

ABSTRACTS

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1. Methanol outbreak in the Czech Republic in 2012: Epidemiology and clinical features

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Objective: Mass methanol poisonings are a challenge for treating physicians due to the unpredictable onset and scenario, diagnostic difficulties, severe toxicity, expensive treatment, high mortality and frequently serious sequelae.^{1–4} We report the features of a large methanol outbreak that started in the Czech Republic in September 2012 due to the illegal production and sale of adulterated spirits.

Methods: Discharge reports and questionnaires of hospitalized patients with confirmed methanol poisoning, received by the Toxicological Information Centre were analyzed. Statistical evaluation used: normality of distribution, arithmetic mean, standard deviation, skew, median, mode, Student's t-test, F-test, confidence intervals, correlation coefficient, and Chi-Square-test.

Results: A total of 73 discharge reports were analyzed. A further 20 patients died at home or before hospital and 5 reports of recently deceased subjects could not yet be analyzed. Among the 73 hospitalized patients, 56 (77%) were males, mean age 51 (range 25–79) years, and 17 (23%) females, mean age 54 (range 23–69) years. Only 9 patients (12%) were admitted within 12 hours of ingestion, 50% after 12–48 hours, and 38% later. All patients who died were admitted 12 or more hours after ingestion. The methanol content of the beverage drunk (25–50%) was known in 42/73 patients (58%), 18/73 (25%) subjects drank other alcoholic beverages (wine, beer, whisky, home-made spirits) in addition. There were 32/73 (44%) daily alcohol users.

Admission data: Median serum methanol was 0.939 g/L (range 0–7.307), i.e. 29.4 mmol/L (range 0–229); median ethanol level 0.437 g/L, (range 0–4.460), i.e. 9.6 mmol/L (range 0–98). Median pH was 7.17 (6.57–7.46; N 7.37–7.43), median pCO₂ 4.07 kPa (0.97–14.9 kPa; N 4.3–6.0), median HCO₃⁻ 8.8 mmol/L (2–25.5; N 21.8–27.6), median base deficit 17.2 mmol/L (range 0.1–38.1; N –3–3), median lactic acid 3 mmol/L (0–19.4; N 0.6–2.1), median anion gap 28.8 mmol/L (range 11.1–54.8; N 16–20), median osmolality 348 mmol/kg (283–529, N 275–295), and osmolal gap 45.8 mmol/kg (2.4–235, N 10–25).

Clinical symptoms: Only 12/73 patients (26%) were asymptomatic on admission, 7 appeared inebriated; at least 3 of them

without measurable ethanol in blood. Among the 61 symptomatic patients, the most frequent symptoms were gastrointestinal (63%), visual disturbances (59%), dyspnoea (46%), coma (29%) and chest pain (17%). Other symptoms included fatigue, headache, dizziness, hangover, somnolence, anxiety, tremor, seizures, alcoholic delirium, respiratory and cardiac arrest.

Treatment included alkalization in 64%, ethanol in 79%, fomepizole in 5%, or a combination of antidotes in 12% patients. Because there was limited availability of fomepizole, it was only recommended for the most severely poisoned subjects with methanol level above 0.500 g/L (15.65 mmol/L) or formic acid above 0.400 g/L (8.7 mmol/L) or pH lower than 7.0. Folates were administered in 72% of subjects (folic acid in 33 patients, folinic acid in 20 patients); whereas haemodialysis was performed in 58/73 (79.5%) subjects and started on average 4 hours after admission to the hospital (range 0.5–44). Continuous veno-venous haemodialysis (CVVHD) was performed in 50% of subjects; lasting a median of 36 hours (range 3.5–95). Conventional intermittent haemodialysis (IHD) was performed for a median duration of 8 hours (range 4–18.5).

Outcomes: There were 13/73 (18%) fatalities, 44/73 (60%) survivors without sequelae, and 16/73 (22%) survivors with sequelae: visual impairment alone in 7/73 (10%), central nervous system (CNS) impairment in 5/73 (6.5%) and both visual and CNS damage in 4/73 (5.5%). The mortality was 75% among the patients admitted with respiratory arrest and 52% among those comatose on admission. The patients who died were more ($p \leq 0.05$) acidotic (median pH 6.75, median base deficit 30 mmol/L) than the survivors with sequelae (median pH 7.02, median base deficit 19 mmol/L) and than those without (median pH 7.26, median base deficit 8 mmol/L), ($p \leq 0.05$). No significant differences were found between the 3 groups regarding serum methanol, osmolal gap, and HCO₃⁻. The groups differed only in pCO₂, pH and base deficit (all $p \leq 0.05$). Among the patients who recovered without sequelae, there was a trend towards lower pCO₂ when pH was decreasing, whilst the trend was the opposite amongst the victims (pH decreased and pCO₂ increased). The difference between these groups was highly significant ($p = 0.001$). Lactic acid was significantly higher in victims than survivors ($p < 0.01$).

Among the 58 patients treated with ethanol, 9 (16%) died, 9 (16%) survived with sequelae, and 40 (68%) recovered fully. Among the 13 patients treated with fomepizole or the combination of antidotes, 3 (23%) died, 6 (46%) survived with sequelae, and 4 (31%) recovered, i.e. the outcome was worse in the second group ($p = 0.023$). There was no difference in survival between the patients treated with continuous veno-venous haemodialysis (CVVHD) and IHD ($p = 0.17$).

Conclusion: In agreement with the findings of previous studies⁵, severe acidosis and coma on admission were strong predictors of an unfavourable outcome, as was the lack of hyperventilation in spite of severe metabolic acidosis. The comparison of the effect of both antidotes cannot be evaluated, as the limited availability of fomepizole made it the antidote of choice in only the more severely poisoned patients. After improvement, therapy was continued with ethanol to save fomepizole. Among the patients treated with fomepizole or a combination of antidotes, 46% of subjects were comatose on admission, whereas only 26% of subjects solely treated with ethanol were comatose. By December 2012, the outbreak had resulted in 38 casualties. Unfortunately it may not yet be over, as 15,000 bottles of adulterated spirits have been sold and are still missing, threatening the consumers.

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2. A long term epidemic of methanol poisoning deaths in Finland

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Objective: Several outbreaks of methanol poisonings have been reported in Europe during recent years e.g. in Estonia, Norway and the Czech Republic. We describe a long term epidemic of fatal methanol poisonings in Finland between 1986–2011.

Methods: A trend analysis of methanol poisoning deaths using the statistics of the causes of death in Finland from 1986 to 2011.

Results: There were a total of 453 fatal methanol poisonings during the study period. Over the period of 1986 to 1994 there were 22 deaths due methanol, on the average 2.44 deaths/year. Over the period of 1995–2011, the total number of methanol deaths was 431, an average 25.35 deaths/year. Extrapolating from the pre 1995 mortality of 2.5 deaths per year the methanol epidemic has caused an excess of 389 deaths in Finland. A typical victim of methanol poisoning in Finland is a 50-year old man with a drinking problem belonging to a group of technical alcohol drinkers. They use car chemicals as surrogates and possible health effects of the substances are of very little significance if a substance has been found to be fit for drinking.¹

Conclusion: Finland has experienced a dramatic methanol poisoning epidemic after the year 1995, when Finland joined the EU and

has had to allow the use of methanol in windscreen washer fluids. The authorities have put in place regulations concerning packaging and storing windshield washer fluids, with limited success. At the moment, sellers should store products containing methanol in a locked place and the selling of these products is prohibited to persons less than 18 years.

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3. Description of 3924 courses of chelation with 2,3-dimercaptosuccinic acid in children with severe lead poisoning in Zamfara, northern Nigeria

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Objective: Lead poisoning on an unprecedented scale was discovered in Zamfara by Médecins Sans Frontières (MSF) in early 2010. The source was artisanal mining and processing of lead-contaminated ore for gold. Remediation was undertaken by other international/national agencies and in June 2010 MSF commenced a treatment programme in a remote field clinic. 2,3-dimercaptosuccinic acid (DMSA) chelation protocols were based on WHO guidelines and expert consensus. The chelation blood lead (BLL) threshold was 45 µg/dL; 28, 19 or five day DMSA courses were administered based on BLL. We describe here data from the first thirteen months of this programme; this is the largest series of DMSA chelation therapy reported to date.

Methods: Inclusion criteria: DMSA chelation courses June 2010–June 2011 in children ≤ 5 years. Venous BLL was measured with Lead Care II. Percentage reduction in BLL from start to end of each chelation course is reported. Variables significantly influencing change in BLL during a chelation course were assessed by multivariable linear regression and BLL change in the DMSA-free period post-chelation was also assessed.

Results: 3924 DMSA courses (in 1193 children) were administered. Thirty per cent of courses were initiated within initial BLL ≥ 80 µg/dL; 24 children had encephalopathy. BLL for 3182 completed courses of 19 or 28 day DMSA declined to a geometric mean of 76.5% (95% CI 75.6, 77.5) of pre-chelation BLL, with inpatient courses decreasing to 39.2% (95% CI 34.8, 44.2). Decline in BLL at the end of 19 day DMSA courses was significantly ($p < 0.0001$) greater in older children (≥ 3 years vs < 6 months), first-ever DMSA course, higher initial BLL, courses with a greater time-interval since previous course and courses

with a greater proportion of directly observed doses. There was no change in the proportion of children with a low total white-cell or neutrophil count. A small (3%) number of children developed an elevated alanine aminotransferase (> 42 IU/L), none of these were of clinical significance.

Conclusion: Oral DMSA is an effective and safe chelator for children with severe lead poisoning, including those with encephalopathy. Findings from this large cohort will help improve chelation protocols and enable clinical toxicologists to adjust DMSA therapy based on the severity of lead poisoning.

4. Long-term follow-up of three cohorts of self-poisoning

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Objective: The long-term mortality of patients admitted to hospital for self-poisoning is high for all causes of death. The effect of follow-up is complicated to evaluate because the elevated risk persists for decades, and it is not known whether the long-term mortality has changed over time as a result of hopefully better aftercare. We therefore compared long-term mortality for hospitalized self-poisonings in 1980, 1985 and 1990.

Methods: Three cohorts of self-poisonings admitted to Ullevål University Hospital in Oslo in 1980 ($n = 855$, median age 31 years, 46% females), 1985 ($n = 463$, median age 33 years, 54% females) and 1990 ($n = 322$, 36 years, 58% females) were obtained, in total 1640 patients. Patients were followed to the end of 2010 using the Central Population Register and the Causes of Death register. Uneven observation time was handled by using survival analysis with Kaplan-Meier calculation and Cox regression analysis.

Results: In total, 787 (48%) died during the follow up period; 445 (52%) from 1980, 212 (46%) from 1985 and 130 (40%) from 1990. No differences in total mortality between the cohorts were found with log rank test, $p = 0.78$. Cox regression gave hazard ratio (HR) for 1985 = 0.98 ($p = 0.85$) and for 1990 1.1 ($p = 0.55$) compared to 1980. Overall, males had higher mortality than females, HR 1.9 ($p < 0.001$), no difference across the cohorts. Suicides in the follow-up period were identified by ICD-codes, from 1980 70 (8.2%), from 1985 38 (8.2%) and from 1990 14 (4.3%). The risk of death by suicide did not differ between the cohorts, over all log rank $p = 0.33$; 1985 HR 1.0 ($p = 0.81$), 1990 HR 0.67 ($p = 0.17$) compared to 1980. When analysing the subgroup of patients with a clear suicidal intent at the index episode, later death by suicide did not differ significantly across the cohorts, HR for 1985 1.2 ($p = 0.51$) and HR for 1990 0.6 ($p = 0.23$) compared to the 1980 cohort.

Conclusion: The long term mortality rates among self-poisoned patients did not differ significantly between the 1980, 1985 and 1990 cohorts, neither in terms of total mortality nor suicides. These high mortality and suicide rates definitely call for better aftercare.

5. Safety of engineered nanomaterials

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Background: The emerging field of nanotechnology has led to substantial advances in energy, medicine, and clean technologies.

Discussion: This area relies on nanomaterials that have been defined as materials where at least one dimension is less than 1 μm . Nanomaterials are used in many different products, and the numbers of engineered products are increasing due to their unique properties. Due to their small size and their unique properties, there has been concern that exposure to these materials is associated with an increased risk for adverse health effects. These concerns were due to increased risk of cardiovascular disease (CVD), cancer and mortality associated with ambient air pollution that also contains ultrafine particles, as well as the similarity of some nanoparticles to asbestos e.g. carbon nanotubes. However in contrast to ambient air particles, nanoparticles are chemically well defined and not a complex mixture of different compounds. In order to address a public concern about using this new technology and the derived products, the European Commission, at an early stage, asked the question, could the safety of nanoparticles be evaluated using the Technical Guidance Documents used for chemicals, or is a new paradigm needed. The major concern was 1) the metric dose required, i.e., weight basis, particle number or surface area, and 2) if the traditional Organisation for Economic Co-operation and Development (OECD) validated test methods could be used or should be modified. Since then, recommendations have been developed for specific applications, e.g. food, cosmetics, medical products by relevant agencies.

Due to their high surface area relative to the weight, it is assumed that the nanomaterials are very reactive, and based upon our knowledge of the toxicology of ambient air ultrafine particles, it is generally assumed that the toxicity of nanoparticles is mediated by reactive oxygen species (ROS), and formation of ROS has been detected following both *in vitro* and *in vivo* exposure to various types of nanoparticles (NP). The consequence of this exposure could be induction of inflammatory responses, or damage to cellular macromolecules by reactive oxygen species. Due to its high reactivity the NP could directly react with cellular macromolecules, e.g. enzymes, DNA and thus interfere with the homeostasis of the cells. A tiered approach to screening for nanoparticle toxicity has been proposed based upon the formation of ROS.¹ Of special concern is genotoxicity testing, as many NP are not mutagenic in bacterial assays, and the fact that the NP interfere with reagents used in standard assays.²

One of the major problems in nanotoxicology has been the characterization of the nanoparticles, both prior to testing and during the testing protocol, e.g. NP tends to react with components in serum and thus changes the size, and also agglomeration of the nanoparticles. In order to characterize these particles several microscopic techniques are used as well as other physical chemical methods. Thus nanotoxicology requires a cross-disciplinary approach involving material scientists, physicists and molecular toxicologists.

The focus of our work has been on the toxicity of silver (Ag) NP particles, as these are used in many different consumer products, mostly related to their antibacterial activity. The toxicity of silver nanoparticles and silver ion has been investigated in both human and animal cells using different parameters for toxicity, e.g. mitochondrial activity (MTT assay), induction of apoptosis, and induction of reactive oxygen species. ROS was demonstrated both by direct measurements and by formation of DNA adducts, e.g. bulky adducts measured by P32 postlabelling, and 8-oxo-dG by mass spectrometry (MS). Potential genotoxicity was assessed by induction of micronuclei detected by flow-cytometry.

The observed toxicity was due to both the Ag NP and the release of silver ions, however using gene array assay, significant differences between Ag NP and silver ion heat maps were noted. This indicates different toxicological mechanisms for the ion and the NP.³

In order to compare the toxicity in cells of different organs and to compare the effect in human and animals cells, pairs of mouse and human cell lines, i.e. lung, colon, macrophage were compared, and the mouse cell lines were significantly more susceptible to the toxicity of Ag NP.

Comparison of different types of nanoparticles in the same cells (lung cancer cells A549) suggests that the toxicological mechanism is more related to the specific chemical properties of the nanomaterial, rather than the nanoparticle structure. A comparison of the gene expression profiles of silica NP and Ag NP showed significant differences.

In vitro studies are the preferred model for assessment of toxicity and determination of the mechanism of action for nanoparticles. Many of the assays used are very sensitive to culture conditions, cell types, serum and media composition due to interaction with the nanomaterial.

Risk assessment normally requires information on hazard characterization and exposure characterization; whereas many studies have been conducted to assess the hazard, limited information is available on exposure to both humans and the environment. A special concern with the use of nanomaterials is the release of the NP into the environment through wear and release from waste. Thus environmental risk assessment is an integral part of the evaluation process.

Conclusion: Regulatory procedures are currently being developed to ensure that exposure to engineered nanomaterials or the released particles are not associated with any health risk.

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6. Mechanistic biomarkers provide early and sensitive detection of paracetamol-induced acute liver injury at first presentation to hospital

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Objective: Paracetamol (acetaminophen) overdose is a common reason for hospital admission and the most frequent cause of acute

liver failure in the Western world. We investigated the potential of new biomarkers - which demonstrate enhanced liver expression or are linked to the mechanism of toxicity - to identify paracetamol-induced acute liver injury at first presentation to hospital.

