whether these cases died in hospital. The European Drug Emergencies Network (Euro-DEN) is a European Commission funded project of 16 sentinel centres in 10 countries collecting data on presentations to Emergency Departments (ED) with acute recreational drug and/or novel psychoactive substance (NPS) toxicity;<sup>1</sup> we describe in-hospital deaths from the first nine months of data collection.

**Methods:** The Euro-DEN project database was searched to identify all deaths between 1 October 2013 and 30 June 2014. Data was extracted on the reported drug(s) used by the deceased, time from ED presentation to death, place of death and, where available, the inquest or analytical screening results.

**Results:** There were fourteen (0.39%) deaths in the 3,573 cases reported to the Euro-DEN project. Eight of the 16 centres reported deaths: in five centres there was one death, in one centre two deaths, in one centre three deaths and in one centre four deaths. 13 of the deceased were male and the median age was 36 years (IQR 30-41 years). Seven patients died in the ED, six died after admission to critical care and one died after admission to a non-critical care ward. The median time from ED presentation to death was 9 hours 53 minutes (IQR 1 hour 9 minutes to 74 hours 19 minutes). The reported drugs used by the deceased prior to death were: opioids (heroin n = 3, methadone n = 2, fentanyl n = 1); cocaine (n = 2); cocaine and MDMA (n = 1); mephedrone (n = 1); cannabis (n = 1) and unknown in 3 cases. Inquest or laboratory reports are currently available for seven cases, and in these cases the analytical screening results corroborated the reported drug(s) used.

**Conclusion:** Deaths are uncommon amongst presentations to the ED with acute recreational drug/NPS toxicity. In the small number of cases reported to the Euro-DEN project the drugs implicated in deaths are similar to those reported in out of hospital drug-related fatalities.<sup>2</sup> Data from projects such as Euro-DEN will provide more information on the circumstances of recreational drug/NPS related death occurring after presentation to hospital.

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### 300. Oxycodone/naloxone preparations can cause acute opioid withdrawal symptoms following intravenous and oral exposure

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**Objective:** Orally administered compound oxycodone/naloxone preparations are designed to reduce the incidence of constipation associated with oxycodone use. The low oral bioavailability (<2%) of naloxone following ingestion of these preparations means that precipitation of acute opioid withdrawal symptoms is unlikely.<sup>1</sup> Opioid withdrawal symptoms following ingestion of oxycodone/naloxone preparations have not been described in patients consulting a Poisons Information Centre (PIC).

**Methods:** A retrospective review of the Victorian PIC electronic call database, using search terms including "oxycodone" or "oxycodone/naloxone", was performed for the period January 2012 to August 2014. Data collected included patient demographics, reported symptoms, type of caller, intentional or accidental exposure.

**Results:** There were 565 reported exposures to oxycodone. Of these, 90 (16% of total) reported exposures were to oxycodone/naloxone preparations. The frequency of calls related to oxycodone/naloxone preparations increased over time from zero in 2011, to 30 in 2012 and 55 episodes in 2013. Forty-one (45%)

of exposures were misuse, 44 (49%) therapeutic errors and 5 (6%) were accidental. The route of exposure was predominantly oral ingestion in 76 (84%), with intravenous injection of crushed tablets in 14 (16%) of cases. Of the 76 oral exposures, 7 (9%) patients developed withdrawal symptoms; all had a history of long-standing opioid use. We noted a temporal relationship between first dose, increased dose (total dose range 10-40 mg oxycodone/5-20 mg naloxone), chewing tablets and the development of opioid withdrawal symptoms. Symptoms reported were agitation (n = 3), tremor (n = 2), increase in pain (n = 2), chills (n = 2), insomnia (n = 1), diaphoresis (n = 1) and nausea (n = 1). One female with end stage liver failure treated chronically with oxycodone-alone developed increased pain, muscle spasm, diaphoresis and agitation necessitating emergency department presentation after ingestion of the oxycodone/naloxone preparation. There were 14 exposures to crushed oxycodone/naloxone tablets injected intravenously; all precipitated an acute withdrawal state. We found 8 cases of parenteral abuse all involving the oxycodone-alone product. No episodes of acute opioid withdrawal were described in these cases.

**Conclusion:** Compound oxycodone/naloxone preparations may result in acute opioid withdrawal symptoms following misuse intravenously by injection of crushed tablets. Withdrawal syndrome was more likely in opioid-dependent patients after oral ingestion of first dose, increased dose or chewing oxycodone/naloxone tablets suggesting that the dose of naloxone may be large enough to allow systematic absorption of the opioid antagonist.

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### 301. Estimating nonmedical use of prescription opioids in the USA from social media

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**Objective:** The non-medical use of prescription drugs (NMUPD) is a significant public health burden that affects users, their families, their peers and society at large. Social media provide data that may help us understand NMUPD in the general population.<sup>1</sup> Until now, social media have played a limited role in public health research, partially owing to a lack of validated methods for estimating essential epidemiological quantities from social media. The aim of this study was to demonstrate that the point prevalence of opioid NMUPD can be accurately and rapidly estimated from publicly available data on Twitter.

**Methods:** This cross-sectional study of the point prevalence of opioid NMUPD used publicly available data from the Twitter API. Institutional Review Board (IRB) approval was obtained at the

authors' institution. We clustered tweets using a novel measure of semantic similarity that we developed that accounts for context. We used the silhouette coefficient to automatically determine the most likely number of clusters in the data. To geolocate the tweet we used latitude and longitude coordinates in the metadata of the tweet. Since only 1-2% of tweets contain explicit information, we used Carmen, a program that infers location from the text and metadata of a tweet, to approximate the location of more tweets. From these data, we calculated the location quotient for each state in the continental US. We validated our estimate by calculating its correlation with the location quotient calculated from the 2012 National Survey on Drug Use and Health as well as controlling for US population density.

**Results:** We obtained 106,422 tweets over a three-month period. Of those, 39,989 were duplicates, allowing subsequent analysis on the remaining 63,090 unique tweets. Tweets discussing opioid NMUPD formed a distinct cluster, with the silhouette coefficient peak at 0.55 for three clusters. The correlation between our estimate of opioid NMUPD and the most recent federal survey data was outstanding ( $R^2 = 0.89$ ). There was no significant correlation with US population density alone.

**Conclusion:** Our results demonstrate that a computational linguistic analysis of social media can yield accurately approach validated epidemiological data on prescription drugs.

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## 302. Dextromethorphan abuse in adolescence: A rising trend

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**Objective:** Dextromethorphan (DXM) is an over-the-counter cough suppressant structurally similar to opioids (it is the dextro-isomer of levorphanol). At recommended doses, the drug produces few adverse effects; however, when abused in large quantities ( $> 2$  mg/kg), it has been associated with a dissociative effect similar to ketamine and phencyclidine. Massive ingestions may be associated with serious toxicity. Since 2012 increasingly recreational use of DXM has been reporting to the National Toxicological Information Centre (NTIC) in Slovakia.

**Methods:** All cases of DXM intoxication were extracted from the NTIC database from January 2012 to October 2014. Data were evaluated for demographic and clinical factors.

**Results:** We studied the outcome of 36 cases of DXM intoxication. The median age of patients was 15 years (1 to 49 years); 61.1% of cases involved females. Recreational abuse prevailed with 47.2%, accidental ingestion occurred in 38.8% and suicidal attempts in 11.1% of cases. The median ingested dose was 250 mg (15 to 2700 mg). The most common co-ingested agent was alcohol. There were no symptoms or signs of toxicity in 14 cases (38.8%), minor toxicity occurred in 18 (50%) and serious toxicity in 4 patients (11.1%). Clinical features were drowsiness (22.8%), ataxia (22.2%), nausea or vomiting (19.4%), mydriasis

(13.8%), tachycardia, hypertension (11.1%), blurred vision (8.3%), agitation (8.3%), nystagmus (5.6%), tremor (5.6%) and coma (2.8%); 55.5% of the patients were treated in a health care facility. The median length of hospital stay was 3 days (1 to 5 days).

**Conclusion:** DXM is often abused by young people seeking its dissociative effects. For adolescents experimenting with drugs, DXM is cheap, easily accessible and legal. Clinicians should be aware of the potential abuse of DXM. Pharmacists might be particularly cognizant of the risks involved with DXM abuse as they control over the counter (OTC) access to the drug. Additionally, implications may exist for authorities in this area that might increase awareness of DXM misuse, control drug availability and improve recognition of cases involving abuse.

## 303. Emergency Department presentations following recreational use of baclofen, gabapentin and pregabalin: A Euro-DEN case series

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**Objective:** There is emerging evidence of recreational misuse of the prescription drugs baclofen, gabapentin and pregabalin in Europe.<sup>1</sup> However there is limited data available on the characteristics of users, whether misuse overlaps with other recreational drugs or novel psychoactive substances (NPS) and on the acute toxicity associated with misuse of these medications. This study describes recreational misuse of baclofen, gabapentin and pregabalin reported to the European Drug Emergencies Network (Euro-DEN), which collects data from 16 sentinel centres in 10 European countries on presentations to Emergency Departments (EDs) with acute recreational drug and/or NPS toxicity.<sup>2</sup>

**Methods:** The Euro-DEN project database was searched for data from 1 October 2013 to 30 June 2014 to identify all cases of acute toxicity involving self-reported use of baclofen, gabapentin and/or pregabalin. Data was extracted on age, gender, other drugs used and outcome (admission and length of stay).

**Results:** There were 3,573 cases reported to the Euro-DEN project over the nine month study period; 60 (1.7%) involved baclofen (13.3%,  $n = 8$ ), gabapentin (8.3%,  $n = 5$ ) or pregabalin (78.3%,  $n = 47$ ). No concurrent use of these drugs was observed. A single case of non-oral administration was reported (intravenous pregabalin). Twenty-six (43.3%) users were female and the mean  $\pm$  SD (range) age was  $36 \pm 10.7$  (19-74) years. No other recreational drugs/NPS were taken in 12 (20.0%) cases (baclofen 4; gabapentin 2; pregabalin 6). Other drugs (range 2-6 drugs) were taken in 48 (80.0%) cases; the most common were opioids (42 cases with at least one opioid), benzodiazepines ( $n = 34$ ) and cannabis ( $n = 10$ ). No deaths were reported; 42 cases (70%) were discharged from the



ED. A total of 18 users (30%) were admitted, including 2 (3.3%) to critical care. The median length of hospital stay was 9 hour 46 minutes (Interquartile range: 9 hours 10 minutes to 41 hours 26 minutes).

**Conclusion:** Recreational misuse of baclofen, gabapentin and pregabalin make up a small proportion of all ED presentations for acute recreational drug toxicity. Pregabalin is the most frequently encountered, with most cases involving polysubstance use, in particular opioids and benzodiazepines. These data together with information from studies looking at other factors such as the source of these drugs for misuse will help to inform harm reduction work.

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### 304. Acute behavioural disturbance associated with phenibut purchased via an Internet supplier

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**Objective:** Access to the Internet has enabled substances unavailable therapeutically in certain geographical areas to be accessed for therapeutic and recreational purposes. We report two cases of the use of phenibut, an agent with structural similarity to baclofen, for recreational effect and the subsequent toxicity produced.

**Case report:** Case 1: A 20-year-old female was brought to the emergency department (ED) at 09:53 hours having been found with a decreased level of consciousness at 07:00 hours that same day. She had ingested phenibut purchased on the Internet, the evening before. She was quite sedated on arrival in the ED though when stimulated would awake briefly and appeared delirious. After several hours observation during which it was deemed that she did not need formal airway protection, she was transferred to the emergency short stay unit overnight. The next day she was awake and no longer confused. She had ingested 25 g of the phenibut in 3 doses the day prior to presentation. She had done this for recreational purposes and not as an act of self-harm. The recommended dose as per the supplier was 250–300 mg. She was discharged from hospital in the care of her parents. Case 2: A 38-year-old male presented to the ED in the company of the police and ambulance service in an agitated delirium. He was believed to have consumed alcohol, tetrahydrocannabinol (THC) and phenibut in the 24 hours prior to presentation. He was administered droperidol 10 mg intramuscularly on 2 occasions and subsequently 4 mg/kg intramuscular ketamine for sedation. This had a modest effect for a couple of hours

but after that time the patient awoke in a somewhat uncontrollable, agitated state once more. It was decided to intubate the patient and manage in ICU until the effects of the drug had worn off. A head CT was undertaken to exclude a physical CNS lesion and this was normal. The patient was ventilated overnight and awoke the next day with a normal sensorium. He indicated that his intention in taking the phenibut was recreational.

**Discussion:** Phenibut is used in certain countries, such as Russia, for therapeutic purposes. Clinicians are unlikely to be aware of the potential toxic effects of such agents but may encounter their toxic effects in an era where Internet purchase makes them readily accessible.

### 305. The rise in prescription parenteral opiate abuse: Cases reported to an Australian Poisons Information Centre

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**Objective:** To describe the epidemiology of parenteral prescription opiate exposures reported to an Australian Poisons Information Centre (PIC), in order to assess the need for abuse deterrent formulations.

**Methods:** A retrospective review of calls made to an Australian Poisons Information Centre from 1 January 2004 to 31 December 2013 of intentional parenteral exposures to opiates.

**Results:** In total 440 cases were identified, with the incidence increasing from 31 in 2004 to 79 in 2013; 70% were male and the median age was 33 years (IQR 26–42; range 13–63 years). The most prevalent opiates abused in order were: oxycodone ± naloxone (n = 121), buprenorphine ± naloxone (n = 90), methadone (n = 87), morphine (n = 68), fentanyl (n = 43) and tramadol (n = 20). In 2008, intentional exposures to oxycodone surpassed morphine, and abuse of oxycodone has continued to rise, reaching a peak in 2013 (n = 36, with 20 of these cases being the oxycodone/naloxone formulation, Targin<sup>®</sup>). The prescription opiate brand most frequently abused over the past decade has been Oxycontin<sup>®</sup> (n = 58). Since 2011, a spike in the abuse of fentanyl patches (Durogesic<sup>®</sup>) has occurred, increasing from 2 cases in 2004 to 9 cases in 2013, and mainly involving the injection of contents from a dissolved or melted patch.

**Conclusion:** Abuse of opiate analgesics poses a significant public health burden worldwide. Prescription opiate misuse has increased over the past decade, in keeping with prescribing trends, and shows no evidence of slowing. Abuse deterrent formulations are effective in minimising diversion. The 2014 introduction of reformulated hydrogelling Oxycontin<sup>®</sup> (claimed to be crush-resistant) will likely deter Oxycontin<sup>®</sup> abuse, however close monitoring is necessary to assess shifting to an alternate opiate. Pharmacovigilance systems utilising PIC data are required in Australia. This retrospective study highlights the importance of analysing PIC data, in collaboration with national epidemiological data, to understand the impact of opiate reformulation on abuse and its consequences.

### 306. Trends over time in population rates of intentional misuse and self-harm mentions with buprenorphine, methadone, and oxycodone as reported to poison centres in Germany, Italy and the UK

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**Objective:** To determine if population rates of misuse/abuse/diversion and self-harm exposures as reported to poison centres (PCs) are increasing for buprenorphine, methadone, and oxycodone in Germany, Italy, and the UK.

**Methods:** Intentional human exposures to buprenorphine, methadone, and oxycodone reported to participating Global Toxicosurveillance Network (GTNet) PCs were examined. Exposures between 2007 and 2013 were obtained from centres in Milan, Italy and Göttingen, Germany, and from centres in the UK between 2008 and 2013. UK PCs provide medical management assistance to health care providers only, while services in Milan and Göttingen are also available to the public. Defined regions of call coverage exist in Germany and the UK, while the Milan center handles 65-70% of all calls in Italy. Rates are expressed as the number of exposures per 100,000 population separately for those with an exposure reason of misuse/abuse/diversion versus self-harm.

**Results:** See Table 1. In Germany, increasing rates were seen for oxycodone self-harm, and misuse/abuse/diversion of oxycodone and methadone. Misuse/abuse/diversion rates were higher for methadone and buprenorphine than self-harm rates, while oxycodone self-harm rates were higher than misuse/abuse/diversion

rates. In Italy, increasing rates were noted for oxycodone self-harm and misuse/abuse/diversion. Rates for misuse/abuse/diversion were higher for methadone and buprenorphine than self-harm rates, while oxycodone self-harm rates were higher than misuse/abuse/diversion rates. In the UK, declining rates were seen for oxycodone and methadone self-harm, while no rates were increasing. Rates of self-harm exceeded rates of misuse/abuse/diversion.

**Conclusion:** As in the USA, increasing rates of reports to PCs of self-harm and misuse/abuse/diversion were evident for some prescription opioids in Germany and Italy. In the UK, where PC reports are only from health care providers, no increases in trends were evident. Increasing rates of self-harm often exceeded rates of misuse/abuse/diversion and may represent an opportunity for public health interventions.

### 307. An Internet snapshot study to investigate the cost and availability of the novel benzodiazepines diclazepam, flubromazepam and pyrazolam in the UK

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**Objective:** There has been increasing concern that non-prescription benzodiazepines are being sold as novel psychoactive substances (NPS) in Europe; diclazepam, flubromazepam and pyrazolam have been detected in Europe since 2013. There is limited data available on the prevalence of use or availability of these drugs. The aim of this study was to determine the availability of these novel benzodiazepines in the UK from Internet NPS suppliers.

**Methods:** The study was undertaken in November 2014 in English using European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) Snapshot Methodology.<sup>1</sup> Three Internet search engines (google.co.uk, uk.yahoo.com and ask.com.uk) were

**Table 1.** Poison centre intentional exposure rates per 100,000 populations in Germany, Italy and the UK.

Country	Drug Class	Exposure reason	2007	2008	2009	2010	2011	2012	2013
Germany	Buprenorphine	Misuse/Abuse/Diversion	0.0097	0.0122	0.0098	0.0049	0.0150	0.0199	0.0137
		Self-harm	0.0061	0.0037	0.0098	0.0122	0.0062	0.0112	0.0062
	Methadone	Misuse/Abuse/Diversion	0.0316	0.0256	0.0306	0.0281	0.0424	0.0485	0.0509
		Self-harm	0.0158	0.0146	0.0159	0.0245	0.0262	0.0336	0.0124
	Oxycodone	Misuse/Abuse /Diversion	0.0012	0.0024	0.0012	0.0049	0.0062	0.0087	0.0025
		Self-harm	0.0231	0.0305	0.0330	0.0416	0.0411	0.0522	0.0596
Italy	Buprenorphine	Misuse/Abuse/Diversion	0.0635	0.0716	0.0288	0.0203	0.0051	0.0236	0.0168
		Self-harm	0.0103	0.0239	0.0153	0.0068	0.0051	0.0017	0.0101
	Methadone	Misuse/Abuse/Diversion	0.0996	0.1057	0.0593	0.0997	0.0438	0.0471	0.0787
		Self-harm	0.0550	0.0477	0.0797	0.0743	0.0303	0.0337	0.0436
	Oxycodone	Misuse/Abuse/Diversion	0.0000	0.0000	0.0169	0.0101	0.0034	0.0101	0.0184
		Self-harm	0.0069	0.0068	0.0407	0.0558	0.0219	0.0421	0.0385
UK	Buprenorphine	Misuse/Abuse/Diversion	NA	0.0146	0.0144	0.0111	0.0047	0.0126	0.0094
		Self-harm	NA	0.0421	0.0241	0.0287	0.0237	0.0126	0.0265
	Methadone	Misuse/Abuse/Diversion	NA	0.0162	0.0257	0.0191	0.0221	0.0094	0.0109
		Self-harm	NA	0.0583	0.0530	0.0446	0.0221	0.0267	0.0156
	Oxycodone	Misuse/Abuse/Diversion	NA	0.0032	0.0000	0.0032	0.0032	0.0016	0.0031
		Self-harm	NA	0.0291	0.0337	0.0414	0.0221	0.0235	0.0203

NA = not available.

**Table 1.** Variable drug forms, dose strengths and pricing ranges of novel benzodiazepines sold by Internet suppliers.

Benzodiazepine	Number of Internet suppliers	% Internet suppliers originating from the UK/Europe	Dose form and quantity purchase range			
			Pellets: Dose strengths available (number of pellets available)	Powder: Dose strengths available	Blotters: Dose strengths available (number of blotters available)	Pills: Dose strengths available (number of pills available)
Diclazepam	50	74	1 mg, 2 mg (1–100,000)	0.05–50 g	2.5 mg (10–500)	1 mg (50–2000)
Flubromazepam	39	84	4 mg, 5 mg, 8 mg (5–100,000)	0.05–50 g	2.5 mg (10–1000)	4 mg (50–2000)
Pyrazolam	32	76	0.5 mg, 1 mg (2–100,000)	0.05–2 g	1.5 mg (10–1000)	None available

searched using the terms “buy diclazepam”, “buy flubromazepam” and “buy pyrazolam”.

**Results:** A total of 56 Internet sites were identified selling these three drugs: diclazepam 50 Internet sites; flubromazepam 39; and pyrazolam 32 sites. All three drugs were available from 24 sites and two drugs from 16 sites. It appeared that 77% of the sites originated from the UK and/or elsewhere in Europe. The drugs were sold in varying strengths and various forms including pellets (52 Internet sites), powder ( $n = 8$ ) and blotters ( $n = 4$ ) (Table 1). One Internet site sold diclazepam and flubromazepam in pill form.

**Conclusion:** These three novel benzodiazepines are widely available from Internet NPS suppliers to potential users in the UK. They are most commonly available as pellets and to a lesser extent, as powder or blotters; however one Internet site sold diclazepam and flubromazepam in pill form, which clearly means they are being sold for intended human consumption. This study could be used to support triangulation of data from other sources to further understand novel benzodiazepine availability, use and toxicity to inform harm minimisation strategies and to tackle their extensive availability.

### 308. Prescription drug overdose resulting from drug abuse: Moroccan Poison Control and Pharmacovigilance Centre data (1980-2011)

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**Objective:** The increased availability of prescription drugs has contributed to a dramatic rise in the non-medical use and abuse of these medications. The most recent National Survey on Drug Use and Health statistics for 2008 reported an estimated 6.2 million (2.5%) persons aged 12 or older using prescription-type psychotherapeutic drugs non-medically in the past month.<sup>1</sup> We conducted a study to analyze patterns of prescription drug overdose resulting from drug abuse reported to Moroccan Poison Control Centre (CAPM).

**Methods:** A retrospective study was conducted including all drug poisoning cases in the context of drug abuse reported to the CAPM between January 1980 and December 2011. The age classification used was the International Programme on Chemical

Safety classification and the drug classification was the Anatomic Therapeutic Chemical (ATC) Classification System.

**Results:** In total 203 cases of medication poisoning in the context of drug abuse were reported to CAPM in the study period. Patients were mostly from urban centres (97.0%). The average age was  $25.6 \pm 9.6$  years. The sex-ratio was 2.4 (59 females, 142 males). Most cases involved adults aged 20-75 years (73.0%) and adolescents aged 16-19 years (22.6%). The drugs implicated in the largest number of poisoning cases were nervous system drugs (60.6%) with benzodiazepines being the most common (37.5%) followed by antidepressants (16.3%). Cannabis was also involved in 4 cases. Gastrointestinal signs occurred in 33.8% and nervous system disorders in 33.1% of cases. The mortality rate was 0.7%.

**Conclusion:** The epidemiological circumstances of drug abuse using medicines are still unclear in our country and the number of cases is probably underestimated. Our study showed that it is a particular problem among young adults and adolescents. Others studies are needed to determine the epidemiology and risk factors of medication abuse and to establish a prevention program.

### Reference

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### 309. Prescription opioids: Reported reasons for non-medical use in an online national survey in the UK

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**Objective:** To describe reasons for non-medical use of prescription opioids reported in an online national survey in the UK.

**Methods:** The survey was undertaken in July 2014 using an online market research company. Data analysed for this study were: non-medical use of prescription opioids and reason for this misuse (using pre-formatted criteria; individuals could select multiple reasons), together with last year misuse of illicit drugs. The prescription opioids included in the survey are listed in Table 1. Prevalence of misuse per 100,000 was calculated using the latest UK Office of National Statistics population estimate.



**Table 1.** Prevalence of misuse and reasons for non-medical use of prescription opioids.

Opioids	Prevalence of non-medical use per 100,000 population	Percent of respondents reporting non-medical use (%)	Number (%) reporting reason for misuse					
			For enjoyment/to get high	To come down	Makes me feel good	I feel unwell if I don't take it	Out of curiosity	Other reason
Buprenorphine (n = 72)	0.11	3	33 (45.8)	36 (50.0)	40 (55.6)	33 (45.8)	26 (36.1)	11 (15.3)
Dihydrocodeine/Codeine (n = 535)	0.83	21	20 (3.7)	28 (5.2)	63 (11.8)	72 (13.5)	21 (3.9)	390 (72.9)
Fentanyl (n = 124)	0.19	5	53 (42.7)	59 (47.6)	77 (62.1)	50 (40.3)	49 (39.5)	16 (12.9)
Methadone (n = 41)	0.06	2	22 (53.7)	19 (46.3)	13 (31.7)	13 (31.7)	10 (24.4)	1 (2.4)
Morphine (n = 45)	0.07	2	17 (37.8)	18 (40.0)	17 (37.8)	13 (28.9)	17 (37.8)	14 (31.1)
Oxycodone (n = 22)	0.03	1	12 (54.5)	11 (50.0)	11 (50.0)	11 (50.0)	9 (40.9)	7 (31.8)
Tapentadol (n = 13)	0.02	1	4 (30.8)	9 (69.2)	6 (46.2)	8 (61.5)	7 (53.8)	3 (23.1)
Tramadol (n = 65)	0.10	3	17 (26.6)	14 (21.9)	21 (32.8)	15 (23.4)	28 (43.8)	33 (51.6)
Other/not-specified opioid (n = 26)	0.04	1	12 (46.2)	10 (38.5)	8 (30.8)	10 (38.5)	7 (26.9)	8 (30.8)

**Results:** In total 2,499 respondents completed the survey; the mean  $\pm$  SD age was  $48.0 \pm 15.6$  years, 49.9% were male. The reported use of any illicit drug in the past year (8.6%) was similar to the 2013/14 Crime Survey for England and Wales (8.8%).<sup>1</sup> In total 968 (38.7%) respondents reported non-medical use of at least one prescription opioid. The reported prevalence of non-medical use was highest for dihydrocodeine followed by fentanyl (Table 1). At least one reason for misuse was specified by 685 (70.8%) respondents; 26.8% reported more than one reason for misuse. Amongst those reporting misuse of methadone, oxycodone, and other/not-specified opioid, "for enjoyment/to get high" was the most commonly reported reason. "To come down" was the most commonly reported reason amongst those that reported morphine and tapentadol misuse. "Makes me feel good" was the most common reason for misuse amongst those reporting buprenorphine and fentanyl misuse.

**Conclusion:** This survey suggests significant misuse of prescription opioids in the UK, and the reasons for misuse appear multi-factorial. Given the limited data available on prescription opioid misuse in Europe understanding the motivation for misuse is important to inform the design of appropriate interventions to tackle this issue.

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## 310. Pregabalin, gabapentin and baclofen: Sources of drug acquisition for non-medical use in an online national survey in the UK

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**Objective:** To describe the source(s) of pregabalin, gabapentin and baclofen in individuals reporting non-medical use of these drugs in an online national survey in the UK.

**Methods:** The survey was undertaken in July 2014 using an online market research company. The data analysed for this study was non-medical use of pregabalin, gabapentin and baclofen and source of drug acquisition (using pre-specified criteria); multiple drug sources could be indicated. Prevalence of misuse per 100,000 was calculated using the latest UK Office of National Statistics population estimate.

**Results:** In total 2,499 respondents completed the survey; the mean  $\pm$  SD age was  $48.0 \pm 5.6$  years and 49.9% were male. The reported use of any illicit drug in the past year (8.6%) was similar to the 2013/14 Crime Survey for England and Wales (8.8%).<sup>1</sup> Whilst the reported prevalence of non-medical use was low, the highest prevalence was for gabapentin, followed by baclofen and pregabalin (Table 1). Respondents reported acquiring these drugs from a variety of sources; 71.4% reported using more than one source. The most common source for all three drugs was a prescription from a medical practitioner (79.2% overall). Sourcing of the drugs from illicit channels (29.2% reported buying from a dealer) and the Internet (16.7%) was less common; interestingly, 33.3% reported

**Table 1.** Prevalence of misuse sources of drug acquisition for pregabalin, gabapentin and baclofen.

Source of drug	Pregabalin N (%)	Gabapentin N (%)	Baclofen N (%)
Prevalence of non-medical use per 100,000 population	0.012	0.016	0.009
Number (%) of respondents reporting non-medical use (%)	8 (0.32)	10 (0.40)	6 (0.24)
Am prescribed it by a medical practitioner	7 (87.5)	6 (60.0)	6 (100.0)
Am given it by friends or family member	2 (25.0)	4 (40.0)	2 (33.3)
Took it from friends or family members without their knowledge	1 (12.5)	1 (10.0)	3 (50.0)
Took it from someone other than friends/family	1 (12.5)	1 (10.0)	3 (50.0)
Bought it over the counter	1 (12.5)	2 (20.0)	2 (33.3)
Bought it in a "high street" pharmacy/shop	2 (25.0)	2 (20.0)	4 (66.7)
Bought it abroad	1 (12.5)	0 (0.0)	1 (16.7)
Bought it from a dealer	2 (25.0)	3 (30.0)	2 (33.3)
Bought it on the Internet	1 (12.5)	1 (10.0)	2 (33.3)

sourcing these drugs from a pharmacy/high street shop despite these drugs being prescription-only medicines in the UK.

**Conclusion:** Non-medical use of pregabalin, gabapentin and baclofen was uncommon in this survey. A variety of sources were reported, the most common was a prescription from a medical practitioner. More work needs to be undertaken to understand this, to determine the most effective interventions for prescription medicine misuse.

## Reference

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### 311. Chronic pain and non-medical use of opioids, benzodiazepines and pregabalin in an online national survey in the UK

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**Objective:** To investigate the relationship between chronic pain and use of illicit drugs and non-medical use of prescription drugs in an online national survey in the UK.

**Methods:** The survey was undertaken in July 2014 using an online market research company. Data analysed for this study was: whether the individual had experienced chronic pain (“pain lasting for at least 3 months that either occurs constantly or flares up frequently”), prevalence of illicit drug use, and prevalence of non-medical use of prescription drugs (use without a doctor's prescription or for any reason other than recommended by a doctor).

**Table 1.** Relationship between reported chronic pain and the prevalence of lifetime use of illicit drugs and non-medical use of prescription drugs.

	Chronic Pain		P-value
	Yes N (%)	No N (%)	
Lifetime use of illicit drugs			
Yes	357 (31.5)	336 (24.6)	
No	775 (68.5)	1031 (75.4)	<0.0001
Lifetime misuse of any prescription drug			
Yes	511(45.1)	473(34.6)	
No	621(54.9)	894(65.4)	<0.0001
Lifetime misuse of opioids			
Yes	507 (44.8)	461 (33.7)	
No	625 (55.2)	906 (66.3)	<0.0001
Lifetime misuse of benzodiazepines			
Yes	34 (3.0)	23 (1.7)	
No	1098 (97.0)	1344 (98.3)	0.0311
Misuse of pregabalin/gabapentin			
Yes	13 (1.1)	2 (0.1)	
No	1119 (98.9)	1365 (99.9)	0.0013

Data on lifetime non-medical use of prescription drugs was studied for opioids, benzodiazepines and pregabalin/gabapentin. Fisher's exact test was used to determine statistical significance with an alpha level of  $\leq 0.05$ .

**Results:** In total 2,499 respondents completed the survey; the mean  $\pm$  SD age was  $48.0 \pm 15.6$  years and 49.9% were male. In total 693 (30.8%) reported lifetime use of an illicit drug and 984 (39.4%) reported lifetime non-medical use of a prescription drug. Chronic pain was reported by 1,132 (45.3%) respondents. As shown in Table 1, lifetime use of illicit drugs and non-medical use of prescription drugs were more common in those with chronic pain; reported non-medical use of opioids, benzodiazepines and pregabalin/gabapentin were all more common in those with chronic pain.

**Conclusion:** Data from this survey suggest that use of illicit drugs and non-medical use of prescription drugs is more common in those with chronic pain in the UK. It is important that clinicians managing patients with chronic pain and those managing patients with drug misuse, including clinical toxicologists, consider this in their clinical assessment. Further work is required to understand the reasons for this association which is important given the high prevalence of chronic pain in Europe and North America.

### 312. Benzodiazepines and “Z drugs”: Reported reasons for non-medical use in an online national survey in the UK

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**Objective:** To describe reasons for non-medical use of benzodiazepines and “Z drugs” reported in an online national survey in the UK.

**Methods:** The survey was undertaken in July 2014 using an online market research company. Data analysed for this study was non-medical use of benzodiazepines/Z drugs and reason for this misuse (using pre-formatted criteria; individuals could select multiple reasons), together with misuse of illicit drugs in the last year. The benzodiazepines/Z drugs included in the survey are listed in Table 1. Prevalence of misuse per 100,000 was calculated using the latest UK Office of National Statistics population estimate.

**Results:** In total 2,499 UK respondents completed the survey; the mean  $\pm$  SD age was  $48.0 \pm 15.6$  years, 49.9% were male. The reported use of any illicit drug in the past year (8.6%) was similar to the 2013/14 Crime Survey for England and Wales (8.8%).<sup>1</sup> Non-medical use of at least one benzodiazepine was reported by 57 (2.3%); the reported prevalence of non-medical use was highest for diazepam, followed by temazepam and lorazepam (Table 1). At least one reason for misuse was specified by 48 (84.2%) respondents; of these, 66.7% of individuals reported more than one reason for misuse and the median (IQR) number of reasons for misuse was 2 (1-4). The most commonly reported reason among respondents reporting diazepam, temazepam and lorazepam misuse was “makes me feel good”. Other reasons

**Table 1.** Prevalence of misuse and reasons for non-medical use of benzodiazepines and Z drugs.

	Prevalence of non-medical use per 100,000 population	Percent of respondents reporting non-medical use (%)	Number (%) reporting reason for misuse					
			For enjoyment/to get high	To come down	Makes me feel good	I feel unwell if I don't take it	Out of curiosity	Other reason
Benzodiazepines								
Diazepam (n = 36)	0.056	1.4	9 (25.0)	8 (22.2)	16 (44.4)	5 (13.9)	8 (22.2)	13 (36.1)
Temazepam (n = 15)	0.023	0.6	4 (26.7)	2 (13.3)	7 (46.7)	3 (20.0)	3 (20.0)	5 (33.3)
Nitrazepam (n = 9)	0.014	0.4	3 (33.3)	5 (55.6)	4 (44.4)	2 (22.2)	3 (33.3)	0 (0.0)
Zopiclone (n = 9)	0.014	0.4	4 (44.4)	3 (33.3)	3 (33.3)	1 (11.1)	2 (22.2)	3 (33.3)
Zaleplon (n = 1)	0.002	<0.1	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
Zolpidem (n = 1)	0.002	<0.1	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Oxazepam (n = 2)	0.003	<0.1	1 (50.0)	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)
Other sedative hypnotics (n = 5)	0.008	0.2	2 (40.0)	2 (40.0)	2 (40.0)	1 (20.0)	3 (60.0)	1 (20.0)
Lorazepam (n = 11)	0.017	0.4	4 (36.4)	2 (18.2)	7 (63.6)	2 (18.2)	4 (36.4)	2 (18.2)
Lormetazepam (n = 2)	0.003	<0.1	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)
Flunitrazepam (n = 3)	0.005	0.1	2 (66.7)	1 (33.0)	1 (33.0)	0 (0.0)	0 (0.0)	3 (100.0)
Etizolam (n = 1)	0.002	<0.1	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
Phenazepam (n = 0)	0.000	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alprazolam (n = 5)	0.008	0.2	1 (20.0)	0 (0.0)	3 (60.0)	1 (20.0)	2 (40.0)	1 (20.0)
Flurazepam (n = 6)	0.009	0.2	4 (66.7)	0 (0.0)	4 (66.7)	2 (33.3)	2 (33.3)	1 (16.7)
Other/not-specified benzodiazepine (n = 1)	0.002	<0.1	1 (100.0)	0 (0.0)	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)

including “to come down”, “for enjoyment/to get high” and “out of curiosity” were also commonly reported as reasons for misuse.

**Conclusion:** Despite a relatively low prevalence of benzodiazepines misuse, there appear to be multiple reasons for their misuse, with the majority of respondents reporting more than one reason. Understanding the reasons for misuse will enable development of better strategies to reduce benzodiazepine misuse in the UK.

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## 313. Characterization of acute opioid overdose in the ToxIC Registry

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**Objective:** The abuse and misuse of prescription opioid analgesics in the USA has risen steeply over the past decade. Trends among gender differences and age groups are described in National Survey data, however, it is self-reported and only includes intentional abuse. Our objective was to compare characteristics of patients reported in the American College of Medical Toxicology's Toxicology Investigator's Consortium (ToxIC) database following opioid overdose. ToxIC is a prospective online registry developed in 2009; currently 46 institutions participate by entering data on bedside consults by medical toxicologists.

**Methods:** This is a retrospective review of opioid overdoses reported to the ToxIC database. All intentional and unintentional pharmaceutical encounters between 1 October 2010 and 1 November 2014 were reviewed. All cases that listed opioids as a primary agent in the ingestion were included for analysis.

**Results:** Within the study period 4,818 cases were classified as intentional and 696 cases as unintentional pharmaceutical encounters. Opioids were listed as the primary agent in 553 (11%) of intentional and 58 (8%) of unintentional cases. In the intentional group, the top five agents were oxycodone (n = 148 cases, 27%), methadone (n = 91, 16%), hydrocodone (n = 80, 14%), tramadol (80, 14%) and heroin (n = 41, 7%). Of the unintentional overdoses, the most common agents were buprenorphine (n = 16, 28%), oxycodone (n = 12, 21%), methadone (n = 9, 15%), morphine (n = 6, 10%) and tramadol (n = 5, 9%). Naloxone was administered to 26 patients in the unintentional category and 203 in the intentional overdose category (44.8% versus 36.7% p = 0.22). Males accounted for 305/611 (50%) and females for 306/611 (50%) of opioid encounters overall. Of intentional cases 279 (50%) were males, and 274 (50%) were females. For unintentional overdoses, males accounted for 26 (45%) and females 32 (55%) of cases. The majority of intentional overdoses (483/553, 87%) occurred in adult patients (age greater than 18 years). However, most unintentional exposures were in children less than 7 years of age (34/58, 59%).