Methods: In plasma from patients (n = 129) at first presentation to hospital following overdose, we measured: microRNA-122 (miR-122; high liver specificity), High Mobility Group Box-1 (HMGB1; marker of cell necrosis), full length and caspase-cleaved Keratin-18 (K18; markers of cell necrosis and apoptosis, respectively) and glutamate dehydrogenase (GLDH; marker of mitochondrial dysfunction). Receiver operator characteristic (ROC) curve analysis was used to compare each marker with current liver injury markers such as alanine transaminase (ALT) and international normalised ratio (INR).

Results: In all patients (n = 129); the biomarkers (miR-122, HMGB1, necrosis K18, apoptosis K18 and GLDH) at first presentation all correlated with peak ALT/INR (all p < 0.0001). In patients with normal ALT/INR at presentation, miR-122, HMGB1 and necrosis K18 identified the development of liver injury (n = 15) or not (n = 84) with a high degree of accuracy (miR-122, HMGB1 and necrosis K18: ROC curve AUC values (sensitivity at 90% specificity); 0.93 (0.83), 0.97 (0.91) and 0.94 (0.90), respectively. All p < 0.0001). In patients presenting within 8 h of overdose, miR-122, HMGB1 and necrosis K18 substantially outperformed ALT and plasma paracetamol concentration for the prediction of subsequently liver injury (n = 11) compared with no injury (n = 52). ROC curve AUC (sensitivity at 90% specificity) values: 0.80 (0.45) for miR-122 (p = 0.002), 0.83 (0.63) for HMGB1 (p < 0.001), 0.80 (0.45) for necrosis K18 (p = 0.002), 0.52 (0.09) for ALT (p = 0.8), 0.54 (0.18) for plasma paracetamol concentration (p = 0.68).

Conclusion: MiR-122, HMGB1, and necrosis K18 identify acute liver injury on admission to hospital, soon after paracetamol overdose, and when ALT is in the normal range. The clinical development of such a biomarker panel could improve the speed of clinical decision making, both in the treatment of acute liver injury and in the design and execution of clinical trials that aim to refine the management of this common poisoning.

7. Adulterated food supplements, health risks and poisons information center data

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Introduction: For many people, using food supplements is a way of treating disorders without having to consult a medical professional. They often have the impression that a product of so-called herbal origin will be safe to use. Although they may have some doubt whether the intended effect will be sufficient, they are confident that the product will not harm their health. Because the product is readily available on the market, potential users conclude it must be safe to use. They wrongly assume that any available product is automatically screened and therefore legally available on the market. Apart from the health risks posed by misdiagnosis of the ailment and/or not treating the illness adequately, serious health risks also arise from the poor quality of many of these

products. It is important to realise that there is little quality control and the composition of the products can vary greatly even between different batches of the same product. Often the concentrations of active substances are variable and contamination with residues from the production process can occur. Moreover, adulteration of food supplements with pharmaceutically active substances is widespread. Food supplements can also interfere with regular treatment and thus have a negative health effect, especially when the use of the food supplements is not declared to the treating physician.

Types of food supplements: In general four main categories of food supplements can be distinguished: vitamins and minerals, relaxing food supplements, energizers (including weight-loss preparations) and erectogens.

Vitamins and minerals: Food supplements from this category are very widely used. Adverse health effects are rare and mostly occur after (chronic) ingestion of high doses (very large amounts or concentrated preparations), especially when metal-salts (mainly iron and copper) or water-insoluble vitamins are involved. The toxicology of vitamins and minerals is well known and health effects from these agents are not of major concern within the food supplements.

Relaxing food supplements: Substances like melatonin, valerian and St. John's wort are used as alternatives to prescription sedatives. No reports of severe health effects were found in 1395 calls to the National Poisons Information Center (DPIC) about overdose with these substances. However for St. John's wort it is well known that induction of metabolic enzymes can occur, leading to interference with the metabolism of other medication and thus possibly disturbing the efficacy of regular treatment.

Energizers: Many different substances are occasionally found in this category, but with the current ideal of beauty being slim, and obesity being a major health-problem in Western society, the main products of concern within the Energizer-category are the weight-loss preparations. From the analysis of confiscated food supplements for weight-loss¹ we know that these preparations mostly contain ephedrine-alkaloids or sibutramine in moderate to high dosage. In the Netherlands, the ban on ephedra did not result in the disappearance of ephedra-alkaloids from food supplements for weight-loss. The decline in the number of enquiries on ephedra to the DPIC is greater than expected based on the analytical results. This is probably due to the fact that ephedra is no longer declared on the label, thus posing an additional health risk for the unwitting user. Despite the obvious risk of using weight-loss food supplements, the prospect of losing weight fast and without effort is still tempting to many. The booming (Internet) trade in dubious weight-loss food supplements is therefore a worrying development.

Food supplements for erectile dysfunction: From the analysis of confiscated food supplements for erectile dysfunction, we know that most of them contain at least one pharmaceutical that is not declared on the label. The pharmaceuticals found are mainly sildenafil, tadalafil, vardenafil and their analogues. These "analogues" are defined as molecules that are structurally similar to sildenafil, tadalafil or vardenafil but have not been evaluated for safety or efficacy. In a Dutch survey² 42 different analogues were identified. In 6 reports to the DPIC (all concerning adults under 50 years of age) reported adverse health effects were: palpitations, irregular pulse, restlessness, vomiting and a burning sensation all over the body. In 4 cases other drugs or alcohol had been used as well and in one case 60 pills were taken at once. The occurrence of adverse effects is associated with overdosing and with concomitant alcohol or drug use. The majority of the analyzed food supplements

for erectile dysfunction contained pharmaceuticals that were not declared on the label. Thus, users are deceived and cannot be held accountable for possible health damage.

Conclusion: The use of food supplements poses a health risk to the users. PICs can monitor their inquiries for reports of poisonings or adverse health effects related to food supplement use. PIC-generated signals can be used as a starting point for laboratory analysis of the products involved. Collaboration with regulatory and enforcing authorities is necessary to insure that adequate measures can be taken if high risk products are detected.

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8. Trends in intoxications of novel psychoactive substances in Sweden during 2012

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Background: The Swedish Poisons Information Centre (SPC) and the Karolinska University Laboratory cooperate in a project called "STRIDA", aiming to monitor trends in acute poisonings with novel recreational drugs in Sweden and collect data of their clinical effects and associated dangers. This study summarizes the results for the first 9 months in 2012, with focus on the stimulants 3,4-methylenedioxypropylvalerone (MDPV), ethylphenidate, 5-(2-aminopropyl)indole (5-IT) and benzofurans (5- and 6-APB).

Methods: Patients from all of Sweden with suspected intoxications by novel recreational drugs were recruited to the STRIDA project by promptings from SPC personnel when consulted by caregivers. Urine and/or blood samples from 321 patients were analyzed with a liquid chromatography-tandem mass spectrometry (LC-MS/MS) multi-component method which is continuously updated to identify novel and traditional psychoactive substances and their metabolites. Analysis for MDPV was prospective during the entire study period while analyses for ethylphenidate, 5-IT and benzofurans were applied retrospectively to samples where these drugs had been suspected, or in unresolved cases with significant toxic symptoms. Positive test results were related to clinical symptoms in medical records sent to the SPC.

Results: MDPV was detected in 86 samples. In 17 cases the symptoms were severe (Poisoning Severity Score - PSS 3) and consisted of extreme agitation, psychosis, hyperthermia, tachycardia, hypertension, myocardial infarction, rhabdomyolysis and renal failure. A few patients needed therapy with sedatives for several days due to prolonged symptoms. Ethylphenidate was detected in 25 samples. In 2 cases the symptoms were severe, resembling those of MDPV intoxication. 5-IT was detected in 16 samples and in 7 cases the

symptoms were severe. Benzofurans were detected in 6 samples and in one case the symptoms were severe. The symptoms caused by 5-IT and benzofurans were similar and included agitation, convulsions, mydriasis, hyperthermia, tachycardia, disseminated intravascular coagulation, rhabdomyolysis, hepatic and renal failure.

Conclusion: These results demonstrated that among people that come to medical attention, the incidence of severe poisonings (PSS 3) was highest for MDPV (20%) and 5-IT (44%), suggesting that these substances are particularly dangerous novel psychoactive drugs. Deaths related to both substances have occurred in Sweden during 2012 (Institute for Forensic Toxicology, Linköping, unpublished data). The comparatively large number of MDPV intoxications is partly explained by a local outbreak.

9. The impact of an MDPV-epidemic on a medium sized Swedish city

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Objective: In the first half of 2012, the number of enquiries to the Swedish Poisons Information Centre regarding intoxications with the amphetamine derivative MDPV (3,4-methylenedioxy-pyrovallorone) rose sharply. Most came from Västerås, a city in central Sweden with a population of 110,000. This retrospective study of medical records attempts to corroborate and quantify the impact of this epidemic.

Methods: Cases of stimulant toxicity at the hospital in Västerås in April-May 2010-12 were identified through a review of medical records of patients either classified as "intoxication" in the emergency room ledger or who received the ICD-10 diagnoses F14-16, T40 or T43. Cases of suspected stimulant consumption were included and patient self-report or care giver suspicion of drug type was recorded. The presence of a history of long standing drug abuse or hepatitis C virus (HCV) infection was also noted. A non-randomized subset of the patients had blood and/or urine tested for "Internet drugs" by liquid chromatography tandem mass spectrometry method (LC-MS/MS) in an ongoing research project.¹

Results: In April-May 2012 the number of patients (n = 45) with stimulant toxicity and their need for hospitalization (109 days) increased 2–5-fold and 5–18-fold respectively, compared with the preceding years. The number of patients treated in intensive care rose from a total of 2 in 2010–11 to 10 in 2012, and the number of ICU days from 2 to 45. MDPV-intoxication was suspected in 82% of cases in 2012. In 2012, 17 of the 45 patients underwent LC-MS/MS analysis and 13 (76%) tested positive for MDPV. Of the patients with confirmed or suspected MDPV consumption 95% were classified as chronic drug users and >60% were HCV-positive.

Conclusion: This study documents a dramatic increase in the need for all levels of hospital care for stimulant toxicity in Västerås in early 2012. Medical records implicate MDPV as the cause of the increased morbidity, a finding supported by the presence of MDPV in 76% of patients who underwent drug testing. No deaths were recorded during the study period, but the increased morbidity in a

population of chronic drug users exposed to a new drug indicates that MDPV is a highly dangerous substance of abuse.

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10. Methoxetamine: A case series of analytically confirmed cases

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Objective: Methoxetamine is a novel recreational drug with reported ketamine-like effects.¹ We retrospectively studied available hospital discharge summaries and poisons centre (PC) records of all methoxetamine cases, from March, 2011 until October, 2012.

Case series: The Swedish PC received enquiries about 71 hospitalized cases with suspected methoxetamine-intake. Half of these patients were under 26 years of age. Route of administration was oral (38%), nasal (37%) and injection i.m./i.v. (7%). Three cases with sublingual and one case of rectal administration were also reported, 13% were unknown. Methoxetamine was analytically confirmed in urine and/or serum in 24 cases. Addition of 14 cases with positive results and no history of methoxetamine-intake made a total of 38 analytically confirmed cases (Table 1). For the "methoxetamine only" group most cases were scored as mild or

Table 1. Analytically confirmed cases of methoxetamine.

	Number of cases	Prominent symptoms	Poisoning severity score (PSS) [#]
Methoxetamine only	11/38	Hypertension (36%), tachycardia (36%), hallucinations (27%), nystagmus (27%), CNS-depression (27%), mydriasis (27%), anxiety (18%), muscular symptoms (18%), agitation/restlessness (9%)	PSS 1 (64%) PSS 2 (18%) PSS 3 (18%)
Mixed poisonings*	27/38	Hypertension (48%), CNS-depression (44%), tachycardia (44%), agitation/restlessness (33%), mydriasis (30%), nystagmus (26%), hallucinations (22%), anxiety (19%), muscular symptoms (11%)	PSS 1 (41%) PSS 2 (37%) PSS 3 (11%) Unknown (11%)

*Additional substances detected were e.g. 5-(2-aminopropyl) indole (5-IT), amphetamine, benzodiazepines, buprenorphine, ethanol, 3,4-methylenedioxy-pyrovallorone (MDPV), morphine, 4-hydroxy-methylethyltryptamine (4-OH-MET), tetrahydrocannabinol (THC) and tramadol.

[#] PSS. Poisoning severity score²

moderate. However, two were severe poisonings presenting unconsciousness, one of them with respiratory depression. In the latter case, a urine sample was not available hence mixed poisoning cannot be ruled out.

Conclusion: This is the first case series with analytical confirmation regarding methoxetamine. These poisonings presented a combined hallucinogenic and sympathomimetic toxidrome. Symptomatic treatment with benzodiazepines was normally sufficient, though one patient required intubation and mechanical ventilation. After legal control of methoxetamine in May 2012 the enquiries have decreased substantially.

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11. Fundamentals of coagulation and new insights into the pharmacology and pharmacogenetics of anticoagulant therapy

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Background: Millions of patients worldwide are taking anticoagulant therapy to treat or prevent thrombosis or embolic phenomena. One of the risks of such therapy is that of bleeding, and coagulation testing traditionally has been used for monitoring therapy. With newer oral anticoagulants now available, this traditional approach is no longer routinely necessary but methods for assessing anticoagulation may still be needed, for instance if bleeding occurs on therapy or compliance is uncertain. In order to be able to interpret the results of coagulation testing, the fundamentals of haemostasis must be understood. Clotting assay results may vary within and between laboratories dependent on the analysers and reagents used. Standardisation for some tests such as the INR (international normalised ratio) has reduced but not eradicated some of the variability.

Discussion: Haemostasis depends upon the integrity of the tissues and vasculature, the number and function of the platelets (primary haemostasis) and the formation of fibrin (secondary haemostasis). Anticoagulant drugs affect secondary haemostasis either by reducing the concentration of coagulation factors or by the inhibition of activated factors. When a vessel is injured, the subendothelial collagen is exposed resulting in platelet adhesion, activation and aggregation forming the primary haemostatic plug. Secondary haemostasis then follows and has been described as a cascade where inactive plasma coagulation factors are converted to their active counterparts in a sequential fashion by cleavage of peptide bonds. Thrombin is generated, converting fibrinogen to fibrin which then stabilises the platelet plug. Activation of factor XIII by thrombin allows cross-linking of the fibrin strands and further stabilisation. Thrombin also activates both the protein C and the fibrinolytic pathways resulting in the inhibition of coagulation and dissolution of the fibrin clot respectively.

The classical coagulation cascade is described as having an extrinsic and an intrinsic pathway coinciding at the activation of

factor X to form the final common pathway. At initiation of the intrinsic pathway, factor XI is activated by the contact factors factor XII, prekallikrein and high molecular weight kininogens. Factor XIa then activates factor IX which in association with its co-factor, factor VIIIa, forms the ‘tenase’ complex which then activates factor X. Factor Xa with activated factor V binds to negatively charged phospholipids forming the ‘prothrombinase’ complex which cleaves prothrombin to form thrombin which in turn cleaves fibrinogen to form fibrin. In the extrinsic system, it is assumed that the release of tissue factor and factor VII by damaged vessels activates factor X directly. The integrity of these assumed pathways is measured *in vitro* using the prothrombin time (PT) for the extrinsic pathway and the activated partial thromboplastin time (APTT) for the intrinsic pathway. The PT is prolonged with low levels of factors VII and X as well as factors II (prothrombin) and V of the common pathway. The APTT is prolonged by deficiencies of factors XII, XI, IX, VIII and X with the greatest prolongation occurring with the factors at the beginning of the cascade i.e. factor XII. Fibrinogen is measured most reliably by the Clauss fibrinogen assay. It is a functional assay, based on the principle that the thrombin clotting time is inversely proportional to the fibrinogen concentration. These clotting tests however are inadequate to explain what happens during *in vivo* haemostasis. In this process, when tissue factor (TF) is released from damaged vessels, it binds to circulating factor VII (FVII) and factor VIIa which activates factor IX and activates and binds factor X (FX); a small amount of thrombin is generated. The TF/FVII/FX complex is rapidly inactivated by Tissue Factor Pathway Inhibitor (TFPI) but the thrombin generated initiates amplification of the coagulation pathway by activating factor VIII through cleavage from von Willebrand factor, factor V, factor XI and platelets. These factors with the activated factor IX generate sufficient thrombin for clot formation. The traditional coagulation tests, although helpful for monitoring warfarin and unfractionated heparin, are also inadequate for the monitoring of the newer anticoagulants, in particular the new oral anticoagulant agents.

Warfarin is a vitamin K antagonist and inhibits the gamma-carboxylation factors II, VII, IX and X. This post-translational modification is needed for calcium binding which itself promotes binding to the phospholipid surface of activated platelets. The dose of warfarin required to achieve therapeutic levels is measured by the PT and needs to be monitored regularly. Warfarin has a narrow therapeutic range and the PT is dependent on the analytical system used. The INR, used to monitor warfarin, allows comparison of the thromboplastin reagent with an international reference standard through a mathematical conversion, so that results can be standardised across laboratories, regardless of thromboplastin reagent used. The intensity of anticoagulation can be influenced by diet, alcohol and genetic factors such as the patients CYP2C and VKORC1 genotype.

Unfractionated heparin (UFH), low molecular weight heparins (LMWH) and fondaparinux exert their anticoagulant effect by enhancing the action of the inhibitor antithrombin. UFH inhibits activated factors II, IX, X, XI and XII and can be monitored using the APTT. LMWH inhibits activated factor X and II and fondaparinux inhibits activated factor X. Although both cause prolongation of the APTT this is not sensitive enough for monitoring and so anti-Xa levels are used to ensure a therapeutic effect. Once this is achieved, routine monitoring is not required but may be needed in patients at extremes of body weight, during long-term therapy, in pregnancy or in those with impaired renal function.

Oral direct inhibitors of thrombin (dabigatran) and activated factor X (rivaroxaban and apixaban) are now available but have been licensed with doses based on clinical criteria rather than coagulation testing. The classical coagulation tests are not suitable for monitoring these newer anticoagulants as the reagents used for the APTT and PT are either too sensitive or insensitive and fail to show a dose response. Although not having to monitor these drugs should make treatment easier, there are situations where accurate assessment of anticoagulant therapy is important such as before surgery or in a patient who is bleeding.

Conclusion: Clinicians also need to become accustomed to managing patients on anticoagulants without the reassurance of monitoring.

12. Management of bleeding associated with vitamin K antagonists

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Background: Even with the recent influx of novel coagulation factor inhibitors, the vitamin K antagonists (VKAs) remain the most commonly prescribed oral medication for systemic anticoagulation. In addition, some VKAs are used as rodenticides due to their potency and protracted duration of action. Warfarin is the primary VKA used by most countries for prophylactic and therapeutic anticoagulation, but other agents such as acenocoumarol and phenprocoumon are also available. Because of their numerous drug and dietary interactions, maintaining the appropriate degree of anticoagulation with the VKAs is challenging. Bleeding is a common complication even when therapeutically anticoagulated.

Objectives: (1) To review management strategies for bleeding associated with VKAs; (2) to understand the advantages and disadvantages of the factor replacement options; and (3) to discuss vitamin K dosing and administration based on clinical scenario and specific agents.

Discussion: The likelihood of VKA-associated bleeding depends on a number of factors including: genetic variability of target enzymes and metabolic pathways; degree of anticoagulation, comorbid conditions, duration of anticoagulation, and age. The most dreaded complications of anticoagulation are intracranial hemorrhage and bleeding at non-compressible sites.

Patients with life-threatening hemorrhage or severe VKA-induced factor deficiency should receive immediate factor replacement with fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC). While packed red blood cells replace lost volume, they do not replace depleted clotting factors or correct underlying coagulopathy. In fact, large volume transfusion of red blood cells alone can exacerbate coagulopathy by diluting existing coagulation factors, inducing a dilutional thrombocytopenia, and depleting calcium concentrations as a result of citrate toxicity.

The British Committee for Standards in Haematology (BCSH) and the American College of Chest Physicians (ACCP) published updated guidelines to reverse VKA-associated anticoagulation in 2011 and 2012, respectively. Both recommend 4-factor PCC as the first-line option for rapid factor replacement^{1,2} Availability of various PCC products differs by country. All PCC products contain

concentrated factors II, VII, IX, and X, but they vary in factor VII content. 3-factor PCC contains a reduced amount of factor VII to limit thrombotic potential. There are no large, prospective trials directly comparing PCC and FFP for this indication; the studies suggesting that PCC completely corrects international normalized ratio (INR) faster than FFP are small and compromised by uneven factor replacement between the treatment groups and subtherapeutic dosing of FFP³. Although considerably more expensive, the BCSH and ACCP recommend utilization of PCC before FFP for several reasons. First, FFP at standard initial doses of 15-30 mL/kg requires longer infusion times and can also cause volume overload. Additionally, large volume transfusion of FFP can induce dilutional thrombocytopenia, thereby worsening hemostasis. Finally, time to infusion of FFP may be significantly prolonged due to blood-type requirements and thawing time. Regardless of the form of exogenous factor replacement, repeat dosing may be necessary since clotting factors have limited half-lives; for example, factor VII has the shortest half-life at approximately 6 hours¹.

Recombinant activated factor VII (rFVIIa) is approved for use only in bleeding patients with hemophilia or inhibitors to factors VIII or IX. Thromboembolic events after rFVIIa administration is a known complication, with 89.9% of the cases reported to the US Food and Drug Administration's Adverse Event Reporting System occurring as a result of off-label use.⁴ Though rFVIIa has been used for warfarin reversal, it is not adequately studied, and the BCSH and ACCP do not recommend its use for treating bleeding from the VKAs. Vitamin K should be administered in VKA-anticoagulated patients with active bleeding or excessively high INRs. The BCSH and ACCP have published specific guidelines on vitamin K at doses of 1-10 mg for these patients, depending on the degree of bleeding and anticoagulation.^{1,2} Vitamin K can be administered orally or parenterally as its active form phytonadione (vitamin K1). Oral administration of phytonadione is safe and effective with overcorrection as the major complication in patients who require systemic anticoagulation. Efficacy may be reduced by poor enteric absorption such as during gastrointestinal hemorrhage. Although intravenous administration of vitamin K1 results in the most rapid onset of action, it still requires several hours to take effect and introduces the risk of life-threatening anaphylactoid reaction. Reducing the rate of administration decreases but does not eliminate this risk. Intramuscular administration, an option in stable patients with poor enteral absorption, may result in unpredictable absorption kinetics. Regardless of the route of vitamin K1 administration, a delay of several hours to the onset of reversing coagulopathy mandates that factor replacement should be instituted early in serious hemorrhages.

Anticoagulation from the long-acting VKAs, such as those constituting many rodenticides, may require prolonged therapy with vitamin K1 because severe coagulopathy may last for several months. High dose vitamin K1 regimens of 50 to 100 mg/day are commonly needed to maintain normal INRs, and case reports of patients requiring maintenance doses up to 600 mg/day are reported⁵.

Conclusion: Supratherapeutic INRs and hemorrhage are common complications of anticoagulation with the VKAs. Although volume replacement is essential in hemorrhaging patients, effective reversal of VKA-induced anticoagulation is achieved by direct factor replacement, followed by vitamin K1 supplementation to promote reactivation of endogenous clotting factors.

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13. Non-hemorrhagic complications of anticoagulation

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Objective: To describe the most common non-hemorrhagic complications of the most commonly used antithrombotics.

Methods: Literature review of existing publications on: 1) Heparin-induced thrombocytopenia and thrombocytosis (HIT); 2) Vitamin K antagonist (VKA; warfarin) skin necrosis and the purple toe syndrome; and 3) Thrombotic thrombocytopenic purpura (TTP) from thienopyridines.

Results: HIT¹ is a disorder that results from an immune response to heparin that has become complexed to platelet factor 4. It is more common in women and with certain clinical disorders and rates range from as low as 0.1% in hemodialysis patients to 3–5% in orthopedic surgery patients. Platelet counts fall as they participate in “white clots” that may occur in both the arterial and the venous system. Skin lesions may result from small vessel coagulation and many patients will develop fever, chills, and respiratory symptoms shortly following heparin injections. The diagnosis is established based on a clinical scoring system that includes platelet count, timing, thrombosis and HIT antibodies. Treatment involves stopping all heparins and treatment with a direct thrombin inhibitor.

V skin necrosis² occurs in about 1–10 patients for every 10,000 treated and typically presents in the first few days following initiation of therapy. Women and those patients receiving large loading doses of VKAs tend to be predisposed and lesions typically develop in areas with high fat content that are under pressure. While the exact mechanism is not known one prevailing theory is that following the administration of a VKA, the levels of both procoagulants (Factors II, VII, IX and X) and anticoagulants (Proteins S, C and Z) fall. If the anticoagulants fall more rapidly than the procoagulants a hypercoagulable condition develops. This would account for the timing of the skin necrosis and the fact that many patients with VKA skin necrosis have true deficiencies in Proteins S or C or antithrombin. Early manifestations can be treated with conservative care and vitamin K, but those patients requiring anticoagulation are traditionally managed with heparins and extensive wound care. Since this is not a true allergic manifestation of VKAs, some patients can be successfully treated with VKAs in the future. The purple toe syndrome³ is a symmetrical abnormality that typically occurs in the feet of patients recently (3–8 weeks) started on VKAs

and other antithrombotics. Although many are painless, some patients report pain. The syndrome results from a showering of cholesterol emboli from large vessel plaques that are no longer covered by their protective layer of fibrin. Pulses are universally present, which distinguishes this from other forms of clot and embolic disease and loss of tissue is exceedingly uncommon. The exact therapy is unknown and many patients are switched to heparin since it is unclear whether they should remain on long-term VKAs.

The thienopyridines are anti-platelet drugs that include ticlopidine, clopidogrel and prasugrel. As a class, they bind to the P2Y₁₂ ADP receptors on platelets to reduce activation and aggregation. Although all three drugs are associated with TTP^{4,5}, the incidence and mechanisms are different for these agents with ticlopidine having the greatest risk with a reported incidence of about 1/5000 uses. The onset is typically within the first few weeks of therapy and patients present with some or all of the classic findings that include; thrombocytopenia from platelet aggregation, kidney injury, neurological findings, and a microangiopathic hemolytic anemia. In addition to stopping the drugs, patients are treated with corticosteroids and plasma exchange.

Conclusion: Although non-hemorrhagic complications of anti-thrombotic agents are far less common than hemorrhage they represent a unique series of events that may present risk to life or limb. The correct diagnosis begins with clinical identification followed by laboratory confirmation when available. In most cases the offending drug should be immediately stopped and other anticoagulants initiated as indicated.

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14. Alternative medicine and toxicology: Are the risks well known?

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Background: The term “complementary and alternative medicine” (CAM) includes several different approaches to treatment, from homeopathy to herbal medicine, acupuncture or spiritual healing; it includes all practices and ideas self-defined by their users as preventing or treating illness or promoting health and well-being. The

boundaries within CAM and between the CAM domain and that of the dominant health systems are, therefore, not always fixed. In fact, several complementary therapies involve the administration of pharmaceutical-type remedies. Herbal medicines are chemically rich preparations of plant material whereas homeopathic remedies are infinitely dilute preparations of material which may be plant, animal, mineral, chemical or biological in origin.

Discussion: A substantial amount of CAM is used worldwide for illness prevention and health promotion purposes, but there is also evidence that CAM is frequently used as an adjunct to biomedical treatment by patients with serious diseases such as diabetes or cancers, and to self-manage long-term health complaints like lower back pain or sleep problems. These types of product are widely available for purchase for self-treatment from pharmacies, health-food stores, supermarkets and via the Internet.

Often in the case of herbal medicines, data are lacking on pharmacology (e.g. active constituents, pharmacokinetics, use in specific patient groups such as children, the elderly or individuals with renal or hepatic disease and in pregnancy and lactation) and toxicology (e.g. adverse effects and their frequencies, interactions with drugs and food). Moreover, the quality of some marketed complementary medicines, including food supplements, is a real concern. First of all, it is important to emphasize that products from different manufacturers are not the same. Herbs are natural products and, thus, do not have a consistent, standardized composition. Different parts of the plant (e.g. roots, leaves) contain a different profile of constituents and the content and concentration of constituents can be influenced by several factors such as climate, growing conditions, storage conditions and processing (e.g. extraction and drying). For these reasons, batch-to-batch and manufacturer-to-manufacturer variation in preparations of the same herb will occur. The quality of plant raw materials can also be influenced by human error or unscrupulous operators. Accidental botanical substitution (misidentification of plant species) or intentional adulteration can occur. An example of this relates to reports of renal failure and renal cancer following the substitution of nontoxic herbs with *Aristolochia* species in herbal food supplements marketed for reducing body weight.¹ Patients suffering anticholinergic toxicity after use of supplements containing *Choleus forskollii* contaminated with scopolamine, lead poisoning after use of Ayurvedic medicines, or microcystin toxicity were recently described in Italy.

Toxicity may also depend on the intrinsic effect of the drug, in the absence of contamination or adulteration. *Ephedra* has been used for thousands of years in China to treat bronchial asthma and other upper respiratory symptoms. More recently, its main use in the US and many other countries has been in dietary supplements for weight loss. *Ephedra* sales prospered in the '80s because the product was perceived by consumers as a "natural" and "safe" alternative to prescription weight loss products without the associated risk of harm. Actually, adverse effects associated with *Ephedra* use include headache, insomnia, anxiety, psychoses, hypertension, seizure and cardiovascular effects such as myocardial infarction, arrhythmias, stroke and death. In 2004, after 117 deaths and 16,000 reports of adverse effects, all *Ephedra* sales were banned and the product was no longer legally available via conventional methods.²

The use of several common herbs and dietary supplements has been also associated with hepatotoxicity, varying from asymptomatic elevations in hepatic enzyme levels to fulminant hepatic failure. Supplements with potential liver toxicity are, for

example, *Garcinia cambogia*, *Camellia sinensis*, *Hoodia gordonii* and kava-kava.³

In other cases, toxicity data about substances proposed for the treatment of serious diseases are totally lacking. This is the case of the scorpion *Rhopalurus junceus* toxin distributed in Cuba and around the world as an anticancer drug.

In addition to the adverse effects associated with the active principles, the risks associated with the use of dietary supplements come also from their wide availability on the Internet and by illegal trade. Thus patients may have access to products contaminated with toxic botanicals, heavy metals, pathogenic microorganisms, pesticides or adulterated with banned drugs or undeclared pharmaceutical ingredients. In a retrospective study conducted by reviewing all poisoning cases suspected to involve use of illicit slimming products, 66 poisoning cases were encountered and 81 products were analysed.⁴ Analysis of the products demonstrated the presence of 12 illicit ingredients comprising undeclared or banned drugs, such as sibutramine.

The diagnosis of intoxications due to the use of herbal medicines is often complex due to many factors. Investigation of the source of the exposure is difficult because these products are often considered "safe" and patients often do not report the taking of such "natural" preparations. Furthermore, poisonings by herbal principles and metals are not well known by emergency department doctors, so the "alternative" cause is investigated late. Moreover the latency time that may elapse between the beginning of taking these products and the occurrence of clinical manifestations (weeks to months or years) often makes it difficult to identify a causal relationship between taking the product and symptoms.

Conclusion: In conclusion, the ethnic background of the patient, the history of the current, recent or past intake of complementary or alternative medicine, and the presence of specific signs and symptoms represent the criteria for a correct and early diagnosis.

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15. Toxicity of traditional Chinese medicines

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Background: The practice of traditional medicine is culture related. For thousands of years, in Chinese society, many plants, animal products and minerals has been used for the purpose of health protection/promotion and/or curing illness. Many of the natural toxins or active ingredients, identified in the herbs being used originated from animals, plants as well as microorganisms which are well

known for having the potential to produce prominent but untoward health effects. Due to the increased morbidity and mortality, the poisoning associated with the use of herbs and/or traditional medicines has raised universal attention in the past few years.^{1,2}

Discussion: In the daily practice of the Chinese community, traditional medicines have been dispensed by health professionals, quacks, layman and other non-medical professionals such as witch doctors, in a form of Dan (capsule), San (powder), Wan (tablet, pill), Gau (paste, cream) and compound recipes (many gross herbs mixed together). The dispensed medicines may contain minerals or any part of plants and/or animals. Upon consumption, the untoward clinical effects may vary from mild to severe toxicity and even life-threatening. Consequently, it may manifest as single or multiple organ dysfunction, and furthermore, be complicated with systemic disorder. The untoward side effects may result from either the toxic effect or an immune dysfunction related to the exposure to the alleged herbs. Allergic and/or autoimmune reactions may explain most of the phenomena of immune dysfunction observed. However, drug overdose, drug interaction, a natural component with toxicity itself, contamination with pesticides or heavy metals, and adulteration with pharmaceuticals are considered to be the risk factors responsible for the toxicity manifested clinically. In the daily practice of Traditional Chinese Medicine, heavy metal contamination and pharmaceutical adulteration are the major concerns but are preventable risk factors in public health. In the clinical setting, the difficulty in handling the poisonings associated with the use of herbs and/or traditional medicines can be categorized as: (1) identification of the proprietary substances and active ingredients; (2) characterizing the kinetic pattern and toxicological effects; (3) the potential interaction between the herbs and modern medicines taken by the patients; (4) uncertainty of the diagnosis and treatment. Since the content and pattern of the use of herbs and/or traditional medicines does vary with the ethnic culture and geography, a monitoring program designed for international use would be useful in creating a systematic international data bank of herbs and/or traditional medicines with potential toxicity.