**Conclusion:** The most common opioid encountered in overdose was oxycodone (26% of all cases). There was no significant difference in naloxone use between intentional and unintentional overdoses in this dataset. More than half of unintentional overdoses occurred in patients 6 years of age and under (34/58, 59%); this emphasizes the importance of overdose prevention targeted towards this age group. Opioid overdose reported in the ToxIC database provides important details including types of pharmaceuticals, user demographics and intent and need for treatment. This information can be used to target at risk populations for prevention programs.



### 314. Cardiovascular toxicity with levetiracetam overdose

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**Objective:** Case reports and case series of levetiracetam in overdose report its toxicity as mild central nervous system depression with only one case report of decreased level of consciousness requiring intubation and ventilation.<sup>1</sup> There are no reports of cardiovascular effects. The aim was to describe a case of cardiovascular toxicity in an overdose of levetiracetam.

**Case report:** A 43-year-old female with a past history of epilepsy presented 8 hours after an overdose of 60-80 g levetiracetam and 10 g/600 mg paracetamol/codeine combination product. Her Glasgow Coma Scale (GCS) was 15 with a heart rate (HR) of 40 bpm and a blood pressure (BP) of 84/56 mmHg. Her electrocardiogram showed sinus bradycardia of 42 bpm with normal QRS and QT intervals. She was administered 1.2 mg of atropine and 3 litres of 0.9% saline. Her HR and BP transiently increased to 80 bpm and 111/57 mmHg, respectively, before falling back to 40 bpm and 88/62 mmHg about 90 minutes later. Despite her bradycardia and hypotension, she remained well perfused with normal capillary return. A bedside cardiac echo the following day demonstrated normal left ventricular contractility. Twenty four hours after presentation her HR remained low at 37-48 bpm, BP between 86/44 and 102/55 mmHg; and urine output between 13-50 mls per hour. Her renal function and serial venous lactate concentrations were normal. Approximately 36 hours post-ingestion her HR and BP started to increase and on discharge (48 hours post-ingestion) her HR was 68 with a BP 131/81. Six serum samples were available and levetiracetam was quantified using liquid chromatography-tandem mass spectrometry (LC-MS/MS). On admission the concentration was 462.5 mg/L. The concentration time data were analysed using MONOLIX<sup>®</sup> version 4.2 (Lixoft, Orsay, France. www.lixoft.com) and included information from a previous pharmacokinetic model of therapeutic dosing.<sup>2</sup> A one-compartment model with first order input adequately described the timed concentration data, with absorption coefficient, 1.32 h<sup>-1</sup>, volume of distribution, 75 L and an elimination half-life of 10.4 hours.

**Conclusion:** This is the first report of cardiovascular toxicity associated with a massive ingestion of levetiracetam. The timecourse of the concentration data was consistent with the clinical course. Levetiracetam appears to cause bradycardia and hypotension that is potentially responsive to atropine and intravenous fluids.

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### 315. Methotrexate exposures reported to the Poisons Information Centre Erfurt, Germany

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**Objective:** Since 2000 the Poisons Information Centre Erfurt has observed gradually increasing numbers of methotrexate exposures, particularly cases due to medication errors. We evaluated the causes and risks of these cases.

**Case series:** Between September 2000 and August 2014, a total of 94 exposures to methotrexate were reported. Of these cases, 24 (25.5%) were suicide attempts, 14 (14.9%) were accidental ingestions (mostly by children) and in 19 cases (20.2%) adverse events at therapeutic doses had occurred. Medication errors were observed in 37 cases (39.4%), of which one third (n = 13) occurred in hospitals or care homes, and two-thirds (n = 24) at home. In 14 cases, daily application of a weekly dose of methotrexate for 4 to 21 days resulted in pancytopenia and mucositis, with one fatality. Severity of adverse and toxic effects appears to increase proportionally to the administered dose. In 2 cases, high-dose cytotoxic therapy resulted in renal failure as a severe adverse effect, and in one case a medication error (300 mg over 10 days) resulted in renal impairment. Moreover, toxic effects after smaller doses were more severe in elderly patients with underlying disease, whereas accidental ingestion of a small dose by healthy children and adults rarely resulted in any symptoms. We describe two cases in elderly patients. A 76-year-old male developed pancytopenia following ingestion of 15 mg/day for 8 days (120 mg in total) in hospital and died 4 days later. No information concerning other symptoms is available. In the other case, a 78-year-old male with rheumatoid arthritis, type II diabetes mellitus, cardiac decompensation and pacemaker implantation after myocardial infarction developed severe symptoms (pancytopenia, mucositis, gastrointestinal bleeding, oesophagitis, hemorrhagic cystitis and methotrexate-induced pneumonia) following ingestion of 10 mg/day for 4 days (40 mg in total) in hospital. He recovered gradually over a period of six weeks.

**Conclusion:** Since 2010, methotrexate is the standard treatment option for rheumatoid arthritis in Germany and is therefore widely used. Despite warnings by the German Federal Institute for Drugs and Medical Devices (BfARM) concerning correct dosage and overdose<sup>1</sup>, medication errors both by patients and by hospital staff are common. Doses exceeding the recommended daily dose can lead to severe symptoms and even death.

#### Reference

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### 316. Unusual management of an inadvertent overdosage of vinorelbine in a child: A case report

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**Objective:** Vinorelbine (VNR), a second-generation vinca alkaloid, is widely used as an antineoplastic drug. To our knowledge, 3 cases of overdose in adults have been published, in 2 cases the patient died.<sup>1</sup> No specific treatment for VNR overdose exists. We report a case of accidental administration of 5-fold overdose in a child, its management and the quantification of VNR and its metabolites in blood, urine and stool samples.

**Case report:** A 4-year-old child scheduled to receive 11.7 mg of intravenous VNR as maintenance treatment for rhabdomyosarcoma, was given 58.3 mg in error. The VNR concentration in the blood after 4.5 hours was 96 ng/mL and the subsequent daily measurements were <0.5 ng/mL. Repeated doses of activated charcoal and intravenous infusion of N-acetylcysteine (NAC) were given. Observable symptoms were grade 3 neutropenia, nausea, mucositis, peripheral neuropathy, muscle aches and intestinal hypomotility. Fluids, lactulose, an antiemetic, antibiotics, analgesics, biotin and granulocyte colony-stimulating factor were administered. No significant alterations in vital signs and in laboratory exams were registered. To monitor the elimination of VNR, concentrations were quantified in urine samples and were 746 ng/mL, 214 ng/mL, 92 ng/mL, 21 ng/mL, <0.5 ng/mL after 24, 48, 72, 96, 120 hours, respectively. In stool samples the concentrations were 753 ng/g and 15,600 ng/g after 96 and 120 hours, respectively. The clinical course was favourable and the patient was discharged 14 days after admission.

**Conclusion:** Even if charcoal is recommended only in oral intake, pharmacokinetic studies have shown that the enterohepatic cycle of the drug occurs even after intravenous administration of high doses of VNR.<sup>2</sup> In addition, an intravenous infusion of NAC was administered in order to prevent cell damage to different target tissues mediated by VNR-induced glutathione depletion as *in vitro* studies demonstrated that the administration of NAC is able to inhibit the production of ROS-induced VNR and the following cytotoxicity.<sup>3</sup> Although further studies are needed to confirm the usefulness of charcoal and NAC associated with symptomatic treatment, they could be possible aids in order to obtain a favourable outcome.

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## 317. "Massive" paracetamol overdose

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**Objective:** To describe the characteristics, treatments and outcomes in "massive" paracetamol overdose.

**Methods:** Observational study of massive paracetamol overdoses, from two clinical toxicology units over 4 years and calls to the New South Wales Poison's Information Centre (NSW PIC) over 2 years. Acute ingestions (immediate release) of  $\geq 40$  g paracetamol taken over less than 8 hours were included. Toxicology unit data was extracted from clinical databases and medical records. Data from NSW PIC calls were collected prospectively as a part of the Australian Paracetamol Project. Information collected included demographic and ingestion data, serial paracetamol concentrations, treatments received and outcomes.

**Results:** There were 55 massive paracetamol overdoses with reported median dose ingested of 50 g (range: 40-150 g). The median age was 22 years (range 14-78 years); 38 (69%) were female and median time to presentation was 2.5 hours (range 0.5-60 hours). Activated charcoal was administered to 11 (20%), at a median time of 1.5 hours post-ingestion (range 0.5-3.25 hours). N-acetylcysteine (NAC) was commenced in all patients, 82% within 8 hours of ingestion. Seven (13%) subsequently had concentrations below the 150 mg/L (4 hour) paracetamol nomogram line. In Australia intravenous NAC is given as a three-stage infusion (300 mg/kg over 20-21 hours).<sup>1</sup> Seventeen (31%) had dose adjustments, most commonly doubling the third infusion from 100 mg/kg to 200 mg/kg over 16 hours. Twenty-three (42%) had prolonged NAC courses either because of abnormal liver function tests (LFTs) or detectable paracetamol concentrations after NAC completion. Thirteen patients developed abnormal LFTs, there was no significant difference in the median dose ingested in those who developed abnormal LFTs and those who had not, 50 g in both ( $p = 0.4635$ ). The median time to commencement of NAC treatment was significantly different in both groups, 4 hours versus 10.5 hours in those who developed abnormal LFTs ( $p = 0.001$ ). Four patients who developed abnormal LFTs had NAC commenced within 8 hours of ingestion. Seven of the thirteen patients developed alanine transaminase  $> 1000$  U/L, including two who had NAC commenced within 4 hours of ingestion, one had a liver transplant. One patient who developed abnormal LFTs was administered activated charcoal. The median paracetamol dose ingested, in those receiving or not receiving activated charcoal, was not significantly different 50 g in both groups ( $p = 0.7890$ ).

**Conclusion:** In this observational study of massive paracetamol overdoses, a significant proportion of patients required prolonged NAC treatment. Furthermore 2 patients developed hepatotoxicity despite early NAC treatment.

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## 318. Tramadol overdose is associated with an increased risk of seizure but not serotonin toxicity

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**Objective:** Tramadol is a commonly used centrally acting analgesic that has been associated with seizures in overdose and suspected to cause serotonin toxicity. This study sought to investigate the clinical effects of tramadol overdose.

**Methods:** This was a retrospective review of tramadol overdoses (> 400 mg) admitted to a tertiary toxicology unit from November 2000 to June 2013. Demographic details, information on ingestion (dose, coingestants), clinical effects, complications (seizures, serotonin toxicity, and cardiovascular effects), length of stay (LOS) and intensive care unit (ICU) admission were extracted from a clinical database.

**Results:** There were 71 cases of tramadol overdose with 43 (61%) being female. The median age was 41 years (range 17-69 years) and the median dose was 1000 mg (range 450-6000 mg). Seizures were dose-related and occurred in eight patients, with one patient having three seizures (12.5%). One of the eight seizure patients (12.5%) co-ingested a benzodiazepine compared to 16 of 63 (25%) patients without seizures. There were no cases of serotonin toxicity that met the Hunter Serotonin Toxicity Criteria. Tachycardia occurred in 27 (38%) patients, mild hypertension (systolic blood pressure > 140 mmHg) in 32 (45%) and one patient had a pre-existing left bundle branch block. Glasgow Coma Scale was less than 15 in 29/71 patients (41%) and less than 9 in five patients, including three co-ingesting tricyclic antidepressants and two ingesting 3000 mg and 900 mg of tramadol who developed respiratory depression that responded to naloxone. Respiratory depression with oxygen saturation < 94% occurred in 13 patients (18%), with a median dose of 2500 mg (500-4000 mg) which was significantly different to patients not developing respiratory depression, with a median dose of 1000 mg (450-6000 mg;  $p = 0.003$ , Mann-Whitney test). The median LOS was 16 hours (range: 1.8-227.8 hours) and eight (11%) patients were admitted to the ICU, but in all cases this was due to toxicity from coingestants.

**Conclusion:** Tramadol overdose was found to be associated with a significant risk of seizures and respiratory depression in more severe cases, both which appear to be related to the ingested dose. Tramadol overdose does not appear to be associated with serotonin toxicity, and opioid-like effects and adrenergic effects were more prominent.

### 319. Levodropropizine overdose: A multicenter analysis of poison center data

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**Objective:** Levodropropizine is a peripherally acting cough suppressant drug which presumably acts on the trancheobronchial system. The drug is approved for children aged over two years and adults. The aim of the study was to evaluate toxicity and the outcome.

**Methods:** In an observation period between 2010 and 2013 case data were sampled from six German and one Austrian poison

center. Follow-up information regarding symptoms and clinical outcome were obtained by means of structured questionnaire. The symptoms were graded according to the Poisoning Severity Score (PSS).

**Results:** The total number of cases was 47. Of these, follow up information was obtained in 41 infant patients (87%). Toddlers ( $n = 40$ ) were the most exposed age group, 16 of them were under 2 years old. The male to female ratio was nearly balanced. The range of stated dose taken was less than the daily dose to a 4-fold daily dose. In the majority of cases the clinical course was benign. In total 29 patients remained asymptomatic, 17 had minor signs. The most reported symptoms were fatigue ( $n = 9$ ), general weakness ( $n = 3$ ), mild confusion ( $n = 3$ ) and paleness ( $n = 3$ ). Nausea, abdominal pain, bedwetting, sweating, restlessness, mild tachycardia and a short bradycardic period were each once reported. One minor allergic skin reaction occurred, a well-known therapeutic side effect.<sup>1</sup>

**Conclusion:** The antitussive levodropropizine appears to be of low toxicity when taken in overdose. In this case series 63% of the children were asymptomatic and 35% had only minor symptoms, mostly as mentioned above in accordance with reported adverse drug reactions. Nevertheless, these data are too limited to rule out more severe poisoning.

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### 320. Accidental intravenous administration of haloperidol decanoate

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**Objective:** Haloperidol decanoate is synthesized by esterification of the active drug to a long chain fatty acid (decanoic acid) and then dissolved in a vegetable oil. After intramuscular administration it is absorbed via the lymphatic system and then hydrolysed to haloperidol. As a result, the haloperidol plasma concentration rises gradually, usually peaking within the first week after injection and falling thereafter with an apparent half-life of about 3 weeks. Haloperidol is available in 5 mg vials, the decanoate formulation in 50 mg vials. We describe two cases of erroneous administration of haloperidol decanoate via intravenous route, with measurement of haloperidol serum concentrations (by high performance liquid chromatography with detection limit of 0.5 ng/mL).

**Case report:** Case 1. A 55-year-old male erroneously received a 50 mg vial of haloperidol decanoate in a 1 hour infusion. After the infusion, he was transferred to ICU to be monitored. Serum haloperidol was undetectable 8 hours later. He remained asymptomatic and returned to the psychiatry ward the day after. Case 2. An 89-year-old woman received 50 mg (1 mL vial) of haloperidol decanoate intravenously instead of intramuscularly. The serum



concentration was 1.1 ng/mL one hour after administration and undetectable 24, 48 and 72 hours later. She was monitored for two days but no neurological impairment or rhythm disturbances were observed.

**Conclusion:** Haloperidol intravenous administration is currently considered contraindicated because of its relation with increased cardiotoxicity. However, the effects of erroneous intravenous administration of the decanoate form are unknown. A previous report described tachycardia in a very agitated patient who received intravenous haloperidol decanoate.<sup>1</sup> In our cases the accidental administration of intravenous haloperidol decanoate was not associated with adverse effects or pulmonary embolism due to the oily vehicle. Serum concentrations were undetectable or very low (1.1 ng/mL, therapeutic range 5.6-16.9 ng/mL and a recommended target concentration of 10 ng/mL).<sup>2</sup> It is possible to speculate that hydrolysis of the decanoate formulation also occurs slowly in the blood.

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### 321. New oral anticoagulants (NOACs): An increasing problem for poison centres?

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**Objective:** An increasing number of patients receive therapeutic anticoagulation to prevent thrombotic or thromboembolic events. Besides vitamin K antagonists (VKAs) since 2009 three new oral anticoagulants (NOACs) are available as alternative therapeutic options. So far there is only little experience concerning poisoning due to these new substances, whose clinical management deserve even more attention due to the lack of a specific antidote therapy.<sup>1-4</sup>

**Methods:** Retrospective analysis of PC data collected between January 2009 and June 2014 on human exposures to oral anticoagulants including VKAs (warfarin, phenprocoumon) and NOACs (rivaroxaban, dabigatran, apixaban). Further analysis including epidemiology, follow up, clinical presentation according to the poisoning severity score (PSS) and outcome.

**Results:** In total 69,232 cases with human pharmaceutical poisonings were reported to the PC within that period. Of these 449 cases (0.6%) involved oral anticoagulants: 349 VKAs and 100 NOACs. These included 212 cases of single substance intoxications and 67 of these had a successful follow up. The average age was 47 years. The overall leading causes of exposure were intended/suicidal (44%) and accidental (33%). Concerning the 67 single substance intoxications with follow up distribution and PSS was: 54 VKAs: PSS 0 or 1 65% (n = 35), PSS 2 or 3 35% (n = 19) and 13 NOACs: PSS 0 or 1 77% (n = 10), PSS 2 or 3 23% (n = 3). The main clinical sign reported were coagulation disturbances and bleeding. Death occurred in 1 case (NOAC).

**Conclusion:** In the context of the widespread use of VKAs and NOACs poisoning seems to be less common compared to other pharmaceutical groups. While prescription of the NOACs is rapidly increasing, the number of cases reported to the PC is still low compared to VKAs. All of the reviewed substances have to be announced as potentially harmful in case of overdose even though most cases of acute poisoning can be treated successfully in a setting of hospital care. Poisons Centres can help to gain more experience to provide risk assessment and clinical management recommendations concerning new anticoagulant classes.

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### 322. A decade of Australian methotrexate dosing errors: What more can be done?

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**Objective:** The use of methotrexate as an immunomodulating drug for rheumatological, dermatological and gastrointestinal disorders has become well established. It is generally well tolerated when used in recommended weekly doses, however severe toxicity can result when erroneously taken daily. We investigated the rates of dosing errors in Australia with methotrexate, specifically where doses were taken on three or more consecutive days.

**Methods:** A retrospective review of calls made to the New South Wales Poisons Information Centre, coronial cases logged in the National Coronial Information System and the reports to the Therapeutic Goods Administration Database of Adverse Event Notifications. The time period examined was 1 January 2004 to 31 December 2013. Exposures to methotrexate were retrieved and then manually reviewed for inclusion. Cases were included if accidental and there was evidence of daily dosing on at least three consecutive days.

**Results:** Five deaths were identified in the coronial dataset (the most recent in 2012), 14 cases were identified in the adverse events database. The NSW PIC dataset contained 43 people who took daily doses of methotrexate in error. The incidence of cases has remained fairly stable at an average of 4 cases per year over the past decade. Errors occurred through patient confusion, pharmacist labeling and pharmacist packaging of dosette packs. Clinical effects experienced were consistent with previously reported chronic methotrexate toxicity.

**Conclusion:** Dosing errors with methotrexate can be lethal and cause significant morbidity and they continue to occur despite a number of alerts which have been issued in the past decade. Further strategies need to be implemented to reduce these preventable harms from occurring. Recent suggestions for improvement

have included reductions in packet size and mandatory labeling on packaging of weekly dosing. Monitoring of medication errors through poisons centre systems can provide more information and yield more cases than through other available systems and are vital for optimal pharmacovigilance.