Conclusion: Further research such as: (1) to facilitate the upgrading of analytic capability in identifying the active ingredients and characterizing their kinetics; (2) to speed up the procedures in evaluating the pharmacological and toxicological impacts does deserve to be reemphasized; (3) an initiative of creating an international data bank of the toxicity of herbs and traditional medicines is worth further discussion.

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16. Clinical toxicology of Ayurvedic medicines

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Background: Ayurveda (Sanskrit for science of life) is a comprehensive holistic medical system which evolved in India more than

5000 years ago. Ayurvedic physicians are encouraged to prepare their own Ayurvedic medicines which are remedies based on natural sources such as herbs, metals and minerals and prepared using traditional methods. They are classified in the Ayurvedic pharmacopoeia according to the constituents, taste, potency, postdigestive effect and any special action.

Discussion: Ayurvedic medicine is widely used as a traditional system of healthcare in Asia and is increasingly used in the Western world. The large increase in immigrant populations from the Indian subcontinent has led to increased availability and utilisation of traditional Ayurvedic medicines which may be purchased from retail stores and over the Internet without medical consultation. In addition, medical tourism and use of Ayurvedic spas has led to increased acceptance of this form of healthcare.

As Ayurvedic medicines are marketed as dietary supplements, they are not subject to the same stringent regulations as pharmaceutical drugs with regards to efficacy and safety.

Reports of toxicity associated with these traditional remedies have increased. Toxicity may arise from use of herbs and plants containing recognised pharmacologically active ingredients e.g. *Papaver somniferum* (Ahipheman for anxiety and diarrhoea) and *Rauwolfia serpentina* (Sarpaghandha for hypertension). Pharmacodynamic drug interactions may arise from concomitant use of such preparations and conventional pharmaceutical drugs. Adverse reactions such as severe hepatotoxicity may occur with certain preparations e.g. extracts of *Psoralea corylifolia* leaves containing psoralens.¹ Some preparations such as Ashagandha contain withanolides which are structurally similar to digoxin and interfere with some digoxin assays, giving a falsely lowered digoxin concentration, potentially leading to unwarranted increase in the digoxin dose.

Ayurvedic formulations may contain inherently toxic plant extracts e.g. *Aconitum* and *Ricinus communis* where the traditional preparation process includes an elaborate detoxification technique (known as samskaras). This process has been shown to be effective in completely eliminating the toxicity of aconite² and oleandrin from *Nerium indicum* roots³ in mice but commercially available Ayurvedic preparations may not adhere to such complex and time-consuming procedures, thereby exposing patients to toxic unprocessed herbal ingredients. Contamination with pesticides such as organochlorine pesticides residues and adulteration of fake Ayurvedic medicines with synthetic drugs such as steroids have also been reported.

Ayurvedic practitioners believe in the healing properties of heavy metals. Bhasmas, Ayurvedic metallic preparations with herbal juices or fruits, contain metals such as mercury chelated with organic ligands derived from medicinal herbs. A study in Boston showed that 20% of Ayurvedic preparations imported from South Asia contained toxic concentrations of heavy metals such as lead, mercury and arsenic.⁴ Studies conducted in India have shown that 64% contained lead and mercury, 41% arsenic and 9% cadmium.⁵ Heavy metal poisoning may result from chronic use of Ayurvedic medicines which accounted for 9 of 12 cases of lead, arsenic or mercury poisoning reported to a toxicology unit in London over a 5-year period.⁶ Severe lead toxicity from Ayurvedic formulations has been reported in Western countries, with features ranging from anaemia and abdominal pain to status epilepticus and fatal encephalopathy⁷ and is associated with significantly higher blood lead concentrations, more basophilic stippling and lower haemoglobin than lead intoxications from lead paint⁸. Mercury poisoning associated with

gastrointestinal and autonomic disturbance occurred after treatment of eczema with Ayurvedic medicines containing 30–42 mg inorganic mercuric sulphide per pill.⁹ Dermatological manifestations of arsenic toxicity, sensorimotor peripheral neuropathy and non-cirrhotic portal hypertension have been reported after use of Ayurvedic preparations with an arsenic content of up to 248 mg/L.^{9,10}

The potential genotoxic and teratogenic effects of Ayurvedic formulations is unknown. *In vitro* genotoxicity testing showed that extracts of *Salacia oblonga* roots used for diabetes may be weakly genotoxic and extracts of *Asparagus racemosus* roots (used as a reproductive tonic) have been shown to be teratogenic in rats. Exposure to lead-containing preparations *in utero* has caused congenital paralysis and sensorineural deafness. Although there are no reported cases of malignancy attributable to use of Ayurvedic medicines, long-term use of preparations containing arsenic may predispose to skin and haematological cancers.

Conclusion: A history of Ayurvedic medicine use should be actively sought in patients presenting with symptoms and signs of heavy metal poisoning. Education of users about the potential risks and more effective regulation of these traditional remedies are required.

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17. Challenges in the investigations and management of herb induced aconite poisoning: Experience of a poison treatment centre in Hong Kong

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Objective: Herb induced aconite poisoning can be complicated by serious cardiotoxicity. Contributory factors should be identified so that preventive measures can be formulated. We reported our experience in the investigations and management of aconite poisoning.

Case series: The Prince of Wales Hospital Poison Treatment Centre (PWHPTC) is a tertiary referral centre for poisoning management in Hong Kong. From April 2004 to October 2012, 17 patients (6 males, 11 females, median age 60 years, range 27–86 years) were admitted to the PWHPTC because of aconite poisoning. The herbal medicines were taken for treatment of musculoskeletal problems (n = 8), gastrointestinal problems (n = 3) and upper respiratory tract illnesses (n = 2) and as a tonic (n = 3). Herbal decoction accounted for 15 cases. Contamination of non-toxic herbs by aconite roots (n = 7), use of greater than recommended doses (n = 3) and inadequate decoction or use of inadequately processed herbs (n = 5) were the main contributory factors. One patient consumed herbal wine made from aconite roots. Another patient consumed a proprietary medicine with undeclared aconite roots. These subjects mainly presented with cardiovascular (n = 14), neurological (n = 12) and gastrointestinal (n = 11) symptoms. Ten patients had hypotension. Two patients developed ventricular tachycardia. Eight patients required management in intensive care (ICU) or coronary care (CCU) units. All patients survived and were discharged after a median of 3 days (range 1–13 days).

Conclusion: Herb induced aconite poisoning often requires ICU or CCU care and can be complicated by ventricular tachycardia. Contamination of herbs by aconite roots, use of larger than recommended doses and inadequate processing of aconite roots after harvest and during decoction are important causes.

18. Risk assessment of poisonous plants

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Background: Of the 90,000 exposures involving children younger than 6 years of age reported to German poison centers (PCs) every year a fifth are caused by plants. A list of especially poisonous plants, which should not be planted in children's playgrounds, was published in the "Bundesanzeiger" (Federal Gazette) in 2000. The BfR-Committee "Assessment of Intoxications" founded a working group to re-assess the toxicity of plants to protect especially children from severe plant poisoning.

Methods: The members of the working group defined criteria for risk assessment of plants in the close proximity of children's playgrounds. Human exposure data, provided by the German PCs in Berlin, Freiburg and Erfurt and by the Swiss PC Zürich were reviewed as well as scientific publications about human exposures and about toxicity of ingredients of plants. Following the assessment of the toxicity of chemicals in analogy to the German Regulations on Dangerous Substances, poisonous plants were re-classified into three categories, namely plants which could lead to minor poisoning, moderate poisoning and severe or deadly poisoning.

Results: Out of 43,000 confirmed accidental plant exposures from PCs in Freiburg and Berlin moderate or severe poisoning was experienced in 1.3% restricted to 39 plants. Altogether, 280 plants were

re-evaluated. Risk assessment changed for some of the especially poisonous plants of the 2000 list. For example the formerly moderate poisonous plants *Lantana camara*, *Ilex spec.*, and *Euonymus spec.* were re-assessed as minor poisonous, and the formerly minor toxic *Chelidonium majus* was re-assessed as moderately toxic for the eyes.

Conclusion: Human data about the risk of health damage after accidental ingestion of small amounts or by accidental dermal or ocular contact are mainly restricted to published case reports. The toxicity of ingredients and of preparations of plants for medical or psychoactive purposes may be completely different. The exposure data of PCs are very useful for risk assessment of plants present in the close proximity of children's playgrounds, kindergartens, etc. The re-assessment and the final table of especially poisonous plants will be published again in the "Bundesanzeiger".

19. Poisoning by *Boletus satanas* causes hyperprocalcitoninemia: Case report

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Objective: *Boletus satanas* belongs to the mushroom group which causes gastrointestinal syndrome. Symptoms: nausea, vomiting and diarrhoea start early after a mushroom meal. In the differential diagnosis we do not have any specific laboratory marker for the large group of mushrooms which causes gastrointestinal symptoms. We present two cases of severe poisoning by *Boletus satanas* which caused a high serum procalcitonine (PCT) level.

Case report: Two girls, otherwise healthy, started with severe vomiting and diarrhoea 45 minutes after their meal. They picked by themselves three "*Boletuses aestivalis*" and prepared them with rice; but in fact they ate *Boletus satanas*. It was not difficult to identify their mistake, since they took a photo of the picked mushrooms. At admission, six hours after the meal the first girl was hypotensive 75/55, both still had diarrhoea; laboratory findings, except for slightly hypokalemia, were normal. They were treated with intravenous fluids; the first girl needed temporary noradrenaline in low dosage. In laboratory findings we noticed an increase in C-reactive protein (CRP) and PCT, which reached peak serum level around 28 hours after meal; for the first girl CRP was 126 mg/L and PCT 49.93 ng/mL, for the second girl 78 mg/L and 28.74 ng/mL respectively. Leukocytes were low. The first girl had temporary high body temperature (38°C). We gave a first dose of antibiotic because of suspicion of sepsis. Microbiological examination of blood, stool and urine were all negative. In the literature, we found one report of CRP and PCT increase in seven family members after *Boletus satanas* poisoning.¹ We discontinued antibiotic treatment. Two days later both girls were discharged without gastrointestinal symptoms and with nearly normal serum CRP and PCT levels.

Conclusion: In differential diagnosis of gastrointestinal syndrome due to mushroom poisoning, we also have to consider infectious gastroenterocolitis. Physicians should evaluate carefully clinical presentation and should be aware, that *Boletus satanas* poisoning can cause a very high level of PCT of non-infectious origin which does not need antibiotic treatment.

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20. Acute liver failure after accidental intake of pyrrolizidine-containing plants

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Objective: Herbal hepatotoxicity is not uncommonly encountered, but presumably veno-occlusive liver disease may determine a serious course.

Case report: A 63-year old female was admitted to an external hospital with vomiting and abdominal pain starting three hours after consumption of approximately 10 leaves (100 g) of self-collected Petasites and Tussilago as a Korean dish. The next day she complained of abdominal pain and showed signs of hepatic failure with highly elevated liver enzymes, low prothrombin time and thrombocytopenia. After consulting our poison centre, the patient was transferred to our intensive care unit (ICU) suspecting a pyrrolizidine poisoning. Here laboratory analysis showed leukopenia and an increased D-dimer. Treatment with N-acetylcysteine was initiated in analogy to acetaminophen-poisoning and low-molecular weight heparin (LMWH) was administered for prophylaxis of thrombosis. Abdominal sonography showed nonspecific hepatopathy and hepatomegaly with moderate ascites. Platelets were given four times due to severe thrombocytopenia (nadir 11 G/L) and even administration of dexamethasone at days 5 to 9 was without any effect on thrombocytes, which finally recovered spontaneously after 21 days. Liver biopsy performed at day 14 showed liver tissue with the pattern of a veno-occlusive disease showing intraluminal fibrin clots in the sinusoides. Full anticoagulation with LMWH was initiated to prevent further progression of the liver disease. Liver enzymes and D-dimer decreased steadily but still stayed elevated at discharge after 24 days. The further course was complicated through a fall-associated cerebellar bleeding which necessitated neurorehabilitation and discontinuation of LMWH. Three months later the patient presented with unchanged but still moderately increased liver enzymes, alkaline phosphatase and gamma-GT. A liver biopsy at that time showed slight progression of the veno-occlusive liver disease with partly obliterated lumina of central veins, perivenular drop out hepatocytes and beginning perisinusoidal fibrosis.

Conclusion: Veno-occlusive liver-disease caused by pyrrolizidine alkaloid containing herbs may account for significant morbidity. Therapeutic options are very limited and are mainly symptomatic.

21. The bitterness ... a sign of alert

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Introduction: The consumption of wild plants in spring exposes the public to the risk of confusion between edible and toxic plants. One of the most serious errors is the confusion between *Allium ursinum* or *Allium polyanthum* and *Colchicum autumnale*.

Case report: A 35-year-old man, who was used to eating wild plants, prepared a dish of vegetables consisting of plantain, stinging nettles and the white part of 9 wild "leeks". He ingested this preparation despite its very bitter taste. Three hours after the ingestion he developed vomiting and myalgia. He called the Poison Information Center which advised him to go immediately to an emergency unit. On admission gastric lavage was performed (Hour 4), then the patient was transferred to the intensive care unit. He presented successively: digestive disorders, cardiogenic then vasoplegic shock, acute renal failure, bone marrow aplasia, bowel obstruction, polyneuropathy, and alopecia. Moderate hepatic cytolysis, renal insufficiency, pancytopenia, and major hypertriglyceridaemia (triglycerides 9.12 grams/L) were also present. Treatment consisted of activated charcoal, artificial ventilation for 27 days, vasopressors, filgrastim and continuous hemofiltration and hemodialysis for renal failure. The concentration of colchicine on admission was 15.9 nanograms/mL in the blood and 1064 nanograms/mL in urine (measured by UPLC-MS-MS). The patient recovered slowly after 3 months of hospitalization and 2 months of rehabilitation.

Discussion: This patient presented the classical complications described in colchicine poisoning but also, more remarkably, occlusive syndrome, polyneuropathy and hypertriglyceridaemia. The plasma concentration of colchicine increased on day 9, probably because of retention of colchicine in the digestive tract as demonstrated by the concentrations in the gastric liquid (76 nanograms/mL) and the stools (368 nanograms/mL) on day 15. The renal clearance of colchicine was 76 mL/min. The elimination by hemofiltration was only about 330 µg/day. The mechanism of the hypertriglyceridaemia was not clear, no administered drug being involved in a possible medicinal interaction.

Conclusion: This observation is remarkable for the complete clinical and biological presentation of this intoxication and the favourable outcome despite the presence of many severe features.

22. *Erycibe henryi* induced acute cholinergic syndrome

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Objective: Chinese herbal therapy is common in Taiwan. Some herbs have been noticed to be toxic. *Erycibe henryi* Prain is one of them. In literature, there were few cases reports of *Erycibe* intoxication. Here, we present a case of acute *Erycibe henryi* Prain poisoning due to misidentification.

Case report: A 42 year-old male presented to the emergency room due to nausea, vomiting, watery diarrhea and diaphoresis, developing acute cholinergic syndrome 30 minutes after ingestion of an *Erycibe henryi* Prain decoction. At the emergency room (ER), he was noted to have hypothermia (body temperature: 34.5 C), miosis, bradycardia (heart rate: 61/min), and hyperactive bowel sounds. Laboratory examination revealed leukocytosis (white blood

cell count: 14,060), elevated blood glucose (160), and normal plasma cholinesterase activity. Atropine was administered under the impression of acute cholinergic syndrome and it improved the patient's condition immediately. He was well after one day's observation.

Discussion: *Erycibe henryi* Prain is a herb commonly used for musculoskeletal pain management in Taiwan. Our case and others reported before¹, all developed acute peripheral cholinergic manifestation. A few reports found that the tropane alkaloid in these plants may work as an agonist on muscarinic receptors. Thus, atropine could work as antidote for *Erycibe henryi* prain poisoned patients. Some other herbs have similar Chinese names and can easily be misidentified. It is important to study how to prevent such misidentification.