### 323. High-visibility warning labels on paracetamol-containing products do not prevent supratherapeutic ingestion

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**Objective:** In Australia, legislation requires package labels warning of co-administration with other paracetamol products, and maximum safe daily dosing (4 g). Labelling style, size and visibility differ, potentially leading to variability in the chance of supratherapeutic misadventure. We studied the likelihood of supratherapeutic misadventure using products with standard labelling (SL) versus products labelled with one of two custom designed warning labels in addition to SL.

**Methods:** The study was a prospective, observational study, conducted from May 2013 to July 2014 of patients and visitors attending a tertiary level Emergency Department. Participants undertook an interview to create a simulated 24 hour scenario in which they chose from a range of labelled lone paracetamol and compound paracetamol-containing medications to treat dental pain on 6 occasions. It was not possible to take 6 standard doses of analgesic medications without taking a supratherapeutic paracetamol dose. Participants were randomised to choose from one of three groups of analgesic medications with different packaging labelling: 1) SL alone, 2) SL + small customised warning label, 3) SL + large customised warning label. End-points were either the participant taking a supratherapeutic dose of paracetamol (> 4 g) or stating that they would not take more paracetamol-containing medication as indicated by the package labelling. Primary outcome was to determine if participants exceeded the recommended maximum dose of 4 g within 24 hours.

**Results:** In total 118 surveys were completed (66% females). The mean age of participants was 53 years. Within the 24 hour scenario period 42 (35% of total) participants took greater than 4 g of paracetamol; 10/43 (23%) of the SL alone group, 13/35 (37%) of the SL + small customised warning label group and 19/40 (48%) of the SL + large customised warning label group ingested greater than 4 g of paracetamol. A statistically significant number of participants in the SL + large customised warning label group ingested > 4 g of paracetamol, compared to the SL alone group ( $p < 0.02$ ). There was no significant difference between the two groups with SL + customised warning labels. Only 38 (32%) of all participants read the product packaging.

**Conclusion:** In this small simulated dental pain scenario, use of customised warning labels in addition to standard labelling on lone and compound paracetamol containing products did not reduce the likelihood of supratherapeutic misadventure.

### 324. Acute toxicity profile of tolperisone in overdose: A consecutive case series

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**Objective:** Tolperisone is a centrally-acting muscle relaxant that acts by blocking voltage-gated sodium and calcium channels. Despite being considered relatively safe in overdose, there is a forensic publication describing three fatalities due to tolperisone poisoning.<sup>1</sup> Information on the clinical features of tolperisone poisoning is lacking in the scientific literature. The aim of this study was to investigate the demographics and clinical features of acute overdoses with tolperisone.

**Table 1.** Signs and symptoms of tolperisone overdose classified according to severity (Poisoning Severity Score).

		Severity (patients n = 75)		
Clinical signs		Mild n (%)	Moderate n (%)	Severe n (%)
Central nervous system	Somnolence	29 (38.7%)		
	Coma <sup>1</sup>		1 (1.3%)	6 (8.0%)
	Seizures <sup>2</sup>		5 (6.7%)	3 (4.0%)
	Agitation	2 (2.7%)	1 (1.3%)	
	Myoclonus		1 (1.3%)	
	Bradykinesia	4 (5.3%)		
	Ataxia	1 (1.3%)		
	Vertigo	4 (5.3%)		
	Tremor	1 (1.3%)		
	Dysarthria	2 (2.7%)		
Cardiovascular system	Dystonic reaction <sup>3</sup>	1 (1.3%)		
	Tachycardia <sup>4</sup>	12 (16.0%)	3 (4.0%)	
	Hypertension	5 (6.7%)		
	Hypotension	2 (2.7%)		
	QT-prolongation <sup>5</sup>	2 (2.6%)		
Respiratory system	Cardiac arrest			1 (1.3%)
	Respiratory depression/apnoea			3 (4.0%)
Various	Tachypnoea	1 (1.3%)		
	Gastrointestinal symptoms <sup>6</sup>	16 (21.3%)	3 (4.0%)	
	Hypokalemia <sup>7</sup>	2 (2.7%)	1 (1.3%)	1 (1.3%)
	Mydriasis	2 (2.7%)		
	Headache	2 (2.7%)		

<sup>1</sup>moderate: GCS 8-9; severe: GCS  $\leq$  7.

<sup>2</sup>moderate: single convulsive episode; severe: multiple seizures.

<sup>3</sup>focal dyskinesia.

<sup>4</sup>adults: mild: 100-139 beats/min; moderate 140-179 beats/min; children (< 2y) moderate: > 205 beats/min.

<sup>5</sup>mild - children (1-15 y): QTc 440-500 ms; - adults: males 430-500 ms, females 450-500 ms.

<sup>6</sup>mild: nausea, mild vomiting, epigastric pain; moderate: repeated vomiting.

<sup>7</sup>mild: 3.0-3.4 mmol/L, moderate: 2.5-2.9 mmol/L, severe < 2.5 mmol/L.

**Methods:** A retrospective review of acute overdoses with tolperisone in adults and children (< 16 years), either alone or in combination with one non-steroidal anti-inflammatory drug in a dose range not expected to cause central nervous effects, reported to our poison centre between 1995 and 2013.

**Results:** In total 75 cases were included: 51 females (68%) and 24 males (32%); 45 adults (60%) and 30 children (40%). Of these 6 adults (13.3% of adults) and 17 children (56.7% of children) remained asymptomatic, and mild symptoms were seen in 25 adults (55.6%) and 10 children (33.3%). There were 9 adults (20.0%) with moderate symptoms, and 5 adults (11.1%) and 3 children (10.0%) with severe symptoms. There were no fatal cases. Signs and symptoms predominantly involved the central nervous system. Furthermore some severe cardiovascular and respiratory signs and symptoms were reported (Table 1). The minimal dose for seizures and severe symptoms in adults was 1500 mg. In 11 cases the latency between the ingestion and the onset of symptoms was known and reported as 30-90 minutes.

**Conclusion:** Acute overdose of tolperisone may be life-threatening, with a rapid onset of severe neurological, respiratory and cardiovascular symptoms. With alternative muscle relaxants available, the current indications for tolperisone should be rigorously evaluated.

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## 325. Sleeping Beauty: Prolonged sedation following an alprazolam and fluconazole overdose

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**Objective:** Alprazolam is a short-acting benzodiazepine with an average half-life of 10-14 hours.<sup>1</sup> We report a case of prolonged sedation following an overdose of alprazolam and fluconazole.

**Table 1.** Alprazolam and fluconazole concentrations during the patient's admission.

Time post arrival to hospital (hours)	Alprazolam concentration (micromol/L)	Fluconazole concentration (mg/L)
On arrival	> 5	5.1
8.5	4.35	–
22	2.92	–
27.5	2.57	–
55	1.31	1.4
65.5	0.73	< 1.0 L
Reference	Ten subjects on alprazolam 0.5mg tds produced a steady-state plasma range of 0.02–0.06 micromol/L.	A therapeutic range for fluconazole has not been established. An oral dose of 100 mg should produce trough concentrations at steady-state of 1–3 mg/L.

**Case report:** A 58-year-old female presented with a decreased level of consciousness after being found at home on the floor, surrounded by empty pill packets. She stated 24 hours earlier she had taken fluconazole 200 mg × 50 and an unknown amount of alprazolam, ethanol and paracetamol. Her past medical history included candidal esophagitis, Sjogren's syndrome and benzodiazepine dependence. Her medications included alprazolam, oxazepam and fluconazole. On presentation she was haemodynamically stable, Glasgow Coma Scale (GCS) 14, respiratory rate 12 breaths/min, oxygen saturation 90% on room air. Naloxone had no effect. No blood ethanol was measured due to the late presentation. Over the next day she became less responsive with a respiratory rate of 9 breaths/min and worsening hypoxia. She required intubation 24 hours after her presentation and remained intubated for 48 hours. She was neurologically normal by day 3. Her admission was complicated by aspiration pneumonia and a mild creatine kinase rise to 3500 IU with a right arm neuropathia secondary to her prolonged period of immobility before being found. Her blood alprazolam and fluconazole concentrations are shown in the Table 1. The calculated half-life of alprazolam was 26.9 hours. Alprazolam is primarily metabolised by cytochrome P450 CYP3A4.<sup>1</sup> All azole antifungals can cause significant CYP3A4 inhibition<sup>2</sup> which can result in a significantly increased half-life of short-acting benzodiazepines such as alprazolam, as in this case.

**Conclusion:** This is a case of overdose with alprazolam and fluconazole that was complicated by a prolonged alprazolam half-life of 26.9 hours, resulting from CYP3A4 inhibition by fluconazole resulting in decreased metabolism of alprazolam.

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## 326. Lack of serious cardiotoxicity in patients with desvenlafaxine overdose

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**Objective:** Desvenlafaxine is the pharmacologically active metabolite of venlafaxine, a commonly prescribed serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant known to cause cardiotoxicity (ECG abnormalities, haemodynamic instability and arrhythmias) in massive overdose. However, there is paucity of literature on the adverse haemodynamic or cardiotoxic effects of desvenlafaxine in overdose. This study aims to identify adverse cardiovascular effects and ECG changes in patients presenting to our regional toxicology service with desvenlafaxine overdose.

**Methods:** Retrospective review of all desvenlafaxine-poisoned patients presenting to our service between 2010 and 2014. All cases of desvenlafaxine ingestion were identified from our service database. Case records were reviewed for dose ingested, co-ingestants, haemodynamic parameters, ECG abnormalities, adverse events



and complications of overdose, in-hospital length of stay (LOS) and treatment modalities. Two investigators independently measured QT intervals manually and maximal QT-heart rate (HR) pairs corresponding to each case were plotted on the QT nomogram.

**Results:** A total of 25 cases of deliberate desvenlafaxine poisoning were identified; in 8 cases only desvenlafaxine was ingested (32%). Median dose was 750 mg (range 150-3400 mg). Amongst co-ingestants, ethanol (n = 6), diazepam (n = 4) and temazepam (n = 4) were the commonest agents. Background history of depression featured in 19 cases. Hypertension (n = 6), tachycardia (n = 9) and low grade fever (n = 4) were the most common clinical features. Hypotension was noted in 2 cases. Vomiting (n = 1) and coma (n = 1) were present in only one case resulting in intubation on arrival (further complicated by aspiration pneumonia). Tremor (n = 1) and hyperreflexia/clonus (n = 1) were noted in two separate patients but neither satisfied the Hunter criteria for serotonin toxicity. No cases of seizures, arrhythmias or QRS prolongation were observed. Only 1 case was found to breach the QT-HR nomogram "at-risk" line. Management in all cases was supportive with the main treatment modality being intravenous fluids (n = 19). Median LOS was 0.5 days (range 0.13-17 days).

**Conclusion:** In this small case series, no serious cardiotoxicity or ECG abnormalities were observed following desvenlafaxine overdose up to 3400 mg.

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### 327. Patterns of toxicity of antiretroviral therapy as reported to the UK National Poisons Information Service (NPIS)

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**Objective:** The number of people in the UK accessing HIV care, including antiretroviral therapy (ART), has increased substantially over the last 15 years.<sup>1</sup> Up to 20% of HIV positive patients self-harm and 2.4% of deaths within this population result from suicide.<sup>2</sup> ART toxicity may result from the complexity of regimens used. Despite some case reports, the patterns and epidemiology of ART toxicity are not well known. This study was therefore performed to assess the epidemiology and features of ART toxicity as reported in UK National Poisons Information Service (NPIS) telephone enquiries.

**Methods:** NPIS telephone enquiry records were reviewed for the period February 2004 to July 2014, analysing demographic details and the Poisoning Severity Score (PSS) for each enquiry.

**Results:** There were 557 enquiries identified, including calls from hospitals (n = 311), public access telephone advisory services (n = 124) and primary care (n = 54). Annual enquiry numbers for

the six complete years from 2008 to 2013 were 74, 74, 78, 61, 75 and 75. Enquiries involved 414 adults (285 males, 127 females, 2 unknown), 49 neonates, 40 children aged from 1-12 years (24 female, 17 male, 1 unknown), 30 teenagers between 13-19 years (24 female, 6 male) and 3 elderly males (over 75 years). The most common circumstances were intentional overdose (n = 243), therapeutic errors (n = 180) and accidental exposures (n = 89). There were 791 exposures to individual antiretroviral agents recorded. The most common products involved in intentional exposures were Truvada<sup>®</sup> (emtricitabine and tenofovir) (n = 68), Atripla<sup>®</sup> (efavirenz, emtricitabine and tenofovir) (n = 44) and nevirapine (n = 38) and for therapeutic errors were Truvada<sup>®</sup> (n = 55), zidovudine (n = 38), tenofovir (n = 22) and nevirapine (n = 21). Many intentional exposures involved co-ingestants such as therapeutic or recreational drugs. PSS was recorded as 3 (severe) in 5 patients (6 enquiries), 2 in 12 patients (13 enquiries), 1 in 128 enquiries, 0 in 315 enquiries and not applicable/unknown in 46 enquiries. Severe features of toxicity were often likely to be related to co-ingestants.

**Conclusion:** Most enquiries about ART arise from intentional overdose or therapeutic error. Severe toxic effects are uncommon and often result from co-ingestants. Further research is needed to evaluate the spectrum of toxicity of individual antiretroviral agents.

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### 328. Overdoses of riluzole reported to the UK National Poisons Information Service

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**Objective:** The UK National Poisons Information Service (NPIS) maintains TOXBASE<sup>®</sup>, an international poisons information database. In order to ensure that it is kept up-to-date telephone enquiries to NPIS are regularly reviewed and those without TOXBASE<sup>®</sup> entries about which 3 or more enquiries are received and those with Poisoning Severity Score (PSS)<sup>1</sup> > 1 are recommended for addition to the database. Riluzole<sup>2</sup>, a glutamine antagonist used for treating the amyotrophic lateral sclerosis form of motor neurone disease, was identified using this method and as there was little information available on its toxicity this study was carried out to review NPIS call records.

**Methods:** Information was extracted from telephone enquiries on UKPID, the UK poisons enquiry database from 1 September 2007 to 30 September 2014, and analysed using Excel.

**Results:** Fifteen enquiries about 14 patients were retrieved. Enquiries came from hospitals (n = 6), UK health telephone advice line nurses (n = 5), general practitioners (n = 2) and nursing homes (n = 2). A 1-year-old child ingested 25 mg but no further details were available. The remaining 13 adults were aged 26–78 years (average 64.3, median 67; males 7, females 6). Accidental exposures: Five of the patients were taking riluzole therapeutically and had accidentally taken or been given 1 or two extra doses (normal dose 50 mg, twice daily). Four were asymptomatic and one was described as tired. A further accidental exposure to 200 mg (features unknown), and 2 accidental exposures to 50 mg (numb mouth; asymptomatic) were reported. One enquiry concerned a 64-year-old on riluzole who suffered a cardiac arrest but there was no evidence of overdose. Deliberate overdoses: A 26-year-old female, taking therapeutic riluzole, took a deliberate overdose of 1500 mg, some citalopram and 1500 mg tolperisone and suffered nausea and tachycardia. A 60-year-old female deliberately ingested an unknown amount of riluzole with a “large” amount of zopiclone and was very sedated (PSS2). A 58-year-old male took 900 mg simvastatin, 12 g paracetamol, 11 x bendroflumethiazide and 3300 mg of riluzole 9 hours previously and was somnolent.

**Conclusion:** There is very little information about riluzole in overdose. Accidental ingestion of 1 or 2 extra doses in adults taking riluzole therapeutically does not seem to cause problems. The deliberate overdoses (ranging from 1500 to 3300 mg) in this small series involved multiple drugs but there were no serious effects.

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### 329. Severe lithium poisoning: A case series from Norway

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**Objective:** Severe lithium poisonings are rare, and the use of dialysis debated. The aim of this case series was to relate our past and present management of severe lithium poisoning to current published guidelines.

**Methods:** Cases of severe lithium poisonings (serum lithium concentration > 2.5 mmol/L) treated between 2003 and 2013 were included.

**Results:** Six cases of severe lithium poisoning with lithium concentration 2.7–9.6 mmol/L were included; there were five females and one male, aged 15 to 62 years. Three cases were acute-on-chronic (AC), two were acute (A) and one was a chronic poisoning (C). The time delay between ingestion and

admission was 2–24 hours, excluding the C. Five patients had altered mental status upon admission. Other neurological features included rigidity and ataxia. The two cases of A had extended QTc (> 500 ms) on their ECGs, but no arrhythmias. Three patients (lithium 5.0 (AC), 8.0 (A) and 9.6 mmol/L (A), respectively) were sedated and ventilated. Gastric decontamination was performed in three cases, of whom two were intubated. Two patients received hemodialysis (lithium 5.0 (A) and 4.1 mmol/L (AC), for 4 and 6 hours respectively), and one patient (lithium 8.0 mmol/L (A)) received hemodialysis (21 hours) followed by continuous venovenous hemodiafiltration (12 hours). One acute poisoning with an initial lithium of 9.6 mmol/L was only given intravenous fluids/electrolytes and monitored closely as lithium rapidly declined. All patients survived. According to guidelines,<sup>1,2</sup> extracorporeal drug removal could have been recommended in all but one of these cases (A with lithium 2.7 mmol/L), since lithium was either > 4.0 (recommended for any type of poisoning) or > 2.5 mmol/L in the case of chronic poisoning. However, recommendation of fluid therapy and no dialysis was based on individual considerations. For the A with lithium 9.6 mmol/L, renal function was normal and the patient was dehydrated. For the C with lithium 2.9 mmol/L, renal function was impaired, but due to capacity problems initially, dialysis was delayed and lithium decreased to 2.2 during the first 24 hours.

**Conclusion:** During the last 10 years, severe lithium poisoning in Norway was managed more conservatively and individually than recommended by the present guidelines, which are about to be implemented.

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### 330. Two years of paracetamol misdosing: The experience of National Milan Poison Control Center

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**Objective:** Paracetamol is present in many products and its easy availability makes it one of the most frequently involved in medication errors (MEs).<sup>1</sup> This study aims to investigate reports of MEs received at the National Milan Poison Control Center (NMPCC) concerning paracetamol, in order to reduce the risk of error.

**Methods:** We analyzed all consultations for MEs related to prescribed and self-prescribed drugs containing paracetamol between July 2012 and July 2014. Each case was re-evaluated to determine: the severity of the symptoms, treatment, patient characteristics, pharmaceutical form and reason and circumstances of

exposure. Severity of effects was graded according to Poisoning Severity Score.

**Results:** A total of 5,401 MEs were received, 811 (15%) concerning paracetamol. Distribution by age was: 76% of patients were aged < 5 years, 17% 5-19 years, 5% 20-69 years and only 2% 70 years or older. Symptoms were absent in 96.8% (n = 785), mild 1.9% (n = 15), moderate 0.9% (n = 7), severe 0.1% (n = 1) and unknown 0.4% (n = 3). The most common symptoms were elevation in transaminases (n = 14), vomiting (n = 4), and single cases of headache, dizziness, confusion, seizures, agitation and aggression. At least one treatment was prescribed in 96 cases, including N-acetylcysteine (n = 36) and charcoal (n = 15). In 89% of cases the error was committed by the caregiver, 8% by the patient and 2% were iatrogenic. The most frequently reported pharmaceutical form was suppositories (42%), caused by the wrong dosage and wrong route of administration, oral drops (21%), syrup (14%) and tablets (10%). All of these MEs were primarily caused by wrong dosage and exchange of drugs. The trend of requests for information showed a decrease of about 1.2 cases/month, with the presence of expected peaks in winter.