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23. The killer from the countryside: Intoxications with hydrogen sulphide in anaerobic digestion plants (Biogasanlagen)

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Introduction: The toxicity of hydrogen sulphide (H₂S) has been well known for centuries. A new setting for poisonings in Germany could be anaerobic digestion sites (so called Biogasanlagen). The number of these sites has increased steadily during recent years. Especially after the Fukushima catastrophe, there is a strong political will in Germany for an energy transition away from nuclear and coal power plants towards solar and wind energy and biogas, which is the most important source for H₂S intoxications in Germany.

Methods: Retrospective analysis of all cases of a poisons centre in northern Germany over a 16 year period concerning demographic data and severity of intoxications according to the poisoning severity score (PSS).

Results: From 1996 to 2012 the poisons centre was consulted 185 times with regard to hydrogen sulphide intoxications. There were 29 prophylactic consultations and 156 exposures. PSS: 5 fatalities, 14 severe, 20 moderate intoxications (n = 39, resp. 25% of all exposures); rest (n = 117, 75%) minor, asymptomatic or not documented. 126 (81%) intoxications happened in an occupational setting; i.e. 56 cases between 20 and 49 years, 27 between 50 and 69 years; rest (n = 43) under 20 years or older than 69 or not documented.

Discussion: The particular poisoning risk of hydrogen sulphide is well documented and is reflected in the poisons centre's cases. The mechanism of action is a blocking of electron transfer within the mitochondria (similar to cyanides). Such a fundamental action explains the broad variety of symptoms consisting of seizures, coma, dysrhythmias and gastrointestinal disorders. Moreover, H₂S is irritating and can cause lesions of the cornea and a toxic edema of the lungs. Therapy is symptomatic and a specific antidote does not exist.

24. Circumstances of lethal Mediterranean thistle *Atractylis gummifera* poisonings: Experience of the Algiers Poison Centre

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Objective: The Mediterranean thistle, *Atractylis gummifera*, is considered as one of the most dangerous plants due to the production of diterpenoid glucosides (attractyliside and gummiferin) which inhibit mitochondrial oxidative phosphorylation. This species is the cause of rare poisonings in Italy, Spain and Greece. However, *A. gummifera* is responsible for numerous human deaths every year in the entire Maghreb region of Northwest Africa¹ where this plant is considered to be a major threat to rural populations. The aim of the present Algerian case reports is to illustrate the various circumstances leading to life-threatening situations after contact with this plant.

Case series: Observation 1, a woman aged 40 years with a previous history of psychiatric disorders was treated by her family with herbal tea (Southeastern Algeria). *Atractylis* roots were added to the herb mix in order to avoid the “evil eye”. After 5 days of this new treatment she complained of vomiting and coma and was transferred to hospital where examination showed hypoglycemia, renal and hepatic failure. She died a few hours after, despite hemodialysis treatment. Observation 2, in rural Algeria, a 2 year old girl with a second degree burn on her buttock was treated by her grandmother with a poultice of several plants including *Atractylis* roots. Symptoms appeared in a few hours: vomiting, agitation, seizure and coma. She died as soon as she arrived at hospital (hypoglycemia, renal and hepatic failure). Observation 3, three brothers aged 9, 10 and 12 years, ate thistles due to misidentification with wild artichokes. In about 3 hours, vomiting, hypoglycemia and seizures were reported and they all died 15 to 28 hours after the meal.

Conclusion: The Mediterranean thistle can cause severe poisoning in few hours after ingestion or skin contact, with digestive features, hypoglycemia and renal/hepatic failure leading to rapid death. This plant must be excluded from local traditional herbal usage but it is often difficult to eliminate popular beliefs.

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25. Neurological troubles after consumption of Mediterranean sea figs of the *Microcosmus* genus

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Objective: Mediterranean sea figs of the *Microcosmus* genus, also called sea violets, are eaten in Southeastern France where these ascidians are a part of local seafood platters (marine animals also eaten in Italy, Croatia and Chile). Recent studies proved that

tunicates are able to accumulate phycotoxins.¹ In Croatia a human collective paralytic shellfish poisoning has been described in 2012 after a meal containing sea violets.² Since January 2011 the Marseille poison centre has been consulted 4 times for patients with unusual features after consumption of sea figs.

Case series: In January 2011, 6 adults shared a seafood platter near Narbonne. Two of them (men, aged 30 and 52 years) ate sea violets: in one hour diplopia, accommodation difficulties, ataxia, dizziness and diarrhea were reported lasting 20 hours in both patients. In December 2011, 2 women aged 70 and 78 years, 30 minutes after eating sea violets in Marseille complained of ataxia, dizziness, sweating, vomiting and diarrhea lasting 24 hours. In January 2012, a woman aged 55 years ate sea figs near Marseille inducing within half an hour diplopia, ataxia, vomiting and diarrhea lasting 24 hours. In March 2012, in a Marseille restaurant, colleagues shared a seafood platter (no alcohol during this professional meal). Two of them (men of 33 and 44 years) ate sea violets: in 30 minutes, they both experienced dizziness, headache and difficulty in walking lasting 24 hours.

Conclusion: The clinical picture reported by the 7 patients was homogeneous and different from other seafood poisonings, with moderate digestive troubles and a cerebellar syndrome appearing 30 minutes to one hour after the *Microcosmus* ingestion. The responsible molecules or toxins are still unidentified but samples were taken during the first episode in order to analyze the implicated sea figs as soon as possible.

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26. Poisonous mushroom ingestions presenting to Northeast US emergency departments from 1996–2010

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Introduction: Poisonous mushroom ingestions are an extremely uncommon occurrence in the US. Fortunately, life-threatening toxicity following these ingestions is extremely rare. The epidemiology of poisonous mushroom presentations to US emergency departments (EDs) is poorly studied.

Objective: To characterize mushroom exposures presenting to New Jersey and New York emergency departments.

Methods: Design: A multi-center retrospective emergency department (ED) cohort. Study setting: 34 New Jersey and New York EDs. Subjects: Consecutive patients with the ED diagnosis of “toxic effect of mushrooms” (ICD9 code = 9881) were identified from January 1, 1996 to December 31, 2010.

Results: Out of 9,488,847 consecutive patients, 91 patients were diagnosed with “toxic effect of mushrooms” (0.00096% of all ED patients) with 24 admitted to the hospital (26.4% admission rate).

Only 68 patients had completed charts for review. The patient demographics were as follows: mean age = 30.9 years (range: 0.8–79.3 years) and gender = 30.9% female. 57.7% of the 68 admitted patients reported gastrointestinal symptoms (e.g. vomiting, diarrhea, abdominal pain). 14.3% of the 68 admitted patients reported neurologic symptoms (e.g. hallucinations, anti-cholinergic toxidrome, headache). Mushroom ingestions among pediatric patients (n = 17, ages 0–10 years) with 88% the result of an ingestion of a wild mushroom by an unattended child. Mushroom ingestions among adolescents and young adults (n = 23, ages 11–35 years) were associated with substance abuse, with the potential ingestion of a psychedelic mushroom in 65% of cases. Finally, mushroom ingestions among older adults (n = 29, ages 36 years and older) were associated with foraging for wild mushrooms and/or onset of gastrointestinal symptoms in 71.4% of cases.

Conclusion: Poisonous mushroom ingestions are a rare presentation to Northeast US emergency departments. Substance abuse, with possible psychedelic mushroom ingestions, is commonly observed among adolescents and young adult ED presentations. Hospital admission is common among patients who present to the ED following a mushroom ingestion.

27. Does *Zamioculcas zamiifolia* cause symptoms by exposure? A 1-year telephone survey

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Objective: *Zamioculcas zamiifolia* has been appearing in Finnish Poison Information Centre (FPIC) statistics since 2001. There are no clinical data available on the plant's toxicity. It is assumed to contain the same irritating oxalates as the other plants in the Arum-family (*Araceae*). According to the queries to FPIC concerning the plant, it seems to cause irritation as a symptom. We wanted to find out the severity of the symptoms and how long they lasted.

Methods: All calls related to a human exposure to *Z. zamiifolia* to the FPIC from 1.3.2011 to 29.2.2012 were eligible. Information about the exposure was collected with the help of a structured form and permission to call back within a week was asked. During the call back the patient was asked if any symptoms developed after the exposure, how fast the symptoms appeared, how long they lasted and whether any other procedures were needed than wash/rinse.

Results: The FPIC received 98 phone calls regarding poisonings by *Z. Zamiifolia*. In 80 cases the consent to call back was given, 2 cases were excluded (1 could not be contacted and 1 case was reported twice) leaving 78 cases included in the study. One of them was an adult, the rest were children aged under 5 years. Seventy-five of the patients were exposed by mouth, 2 by skin, 1 by eye. Three patients were exposed by both mouth and skin and 1 by both mouth and eye. Symptoms developed in 45 cases. All the patients (7) who had either bitten or chewed the stem of the plant developed symptoms. Irritation (mouth, skin or eye) was the most common symptom (75.6%) among all the patients reporting symptoms. Seventy-six children and one adult were treated at home. Two children had been seen by a doctor.

Conclusion: *Zamioculcas zamiifolia* causes mostly local irritation to mouth, skin or eye or no symptoms at all. All patients who tasted or swallowed the stem of the plant developed symptoms.

The recommended treatment in exposure to *Z. Zamiifolia* is wash/rinse and cold applications to the exposed site if needed.

28. Retrospective poisons centres-based study on adverse effects due to plant food supplements

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Objective: Plant Food Supplements (PFS) are products of increasing popularity and wide-spread distribution. Nevertheless, information about their risks and benefits is limited. To fill this gap, the PlantLIBRA-project - a part of the EU's Seventh-Framework-Programme - was started. Within this project, a poisons centre-based study on the risks of PFS was performed.

Methods: Through a systematic multicenter retrospective review of data from selected European and Brazilian poisons centres (PCs), documented human cases of adverse effects or poisoning due to plants consumed as food or ingredients of food supplements or due to misidentified poisonous plants consumed as food were collected for the period 2006–2010.

Results: From the 66 contacted PCs, 11 were able to provide a total of 153 cases: 76 cases of adverse effects after intentional ingestion, 76 cases of poisoning due to misidentification, and one case of interaction between a PFS and a pharmaceutical. A total of 249 plants and plant-related substances (e.g. caffeine, naringin, olive oil) were involved. The 10 most frequently reported plants were *Mandragora officinarum*, *Valeriana officinalis*, *Aesculus hippocastanum*, *Colchicum autumnale*, *Camellia sinensis*, *Melissa officinalis*, *Passiflora incarnata*, *Paullinia cupana*, and *Mentha piperita*. Most cases occurred in adults (91%). The plants most frequently involved in the 76 cases of adverse effects due to intentional ingestion were *Valeriana officinalis* and *Camellia sinensis*. Irritation of skin or mucosa, gastro-intestinal symptoms, signs of neurotoxicity (e.g. dizziness, somnolence, restlessness), and hepatotoxicity were the most frequently observed clinical events. Most cases showed a benign clinical course, however, a severe outcome was recorded in 5 cases. In the 76 cases of misidentification only 6 different identified plants were recorded: *Mandragora officinarum*, *Aesculus hippocastanum*, *Colchicum autumnale*, *Digitalis* sp./

D. purpurea, *Allium ursinum*, *Datura stramonium*. Severe symptoms were only observed with *Colchicum autumnale* (multi-organ failure) and *Mandragora officinarum* (anticholinergic syndrome). In the remaining cases, mostly mild gastro-intestinal symptoms were recorded.

Conclusion: PFS-related adverse effects seem to be relatively infrequent issues for PCs. Most cases showed mild symptoms and a benign clinical course. Nevertheless, the occurrence of some severe adverse effects and the increasing popularity of PFS require continuous active surveillance, and further research is warranted.

29. Two fatal cases following use of plant mixtures for weight gain

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Objective: The use of plants and corticosteroids for weight gain is a common practice among young Moroccan women, particularly in the southern region of the country. These plants are purchased mainly as mixtures prepared by herbalists who may use toxic species in their ignorance of the dangers that can lead to death. We report two cases of young women with fatal fulminant hepatitis due to the consumption of plant mixtures in order to gain weight.

Case series: A 16 year old girl consumed an infusion of a mixture of plants containing *Atractylis gummifera* L, *Trigonella foenum-graecum* and almond leaves mixed with contraband corticosteroids and an antihistamine and sold under the name “Derdag”. The second case was a previously healthy 22-year-old woman who used suppositories made of a mixture of plants procured from a herbalist in order to gain weight. Both patients experienced severe nausea and vomiting, central nervous system depression with coma, hepatitis, severe hypoglycemia, coagulopathies and renal failure. The nature of the plants in the first case was determined from interview with the mother. In the second case, the identification of the composition of the suppositories was difficult; the Agronomic Institute of Rabat identified a single plant: *Artemisia absinthium*. In spite of all treatment and therapeutic efforts including N-acetyl-cysteine, the adolescent girl died 24 hours later and the young women 72 hours after admission.

Conclusion: Plants used among young Moroccan women are not trivial because of the ignorance of consumers and herbalists as to the potential toxicity of some plants. Real awareness in schools and for housewives must be initiated. Unfortunately, the legal vacuum maintains anarchy in the marketing of medicinal plants. Adequate regulation must be put in place to prevent this kind of intoxication.

30. Aconite poisoning following the consumption of herbal soup

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Objective: To report three family members with acute aconite poisoning following the consumption of homemade soup prepared from herbs contaminated by aconite roots.

Case series: A mother and her 14-year-old son had neurological (mainly generalised numbness and weakness) and gastrointestinal (mainly abdominal pain) symptoms. Her 13-year-old son had neurological symptoms (mainly generalised numbness). All the symptoms in the three subjects subsided 16–32 hours after ingestion. In the two packs of unused herbs, a total of 14 different herbs were present in each, but aconite roots were not found. Toxicological analysis of the herbal remnants revealed yunaconitine, crassicauline A and other substances. Yunaconitine and crassicauline A are *Aconitum* alkaloids found in the *Aconitum* species from Yunnan.

Conclusion: As inspection of the unused herbs did not reveal aconite roots, it was most likely that the pack of herbs used to make the herbal soup was contaminated. In patients with acute onset of neurological, gastrointestinal and/or cardiovascular symptoms occurring after the use of herbal medicines, aconite poisoning should be excluded, even if aconite roots are not found in the herbal formula and unused herbs. The diagnosis of herb-induced aconite poisoning can be confirmed by toxicological screening of the herbal remnants and the patients' urine for the presence of *Aconitum* alkaloids and their metabolites.

31. Acute hepatitis and jaundice due to *Tinospora sinensis* or *Tinospora crispa*

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Background: *Tinospora sinensis* and *Tinospora crispa* are commonly known as ‘Kuan Jin Teng’ in Chinese and they belong to the family *Menispermaceae*. Pharmacological studies on plants from the family *Menispermaceae* have demonstrated anti-inflammatory, anti-infective, immunomodulatory, hepatoprotective, and antidiabetic activities. The stems of *Tinospora* have been used in the treatment of rheumatism, bruises with pain, fever, inflammation, edema, dyspepsia and “liver fire” in Traditional Chinese Medicine. The reported cases of *Tinospora* poisoning are rare and usually came from *Tinospora crispa*.^{1,2} We present three cases of acute hepatitis with jaundice after ingestion of *Tinospora*.

Case series: The patients were all male and their ages were 54, 64 and 65 years. Two cases took *Tinospora sinensis* to treat upflaring “liver fire” and edema for 3 months and 18 days. One case took *Tinospora crispa*, *Chenopodium ambrosioides* and *Tithonia diversifolia* for the purpose of gout and liver-protection over a period of 4 weeks. All cases had marked elevation of liver enzymes and bilirubin. The peak levels of bilirubin were 19.7 mg/dL, 18.3 mg/dL, and 27 mg/dL, respectively. Two cases of *Tinospora sinensis* poisoning also had leukocytosis, monocytosis, coagulopathy and duodenal ulcer with bleeding; and one case had eosinophilia. The patients subsequently recovered after supportive care.

Conclusion: *Tinospora* species have many pharmacological substances and multiple actions. Patients receiving *Tinospora sinensis* or *Tinospora crispa* may develop toxic hepatitis and jaundice.

References

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32. Paracetamol-induced hepatotoxicity despite paracetamol concentrations below treatment threshold

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Background: Severe paracetamol-induced hepatotoxicity has rarely been reported despite paracetamol concentrations below the historical UK nomogram treatment lines (200-line and 100-line for patients without and with risk factors respectively).¹ In September 2012, a single treatment line (100-line) for single acute paracetamol overdose, regardless of risk factors was introduced in the UK. We report a case of acute hepatic failure in a patient whose 4 hour paracetamol concentration was below the revised treatment line.

Case report: A 39-year-old man weighing 91 kg presented to the emergency department 90 minutes after an acute single overdose of 15 g (165 mg/kg) paracetamol. He had taken cocaine, cannabis and over 40 units of alcohol the day preceding his overdose. He admitted to excessive alcohol intake of 70 units weekly. At 4 hours post-ingestion, his serum paracetamol concentration was 75 mg/L (below 100-line) prothrombin time 13 s, bilirubin 17 µmol/L and mildly elevated ALT 59 U/L. He discharged himself from hospital before a psychiatric assessment and re-presented at 21 hours post-ingestion with increased right upper quadrant abdominal pain and vomiting at which time his serum paracetamol concentration was 16 mg/L (above 100-line), prothrombin time 23 s, serum bilirubin 174 µmol/L and ALT 1544 U/L. He recalled the precise time of overdose and denied ingestion of additional paracetamol or other drugs before he re-presented to hospital. He received intravenous ondansetron/placebo before starting on a 20.25 hour acetylcysteine infusion (Scottish and Newcastle Anti-emetic Pre-treatment for Paracetamol Poisoning Study (SNAP) trial protocol). He developed hepatic failure and grade 1 encephalopathy and was transferred to the regional liver unit where he received further acetylcysteine and vitamin K. He had a normal abdominal ultrasound. His peak prothrombin time was 37 s and ALT 18491 U/L (46 hours post-ingestion). He recovered with supportive treatment and was discharged with no sequelae 5 days post-ingestion after a psychiatric assessment and counselling relating to drug and alcohol misuse.

Conclusion: This patient developed significant hepatotoxicity and had a prolonged paracetamol elimination half-life of 7.6 hours. Excessive chronic alcohol consumption and recreational drug use may have increased this patient's susceptibility to paracetamol.

Reference

1. Beer C, Pakravan N, Hudson M, et al. Liver unit admission following paracetamol overdose with concentrations below current UK treatment thresholds. *QJM* 2007; 100:93–6.

33. Paracetamol-induced hepatotoxicity at therapeutic doses

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Background: The maximum licensed daily dose of paracetamol in the UK is 4 g in adults, irrespective of weight. Severe paracetamol-induced hepatotoxicity has rarely been reported after therapeutic doses, although the dose ingested is often uncertain in most cases.¹ We report a case of hepatotoxicity in a patient who received therapeutic doses of paracetamol in hospital.

Case report: A 53-year-old man with severe emphysema was admitted with an infective exacerbation. He had a history of excessive alcohol consumption and was severely malnourished (weight 36.6 kg, body mass index 13 kg/m²). He had a normal alanine aminotransferase (ALT) and prothrombin time on admission. He was treated with amoxicillin and received 8 doses of paracetamol 1 g orally at intervals of at least 4 hours over a 48 hour period (109 mg/kg/24 hours) for pyrexia. Blood tests 3 hours after the last paracetamol dose revealed ALT 1124 U/L, prothrombin time 18 s and paracetamol concentration 23 mg/L. An abdominal ultrasound was normal and viral hepatitis screen negative. As he was not taking any other potentially hepatotoxic drugs, paracetamol-induced hepatotoxicity was suspected. Amoxicillin and paracetamol were discontinued and he was treated with intravenous acetylcysteine. His peak ALT was 2112 U/L and prothrombin time 22 s and occurred 24 hours after the last paracetamol dose. Acetylcysteine was discontinued 42 hours after the last paracetamol dose when his ALT had fallen to 1636 U/L and prothrombin time to 16 s. He made a complete recovery.

Discussion: The pattern of ALT and prothrombin rise was very suggestive of paracetamol-induced hepatotoxicity which occurred after supervised therapeutic doses of paracetamol in this patient, probably as a result of increased susceptibility due to excessive chronic alcohol consumption and severe malnutrition. A weight-based maximum daily dose of paracetamol may help avert these rare adverse events in susceptible patients.

Reference

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34. Severe paracetamol poisoning with methemoglobinemia

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Objective: We present a case of massive paracetamol ingestion with coma, metabolic acidosis, methemoglobinemia, rapid onset of multiorgan failure and death within 48 hours.

Case report: A 45-year old woman with a history of gastric bypass surgery and depression was found after an estimated intake of 190 grams paracetamol. She had not been in contact with her relatives for 24 hours. On hospital arrival she was comatose, hypotensive with systolic blood pressure 45 mmHg and hypothermic 26 degrees C. She had severe metabolic acidosis with pH 6.96, base excess -23 mmol/L and serum lactate 18 mmol/L. Blood glucose was 1.0 mmol/L. ASAT was <0.2 microkat/L, ALAT 4.69 microkat/L and PK (INR) 1.2. Serum paracetamol was initially 11,812 micromol/L, and 2 hours later 10,314 micromol/L. She also had a methemoglobinemia of 28.6%. A computed tomography scan of the brain showed no bleeding or signs of cerebral edema. Treatment with intravenous N-acetylcysteine (NAC) was started within an hour. In addition to other intensive supportive treatment, continuous veno-venous hemodialysis (CVVHD) was initiated. Infusion with NAC was doubled during dialysis. The methemoglobinemia was treated with methylene blue in repeated doses and fell from 28 to 16%. The patient was transferred to a university hospital for possible Molecular Adsorbents Recirculation System (MARS) treatment and acute liver transplantation. On arrival the serum paracetamol was 6100 micromol/L, ASAT 19.1 microkat/L, ALAT 7.21 microkat/L and PK (INR) 2.6. A few hours later her circulation failed and was unresponsive to resuscitation.

Conclusion: This is, to our knowledge, the first case presenting with massive paracetamol poisoning and methemoglobinemia. Since there were no other known substances involved it is likely that the methemoglobinemia was a direct consequence of the paracetamol poisoning. Methemoglobinemia is a well known toxic symptom of paracetamol in animals but is extremely rare in humans. It is also remarkable that the patient went into terminal circulatory failure prior to developing the expected fulminant liver failure, suggesting direct toxic effects of paracetamol or its metabolites. The mechanism of methemoglobinemia in paracetamol poisoning needs to be studied further.

35. Management of intravenous paracetamol overdose

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Objective: Paracetamol poisoning is well studied worldwide and treatment guidelines are generally quite similar. Nevertheless there are still questions to be answered regarding intravenous paracetamol poisoning. Overdoses are most common among small children, where calculation errors occur due to vial size and concentration, but hardly exist in adults. It has become necessary to have a regime on how to manage intravenous overdoses. We report here the strategy chosen in Sweden based on current published knowledge and our own experience.

Methods: All cases of intravenous paracetamol poisoning for which our centre has been consulted were collected. Outcomes related to our current recommendation on treatment with N-acetylcysteine have been evaluated.

Results: During 2005–2012 we were consulted in 14 cases of accidental overdoses in children < 10 years of age. The range was

35–136 mg/kg, 7 cases involved overdoses > 75 mg/kg. None of the cases received treatment with N-acetylcysteine and none developed any liver impairment.

Conclusion: Different strategies have been suggested on management of intravenous paracetamol poisoning.¹ In the few published cases where liver impairment is reported there have been significant risk factors present, indicating glutathione depletion. It has been suggested through pharmacokinetic modelling that liver exposure to paracetamol is less if given intravenously despite the higher early peak concentration, since there will be no first pass metabolism.² Our treatment regime is based on our cases presented above, collaboration with a pediatric acute pain unit with considerable experience of paracetamol treatment and overdosing and the theory of possible reduced liver exposure if given intravenously. For children without risk factors 200 mg/kg is probably a tolerable dose when given as a single oral dose. To increase the safety margin we have chosen 175 mg/kg as the limit for treatment with N-acetylcysteine. Due to the relative lack of safety data the limit is presently lowered to 150 mg/kg after intravenous administration. More pharmacokinetic studies are needed to evaluate the differences in management between intravenous and oral administration.

References

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36. Acetaminophen and N-acetylcysteine dialysance during hemodialysis for massive ingestion

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Objective: To determine the effect of hemodialysis on acetaminophen and N-acetylcysteine kinetics in a massive acetaminophen overdose.

Case report: An 18 year old female arrived at our centre 1.5 h after reported ingestion of 100 g of acetaminophen and an unknown amount of ibuprofen and alcohol. Biochemical analyses 3 h post ingestion showed metabolic acidosis (lactate 8.6 mmol/L, bicarbonate 11.2 mmol/L). At 4 h post-ingestion, acetaminophen serum concentration from blood drawn on arrival was 6496 μ mol/L. She was intubated for decreased mental status, received 100 g of activated charcoal and an N-acetylcysteine bolus of 150 mg/kg over 1 h. N-acetylcysteine infusion followed at 12.5 mg/kg/h before and during dialysis. Screening for co-ingestants including toxic alcohols was negative. Seven hours post ingestion, intermittent hemodialysis was started for 7 h duration that resulted in correction of the metabolic acidosis. Post dialysis, acetaminophen concentration

was 335.7 $\mu\text{mol/L}$ and N-acetylcysteine infusion was continued at 6.25 mg/kg/h for a total duration of 28.5 h. Acetaminophen concentration was under 66 $\mu\text{mol/L}$ at 25.5 h post ingestion. The patient was extubated 4 h after dialysis and later transferred to the ward for psychiatric assessment. She was discharged home 48 h post ingestion. Liver, renal and coagulation profiles remained normal throughout her admission.

Results: Apparent acetaminophen elimination half-life was 5.2 h prior to, 1.9 h during and 4.6 h after hemodialysis. Acetaminophen clearance during hemodialysis (7 h; blood flow rate = 400 mL/min, dialysate flow rate 1000 mL/min) was 160.4 mL/min with an extraction ratio of 57%. N-acetylcysteine clearance during hemodialysis was 190.3 mL/min with an extraction ratio of 69%. N-acetylcysteine serum concentrations fluctuated during hemodialysis between 162.7 and 364.9 $\mu\text{mol/L}$, which was comparable to concentrations following dialysis. Hemodialysis removed 20.6 g of acetaminophen and 17.9 g of N-acetylcysteine.

Conclusion: In massive acetaminophen overdose, hemodialysis corrects metabolic acidosis and significantly accelerates acetaminophen clearance. Doubling the acetylcysteine dose during hemodialysis (to 12.5 mg/kg/h) resulted in serum concentrations similar to those seen post-hemodialysis at a rate of 6.25 mg/kg/h.

37. Dissemination and uptake of new UK guidance on the management of paracetamol poisoning: A survey of healthcare professionals

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Objective: In September 2012, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) issued guidance changing the license and administration instructions for acetylcysteine for paracetamol poisoning with immediate effect.¹ We sought to evaluate awareness of the new guidelines amongst UK healthcare professionals.

Methods: We surveyed healthcare professionals in specialties managing patients with paracetamol poisoning in the 1–8 week period following guidance implementation. Participants were identified through e-mail distribution lists and from attendees at an educational meeting.

Results: 260 individuals, from 42 institutions, responded; 154 (59%) were aware of the guidance changes. Awareness differed significantly among professional groups and between specialties ($p < 0.001$ in both cases; Table 1). There was no variation by sampling week ($p = 0.096$). For respondents aware of the changes, the main sources of information were internal hospital alerts (57%); the MHRA (26%); and other professional bodies (23%). Twenty-four (16%) of the individuals aware of the changes had not adopted them in practice; 18 of these (75%) had not seen any practical instructions (e.g. protocols, acetylcysteine dosing tables) to support the changes.

Conclusion: Over one-third of healthcare professionals in specialties managing patients with paracetamol poisoning were unaware of important changes to its management in the 8 weeks after they took effect. The most effective means of communicating this information appeared to be via internal alerts, which, for maximum effect, should be supported by practical guidance.

Table 1. Awareness of new UK guidance on the management of paracetamol poisoning among professional groups and between specialties.

	All respondents	Aware of changes	Unaware of changes
Total numbers	260	154 (59%)	106 (41%)
<i>Professional category</i>			
Consultant/associate specialist	68	46 (68%)	22 (32%)
Junior doctor	72	33 (46%)	39 (54%)
Pharmacist	58	45 (78%)	13 (22%)
Nurse	49	23 (47%)	26 (53%)
Other	13	7 (54%)	6 (46%)
<i>Specialty*</i>			
General medicine	58	28 (48%)	30 (52%)
Acute medicine	19	14 (74%)	5 (26%)
Emergency medicine	83	59 (71%)	24 (29%)
Intensive care	37	14 (38%)	23 (62%)
Paediatrics	37	14 (38%)	23 (62%)
Other	100	53 (53%)	47 (47%)

*Some respondents had more than one specialty

Reference

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38. A new line - the potential impact of decreasing the paracetamol treatment line

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Objective: Paracetamol (APAP) remains one of the most common causes of overdose. The Rumack-Matthew nomogram is used to guide therapy. N-acetylcysteine (NAC) is typically indicated in the US when the [APAP] falls above the “150 micrograms/mL treatment-line” Recently, the UK lowered their treatment-line to 100 micrograms/mL. We reviewed the Poison Control Center (PCC) database to assess the impact of changing the treatment-line in our patient population.

Methods: The PCC database of all home and hospital calls for single agent APAP ingestions was retrospectively reviewed for a two-month period (9/1/12–10/31/12). The birth year, gender, weight, relevant medications, and suicidality were recorded in addition to the mg/kg dose (if known) and if the caller was from home, whether it was recommended to go to the hospital. Dose extrapolation was used for home calls to predict location on the nomogram. For hospitalized patients, additional variables included AST/ALT, international normalized ratio (INR), NAC administration, and adverse reaction to NAC. Outcome was defined as any patient whose management would have changed based on the newer treatment-line.

Results: 436 total records were reviewed; 17 were excluded as duplicates or incomplete charting, leaving 419 cases for

evaluation. There were 231 home calls, of which 68 were sent to the hospital for evaluation. Of the 163 cases that were managed at home, 9 would have been sent to the hospital based on extrapolation of ingested dose to be over the proposed 100 micrograms/mL treatment-line. There were 188 hospital calls, 74 of which could not be placed on the nomogram, leaving 114 cases for evaluation. Four patients who were not treated would have received NAC based on the 100 micrograms/mL treatment-line. There was a 6.5% incidence of adverse reactions to NAC noted in the PCC records for that two-month period. During this period we were unaware of any cases of hepatotoxicity in either group of untreated patients.

Conclusion: If the proposed 100 micrograms/mL treatment-line was established, at least 9/163 (5.5%) of home calls and 4/114 (3.5%) of hospital calls would require additional evaluation or therapy. Although this percentage is small, it represents only 2 months' data from a single PCC. A formal cost-benefit analysis is indicated to assess the impact.

39. Management of acute paracetamol poisoning: The effect on the numbers of patients needing N-acetylcysteine of adopting a single treatment line

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Objective: Treatment of single-time-point ingestion of paracetamol poisoning with N-acetylcysteine (NAC) is guided by plotting a timed plasma paracetamol level on established nomograms, and considering the presence or absence of risk factors for hepatotoxicity. This study examined the effect on the numbers of patients needing NAC if a single treatment line were adopted, regardless of their risk for hepatotoxicity.

Methods: Data were recorded from 107 patients with non-staggered (ingestion over less than 1 hr), single-time-point ingestion paracetamol overdose from January 2008 to October 2012. Information was recorded about the patients' hepatotoxicity risk stratification, plasma paracetamol levels, and time elapsed from ingestion to paracetamol measurement (t in hr). ANAC (mg/L) is the timed paracetamol level above which treatment with NAC may be warranted. Based on the Rumack-Matthew nomogram, ANAC was calculated by the equations $400(0.84)t$, $300(0.84)t$ and $200(0.84)t$, for the 200-line, 150-line and 100-line, respectively, where t ranged 4 to 24 hr.¹ The numbers of patients needing NAC were modeled and compared for three scenarios: 200/100-line (200-line for normal risk and 100-line for high risk patients), 150-line and 100-line (single treatment line regardless of risk for hepatotoxicity). Cases were excluded where the time of paracetamol ingestion was uncertain, or paracetamol levels were measured within 4 or beyond 24 hr of ingestion. Between-group comparisons were made by two-tailed chi-square proportional tests.