**Conclusion:** PCCs, with ongoing surveillance of MEs, are able to detect old and new contributing factors. In this series suppositories were the most common form involved in MEs; this is probably due to the frequent exchange between suppositories of different dosages and similar packaging. Also, the exchange between liquid oral formulations with different concentrations of paracetamol was common which could potentially lead to severe intoxication. Only the cooperation of PCCs, citizens, health professionals and pharmaceutical companies would be instrumental in reducing MEs.

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## 331. Duloxetine overdose: A case series

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**Objective:** The purpose of the study was to assess the toxicity and clinical feature of duloxetine in overdose. Case series previously described show that the majority of ingestions are generally benign but give insufficient information about toxic dose.<sup>1-4</sup>

**Methods:** Cases of overdose of duloxetine from eight Poisons Information Centres in Austria, Germany and Switzerland were

analysed retrospectively. Inclusion criteria were single drug ingestion, defined dose and documented follow-up. Severity of symptoms was assessed according to Poisoning Severity Score (PSS).

**Results:** A total of 82 cases met the inclusion criteria. Nineteen patients were children (age 0.75-4 years), and 63 patients were adolescents or adults (age 14-82 years). Dose ranged from 15 to 240 mg (1.0-13.5 mg/kg) in children and 60 to 6300 mg in adolescents/adults. Thirteen children remained asymptomatic, whereas in six cases mild or moderate symptoms were observed with doses of 15 mg and 120 mg (1.0 and 10.9 mg/kg), respectively. Most adolescents/adults developed no or only mild symptoms (81%); ten patients suffered from moderate and two from severe symptoms. Mild and moderate effects in adolescents/adults were caused by doses from 60 and 300 mg, respectively. In contrast, adults tolerated doses up to 1800 mg without adverse effects. The minimum dose causing severe intoxication with recurrent seizures was 1800 mg. Most frequent symptoms were nausea/vomiting (48%), somnolence (29%) and tachycardia (24%). Seizures and hypertension occurred in 7% and 5% of all symptomatic cases, respectively.

**Conclusion:** Overdose of duloxetine frequently resulted in altered mental status. Consistent with previously reported case series and case reports neurological and gastrointestinal symptoms were the most frequent symptoms described.<sup>2,3,4</sup> In most cases only mild symptoms occurred. As shown by other authors there is no clear correlation between dose and severity of symptoms.<sup>2,3</sup> However, in this study doses causing moderate symptoms were slightly lower. For a comprehensive assessment of the toxicity of duloxetine further investigations are necessary.

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## 332. Changes to prescribed psychotropics following intentional overdose

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**Objective:** Psychiatric guidelines regarding suicide risk include prescribing psychotropics with low risk of lethality.<sup>1,2</sup> Time of hospital discharge following medication overdose, is a potential opportunity to re-evaluate a patient's medications and choose medications with lower toxicity. Our objective was to determine how frequently hospitalization for intentional drug overdose results in changes to prescribed medication regimen.

**Methods:** This retrospective study was conducted at an urban tertiary care center and approved by the local Institutional Review



Board (IRB). Patients were identified using TOXIDARE, a pre-existing database of all patients receiving a medical toxicology consult. Consults are called at the discretion of primary medical providers. TOXIDARE patients with at least two visits for an overdose were identified. Cases involving accidental ingestion, recreational use, non-medicinal ingestion, or incomplete records were excluded. Admission and discharge medication lists were recorded for each patient and compared for each patient's visit; any medication changes at discharge or a subsequent presentation were identified. Additional data collected included the drugs used in overdose, demographics, and presence of suicidal intent.

**Results:** Forty-four patients were initially identified, with 18 cases, accounting for 38 encounters, meeting inclusion criteria. Of these, 17 had a single repeat presentation, and one had 4 presentations. Median age was 38 years (range 18-59); 61% were female. Average time between presentations was 48 days (range of 3-177; median 36). Twenty-eight encounters (73.68%) involved a change in prescribed medications. Twenty-seven encounters (71.05%) noted a change in psychotropic medication prescriptions; 20 (52.63%) had a psychotropic added, 19 (50%) had a psychotropic discontinued, and 12 (31.57%) had psychotropic medications both added and discontinued. Eighteen encounters (47.37%) recorded no medication changes. Four patients (22.2%) subsequently overdosed on the same prescribed medication(s); 5 (27.78%) used at least partially the same medications and 8 (44.4%) used different medications.

**Conclusion:** In this retrospective review, a majority (71%) of patient encounters for medication overdose involved a change in prescribed psychotropics during the encounter, or at the next presentation. Study limitations include incomplete capture of representing overdose patients and incomplete medical records. In future efforts we hope to collect greater numbers of patients and characterize whether the specific medication changes involve a change to medications associated with lower toxicity in overdose.

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### 333. Serum warfarin concentrations and corresponding INR after intentional warfarin overdose

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**Objective:** Over-anticoagulation with warfarin is a common complication of anticoagulant therapy. Fortunately, intentional overdoses are less common. While elevated international normalized ratio (INR) values associated with intentional warfarin overdoses

have been previously reported, quantified serum warfarin concentrations corresponding to INR values have rarely been described.<sup>1,2</sup> We report measured serial serum warfarin concentrations and correlating the INR following an intentional warfarin overdose with persistently elevated INR.

**Case report:** A 63-year-old-male with a history of a prosthetic heart valve replacement presented to the Emergency Department (ED) 2 hours after ingesting "3 handfuls" (20-30 tabs) of 5 mg warfarin tablets with alcohol as a suicide attempt. On arrival to the ED, he was asymptomatic without evidence of bleeding. He was treated at an outside hospital where INR values were determined; then all samples were sent to our laboratory for analysis. Our laboratory used a liquid chromatography-mass spectrometry/mass spectrometry method to quantify warfarin in serum using diclofenac as an internal standard. The patient's initial INR was 10.9 with a corresponding serum warfarin concentration of 25.1 mcg/mL. Five hours after ingestion, his INR was undetectably high with a warfarin concentration of 28.6 mcg/mL despite receiving 5 mg of vitamin K orally. After receiving 2 units of fresh frozen plasma (FFP), the patient's INR transiently improved to 6, but rose again to undetectably high levels and he received an additional 2 units of FFP and 10 mg of vitamin K subcutaneously. The patient's serum warfarin concentrations declined steadily; however, the INR fluctuated and remained elevated until it fell below 5 by hospital day 7. The patient had no clinical evidence of bleeding during his admission.

**Conclusion:** Serum warfarin concentrations do not correlate well with INR values in overdose. This may be explained by the effect of warfarin on the half-lives of the coagulation factors affected by warfarin therapy rather than a direct effect of the parent drug.

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### 334. Prolonged, refractory glyburide and nateglinide toxicity in the setting of acute renal failure

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**Objective:** Glyburide (glibenclamide) and nateglinide are known to cause symptomatic hypoglycemia in overdose; however, toxicity due to acute renal failure may be under-recognized. Glyburide, a sulfonylurea, acts similarly to nateglinide, a meglitinide. Both drugs bind to the ATP-dependent potassium channels in pancreatic beta cells, increasing insulin secretion. They are metabolized to active metabolites by CYP2C9 and CYP3A4 and undergo renal excretion. The half-life of nateglinide is shorter than that of glyburide (1.5 versus 10 hours, respectively), but renal failure may prolong both half-lives considerably. This case report describes a patient with refractory and prolonged (>48 hours) symptomatic hypoglycemia due to glyburide and nateglinide toxicity in the setting of acute renal failure.

**Case report:** A 65-year-old man with hepatitis B and diabetes mellitus, on tenofovir 300 mg daily, glyburide/metformin 5/500 mg four times daily and nateglinide 120 mg orally twice daily, was brought to the emergency department with altered mental status, left-sided weakness and left facial droop for 1 day. On arrival, his blood glucose concentration was 20 mg/dL. After a 2 mEq/kg dextrose IV bolus, this improved to 220 mg/dL, and his neurologic symptoms resolved. The patient reported 8 days of vomiting prior to presentation and noncompliance with glyburide/metformin for 2 days. He had taken his other medications. Laboratory tests revealed BUN 120 mg/dL, creatinine 10.4 mg/dL (baseline 1.4 mg/dL), pH 7.05, anion gap 30 mEq/L and lactate 10.1 mmol/L. His urine demonstrated protein and blood, and a urine culture was negative. Head computed tomography and renal ultrasound were unremarkable. A dextrose infusion and hemodialysis were initiated in the ICU. Over the next 24 hours, his mental status fluctuated between a Glasgow Coma Scale (GCS) of 6 and 15 despite the dextrose infusion. Glucose concentrations ranged from 30 to 300 mg/dL. On hospital day 2, octreotide 50 mcg was given subcutaneously, and the patient's mental status normalized within 1 hour. Octreotide 50 mcg was given every 6 hours for 4 doses with no further fluctuation of his mental status or glucose concentrations. He was discharged with a normal neurologic exam.

**Conclusion:** This patient developed severe renal failure, leading to refractory hypoglycemia primarily due to nateglinide toxicity. Hemodialysis was ineffective, as glyburide and nateglinide bind extensively to albumin. In contrast, octreotide effectively decreased insulin release in this patient. This case highlights the importance of recognizing glyburide and nateglinide poisoning in patients with renal failure, as well as the futility of hemodialysis to reverse toxicity.

### 335. A survey of doctors' knowledge and confidence in managing paracetamol toxicity

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**Objective:** Paracetamol toxicity is one of the most commonly encountered poisoning locally. The aim of this study was to assess the confidence and knowledge of doctors concerning management.

**Methods:** A paper questionnaire was designed to evaluate the confidence and knowledge of Emergency Department (ED) doctors on paracetamol toxicity.

**Results:** In total 50 doctors participated, consultants 20%, registrars 22%, junior doctors 42% and 8% who did not disclose their designation. Of these 60% reported managing paracetamol poisoned patients at least monthly, 32% hardly ever managed such patients and 8% did not answer. 42% agreed that paracetamol toxicity was easy to manage and 30% enjoyed treating such patients. There was generally adequate knowledge in identifying the signs, symptoms and biochemical markers of paracetamol toxicity; 96% correctly identified renal failure, liver failure, metabolic acidosis and coma as complications associated with paracetamol toxicity and 90% recognized that aspartate aminotransferase (AST) elevation is a sensitive marker of hepatotoxicity. Most (86%) knew the Rumack-Matthew nomogram is used to predict hepatotoxicity in single acute overdose and 84% were aware that serum paracetamol concentration is best drawn at 4 hour post-ingestion. Also 84% knew the AST and paracetamol concentrations are used to predict toxicity

in patients who ingest a toxic dose of paracetamol over a 36 hour period. However there was poorer knowledge in identifying at risk groups and on antidote use. At risk groups were correctly identified by 70%. All identified N-acetylcysteine (NAC) as the antidote and 78% knew it should be started within 8 hours post-ingestion. Only 68% knew the indications to terminate NAC treatment and 46% knew how to manage an NAC-induced anaphylactoid reaction. Only 4% were aware that the risk of an anaphylactoid reaction is higher with low serum paracetamol concentration. Senior doctors (consultants and registrars) were more likely to identify complications of paracetamol toxicity than junior doctors (odds ratio 4.71, 95% CI 1.1 to 20.2). No significant difference in knowledge was demonstrated between doctors who liked treating paracetamol poisoned patients, who found its management easy, who treated these patients at least monthly and those who do not.

**Conclusion:** The majority of the ED doctors can identify the clinical signs, biochemical markers and antidote to manage paracetamol toxicity. However their knowledge in identifying at risk groups, NAC use and managing NAC complications was weak. These results suggest a need for more training in this area or input from clinical toxicologists to ensure optimal management of this commonly encountered poisoning in the ED.

### 336. Acute poisoning with diuretics, antihypertensive and antiarrhythmic medicines

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**Objective:** To study the characteristics of acute poisoning with diuretics, antihypertensive and antiarrhythmic medicines, in patients admitted to the Toxicology Clinic, Emergency University Hospital NI Pirogov, Sofia.

**Methods:** A retrospective study, from January 2011 to December 2013, in which all cases of diuretics, antihypertensive and antiarrhythmic drug poisoning were analyzed. Demographic data, previous illness, laboratory tests, presenting syndromes, were obtained retrospectively from the patients' charts. The cases of poisonings were evaluated with respect to clinical course, therapy and outcome.

**Results:** A total 896 patients with acute exogenous intoxications were treated in the Toxicology Clinic, Department for Adults in the study period. Of these, 136 cases (15.2%) were poisoning with diuretics, antihypertensive and antiarrhythmic medicines including beta-blockers, calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors. Most patients were female (n = 95, 69.9%, male n = 41, 30.1%); patients were aged between 18 and 98 years. Only one drug was taken by 61 individuals (44.9%) but in the 75 (55.1%) cases, intoxications were mixed, including other medications or psychoactive substances. Ingestion was intentional in 112 cases (86.8%), as a result of a suicide attempt. The main causes of suicide attempts were various kinds of depression as well as anxiety disorders, schizophrenia, personality disorders and cognitive disorders. The severity of poisonings varied from moderate to extremely severe. In 17 patients poisoning occurred with the signs of exotoxic shock and 3 of them had a fatal outcome. In the examined group three patients died of cardiogenic shock and secondary

acute respiratory failure resistant to therapy. The mortality rate was 2.2%.

**Conclusion:** Patients with acute poisoning from diuretics, anti-hypertensive and antiarrhythmic medicines represent a large proportion of all patients with acute poisoning. The combination of medicines increases the severity of poisoning and consequently the length of hospitalization.

### 337. A case of severe overdose with valproic acid treated with carnitine and continuous renal replacement therapy (CRRT)

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**Objective:** Valproic acid is an antiepileptic medication that is increasingly being used in the treatment of bipolar disorders and depression. An overdose is associated with hypotension, respiratory failure, and somnolence and may cause hepatic injury. Lactic acidosis and increased ammonium ion concentrations may be present. Treatment with carnitine has been suggested to improve metabolism and reduce hepatic injury and hemodialysis may improve elimination of valproic acid. We report a case of valproic acid overdose where treatment with continuous renal replacement therapy (CRRT) and carnitine was successfully used.

**Case report:** A 24-year-old woman with a bipolar disorder but no history of psychotic episodes was admitted to the Emergency Department (ED) after being found drowsy at home, after an estimated ingestion of 30 g of a slow-release valproic acid (approximately 100 tablets). She was initially cardiorespiratory stable and responsive. During gastric lavage at the ED where 25 g of activated charcoal was administered she became unconscious and was hastily intubated, due to loss of airway. The patient presented to the ICU with hypotension, and vasopressor treatment and volume resuscitation was initiated. Sodium valproic concentrations was initially 1970  $\mu\text{mol/L}$  and increased shortly to 2990  $\mu\text{mol/L}$ . Ammonium concentrations increased from 190 to 640  $\mu\text{mol/L}$  during the first day. Carnitine was initiated at the dose of 100 mg/kg and thereafter 15 mg/kg was given every 4 hours. The patient was kept on a ventilator and blood pressure was stabilized with a low dose of norepinephrine. She developed a few episodes of seizures. In the second day ammonium concentrations increased from 60 to 150 to 430  $\mu\text{mol/L}$  and CRRT was started. After 24 hours with CRRT and repeated doses of carnitine the concentration of valproic acid decreased from 430 to 81  $\mu\text{mol/L}$  and ammonium concentrations decreased from 1030 to 360  $\mu\text{mol/L}$ . She was extubated after seven days on a ventilator and transferred to a medical ward. At that stage she still hallucinated and presented paranoid delusions which resolved completely two weeks later. A psychiatrist attributed her psychotic episode to medical treatment with valproic acid. She had no history of previous psychotic episodes.

**Conclusion:** Carnitine may be of help in reducing hepatic injury after overdose of valproic acid. CRRT may be helpful in reducing toxicity and increasing elimination. It is possible that psychosis may be an inadvertent effect of valproic acid.

### 338. Acute liver injury after low doses of acetaminophen by intravenous route in an alcoholic patient

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**Objective:** We report unexpected acute liver injury (ALI) after low doses of intravenous acetaminophen (APAP) in an alcoholic patient.

**Case report:** A 60-year-old Caucasian alcoholic male arrived at the emergency department after binge drinking. The blood alcohol concentration was 0.75 g/L, aminotransferases were unremarkable; the prothrombin time (PT) was 96%, white cells count was 8400/mm<sup>3</sup>, platelets 375,000/mm<sup>3</sup>, bilirubin 13  $\mu\text{mol/L}$  and creatinine 61  $\mu\text{mol/L}$ . He complained of pain due to peripheral vitamin B12 deficiency neuropathy and APAP was given 3 g/daily by infusion corresponding to 50 mg/kg/day. On day 2-3 ALT increased to 1671 UI/L, AST to 4872 UI/L, bilirubin to 70 UI/L, lipase to 21 UI/L and lactate to 3.81 mmol/L. The PT decreased to 30%, factor V to 20%, factor VII to 15%, platelets to 48,000/mm<sup>3</sup>. Acute liver injury after low dose acetaminophen was suspected because his past history and the presence of abdominal pains and increased nausea, which are known to be the result of APAP toxicity. All drugs were stopped and N-acetylcysteine (NAC) was prescribed and continued at 100 mg/kg/day for 2 days more. He had a good outcome on day 6 and liver recovery was complete on day 30. Other ALI hypotheses were ruled out.

**Conclusion:** APAP is well-known for increasing the risk of ALI in chronic alcoholics or after binge drinking, also in conditions of obesity, chronic malnutrition or in patients taking cytochrome P450 inducing drugs. This patient with no previous liver disease developed ALI in spite of using, as recommended<sup>1</sup>, a low dose APAP. This APAP-related hepatotoxicity was probably enhanced by alcoholism.<sup>2</sup> However, the role of alcohol in enhancing the hepatotoxic effects of APAP is variable and the effect of acute alcohol P-450 induction may differ from chronic exposure.<sup>3</sup> It seems that a mechanism other than induction of CYP2E1 may be responsible.<sup>2</sup> We can also suggest preventive NAC (e.g. 100 mg/kg for one day) in alcoholics when surgery is needed, to limit adverse events of drugs (APAP, painkillers or anesthetics) requiring hepatic metabolism.<sup>2</sup>

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### 339. The incidence of tramadol-related seizures is affected by co-ingestants

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**Objective:** The incidence of tramadol-related seizures has been reported in the literature to range widely from 4 to 36%. The objective of this study was to look at a large cohort of patients who reported ingestion of tramadol alone and tramadol with co-ingestants to determine the overall rate of seizures under both situations.

**Methods:** Cases were acute tramadol exposures reported to a USA, Texas poison center system during the years 2000-2013 were analyzed. Data collected included the reason for exposure, patient demographics, incidence of seizures, medical outcome and a list of co-ingestants.