Results: Among 107 cases identified, 15 were considered high risk. A 200/100-line would result in 6 (5.6%) high risk cases and 19 (17.8%) normal risk cases needing treatment (total 25, 23.4%). Comparing with the 200/100-line, the 150-line would result in

4 (3.7%) high risk cases and 32 (30.0%) normal risk cases needing treatment (total 36, 33.6%), corresponding to an additional 11 (10.3%) cases being treated (chi-square, $p < 0.05$); the 100-line would result in 6 (5.6%) high risk cases and 40 (37.4%) normal risk cases needing treatment (total 46, 43.0%), corresponding to an additional 21 (19.6%) cases being treated (chi-square, $p < 0.05$).

Conclusion: Both the 150-line and the 100-line would increase the numbers of patients needing treatment comparing with the 200/100-line.

Reference

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40. Audit of admission and acetylcysteine administration rates for paracetamol overdose following licence changes recommended by the UK's Commission for Human Medicines

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Objective: Paracetamol overdose is the leading cause of acute liver failure in the UK and assessment of risk of hepatotoxicity can be difficult. Historically, a nomogram with two treatment lines together with the assessment of risk factors has been used in the UK. On 3rd September 2012 the Commission for Human Medicines (CHM) changed the licence indication for acetylcysteine to simplify treatment decisions. The principal recommendations were for one treatment line for single acute overdose, regardless of risk factors, and administration of acetylcysteine following staggered ingestion irrespective of plasma paracetamol concentration. The aim of the audit was to examine the impact of this change on admission and acetylcysteine administration rates following paracetamol overdose.

Methods: A prospective case note audit was carried out for all patients presenting to the Royal Infirmary of Edinburgh (RIE) following a paracetamol overdose for an eight-week period before and after the licence change. Statistical analysis was undertaken using the two-tailed Fisher's exact test.

Results: Presentations to hospital were similar with 174 in the pre-change group and 175 in the post-change group. Admission rates increased from 77/174 (44%) pre-change to 103/175 (58%) post-change ($p = 0.007$). Treatment requirement increased significantly following the change, from 51 patients (29%) in the pre-group compared to 86 (49%) in the post-group ($p = 0.0002$). Closer examination revealed that 13 patients were treated with acetylcysteine in the post-group who would not have been treated under the previous guidelines. A further four patients received a full course of acetylcysteine based on history of amount ingested and continued on receipt of blood results. If presentation had been before the change acetylcysteine would have been discontinued. Admissions of staggered ingestions also increased following the change from pre 13/174 to post 31/175 ($p = 0.005$). Treatment was administered for 11 patients in the pre-group and 29 in the post-group ($p = 0.004$).

Conclusion: The new licence indication for acetylcysteine has increased admission and acetylcysteine administration rates for patients with paracetamol overdoses.

41. Online behaviour of TOXBASE® users seeking advice on paracetamol poisoning management

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Objective: To examine the online behaviour of users of an Internet clinical toxicology database, TOXBASE®, after a major change in paracetamol poisoning management advice.

Background: The UK National Poisons Information Service provides TOXBASE® to healthcare facilities in the UK, to emergency departments in the Republic of Ireland, and to overseas subscribers. Paracetamol is the substance accessed most frequently. Following recommendations from the Commission on Human Medicines, new license indications were introduced for acetylcysteine on 3/9/2012 resulting in major revisions to TOXBASE® management advice for UK users. Management advice for Irish users remained the same; an index page directing users according to country of origin was made available.

Methods: For the period 4/9/2012 to 21/10/2012, we looked at the behaviour of 556 UK-based TOXBASE® users that viewed paracetamol management pages applicable to Ireland on at least one occasion. One thousand three hundred and fifty-eight TOXBASE® sessions were analysed. We also looked at 146 Irish-user sessions during the same period.

Results: For 94.5% of sessions, UK-based users only consulted UK advice. However, on 2.9% and 2.7% of occasions, they consulted only Irish advice or both UK and Irish advice, respectively. Of the Irish users, a smaller proportion (63%) looked only at Irish advice, while 28.8% and 8.2% consulted only UK advice or UK and Irish advice, respectively. Many readers did not read just one set of management advice that would be specific to a single patient. In the UK, 14.4%, 2.9%, and 1.8% of sessions involved viewing 2, 3, or at least 4 separate paracetamol management pages, respectively. In Ireland, 19.2%, 4.1%, and 5.5% of sessions involved viewing 2, 3, or at least 4 separate paracetamol management pages, respectively.

Conclusion: Although the majority of UK user sessions in this sample accessed only the UK advice after the change, 1 in 20 users viewed the Irish advice. Conversely, 37% of Irish users accessed UK advice. Furthermore, in both the UK and Ireland, 20–30% of viewers accessed more than one set of paracetamol management pages. These findings suggest uncertainty concerning the best management regimens for their patients.

42. Consequences of changing the referral threshold for acetaminophen-related calls to the Quebec poison control centre

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Objective: The United Kingdom Commission on Human Medicines (CHM) published in September 2012 a revision of the indications for N-acetylcysteine in the treatment of acute paracetamol overdoses.¹ Following these recommendations, TOXBASE changed their referral threshold to 75 mg/kg.² Our study evaluates the potential impact of such changes for the acetaminophen-related calls to our poison control center (PCC).

Methods: Retrospective observational study of acetaminophen ingestion cases reported to our poison control center between August 1st and 31st 2012. The following variables were extracted on a standardized sheet; age, gender, dose ingested, weight and referral to hospital status. We refer ingestions above 200 mg/kg in children younger than 6 years and above 150 mg/kg or 7.5 grams for anyone above 6 years. The difference in proportion of patients that would have to be sent for acetaminophen measurements between TOXBASE advice and ours was calculated.

Results: Of 308 charts, 118 were for patients under the age of 6 and 190 for patients older than 6 years. One hundred and thirteen were incomplete for ingestion data. Under 6 years of age none were suicidal, non-suicidal; 52 were under 74.9 mg/kg, 44 between 75–200 mg/kg and 1 above 200 mg/kg. Over 6 years of age, 130 were suicidal, non-suicidal: 11 under 74.9 mg/kg, 10 between 75–149.9 mg/kg and 4 above 150 mg/kg.

Conclusion: Suicidal patients are sent to hospitals regardless of their ingestion history and are not included in the difference calculation. Should the Quebec PCC adopt the same referral threshold as what TOXBASE is recommending, 59 (19%) more patients per month would have to be sent for acetaminophen measurements, 45 of which are children. Our poison centre has not received any calls pertaining to patients with an ingestion under 150 mg/kg becoming symptomatic. A cost-effectiveness analysis is needed to determine the social and resources use consequences of such recommendations with regards to the risk of hepatotoxicity reported with ingestion histories between 75–150 mg/kg.

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43. Snake bites in Sikasso, Mali

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Objective: Envenoming resulting from snake bites is a serious public health problem in many regions of the world. The aim of this study is to describe the difficulties in the management of envenomation in the prefecture of Sikasso in Mali.

Methods: In 2010–2011, a prospective study of snake bites cases, recorded in the Health Reference Center of Sikasso, was conducted.

Results: During the period of study, 204 victims (from Kléla) were received and treated at the Health Reference Center of Sikasso, including 115 cases in serious condition (pain, edema, bleeding and/or vomiting). Of these, 21 died, including 17 cases while on the way to the center. However, 68 of 204 patients did not present any signs of envenomation. Adults 15 years and over were most commonly involved because of their socio-professional activities (agriculture, cattle breeding, gathering). The majority (78% of reported cases) occurred in the fields and pastures, 19% during walks and 3% in and around the house. Snakes belonged to the *Viperidae* family (*Bitis arietans*, *Echis ocellatus*) and the *Elapidae* family (*Naja nigricolis*, *Naja katiensis*). According to data available, 92 envenomed patients were cured by 10 mL of antivenom administered intravenously and 23 patients by 20 mL of antivenom. The average length of stay in hospital was 3 days, with a range of 8 hours to 14 days.

Conclusion: Concerted action is needed to ensure adequate supplies of effective antivenom and to develop systems that deliver high quality health care.

44. Scorpion stings in Gao, Mali

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Objective: Scorpion envenoming is a major public health problem in many tropical and subtropical countries. The aim of this study is to determine the epidemiological features of scorpion stings in the city of Gao in Mali.

Methods: A descriptive retrospective analysis of scorpion sting cases, recorded between 2002 and 2009 in three health Centers of Gao, was performed.

Results: A total of 148 scorpion stings cases were recorded during the study period. Of these, 46% were in the Health Reference Center, 35% in the military hospital and 19% in Gao regional hospital. The cases occurred principally during the months of April and June (respectively 18% and 13%) and between 14 h and 18 h in 57.4% of cases. The average age of the patients was 34 ± 12 years, with a sex ratio (M/F) of 8. According to the results obtained, 5% of victims were under the age of 15 years. In 66% of cases, the sting was on the upper limb, 33% on the lower extremity and 1% on the trunk. The median delay in presentation to hospital was 2.4 hours. Among the 11 patients for whom the outcome is known, one of them died. **Conclusion:** Scorpion envenomation is a serious public health threat in Gao due to the presence of dangerous species: *Leiurus quinquestriatus*, *Androctonus australis* and *Androctonus amoreuxi*.

45. Dying for delicacy – tetrodotoxin poisoning from dried preserved puffer fish

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Objective: We report a case of tetrodotoxin poisoning from dried preserved puffer fish. Such poisoning has only been reported once previously and serves as a reminder that this marine toxin is heat-stable and not destroyed by drying, preservation or cooking process.

Case report: A 25-year-old Chinese male brought some dried preserved puffer fish a month prior. He cooked three of these fish. After consuming half a fish, he developed peri-oral numbness, nausea and watery stools. Two hours later, he developed facial numbness, upper and lower limb numbness and weakness. At the hospital, his heart rate was 78/min, blood pressure 133/58 mm Hg, respiratory rate 18/min, oxygen saturation on room air 98%. These remained normal and stable. Examination showed slightly decreased upper and lower limb power bilaterally, but normal reflexes. The rest of the neurological and all other organ examinations were normal. Electrocardiogram, full blood count, and serum electrolytes including calcium, magnesium and phosphate tests were all unremarkable. The patient discharged himself against medical advice. On follow up, he revealed that he continued to have giddiness, nausea, recurrent vomiting and generalized numbness for three days after discharge.

Conclusion: Tetrodotoxin is produced by marine bacteria and bio-accumulated in marine creatures, especially fish of the *Tetraodontidae* family. It blocks neuronal sodium channel resulting in parasthesia, ataxia, vomiting, diarrhea, and ascending paralysis. Onset of symptoms can be within 30 minutes from ingestion and death from respiratory paralysis can occur within an hour.¹ Poisoning usually results from consuming fresh fish parts; pre-packaged ready-to-eat fish has also caused poisoning.² However, dried fish poisoning has only been reported once previously.³ Tetrodotoxin is heat-stable and will survive normal cooking. These cases also show that it remains viable and dangerous after drying and preservation. Health, food safety authorities and physicians should be aware of this, and sale of these preserved products should be closely regulated.

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46. Severity of *Vipera berus* bites in Finland

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Objective: *Vipera berus* (adder) is the only poisonous snake in Finland and Scandinavia. The last fatal case was in 1998 in Finland but complicated bites are treated in hospitals every year. The treatment consists of symptomatic treatment and a specific antidote. However, we have no data on the use of the antidote. No randomized study can be performed with snake bites and the objective of this retrospective, epidemiological study was to find out the character of *Vipera berus* bites.

Table 1. Severity of *Vipera berus* bites in adults and children.

PSS	Adults	Children
0	22	14
1	41	65
2	34	19
3	28	6
Total	125	104

Methods: This study was performed in Turku University Hospital area (population around 500,000) because it covers the whole Finnish archipelago where *Vipera berus* is most common in Finland. All patients hospitalized because of *Vipera berus* bites during the years 2000–2010 were included and the data were collected from the patient records. The records were double checked by hand to exclude the cases which later proved to be non-snake bites. Poison severity score (PSS) was used to evaluate the severity of the cases.

Results: There were 125 *Vipera berus* bites in adults and 104 in children. All the bites happened between May and October; 48% occurred in July. The median length of hospital stay was 3 days for both groups. However, the severity of the bite varied between the groups (Table 1). Antivenom was given to 12 adults and 16 children. Cortisone was given to 44 children and an antibiotic was started in 40 children. With adults cortisone and antibiotics were not as common. There were only a few cases where symptoms remained for weeks and none of these happened in children.

Conclusion: Antivenom was given more liberally to children than adults even though the PSSs were not worse in children. The time interval from a bite to the antivenom varied from a couple of hours to even 12 hours and it is possible that the antivenom in some cases stopped the development of complications. However, 93% of the patients treated with antivenom had moderate or severe symptoms at some point.

47. Neurotoxicity caused by *Vipera ammodytes* bite: A case report

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Objective: There are three venomous snake species known in Slovenia: *Vipera ammodytes*, *Vipera berus* and *Vipera aspis*; the last one is very rare. Life threatening envenomings by snake bite are rare. This is the first reported case of neurotoxicity caused by snake bite in Slovenia.

Case report: A 56-year old female was admitted to the General Hospital 2 hours after she was bitten by a horned viper (*Vipera ammodytes*) on her left palm, while she was gathering hazel nuts. At admission local oedema at the bite site, dizziness, nausea, vomiting, urinary and faecal incontinence were present; laboratory findings showed thrombocytopenia $17 \times 10^9/L$, international normalized ratio (INR) 1.41. She was treated with fluids, antiemetics, analgesics, Konakion and fresh frozen plasma. During the next twelve hours she developed progressive neurological symptoms: dysarthria, dysphagia, ophthalmoplegia, ptosis, distal neuromuscular weakness; oedema and haematoma spreading over the elbow. She was moved to our Poison Control Center (PCC). Computed tomography (CT) of the head was normal,

microelectromyography of musculus ocularis oculi showed 40% increase of M wave after she had closed her eyes for 20 seconds. Serum acetylcholinesterase level was normal. She was treated with 40 mL of European Viper Venom Antiserum altogether; neurologic symptoms soon started to improve, thrombocytes normalised; she was cardiocirculatory stable throughout. Twenty-four hours after antidote treatment only ptosis and walking incoordination were still present. Intravenous administration of 1 mg of neostigmine methylsulfate improved ptosis. She then received pyridostigmine bromide 30 mg for the next three days orally. At discharge, six days after the bite, only mild ptosis and a haematoma of her left hand was still present, but within the next few days the symptoms completely disappeared.

Conclusion: Neurotoxicity of *Vipera ammodytes* venom is mostly related to ammodytoxin A (AtxA), which belongs to secreted phospholipases A2.¹ The exact mechanism of its presynaptic actions in humans is still not clear. Prompt and effective response to neostigmine treatment confirms at least partial involvement of acetylcholine-nerve transmission failure in neurotoxicity of AtxA.

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48. Coagulopathy as the sole systemic manifestation after envenoming by a juvenile South American rattlesnake (*Crotalus durissus terrificus*): Case report

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Objective: To report an unusual case of envenoming by a juvenile South American rattlesnake (*Crotalus durissus terrificus*) that involved only coagulopathy.

Case report: A 19-year-old male was bitten on the third finger of the left hand by a “small brown striped snake” while handling timber in a rural setting; his uncle tried to kill the snake but only injured it and it escaped. The patient was admitted to the local emergency unit (EU) stating that he had been bitten by a lancehead (*Bothrops spp.*). Although he presented only slight pain, edema and erythema, with no coagulopathy (international normalized ratio (INR) = 1.06; whole blood clotting time (WBCT) = 8 min), he was treated with five vials of bothropic antivenom (Inst. Butantan, Brazil) IV, and discharged on the same day. Four days after the bite he returned to the same EU complaining of nausea, vomiting and sweating. Meanwhile, the snake that caused the bite had been found dead, but was not brought to the EU. The WBCT revealed incoagulable blood (WBCT > 30 min). Total serum creatine kinase activity (CK; 87 U/L) was within the reference values (26–189 U/L), and two more vials of bothropic AV were infused. Five days post-bite the patient was admitted at our EU with incoagulable blood (incoagulable PT, aPTT and INR) more than 24 h after the last dose of AV, showing no increase in serum CK. In view of the possibility of a rattlesnake bite, the patient was treated with five vials of crotalic AV (CroAV; Inst. Butantan)

which improved the coagulation (INR 12 h post-CroAV = 2.11; 33 h post-CroAV = 1.41). During hospitalization, relatives brought the snake which was identified as a 38-cm long *C. d. terrificus*.