**Results:** There were 6,952 acute tramadol exposures reported for the years analyzed, of these 65% involved patients aged 20 years or more. The most common reported effects for single agent tramadol exposure were sedation (18%), tachycardia and vomiting (9% each). There were 3 deaths, and 268 patients (3.9%) with major effects. Suspected suicide was involved in 41% of cases and 72% of cases were managed at a health care facility. The seizure rate (SR) for all tramadol exposures was 4.6% (318/6952). For tramadol products alone the SR was 5.3% (211/3774). The highest SR was seen in those reporting intentional abuse (18%, 33/148); for suicidal patients the SR was 5.9% (136/2278); for unintentional therapeutic error the SR was 0.5% (4/775). Analysis of specific co-ingestants showed statistically decreased SR for those patients who also ingested alprazolam (SR 1.3%, 3/231), carisoprodol (SR 0.6%, 1/158), clonazepam (SR 0.6%, 1/173) and hydrocodone (SR 2.9%, 13/448). Increased rates of seizures were seen with cocaine (SR 7%, 3/41) and amphetamine (SR 11%, 2/19) co-ingestants.

**Conclusion:** In a group of acute tramadol exposures reported to poison centers the incidence of seizures is low (between 4.6 and 18%). This may reflect a lower dose effect for this population compared to other studies reporting higher seizure rates. Misuse and suicidal ideation is associated with a higher seizures rate. Co-ingesting a benzodiazepine may decrease the risk of seizures while co-ingestion of amphetamines or cocaine may raise seizure risk.

### 340. APAP x AT in staggered, chronic and time unknown acetaminophen overdoses

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**Objective:** The product of serum acetaminophen concentration (APAP) and aminotransferase (AT) concentration (APAP x AT)

has been evaluated in the acute acetaminophen overdose setting, and growing data suggests that it may be useful. It is believed that the product of the initial acetaminophen concentration and the higher of the two aminotransferases is predictive of hepatotoxicity if greater than 1500 IU x mg/L<sup>2</sup>. It has not yet been evaluated in the setting of chronic, staggered or time unknown ingestions. In these contexts the Rumack-Matthew nomogram is not useful and alternative tools would be welcome to help identify patients that may require treatment with N-acetylcysteine (NAC). Given the safety profile of NAC, a prospective study withholding NAC in these non-acute or time unknown ingestions may be unethical without adequate supportive retrospective data.

**Methods:** This was a retrospective chart review of cases identified by ICD-9 codes. All acetaminophen overdoses in patients aged 0-99 cared for at a university hospital between 1 July 2011 and 1 July 2014 were analyzed. Patients were excluded if there was a clear time of ingestion, no initial aminotransferase available, clear alternative reasons for transaminitis, hepatotoxicity (defined by AST > 1000 IU/L) upon arrival or incomplete data. In total 162 cases were identified; 122 (75%) were single acute ingestions of acetaminophen containing products, 5 cases had acetaminophen toxicity erroneously applied, 4 cases were excluded for incomplete data and 2 cases had hepatotoxicity upon presentation. Therefore 29 cases met inclusion criteria.

**Results:** Of the 29 (17%) of cases that met inclusion criteria, 11 patients were identified as unknown, chronic or staggered ingestion of acetaminophen with an APAP x AT product below 1500 IU x mg/L<sup>2</sup> on initial testing. These 11 patients of interest were not treated with NAC. Though repeat aminotransferases were not available on all patients, none of these patients went on to develop clinical signs and symptoms of hepatotoxicity. Of the remaining 18 cases, 7 had an APAP x AT product below 1500 IU x mg/L<sup>2</sup>, were treated with NAC and did not manifest hepatotoxicity; 11 cases had an APAP x AT product greater than 1500 IU x mg/L<sup>2</sup>. Ten of these 11 received NAC and one developed hepatotoxicity. The 11th patient was not treated with NAC and did not develop hepatotoxicity.

**Conclusion:** The APAP x AT product may be a useful tool in cases of chronic, staggered, or time unknown of acetaminophen overdose. Further investigation with larger data sets may provide the groundwork for a prospective study.

### 341. 5-Oxoproline concentrations in acetaminophen overdose

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**Objective:** 5-Oxoproline (pyroglutamic acid) is an amino acid that is a metabolite in the glutathione cycle; increased blood and/or urine concentration of 5-oxoproline can occur in patients with deranged glutathione metabolism. Metabolic acidosis after acetaminophen

**Table 1.** The concentrations of 5-oxoproline and liver enzymes in patients with elevated acetaminophen concentrations (n = 24).

	APAP mcg/mL	Total bilirubin mg/dL	AST IU/L	5-Oxoproline mmol/L (normal < 100)
Median	37.5	0.5	32	45
Mean	72.3	1.08	2682.0	81
Range	< 0.8–234.9	0.2–5.2	14–31150	0–300
Correlation to 5-oxoproline	–0.27	0.93	0.67	–
R-Squared	0.07	0.86	0.45	–

(APAP) ingestion has been documented in case reports. No formal studies have been done to look at the kinetics of 5-oxoproline in acetaminophen toxicity or the degree of metabolic acidosis related to these concentrations. The effect on patients is also unknown. Therefore, we enrolled consecutive patients with documented elevated acetaminophen concentrations and measured the concentration of 5-oxoproline in patients admitted for treatment.

**Methods:** We performed a prospective, institutional review board (IRB) approved study, of adults and children admitted to the hospital for acetaminophen overdose. We obtained an aliquot of plasma left over from routine blood draws obtained in the course of clinical care and measured 5-oxoproline by mass spectrometric analysis using a HP GC/MS 6890/5793 with a HP-5MS capillary column (30 meters, 250  $\mu$ m ID, 0.25  $\mu$ m film thickness) and a flow rate of 0.4 mL/min 2.0  $\mu$ L of standard or sample was injected using a HP7673 Injector. Calibration was performed in duplicate using solutions containing 0.00, 0.05, 0.10, 0.25, 0.50 or 1.00 mmol/L 5-oxoproline. O-hydroxyphenylacetate (o-OPA) was used as an internal standard for patient samples, calibrators and quality control preparations. We compared the concentration of 5-oxoproline to other laboratory values including transaminases, total bilirubin and acetaminophen concentration.

**Results:** We enrolled 20 adults and 4 children who presented to our medical center with an elevated acetaminophen concentration. The results are summarized in Table 1.

**Conclusion:** Patients with elevated aspartate aminotransferase (AST) concentrations after acetaminophen overdose generally have normal 5-oxoproline concentrations. Minor and clinically insignificant elevations in 5-oxoproline occur in patients with hepatic dysfunction indicated by elevated bilirubin.

### 342. Toxicity of desvenlafaxine in overdose

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**Objective:** There is limited information on desvenlafaxine overdose, but cases of serotonin toxicity have been reported. Desvenlafaxine is the active metabolite of venlafaxine, so it is expected to cause similar toxicity but at lower doses. We aimed to investigate the clinical effects and complications of desvenlafaxine overdose.

**Methods:** This was a retrospective observational case series of desvenlafaxine overdose managed through the Western Australian

Toxicology Service between January 2010 and December 2014. Demographic information, details of ingestion, clinical effects and length of stay were extracted from a clinical database. Serotonin toxicity was considered mild in the presence of hyperreflexia, clonus, tachycardia < 120/min; moderate if the patient had seizures or tachycardia > 120/min and severe if muscle rigidity and hyperthermia were also present.

**Results:** There were 93 cases of desvenlafaxine ingestion recorded in the database. Fourteen patients were excluded either because of incomplete data, or because the amount ingested was less than 200 mg. Out of the 79 patients included in the study, 8 patients (10.1%) were younger than 16 years of age; 46 (58%) patients were female. Eleven (14%) patients ingested only desvenlafaxine (range 350–9800 mg). Twenty four (30.4%) patients ingested other serotonergic agents (tramadol, SSRIs, lithium, lamotrigine). The most common co-ingestant was alcohol (14 patients, 17.7%). Of the patients who ingested only desvenlafaxine as a sole agent, only one (7%) developed moderate serotonin toxicity; 2 (14%) developed mild serotonin toxicity and 11 (79%) did not develop any signs of serotonin toxicity. Four patients (5%) developed severe serotonin toxicity, and all had also ingested other serotonergic agents (escitalopram, sertraline, lamotrigine, paroxetine). Nine patients (11.4%) developed transient hypotension that was responsive to fluids. Four patients (5%) developed seizures (three co-ingested escitalopram, paroxetine or duloxetine and one had a pre-existing seizure disorder). Three patients (3.8%) developed mild (2.1–2.8 mmol/L) hypoglycaemia (dose of desvenlafaxine ingested 9800, 4900 and 2000 mg).

**Conclusion:** Despite being the active metabolite of venlafaxine and toxicological advice usually extrapolated from venlafaxine, it appears that desvenlafaxine causes moderate to severe serotonin toxicity only if taken in a very large dose or in association with other serotonergic agents. Hypoglycaemia, although rare, can occur after a large desvenlafaxine overdose.

### 343. Mortality predictors in lactic acidosis with confirmed serum metformin concentration

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**Objective:** Metformin's main mechanism of action is related to the inhibition of a specific mitochondrial isoform of glycerophosphate dehydrogenase,<sup>1</sup> which causes an accumulation of lactic acid. Although lactic acidosis is an uncommon adverse effect, it is associated with a 25% mortality rate.<sup>2</sup> The causal association between elevated serum concentrations of metformin and lactic acidosis is not completely understood.<sup>3</sup> We investigated the parameters predictive of mortality in patients with chronic

metformin therapy and lactic acidosis and the correlation with serum concentrations of the drug.

**Methods:** A retrospective observational study was performed at two reference hospitals. Clinical and demographic data from a series of 26 patients with type 2 diabetes receiving metformin treatment admitted to the hospital due to lactic acidosis was obtained from clinical charts. Serum concentrations of metformin were measured using high pressure liquid chromatography (HPLC). The correlation between metformin concentrations and pH, glucose, lactate and creatine were measured using Spearman's Rho. Serum concentration and the clinical and demographical variables in survivors versus non-survivors was compared using U-Mann-Whitney or Fisher's test, with significance at  $p < 0.05$ .

**Results:** Total mortality observed was 23%. Factors associated with mortality were sepsis at admission ( $p = 0.03$ ) and the presence of one or more comorbid conditions ( $p = 0.003$ ). In the subset of patients with severe lactic acidosis ( $\text{pH} < 7$ ; lactate  $> 10$  mmol/L), there was no association between mortality, metformin concentration, pH, lactate, glucose or creatinine. Metformin concentrations correlated with lactate concentrations ( $r = 0.548$ ;  $p = 0.0017$ ), creatinine ( $r = 0.481$ ;  $p = 0.007$ ) and pH ( $r = -0.611$ ;  $p = 0.0003$ ).

**Conclusion:** The presence of a combination of factors including sepsis and comorbid conditions may be better predictors of mortality due to metformin-associated lactic acidosis than metformin concentration, despite the correlation between drug concentration and other markers of severity.

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### 344. Lithium chronic and acute-on-chronic poisoning: A retrospective case series

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**Objective:** Lithium is a first line drug for treatment and prevention of bipolar disorder and it is effective in reducing relapse and the risk of suicide. Chronic lithium treatment is often associated with toxicity since the drug commonly induces nephrogenic diabetes insipidus or interstitial nephritis, due to its action on tubular renal function. This condition can lead to progressive lithium accumulation followed by lithium-induced adverse reactions.<sup>1</sup> The aim of this study was to retrospectively evaluate the patients admitted to Florence Toxicology Unit in the last twenty years (1994-2014) for lithium intoxication. The age, dose ingested and plasma lithium

concentration at admission were evaluated. Renal impairment, neurological symptoms, and average length of stay (days, ALOS) in hospital were also investigated.

**Case series:** In total 71 patients were included in the study. Chronic progressive lithium accumulation due to renal or gastrointestinal dysfunction and to circulating volume decrease occurred in 29 out of 71 patients (41%). All cases (100%) presented with neurological symptoms (agitation, mental confusion, tremors, hyperreflexia), while renal impairment was present in 19 out of 29 (65%) patients. Furthermore, magnetic resonance imaging (MRI) or positron emission tomography (PET) documented brain neurodegeneration in 7 cases (24%) leading to an irreversible lithium-neurotoxic syndrome.<sup>2</sup> In this group the ALOS was 8.5 days. In addition, suicide attempts in patients on chronic lithium therapy occurred in 42 out of 71 patients (59%) and neurological symptoms and renal impairment were present in 2 (4%) and 2 (4%) patients, respectively. In this group the ALOS was 3.5 days.

**Conclusion:** Lithium toxicity is more severe in patients with chronic progressive lithium accumulation compared to acute lithium poisoning for suicide attempt in patients on chronic lithium therapy as documented by the ALOS. Indeed, intracellular lithium accumulation poses a substantial risk for neurological symptoms, renal impairment and brain neurodegeneration. Lithium plasma concentration and renal function should be closely monitored<sup>3</sup> in order to obtain a prompt diagnosis and limit brain damage.

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### 345. A severe adverse drug reaction related to deferasirox

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**Objective:** Deferasirox (DFR) is an oral iron chelator; common adverse effects are vomiting, abdominal pain, increased transaminases, fever, nausea, diarrhoea and liver damage. We report a 3-year-old (12 kg) with thalassemia major that developed a severe adverse drug reaction (ADR) during chelating therapy with DFR.

**Case report:** DFR therapy (41 mg/kg/day) was started at age 2 years for the management of thalassemia major. During the following months behavioral changes, weight loss, vomiting, metabolic



acidosis, transaminases increase and fever appeared. Symptomatic therapy (rehydration and antibiotics) was applied. One year later because of persistent vomiting, worsening level of consciousness (up to stuporous state), lockjaw and myoclonus she was moved to the intensive care unit (ICU), with discontinuation of DFR. Laboratory tests results showed hyperammonemia 741 mcg/dL, hyperchloraemic metabolic acidosis (pH 7.19, sodium 142 mmol/L, potassium 3.9 mmol/L, chloride 122 mmol/L, base excess -17 mmol/L, bicarbonate 11 mmol/L) and glucose 36 mg/dL. A cerebral CT scan was normal. A urea cycle alteration was initially suspected and arginine and sodium benzoate infusion was started. Continuous veno-venous hemofiltration (CVVH) treatment was applied because of persistent metabolic acidosis and oligo-anuria. Urinary organic acids showed an increase of lactic, 3-hydroxybutyric, pyruvic, citric, succinic and fumaric. The patient also had glycosuria, proteinuria, hemoglobinuria and ketonuria. Hyperammonemia and urinary organic acids normalised after the first 24 hours and metabolic disease was excluded. Her clinical condition improved and she was extubated, and discharged from the ICU after two weeks.

**Conclusion:** The recommended dose of DFR is 20-30 mg/kg/day (plasma ferritin > 500 mcg/mL). The European Medicines Agency (EMA) indicates an increase of ADR at doses greater than 30 mg/kg/day. Post-marketing reports show gastrointestinal symptoms, acute renal failure, cytopenia, thrombocytopenia, acute liver failure, rash, fever, pneumonia, myocarditis, thyroiditis and arthralgia. Our patient presented with severe ADR to DFR with Fanconi syndrome associated and non-hepatic hyperammonemia. Naranjo Scale<sup>1</sup> (score 9) showed a relationship between DFR-therapy and clinical state. This case, although it had a good outcome, underlines a potential toxic risk in patients receiving iron chelating therapy that requires careful monitoring.

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### 346. Severe adverse drug reactions and anaesthesiologic intervention: Experience of the National Milan Poison Control Centre

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**Objective:** Adverse drug reactions (ADR) are hazardous and unwanted responses, which can occur after medication, used at normal doses for prophylaxis, diagnosis or therapy.<sup>1</sup> ADRs can vary in severity. Our aim was to analyze consultation requests to the National Milan Poison Control Center between 2011 and 2013 about severe ADRs which required hospitalization in an Intensive Care Unit (ICU). Drug-drug interactions (DDI) were also analyzed.

**Methods:** All the consultation requests about severe adverse drug reactions which needed hospitalization in ICU occurring between January 2011 and December 2013 were analyzed. For each medical

case considered we analyzed: medications which possibly caused the adverse reaction, comorbidities, risk factors, possible drug-drug interactions and outcome. The analysis of possible DDIs was supported by the use of the software DrugReax<sup>®</sup>, a drug interaction tool which allows the analysis of interacting drug ingredients, their effects and clinical significance.

**Results:** Overall 1,015 ADRs were identified for this study between 2011 and 2013. The selected population included 107 patients who experienced a severe adverse drug reaction treated in ICU. Considering the treatments, among the patients who were admitted to ICU, 36% were intubated, 14% had a major sedation, 25% received haemodialysis and 7% hemofiltration, 5% of the patients were admitted to ICU after cardiopulmonary resuscitation and 6% of patients received epinephrine, norepinephrine or dopamine. In total 11 patients died (3 patients before admission to ICU) despite medical attention. The most common causes of hospital admission for ADRs were central nervous system drugs (especially lithium carbonate) and endocrine system drugs (particularly metformin). Of 45 drug-drug interactions observed, 20 of them were defined as high risk and 25 as moderate risk.

**Conclusion:** A significant percentage of ADRs were caused by well-known DDIs and risk factors; therefore these should be taken into account when considering the addition of new drugs in a patient's current therapy regimen. This implies the need for adequate prevention measures and careful drug monitoring.

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### 347. Abstract withdrawn

### 348. Supratherapeutic doses of opiates for acute pain crisis in the ED are safe

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**Objective:** Assessing analgesic requirements in patients with acute pain crisis from sickle cell disease can be difficult as such individuals are usually on chronic opioid therapy. While it is well established that opioid tolerant patients require larger doses of opioids for pain relief as compared to opioid naïve patients, the actual opioid doses administered and the safety thereof have not been well established in the Emergency Department (ED) setting.

**Method:** A retrospective chart review was performed to identify adult patients who had presented to the ED with a chief complaint of acute painful sickle cell crisis on at least 4 occasions between July 2010 and July 2011. Opioid doses were converted to intravenous (IV) morphine equivalent doses (MED) using a standard conversion factor for chronic opioid users of 5:1 IV morphine to IV hydromorphone, 1:2 IV morphine to oral oxycodone and 1:3 IV morphine to oral morphine. Data analysis included average IV MED per visit, time period over which those medications were administered, and IV MED per kilogram body weight.

**Table 1.** Morphine equivalent doses (MED) intravenously administered in the ED.

Patient age (years)	Number of ED visits	Average total opioid per ED Visit (mg)	Average opioid per hour (mg/hr)
34	76	20	10
31	43	26	7
38	26	80	13
28	20	31	12
18	16	132	21
28	8	35	9
40	35	48	7
23	8	50	18
20	9	86	14
29	9	25	4
35	8	32	6
36	6	21	4

**Results:** Twelve patients were identified, 6 males and 6 females. Average IV MED administered per visit was 65 mg for an average length-of-stay of 5 hours. Results are summarized in Table 1. The maximum IV MED administered was 253 mg during an 11 hour length-of-stay. The greatest number of ED visits for any one patient over the study period was 76 visits. No patient was reported as having an adverse drug event or overdose and none required naloxone administration. Medical reconciliation demonstrated that all patients were on chronic outpatient opioid therapy.

**Conclusion:** While it has been established that opioid tolerant patients require non-standard doses of opioids for pain relief, our study demonstrates that safely administered doses may be much larger than those previously recommended in the peer-reviewed medical literature.

### 349. Post-injection delirium/sedation syndrome after olanzapine long-acting injection: Experience of the Milan Poison Center

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**Objective:** Long-acting depot injections of antipsychotic agents are an important tool for the management of patients with schizophrenia who have difficulty with adherence to other medication. Olanzapine long-acting injection (OLAI) is a recent depot antipsychotic formulation with flexibility in dosing ranging from 2 to 4 week intervals.<sup>1</sup> Injection site complications are mild but, with an incidence rate per injection of 0.07% (incidence rate per patient of 1.4%),<sup>2</sup> patients experience symptoms suggestive of olanzapine overdose, a phenomenon called "post-injection delirium/sedation syndrome" (PDSS). We conducted an analysis of Milan Poison Center database enquiries about PDSS focussing on comorbidity, management and clinical outcomes.

**Methods:** We analyzed all the consulting requests made to the National Milan Poison Control Centre (NMPCC) from January

2013 to October 2014 about suspected PDSS. Several follow-ups were made in order to gather demographic, clinical, therapies and outcome were recorded. We collected data on 4 cases of PDSS and examined gender, average age, co-morbidities, concomitant medications, latency and symptoms.

**Results:** Three patients were naive for olanzapine long-acting injection but in the fourth case the drug had previously been administered several times. All the patients presented with a progressive loss of consciousness and then coma; one patient required mechanical ventilation and another developed seizures, cyanosis, tachycardia and finally cardiac arrest.

**Conclusion:** The consistency and seriousness of PDSS impose mandatory administration and continuous monitoring of patients by health care professionals for an adequate observation period in a suitable clinical facility. Importantly, the risk of PDSS is the same with any injection thus the overall risk per patient is cumulative.

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### 350. Overdose or drug interaction? Reducing risks when starting and stopping rifampicin therapy

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**Objective:** Rifampicin is widely prescribed by Infectious Diseases specialists to treat tuberculosis and methicillin-resistant *Staphylococcus aureus* (MRSA). Rifampicin is a potent inducer of drug metabolism, with the potential for a range of clinically significant drug interactions. Two undetected rifampicin drug interactions, both resulting in hospitalisation, prompted a review of incidents and the identification of risk factors to manage rifampicin drug interactions and minimise patient harm.

**Methods:** Two cases involving rifampicin were reviewed. Multidisciplinary discussions took place to identify risk factors and devise strategies to prevent future incidents involving both prescribers and patients.

**Results:** The sentinel case involved a patient taking warfarin from a residential care facility with an INR > 20 after requiring admission following a minor fall. He had completed a rifampicin course several weeks prior to the incident. The second case involved a male patient with haemophilia prescribed methadone tablets for severe joint pain. He was admitted suffering severe insomnia, agitation and night sweats two days after starting rifampicin. Common factors in these incidents included multiple prescribers, dispensing of rifampicin from the hospital but other medications from community pharmacy, lack of clinician awareness of rifampicin interactions and lack of review of all medications when starting or ceasing rifampicin. Interventions implemented: 1) Medical focus: Education about drug interactions through intern orientation, Grand Rounds, prescriber newsletter and case publication.<sup>1</sup> 2) Patient focus: Patients are now

provided with an alert card with each rifampicin dispensing to ensure they are informed of the potential for drug interactions and are a part of the communication process with their other health care providers.

**Conclusion:** Multiple providers, lack of awareness of drug interactions and poor communication of medication-related information were risk factors for interactions causing harm when rifampicin therapy is initiated or ceased, leading to a relative overdose of the interacting medication. To address these risks, targeted prescriber education was provided and an alert card for patients developed to prompt clinicians to review medications when rifampicin therapy is both initiated and ceased.

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### 351. Telephone-based product identification by poisons centers

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**Objective:** Correct hazard identification is an essential part of toxicological risk assessment and prerequisite of appropriate poisons centre (PC) medical advice. Exact product identification is even more important if PC case data are processed within scientific studies or for monitoring product-related poisoning profile changes caused by safety measures or new formulation. In many cases, product name is not enough to identify a formula in the PC database. Therefore, the EAPCCT Working Group on PC Activities proposed a Unique Formula Identifier (UFI) to be printed on all packages in the discussion on Article 45 of the CLP Regulation (EC1272/2008). Within the multi PC study, MAGAM II, it was tested to what degree exact product/formula identification is possible during a PC telephone call.

**Methods:** MAGAM II is a prospective observational study of acute eye exposures to cleaning products and nine PCs recruited cases in 2013/2014. During the emergency call or follow-up calls exact product name and additional product identifiers (PRIN) were requested carefully, registered in the study database and statistically analysed.

**Results:** In total 586 cases were included in MAGAM II. Products intended for consumer or professional use (540) dominated, while products for professional use only (44) were rarely notified (unknown category, n = 2). Both exact product name and PRIN, were documented in 304 cases and exact product name without PRIN was registered in 229 cases. Incomplete or ambiguous product names were documented in 24 cases; in 29 cases only the product category could be registered. The types of PRIN recorded were

European Article Number (EAN) in 179 cases, company-defined formula identifier (e.g. I Number, U Number or Article Number) in 148 cases. A production batch code, usually printed on the packaging outside the label, was rarely collected (33 cases). In 53 cases more than one PRIN was documented.

**Conclusion:** MAGAM II has shown that PCs perform high quality identification of formulas as needed for product-directed toxicovigilance. In the majority of cases product identification by name and additional PRIN was successful (52%). Mostly commonly EANs (not formula-specific) were collected and could easily be identified (below barcode). To enhance exact product identification and thus improve toxicological risk assessment and facilitate product safety monitoring the design of packaging should include an easily identifiable PRIN, like the UFI proposed. The results underline the possibility of using PC exposure case data for product safety monitoring of products.

### 352. EPCCASES: Development of an automated case data collection tool for European poisons centres

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**Objective:** About 80 European poisons centres (PC) serve a population of 505 million people of the European Union. All PCs collect cases locally or nationally using different database systems, most of which are custom-made. Currently there is hardly any exchange or collation of European case data. As part of the tasks of the European Public Health Research Project "Reporting and Surveillance System for Chemical Health Threats Phase III (ASHT III)" a tool was developed to automatically collect poisoning case data from heterogeneous local databases (Work Package 7a). Poisoning cases caused by biocides or plant protection products were chosen as a small model case series to test the function of the newly developed system as these intoxications have to be reported to the European Commission by all EU member states (according to Regulation EC 528/2012).

**Methods:** A relational, Web-based database EPCCASES was developed, substantially grounded on final results and experiences of Phase II of the ASHT Project including a XML case data exchange format. The biocide/plant protection agent category system (describing intended use) developed in ASHT III Work Package 5 was included in the system. In October 2013, five European PCs, Milan (Italy), Lille (France), Vilnius (Lithuania), Prague (Czech Republic) and Göttingen (Germany), were recruited for participation in case data collection.

**Results:** Between December 2013 and July 2014 the PCs submitted 262 cases. All submitted datasets were processed and integrated in EPCCASES. A series of basis tests were performed to check



completeness, plausibility and statistical distribution of parameter values. All tests were successfully completed and have indicated high data quality.

**Conclusion:** In ASHT III Work Package 7a it was possible to develop an automated case data collecting tool for European PCs that works in multiple languages, across borders and continuously in real time. This database is a powerful tool for surveillance of health risks including major cross-border chemical threats. The combination of Work Package 5 categorisation with Work Package 7a data collection, makes EPCCASES an efficient tool for harmonised EU member state reporting of pesticide poisonings.

### 353. Review of calls concerning human medicine to the poisons center of the northern France: How many calls concern the scope of pharmacovigilance?

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**Objective:** In France, pharmacovigilance concerns adverse drugs reactions (ADRs) that happen in normal conditions of drug use or in some particular circumstances: overdose, medications errors, misuse. The aim of this study was to evaluate the proportion of calls concerning the scope of pharmacovigilance received by the poisons centre (PC) of Lille in the Nord Pas de Calais region of France.

**Methods:** A retrospective review of calls made to the Lille Poison Center during a 6 week period from 4 November 2013 to 15 December 2013 involving human medicines was made by the regional pharmacovigilance center (RPVC) of Lille. Suicidal attempt were excluded from the analysis. Data on patient demographics, drugs involved, circumstances of the call and consequences of drug intake were collected.

**Results:** During the period, the total number of calls was 1,315, but only 427 of them concerned human medicines and were not related to a suicidal attempt (32.5% of the total number of calls). The mean age of patients was 18 years old and the median age was 3 years. The sex ratio was 1.01. Most of the calls (51.2%, n = 219) were made by patients or family. Calls were classified as accidental exposure for 193 (45.2%) calls, medications errors for 182 (42.6%) calls, misuse or abuse for 31 (7.3%) calls and other reasons i.e. enquiries about the dose, breastfeeding or an ADR for 21 (4.9%) calls. The main drug involved was paracetamol (n = 51). At least one ADR was reported for 76 calls (17.8% of the calls); 25 ADRs occurred after an accidental exposure, 25 after a medication errors, 12 after a misuse or abuse and 14 in normal conditions of use. There were 11 reports of serious ADRs including one death.

**Conclusion:** Few ADRs were reported or collected by the PC (5.8% of the total calls) and most of them were non-serious. More than half of the calls to the PC come from patients or their family, and this gives a good idea of what happens in ambulatory care. The RPVCs are mainly known by healthcare professionals (rather

than patients) and data collected by RPVCs are probably different. These data are of particular interest for drug accidental exposure or medication errors and can be helpful in developing an educative tool about medication risk.

### 354. Cloud and business intelligence technologies in the poison center consulting service and national reporting system

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**Objective:** Slovenia's Poison Control Center (PCC) provides a telephone toxicology consulting service and manages the Slovenian poisoning register in which all poisonings have to be reported on a special form by physicians. The aim is to present a cloud technology connected to business intelligence software that provides an exposure surveillance database and reports and alerts on poisonings.

**Method:** Presentation and description of information technology used in the toxicology consulting service and national poisoning data reporting system.

**Results:** PCC toxicologists regularly report all telephone consultations in a cloud database using a web form. Physicians are also supposed to report all poisoned patients admitted at their emergency departments and hospitals using the same form. The protected web form for reporting data on consultations and poisoned patients can be accessed over the Internet or hospital information systems. All personal data, circumstances, poisons, symptoms and signs, laboratory results, antidotes and outcomes can be reported over the web form with a 5-level dropdown flyout menu using click-to-open access. All data collected over the web form is standardized, allowing analysis and comparison between different languages. Furthermore, information not included in dropdown menus can be reported in a special field as text to avoid loss of data in cases of particular interest. In the PCC the toxicologists subsequently extract data presented as free text and add it to dropdown menus. They also merge calls and reports since some patients can be reported twice. Physicians' poisoning reports are generally made at the end of hospitalizations and are more complete and consistent as they can contain toxicology results, complete treatment and outcome. On the other hand, data gathered by calls is presented earlier in the cloud surveillance database. The cloud database including all calls and reports is connected to business intelligence software that provides reports, trends and alerts on poisonings in Slovenia in real time. The large database can be analyzed regarding all data fields included in the web form.

**Conclusion:** Toxicovigilance is the active process of identifying and evaluating the toxic risks that can be improved by combining cloud technology and business intelligence software. The presented system proved its usefulness in recent bad weather, when carbon monoxide poisoning due to the practice of burning materials in an enclosed space was detected and enabled early public warning. This approach can also be useful in standardizing European poisoning data and could easily be introduced in countries without a developed toxicovigilance system.

### 355. TOXBASE® and its use in collecting data on new and uncommon products of interest

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**Objective:** To describe reports submitted to TOXBASE® relating to new, uncommon and other products of interest.

**Methods:** From 2000 a link to an optional electronic questionnaire was added for completion by healthcare professionals accessing new TOXBASE® entries of interest. This included new products (e.g. black triangle drugs), uncommon agents and novel treatments such as the use of intravenous lipid emulsion. Reports were collated and entered into Microsoft Access.

**Results:** From July 2000 to April 2014 1,246 product questionnaires were received, relating to pharmaceuticals (855, 68.6%), novel psychoactive substances (NPS) (153), household products (143), drugs of abuse (34), other (22), unlicensed pharmaceuticals (10), water proofers (9), weight loss agents (5), plants (5), unknown (4), antidotes (3) and veterinary products (3). Of 143 household products 132 were detergent capsules. Of these 16 patients were asymptomatic (12.1%). Symptomatic patients reported eye pain (64, 48.5%), of which 10 (15.6%) reported corneal damage, gastrointestinal symptoms (25), CNS depression (7), skin damage (5) and reduced respiratory rate (1). The first report about an NPS ("Bolts Extra Strength") was received in 2006. The patient was tachycardic and agitated. Between 2007 and 2009 6 reports related to benzylpiperazine. Since 2009 there have been 78 reports related to mephedrone and a further 69 reports about 30 other NPS. Two deaths (from cardiac arrest) have been reported (benzo fury, 5,6-methylenedioxy-2-aminoindane [MDAI]). Only 3 reports involved asymptomatic patients. Symptoms reported were cardiac features (78, 51%), agitation (42, 27.5%), hallucination (33), gastrointestinal symptoms (27), convulsions (14) and acute psychotic episode (5). Additional features were reported in 135 (88.2%) cases. Unlicensed pharmaceuticals were melanotan (7), "melanotan 2" (2) and flupirtine (1). All patients exposed to melanotan reported gastrointestinal symptoms (nausea, vomiting, abdominal pain). Other symptoms included dizziness (3), flushing (2) and chest discomfort (2). Across Europe in 2003 a sharp increase in respiratory symptoms (cough, dyspnoea, alveolitis and pulmonary oedema) was reported after the use of some water-repellent aerosols. Subsequent to this, 9 reports of adverse features were collected following exposure to waterproofing sprays reported via TOXBASE, 8 between 2004 and 2009 and the most recent in 2013. Symptoms reported included persistent cough (7), dyspnoea (6) and rigors (2). Reports were received on 128 pharmaceutical products, most frequently montelukast (85), bupropion (61), orlistat (54), quetiapine (48), paracetamol (48), pregabalin (36), sildenafil (33), melatonin (31), levetiracetam (29) and escitalopram (28).

**Conclusion:** In addition to alerting, TOXBASE® provides a useful route to collect user generated data on products of interest. This data can be used to monitor exposure prevalence

over time and to gather symptom profile data on agents of concern.

### 356. TOXBASE®: Its use in answering poison information enquiries in the UK

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**Objective:** TOXBASE® is a poisons information database and helps to ensure poison information enquiries made to the National Poisons Information Service (NPIS) in the UK are answered safely, efficiently and consistently between units. We compared the sources of information used to answer poisons information enquiries in the UK for the fiscal years 2008/09 and 2013/14.

**Methods:** In the UK, poisons information enquiries are answered by Specialists in Poisons Information Officers (SPIs). SPIs enter enquiry data into the UK Poisons Information Database (UKPID). UKPID data were analysed with respect to sources of information used by SPIs when answering poisons information enquiries in the UK between 1 April 2008 and 31 March 2009 and between 1 April 2013 and 31 March 2014. In addition to TOXBASE® other possible sources of information include the Internet, safety data sheets (SDS)/NPIS Product Data Centre, Poisindex®, reference books and TicTac® (a tablet/capsule identification system). The NPIS Product Data Centre (PDC) is the repository for safety data sheets and helps UK SPIs quickly access SDSs as a source of information when answering poisons information enquiries.

**Results:** Between 1 April 2008 and 31 March 2009 there were 55,541 telephone enquiries answered by the NPIS that related to cases. TOXBASE® was the primary source of information in 93% (51,719) of these enquiries. In 90% (50,114) of all enquiries TOXBASE® was the only source of information referred to. Between 1 April 2013 and 31 March 2014 there were 51,594 telephone enquiries answered by the NPIS that related to cases. TOXBASE® was the primary source of information in 93% (48,055) of these enquiries. In 90% (46,644) of enquiries TOXBASE® was the only source of information referred to. Of note there has been an 83% increase in use of safety data sheets/PDC as a primary and secondary source of information when answering poisons information enquiries comparing 2013/14 (1180) with 2008/09 (644). Other sources of information used include the Internet, Poisindex, reference books and TicTac®.

**Conclusion:** There were no differences in the use of TOXBASE® by SPIs to answer poisons information enquiries in 2013/14 compared to 2008/09. The increased use of safety data sheets via the NPIS PDC as a primary and secondary source of information in 2013/14 compared to 2008/09 may reflect increased use of the NPIS PDC since its online launch in 2006, although it had been available on CD previously. TOXBASE® continues to be the primary and often the only source of information

used to answer poison information enquiries made to the NPIS in the UK.

### 357. TOXBASE®: Keeping a poisons information database current and meeting UK demand

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**Objective:** To analyse the demand for new additions to TOXBASE®, the UK's online poisons information database 15 years after its Internet launch.

**Methods:** In the UK, poisons information enquires are answered by Specialists in Poisons Information (SPIs) in four National Poisons Information Service (NPIS) Units. SPIs primarily use TOXBASE®, the NPIS poisons information database, to answer these enquiries and enter telephone enquiry data into the UK Poisons Information Database (UKPID). UKPID data are regularly reviewed in order to ensure that TOXBASE® is kept up-to-date. Agents that are identified in the UKPID data as not on TOXBASE® (NTXB), which appear with frequencies greater than 2 are considered for addition. A retrospective analysis of potential new agents identified from UKPID data between 1 February 2012 and 20 October 2014 was performed.

**Results:** A total of 6,272 agents were identified as not being on TOXBASE® in the study period, of which 219 agents were enquired about on 3 or more occasions. Therefore a total of 5,205 new agents were identified (~1900 per annum). These potential new entries can be summarised by category and are predominantly household products (2,429; 39.0%) that are identified as being NTXB, followed by cosmetics (642; 10%), over-the-counter products (602; 9.6%) and pharmaceuticals (582; 9.3%). Of note, only 201 (3.2%) of all possible new entries were drugs of abuse. Agents that were identified as NTXB and are now available include Mr Muscle Toilet Power Strips, Haliborange Kids Vitamin D Calcium Softies, entacapone and argan oil.

**Conclusion:** Searching enquiry records is one way in which the NPIS keeps TOXBASE® current and up-to-date. It is an important source of information as it reflects UK demand. As the household product market is vast and ever changing, it ensures NPIS can clearly identify what is needed, when it is needed, and promptly publish it on TOXBASE®. In future, UKPID data will also be used to identify those agents that have been enquired about only once but were associated with a moderate or severe Poisoning Severity Score<sup>1</sup>; the NPIS will also consider adding these agents to TOXBASE®.

### Reference

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### 358. Organizational peculiarities of poison information and advisory help in Russia

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**Objective:** In Russia medical aid in acute poisonings is provided by poisoning treatment centers (PTC), organized in cities with a population of more than 500,000. A poison information center (PIC) as a separate organization and federal institution is only found in Moscow, thus the study of the situation with poison information in other Russian territories is of interest.

**Methods:** In addition to the PIC we selected Sverdlovsk, Rostov and Omsk regional PTCs, comparatively similar in the respect of the number of residents. Statistical PIC and PTC reports from the period of 2009-2013 were studied and poison information aid was compared for organization principles, number of calls per 100,000 population, structure of the requests, enquirers and results.

**Results:** The PIC provides information mainly for the territory of Moscow region with population of 11.98 million whereas Sverdlovsk, Rostov and Omsk centers and their regions have populations of 4.7, 4.3, 3.38 million, respectively. In both the PIC and PTCs poison information and consultations are provided by certified clinical toxicologists and also resuscitators certified for toxicology (Sverdlovsk and Omsk), available by telephone 24 hours a day, 7 days a week. All centers provide information to physicians (82-97%) and members of the public (3-8%). The PIC also provides information and consultations in cases of animal poisonings, as well as to non-medical organizations. The most common reasons for information requests are (in descending order) diagnosis, therapy recommendations, necessity of hospitalization, choice of hospital, poisoning prevention measures, antidote use, necessity of calling an ambulance and information on the poison. In total, 77% of enquiries to the PIC concerned poisonings by medicines and narcotics, and 23% involved non-medical chemicals; in other centers poisonings by medicines and narcotics constituted 31-43% and non-medical chemicals 57-69%. In different centers the diagnosis of poisoning was confirmed in 47-90% of enquiries, excluded in 27-52%, correction of treatment provided in 60% of cases (PIC) and hospitalization not required in 15-20%. The average number of requests a year per 100,000 of the population to the PIC was 97.65 in Moscow, 11.02 in Sverdlovsk, 8.64 in Rostov and 17.34 in Omsk, compared to the PTC requests which were 139.27 in Sverdlovsk, 168.67 in Rostov and 81.88 in Omsk.

**Conclusion:** Poison information and advice in Russia is organized and fulfils its functions, except the PIC is additional to the PTC. Most patients with poisoning are managed by PTCs rather than the PIC, as confirmed by the small number of requests to the PIC compared to the rate of hospitalizations to PTCs.



### 359. A glimpse of trends in the Poisons Information Centre of Vienna, Austria

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**Objective:** The Poisons Information Centre (PIC) in Vienna serves the total Austrian population of approximately 8 million inhabitants. To obtain information about trends regarding the reasons for emergency calls to the PIC we performed an analysis of some substances and modification in therapy recommendations from 1996 until 2013.

**Methods:** In our centre, the emergency calls have been documented electronically since 1996. We identified substances with a high number of calls, for which the frequency was perceived to have changed over time. For each year the frequency of telephone calls for twelve different substances was calculated and yearly changes were statistically evaluated.

**Results:** Twelve substances were selected and the possible reasons for changes are discussed: Descaling agents: There was a marked increase of calls concerning descaling agents, which may reflect the rising use of electric water boilers and coffee machines in households. Antidepressants medications: Enquiries regarding amitriptyline and combination of flupentixol/melitracen decreased, whereas quetiapine increased. These changes reflect the change in prescription patterns, which are influenced by the introduction of new medications, availability and prices on the market. The marked decreasing numbers of digoxin and digitoxin are definitely caused by decreasing prescriptions. There is a continuous increase for the neuroleptic prothipendyl, which reflects its increased use as a sleep-inducing drug. Enquiries concerning mefenamic acid increased from 1996 until 2005 and have remained constant. The use of sodium fluoride in children for prophylaxis against dental caries has not changed, although a clear decrease in enquiries was found. This is due to the improvement of the child resistant package of the medication. *Zamioculcas zamiifolia* is an indoor plant, which has become more popular in recent years. This corresponds with the rising enquiries regarding this plant. There is no change in number of emergency calls for silica gel, cigarettes and oral contraceptives in relation to the total number of calls. Regarding the therapy recommendations over 18 years we found a decrease in the frequency of activated charcoal administration and indications for gastric lavage have been strictly reconsidered.

**Conclusion:** These data show that subjective changes in enquiries to poisons information centres can be verified by the statistical analysis of the data. Changes may have several reasons such as introduction of new drugs, plants or other substances, modification of prescriptions or change of packaging.

### 360. The Global Educational Toxicology Uniting Project (GETUP)

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**Objective:** The international boundaries to medical education are becoming less marked as new technologies such as multiuser video conferencing are developed and become more accessible to help bridge the communication gaps. The Global Educational Toxicology Uniting Project (GETUP) is a project aimed at connecting clinicians in countries with established clinical toxicology services around the globe to clinicians in countries without clinical toxicologists. We describe the first six months relating to the set-up of the project.

**Methods:** New sites (medical centres that manage or consult on toxicology cases) registered through the American College of Medical Toxicology website via SurveyMonkey<sup>®</sup>. Data was analysed retrospectively from February to July 2014. Google hangouts<sup>®</sup> was used as the main conferencing software, but some sites preferred the use of Skype<sup>®</sup>. Registration data included contact details and toxicology background and qualifications. Data collected included the number of sites matched, number of conferences completed, expectations of sites registering and limitations of the project.

**Results:** In total 29 sites in 18 different countries in Australasia, Europe, Africa and America were registered. Of these 27 (93%) sites were located in a major urban centre, 1 (3.5%) site in a major rural centre and 1 (3.5%) an urban practice; 15 (52%) sites had both a poison information centre and toxicology service on-site. Three (10%) only had a toxicology service and 3 (10%) only had a poisons information centre; 8 (28%) sites had no access to any poisons information centre or toxicology service. Expectations of GETUP included sharing toxicology cases and education (29, 100% of sites), assistance with toxicology management guidelines (n = 2, 7%), assistance with providing a toxicology teaching curriculum in languages other than English (n = 2, 7%), managing toxicology presentations in resource poor settings, international collaboration and toxicovigilance (n = 2, 7%). Of the 29 sites, 25 (86%) have been matched in this period and begun communication and video conferencing. During the first 6 months 14 conferences were performed with a mean of 3 cases per conference.

**Conclusion:** The Global Educational Toxicology Project (GETUP) has connected countries and clinical units with and without toxicology services through video conferencing and will provide a platform to improve international collaboration in clinical toxicology.

### 361. Correlating physical exam findings on poisoned patients through Google Glass

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**Objective:** Toxicologists help assess poisoned patients to determine correct antidotes and management strategies. A simple head-mounted device can effectively link a toxicologist to a virtual bedside evaluation of the poisoned patient. We sought to determine

**Table 1.** Questionnaire results after assessment of 6 patients using Google Glass.

Characteristic	Agree (n = 6)	Disagree (n = 6)
Needed to prompt for additional information over telephone tox consult	4 (66%)	2 (33%)
Confident in diagnosis after Google Glass consult	6 (100%)	0 (0%)
Glass changed my management of the patient	5 (83%)	1 (17%)
Strong audio/visual connection during consult	4 (66%)	2 (33%)

the feasibility and efficacy of Google Glass to evaluate the poisoned patient.

**Methods:** This is a prospective descriptive study. After training to use Glass, Emergency Medicine residents rotating on the toxicology would receive verbal reports of new toxicology consults. Before seeing the patient, residents would complete a survey regarding information gleaned from the case. Next, the resident examined the patient at the bedside while wearing Glass. Using a Health Insurance Portability and Accountability Act (HIPAA) compliant software on a modified version of Google Glass (Pristine IO, Austin TX), the attending viewed the consult remotely and provided guidance to the resident. Residents obtained static photos of pertinent findings through Glass. Residents then completed a survey regarding feasibility and connectivity of Glass at the end of the consult.

**Results:** Six patients were assessed through Glass (Table 1). Video feed was stable during all consults and audio was clear without interruptions. Users experienced minor lag of video feed. All users preferred Glass to traditional video camera feeds. Antidote (naloxone) was recommended for one patient, while management changed in 5 of 6 patients. Use of Glass increased the confidence of users in identification of toxidrome.

**Conclusion:** Google Glass can augment recognition of the poisoned patient. It has the potential to extend the reach of toxicologists to hospitals where no specialized toxicology consult exists. The visual component of Glass increased confidence among users. Further studies will be needed to investigate cost effectiveness, and advanced triage abilities of Google Glass.

### 362. Globalization and international collaboration in toxicology researches: Viewpoint from publications in Clinical Toxicology, 1968 to 2013

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**Objective:** Clinical Toxicology is the leading journal in toxicology. This study aims to evaluate the global contribution and collaboration in toxicology research since 1968 by analyzing the publications in Clinical Toxicology.

**Methods:** This was an observational study. All of the data were collected from the SciVerse Scopus database. All of the articles

published in Clinical Toxicology were included. We collected data including publication year, authors' affiliated country, document type, and cited times. The publication's origination was classified according to the first author's nationality. The international collaboration publication was defined as the authors' affiliated countries were more than two (included). Linear regression was used for trend evaluation and the slope ( $\beta$ ) was adopted as representative of trends. The cited time difference between single nation and international collaboration publications were analyzed by Wilcoxon rank-sum test. The publication type analysis was analyzed by chi-square test. NodeXL software was used to calculate international collaboration network metrics and create visualization graphs.

**Results:** A total of 4,235 publications were retrieved for analysis. In 1968, the publication number was 40 originating from 5 countries but lacking international collaboration publications. The USA contributed 85% of the publications. In 2013, the publication number increased to 164 which originated from 27 countries. There were 25 (15%) international collaboration publications. The USA contributed 42.7% of the publications. The trends of publication origination numbers and international collaboration publication numbers were 1.352 and 1.422, respectively ( $p < 0.001$ ). A total of 266 (6.28%) publications were international collaboration research. In international collaboration publications, the USA, UK, Australia are the leading first authors' nationalities and the USA, UK, Denmark are the leading co-authors' nationalities. The cited times of international collaboration publications were more than single nation originated publications (average: 12.71 versus 9.66,  $p < 0.001$ ). There was no statistical difference of publication type between the international collaborated and single nation originated publications.

**Conclusion:** Globalization and international collaboration in toxicology research has increased in the past four decades. The US has been the leading contributor of both international collaboration and single nation originated publications. International collaboration publications were more frequently cited than single nation originated publications.

### 363. Hard to swallow: Intravenous botulinum toxin A administration

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**Objective:** Intramuscular injections of botulinum neurotoxin are used to treat various medical and cosmetic conditions. We describe the first reported case of inadvertent botulinum toxin A (BTX-A) following intravenous administration.

**Case report:** A 56-year-old man with long-standing achalasia was receiving BTX-A preparations every 6-12 months for 15 years to relieve dysphagia. He was scheduled to receive endoscopic submucosal injection of incobotulinumtoxinA (Xeomin<sup>®</sup>) into his gastroesophageal junction. BTX-A, 100 Units, (the intended submucosal dose) was drawn into an emptied, unlabeled, sodium chloride-flush syringe, and then unintentionally administered intravenously. This corresponds to approximately 100 mouse median intraperitoneal lethal doses (although biological activity of different BTX preparations cannot be directly compared). Twenty minutes later, the mistake was realized, and the procedure aborted.

The patient remained asymptomatic, refused hospital observation and left against medical advice. The poison control center (PCC) was contacted for assistance. The PCC contacted the patient and encouraged medical evaluation; he presented to the emergency department 48 hours after exposure. Except for his baseline dysphagia, neurological or pulmonary symptoms were absent. His physical examination, pulmonary function tests and laboratory values were normal. Because of the uncertain nature of the case, the Centers for Disease Control and Prevention (CDC) recommended Heptavalent Botulinum Antitoxin (HBAT) treatment. The patient received one vial (20 mL) of the antitoxin without complications. Prior to antitoxin administration, the patient's serum was sent to the CDC for testing for BTX-A and to a specialized laboratory (Pacific BioLabs, California, USA) for neutralizing antibodies to BTX-A. The serum was negative for BTX-A, but positive for neutralizing antibodies.

**Conclusion:** Botulinum toxin is among the most potent toxins known, causing a potentially fatal neuroparalytic illness. The vast majority of cases result from ingestion of either botulinum spore or toxin. Less commonly, the spore or toxin can be inoculated in wounds or inhaled. This is the first reported case of a direct intravenous exposure to botulinum toxin in a human. Three forms of BTX-A are commercially available, each with different formulations and potencies. The dose and potency of incobotulinumtoxinA and delay in testing may account for the patient's negative serum BTX-A test. Formation of neutralizing antibodies, which inactivate the biological activity of botulinum toxin type A, and clinical resistance have been previously reported. Given the patient's long history of BTX-A injections, his serum antibodies to BTX-A may have neutralized the toxin burden and served a protective role. The efficacy of HBAT in this case is unclear.

### 364. High-fidelity simulation improves knowledge and self-confidence of junior emergency resident

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**Objective:** Acute poisoning patients account for 2.5-4.8% of emergency department visits yearly in our medical center. In these populations, less than 5% are exposed to highly toxic agents and have substantial risk of severe intoxication. Junior residents lack experience to manage this patient group. High-fidelity patient simulators are being used in the training of medical residents because they promote the knowledge and clinical skills in a safe environment. Our study examines the effectiveness of high-fidelity patient simulators as a training tool to enhance the clinical ability and confidence of medical residents.

**Methods:** This was a prospective study of 60 emergency residents who completed a written test and confidence questionnaire before and after the simulation courses. The written test consisted of 5 multiple-choice questions testing the knowledge of toxic syndromes, application of an antidote and resuscitation. The questionnaire contained 5 questions about their confidence level in treating the acute poisoning patient. We recorded important checkpoints such as basic life support, toxidromes, antidotes, and used team resource management and provided video-assisted feedback after the courses.

**Results:** The simulation courses increased the correct answer rate of written tests from 73% to 87% ( $p < 0.0001$  by paired t-test). The mean confidence in identifying toxidromes, managing the patients with severe poisoning, and using the correct dosage of antidotes increased from 2.2 to 4.0 ( $p < 0.0001$  by paired t-test) using a 5-point rating scale (1-very low and 5-very high).

**Conclusion:** High-fidelity simulation can be used to increase knowledge and self-confidence of medical residents in managing cases of poisoning.

### 365. Impact of clinical toxicology in emergency medicine in Spain: Review of articles published in the journal EMERGENCIAS

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**Objective:** Clinical toxicology, mainly the diagnosis and treatment of acute poisonings, represents 2-3% of hospital emergencies. We analysed the relationship between clinical toxicology and emergency medicine in Spain, by review of toxicological articles published in EMERGENCIAS, the official journal of the Spanish Society of Emergency Medicine, in the last 25 years.

**Methods:** EMERGENCIAS is indexed by Journal Citation Reports. Its 2013 impact factor was 2.583, placing it in the first quartile of journals in its specialty (Emergency Medicine). After accessing the EMERGENCIAS website ([http://www.semes.org/revista\\_EMERGENCIAS/](http://www.semes.org/revista_EMERGENCIAS/)), we read all titles of articles published between 1988 and 2013 and identified articles containing the words toxic, intoxication, poisoning or any potentially-poisonous source including medicines, drugs of abuse, domestic, agricultural or industrial products, plants, fungi and animals. Adverse reactions to medications and foodborne infections were excluded. We extracted the main characteristics of each article identified, and included them in a SPSS database for statistical analysis. Articles selected were grouped in five-year periods to analyse the temporal evolution.

**Results:** Twenty-five volumes (154 numbers) of EMERGENCIAS, with 2160 articles, were reviewed. We identified 192 (8.9%) articles on toxicology, including Letters to the Editor (57), Original or Short original articles (54) and Clinical notes (31). There were no significant differences ( $p > 0.05$ ) according to five-year periods, in the proportion of toxicological articles published or the type of article. Of the articles selected, 86.4% were of hospital origin, 9.4% involved nurses as authors, 9.6% were related to children and 47% came from Madrid or Barcelona. Intoxications due to medicines and drugs of abuse were the most prevalent subjects. In recent years there has been a significant reduction in articles on intoxications due to medicines ( $p < 0.001$ ), more articles on drugs of abuse and more articles with the collaboration of two or more centres ( $p < 0.001$ ).

**Conclusion:** Clinical toxicology was present uniformly in EMERGENCIAS in the last 25 years, confirming the ongoing relationship between Spanish toxicologists and emergency physicians. Most articles came from hospitals and referred to medicines or drugs of abuse.



### 366. Tattoo-associated granulomatous inflammatory reaction with intensive keloid formation

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**Objective:** The trend of tattooing means an extensive destruction of the epidermis and injection of ink components representing unphysiological substances into the subcutis for a large proportion of the population. Against this background, consumer safety becomes a challenge because currently, neither a “positive list” of safe substances nor an authorization procedure for tattoo agents is available. We describe a case of poisoning reported to the BfR in the context of notifications enforced by the German Chemicals Act § 16e.

**Case report:** A 57-year-old patient who already had several tattoos had a special tattoo applied with magenta colorant in an area of about 20 x 10 cm on his right lower leg. On the next day, he experienced extensive reddening and swelling, hyperthermia, itching and scaling of the skin in this area. After outpatient care for about eight months, the patient was admitted to a university hospital specializing in dermatology. The skin with the coloured tattoo was purulently infiltrated, erythematous and exhibited scaly changes, particularly in the lower part. Histological findings revealed a tattoo-associated granulomatous inflammatory reaction with intensive keloid formation. Large parts of the tattoo were excised, and the wound was covered with split skin graft transplanted from the upper leg. After three weeks of inpatient treatment, the patient was discharged in a stable general condition with the wound being free from irritation.

**Conclusion:** Tattoo application is in a regulatory vacuum; it is not medical treatment and not cosmetic treatment. The Council of Europe Committee of Ministers has taken up the issue in the resolution ResAp(2008)1. They recommend a “positive list” of substances proved safe for this use under certain conditions. Also the resolution applies to composition and labelling, the risk evaluation, the conditions of the application and the obligation to inform the public and consumers. This might be a first step towards regulating these hazardous substances but there is a research need to obtain information on the metabolism of these substances (circulation of the substances in the body), the risks of long-term exposure, epidemiology of tattoo-related skin diseases and the toxicokinetic aspects for intradermal application, target organs, skin and lymph nodes. Finally, a risk assessment requires knowledge of the exact ingredients of tattoo inks such as colorants and other agents, methods for detecting and quantification as well as toxicological data for such ingredients.

### 367. Hemoglobin anomalies: Unrecognized differential diagnosis of methemoglobinemia

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**Objective:** When a patient has a difference between “low” measured oxygen saturation from pulse oximetry and the “normal” calculated oxygen saturation from arterial blood gas analysis or a “saturation gap”, methemoglobinemia or sulfhemoglobinemia diagnosis would be investigated.<sup>1</sup> When those conditions were excluded, other differential diagnosis should include hemoglobin anomalies.<sup>2</sup> This study was designed to identify the “saturation gap” with normal methemoglobin concentration cases in Ramathibodi Poison Center (RPC), Thailand.

**Methods:** We carried on an observational study of cases from the RPC toxic surveillance system during a 3-year period.

**Results:** Patients with a “saturation gap” where the conditions of methemoglobinemia or sulfhemoglobinemia had been ruled out were included in our study. Hemoglobin typing with thalassemia DNA analysis and DNA sequence analysis were investigated. In total we found 4 families of rare hereditary hemoglobin anomalies as the cause of the “saturation gap”. These included one each of hemoglobin Cheverly family, hemoglobin La Desirade/Louisville family, hemoglobin Bonn/Westmead family and hemoglobin Bonn family. One patient with methemoglobin Cheverly presented to the hospital with methemoglobinemia without a definite history of exposure to oxidizing agents. The clinical characteristic and pedigree of these families were described in detail.

**Conclusion:** Hemoglobin anomalies should be included in differential diagnosis as a potential cause of a “saturation gap”, especially when methemoglobinemia or sulfhemoglobinemia have been excluded. More investigation such as DNA sequence analysis is warranted.

#### References

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