Discussion: Rattlesnake bites in Brazil are generally caused by adult individuals, with most of the envenomed patients showing systemic manifestations that include varying degrees of neurotoxicity (acute myasthenia), rhabdomyolysis and coagulopathy, and only mild local manifestations. This is the first report of a confirmed bite by a juvenile *C. d. terrificus* with coagulopathy as the sole systemic manifestation, successfully treated with CroAV five days post-bite.

49. Cantharidin intoxication: A rare but lethal case in Taiwan

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Background: “Spanish fly” (cantharidin) has a reputation as an aphrodisiac, skin irritant, vesicant and abortifacient. However, it is extremely toxic and the minimum lethal dose may be 10~65 mg.

Case report: We report a 60 year-old male presenting to the emergency department with acute onset of gastrointestinal bleeding. The patient ingested a soup made from a large amount of dried Spanish flies. The most common and typical symptoms included hematemesis, abdominal pain, hematochezia, dysuria, and hematuria. In addition, rapid deterioration of renal and cardiac function were also observed in our patient.

Conclusion: From the review of the literature, cantharidin intoxication is very rare around the world. In this case, the detailed toxidrome of cantharidin intoxication and its cause of death were described. Unlike in Hong Kong, selling dried Spanish fly is without regulation in Taiwan. Educating the public about the toxicity of Spanish fly is important in preventing accidental poisoning.

50. The effect of neostigmine on in-hospital mortality of adult patients with severe puffer fish poisoning: A pooled analysis of case reports and case series

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Objective: Among patients with severe tetrodotoxin (pufferfish) poisoning, neostigmine has been suggested to improve the patients’ prognosis. Yet, the evidence base for this practice remains unclear. We aimed to systematically review the available literature and to evaluate the effectiveness of neostigmine use on in-hospital mortality in pufferfish-associated acute respiratory failure.

Methods: We searched in PubMed, EMBASE, Google Scholar and other databases for all case reports or series of acute pufferfish poisoning ever published up to December 2012. We included only severe adult cases (age 16 years or older, with Fukuda grade IV severity or with acute respiratory failure). The main exposure variable was the use of neostigmine or not. Primary outcome was in-hospital mortality.

Results: We identified 377 publications, retrieved 67 full-text articles and selected 34 articles, including 13 case reports and 21 case series. We assessed the quality of reporting based on the completeness of key variables described, resulting in 35 cases eligible for the pooled analysis. Although we did not observe a statistical association between neostigmine use and in-hospital mortality, we noted that severely poisoned patients who used neostigmine tended to have a shorter duration of ventilator support (median: 12 vs. 30 hours) or intensive care requirement (median: 12 vs. 72 hours) than non-users did (p -value > 0.05). Most of the case reports and case series had the following neostigmine regimen: neostigmine 0.05 mg/kg body weight along with atropine 0.025 mg/kg body weight, six hourly for one day.

Conclusion: There is insufficient evidence to recommend or discourage the use of neostigmine in treating patients severely poisoned with pufferfish. Future investigations with rigorous design and adequate reporting quality are needed to provide robust evidence for the clinical benefit of neostigmine use in severe acute pufferfish poisoning.

51. Clinical evidence of Italian viper venom neurotoxicity: 11-year experience of the Pavia poison control centre

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Objective: To study neurotoxic effects after viper envenomation in Italy.

Methods: All human cases of snakebite referred to Pavia Poison Centre (PPC) presenting peripheral neurotoxic effects (PNE) from Jan 2001 to Dec 2011 were included. Cases were assessed for: time from bite to PPC evaluation, Grade Severity Score (GSS)¹, onset/duration of clinical manifestations, severity/time course of local, non-neurological and neurological effects, antidote treatment.

Results: Twenty-four were included (age 3–75 years) and represented an average of 2.2 cases/year (about 7% of total envenomed patients). The mean time interval of PPC evaluation from snakebite was 10.80 ± 19.93 hours. GSS at emergency department admission was 0 (1 case), 1 (10 cases) and 2 (13 cases). All patients showed local signs: 41.6% minor, 58.4% extensive swelling and necrosis. The main systemic non-neurological effects were: vomiting (86.7%), diarrhoea (66.7%), abdominal discomfort (53.3%) and hypotension (20%). PNE were: accommodation troubles and diplopia (100%), ptosis (91.7%), ophthalmoplegia (58.3%), dysphagia (20.8%), drowsiness (16.6%), cranial muscle weakness (12.5%), dyspnoea (4.2%). PNE were the only systemic manifestation in 9 cases; in 4 cases they were associated with only mild local swelling. In 10 patients the onset of PNE followed the resolution of systemic non-neurological effects. Antidote was administered intravenously in 19 (79.2%) patients. The mean duration of manifestations in untreated vs treated group was 53.5 ± 62.91 vs 41.75 ± 21.18 hours ($p = 0.68$) (local effects) and 9.77 ± 3.29 vs 8.25 ± 12.23 hours ($p = 0.1$) (systemic non-neurological effects) and 43.4 ± 14.69 vs 26.58 ± 20.62 hours ($p = 0.03$) (PNE).

Conclusion: PNE may appear late (11 hours after the bite in 58.3% of cases), in contrast with the data reported in the French medical literature². PNE was reversible in all cases and may be the only systemic manifestation of envenomation. PNE are shorter in the treated group. Antidote treatment of patients considered as GSS 2 only for PNE (with mild local effects) may not be necessary. Variable factors such as the different amount of venom injected, concentration of PLA2 component and individual susceptibility may explain the lower percentage of patients presenting neurotoxic effects.

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52. Deleterious outcome following prolonged ice application of an *Agkistrodon contortrix* envenomated finger

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Objective: The outcome for victims of *Agkistrodon contortrix* envenomations is typically full recovery with rare reports of permanent injury. Evidence suggests that cryotherapy of crotalid envenomated tissue is potentially harmful. We report a case of prolonged cryotherapy application to an *Agkistrodon contortrix* envenomated finger with subsequent adverse outcome.

Case report: A 55 year-old previously healthy male was bitten on his left ring finger at the proximal interphalangeal joint by a snake positively identified as an *Agkistrodon contortrix*. He subsequently submerged his hand in an ice water bath for 90 minutes before presenting to a local hospital. Due to progressive finger and hand edema, he was treated with Crotalidae Polyvalent Immune Fab. He developed no laboratory abnormalities. At discharge the next day, he was noted to have 2 large bullae over the bite site with adjacent ecchymosis. Five days following discharge, he returned to the hospital due to progression of ecchymosis and necrotic tissue over the distal portion of his finger. His laboratory values remained normal. Despite local wound care and antibiotic therapy, he continued to have significant necrotic finger tissue and subsequent decreased range of motion of his finger. One week after the envenomation, plastic surgery determined that his finger was not viable and his finger was amputated.

Discussion: Current literature recommends against the use of cryotherapy in the treatment of snake envenomation victims as such therapy may worsen outcomes.¹ Despite these recommendations, first aid Internet sites continue to recommend ice application following snake envenomations.²

Conclusion: Clinicians and the public require increased education as to the proper first aid management of snake envenomations to avoid potentially inducing adverse outcomes.

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53. Intravenous lipid emulsion does not improve hemodynamics or survival in a rodent model of oral verapamil poisoning

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Background: Lipophilic drugs such as verapamil may cause cardiotoxicity in overdose. Intravenous lipid emulsion (ILE) is recommended as a rescue-therapy for the treatment of refractory haemodynamic compromise. The lipid-sink theory is the most supported explanation for mechanism of action. Little is known about the effects of ILE-infusion on blood-drug concentration and haemodynamics in the early/absorptive phase after oral poisoning. Previously, we have reported that ILE-treatment resulted in decreased survival and increased blood-concentrations of amitriptyline over time compared to treatment with sodium bicarbonate in a rodent model of oro-gastric amitriptyline poisoning. Amitriptyline is more lipophilic than verapamil. We aimed to assess whether intravenous administration of ILE affects survival, blood pressure and blood-verapamil concentration after oro-gastric administration of verapamil.

Methods: Thirty minutes (T30) after oro-gastric administration of verapamil (54 mg/kg) (T0), one of 20% Intralipid® (ILE), 0.2 mmol/kg calcium chloride or Hartmann's Solution were infused as an initial loading dose of 4 mL/kg over 10 minutes followed by infusion at 4 mL/kg/h to anaesthetised and ventilated rodents (n = 10 per group). Heart rate (HR), mean arterial pressure (MAP), and survival were recorded over 120 minutes. Blood-drug concentrations were collected serially. MAP, HR and blood concentrations were compared at each time point by 1-way ANOVA and Newman-Keuls post-test (significant if p < 0.05).

Results: ILE-infusion was associated with significantly decreased survival compared to other treatments (20% ILE v 90% Calcium v 100% Hartmanns, p < 0.0001 - Mantel-Cox Test). ILE-treatment resulted in persistent hypotension and lower HR, similar to Hartmanns infusion, compared to Calcium-treatment. MAP was significantly higher with Calcium-treatment at T45, 60, 75, 90 min (p < 0.02) as was HR at T75 and T90 (p < 0.02). Blood-verapamil concentrations were, on-average 50% higher with ILE-treatment at T45, 60, 90 and, 120 mins. However, these were not statistically significant compared with calcium or Hartmann's treatment.

Conclusion: Early administration of ILE after oro-gastric overdose resulted in lower survival than both control treatments and did not improve haemodynamics compared to calcium infusion. Blood-verapamil concentrations were higher in the ILE-treated group, however unlike our amitriptyline model, the increase was not significant. Drug absorption from the gastrointestinal tract may be facilitated if ILE is administered early after oral poisoning. This may increase toxicity after lipophilic drug poisoning.

54. An animal model demonstrating significant bladder inflammation and fibrosis associated with chronic methoxetamine administration

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Objective: Methoxetamine is a novel psychoactive substance that is an arylcyclohexylamine derivative of ketamine. Chronic ketamine use is associated with bladder/renal toxicity and there is the potential that methoxetamine will have similar effects. We used an animal model to investigate the potential for bladder toxicity with chronic methoxetamine use.

Methods: Two month old Institute of Cancer Research (ICR) mice were administered 30 mg/kg/day methoxetamine intra-peritoneally (n = 5) or saline (n = 3, control) for three months. The animals were then sacrificed and histological examination, immunocytochemistry using polyclonal anti-CD4 antibodies [mAb51312] and Sirius red staining for collagen were performed. The density of mononuclear cells in the lamina propria and submucosal layers was calculated using areas of 25 square micrometres. The study was approved by the Animal Experimentation Ethics Committee of the Chinese University of Hong Kong.

Results: The bladder of all methoxetamine-treated animals showed infiltration of fibroblasts and mononuclear cells (lymphocytes and macrophages) in the lamina propria and submucosal layers. Halo-like muscle degeneration was seen in two of the methoxetamine treated animals. There was increased density of mononuclear cells in the methoxetamine treated animals (43.04 ± 10.3 per $25 \mu\text{m}^2$) compared to controls (7.13 ± 5.75 per $25 \mu\text{m}^2$), $p < 0.001$. CD4-positive staining by immuno-cytochemistry was seen in the submucosa and lamina propria of all methoxetamine treated animals and the muscle layer in two methoxetamine-treated animals. There was also increased aggregation of Sirius red positive collagen fibres in the muscular and submucosal layers of methoxetamine treated animals. None of these changes were seen in control animals.

Conclusion: This mouse model of chronic methoxetamine exposure has demonstrated significant inflammation and mononuclear cell infiltration of the bladder and associated fibrosis following chronic methoxetamine administration. These changes are similar to those seen in animal models of chronic ketamine administration, suggesting that it is likely that similar clinical features may be seen in chronic human users of methoxetamine. The time-frame to collect data for legislative authorities on novel psychoactive substances such as methoxetamine is often limited, particularly for chronic toxicity. Animal models such as this provide vital information to ensure accurate data for legislative authorities and clinicians.

55. Neutralization with proteolytic enzyme and a phospholipase A₂ inhibitor reduces the toxicity of *Micrurus fulvius* venom

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Objective: Antivenin is expensive and not available in some countries. Coral snake antivenin is unavailable in the United States. Effective inexpensive treatments are needed. The effects of trypsin, a proteolytic digestive enzyme, and rosmarinic acid (RA), a phospholipase A₂ inhibitor, on the toxicity of *M. fulvius* venom were investigated in a murine model.

Methods: A randomized controlled blinded study was conducted. Fifty mice (20–30 g) were randomized to receive intraperitoneal (IP) injections of: 1) 2 mg/kg *M. fulvius* venom (approximately twice the LD50 for mice; n = 10); 2) 2 mg/kg *M. fulvius* venom incubated *in vitro* for 1 hour prior to injection with RA at a 1:10 ratio (n = 17); 3) 2 mg/kg *M. fulvius* venom incubated *in vitro* for 1 hour prior to injection with 1 mg of trypsin (n = 17); 1 mg trypsin IP without venom (n = 3); and 4) RA IP without venom (n = 3). Animals were observed continuously for 12 hours and assessed for signs of toxicity including respiratory distress (< 25 breaths/min.), loss of spontaneous locomotor activity and/or inability to upright self. Animals were euthanized at the onset of toxicity, as determined by a blinded observer. Comparison of time to euthanasia across groups was performed using Tukey-Kramer HSD (honestly significant difference). The proportion of animals surviving to 4, 6, and 12 hours was compared across groups using Chi-square analysis.

Results: Time to euthanasia for controls (venom alone) was 120.3 min. Pre-incubation of the venom with RA provided a non-significant increase in time to sacrifice vs. controls (238.1 min; $p = 0.15$). Pre-incubation with trypsin significantly increased survival time vs. controls (319.7 min; $p = 0.007$). Pre-incubation of venom with trypsin increased the number of animals that survived to 4 hours vs. controls ($p = 0.023$). This effect was not seen with RA. The proportion of animals surviving to 6 and 12 hours was similar across groups ($p = 0.12$, $p = 0.37$, respectively). Two mice in the trypsin group and 1 mouse in the RA group survived to twelve hours. Mice receiving trypsin alone or RA alone survived to 12 hours.

Conclusion: *In vitro* neutralization of *M. fulvius* venom by trypsin justifies progressing to an *in vivo* model in future studies.

56. Persistent neurotoxic effect of aluminum exposure on Wistar rats: Neurocognitive and histological aspects

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Objective: Aluminum is an abundant metallic element which is present naturally in the environment and also frequently found in numerous sources, including air, food, drugs, cosmetics, vaccines, household materials and water. It was considered, for long time, as a non toxic element and completely excreted out of the body by the renal route. However, currently, its toxicity appears more and more threatening to exposed populations and its principal target is the nervous system. The objective of this study was to investigate the impact of aluminum nitrate toxicity on memory performance after stopping the exposure and on the nervous system's structures among adult Wistar male rats.

Methods: Two groups of Wistar male rats were used. The intoxicated rats received 120 mg/L of aluminum nitrate and the controls received tap water. The intoxication lasted 10 months and the study lasted for a further 3 months after stopping the treatment. The memory abilities were evaluated using novel object recognition memory test and object location task and the structural study was carried out using histological techniques in hippocampus and entorhinal cortex of rat brain.

Results: The results showed that the effect of aluminum on memory abilities remained, even after the intoxication ceased. Highly significant decrease in the memory index of short ($p < 0.01$) and long term ($p < 0.001$) memory and in the location memory index ($p < 0.01$) was registered in studied rats compared to the controls. Also, the histological study demonstrated the presence of nuclear pyknosis, cell shrinkage and eosinophilic cytoplasm, in hippocampal and entorhinal cortex cells of intoxicated rats compared to the controls.

Conclusion: Aluminum toxicity remains harmful to the nervous system's neurocognitive performances and structures, even after the exposure is stopped.

57. Role of insulin-like growth factor 1 signaling in statin-induced myotoxicity

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Objective: To shed light on the molecular mechanisms of statin-induced myotoxicity.

Methods: Evaluation of the role of insulin-like growth factor (Igf-1) in simvastatin-induced myotoxicity on the cell viability, Mafbx and MuRF1 expression and protein activation in C2C12 myotubes.

Results: Statins are drugs used to lower the serum cholesterol level. They are generally well tolerated but their use is frequently associated with skeletal muscle myopathy. The molecular mechanisms driving statin myopathy are not established yet. Statins have been shown to negatively regulate the PI3K/Akt signaling cascade through a so far unknown mechanism.¹ Igf-1 is known to activate PI3K/Akt signaling. We found that simvastatin impairs Igf-1 signaling inducing protein degradation and blocking protein synthesis. Moreover, the addition of Igf-1 completely rescues C2C12 myotubes reversing the simvastatin-induced toxic effects. In addition, we investigated the role of the glycosylation of the Igf-1 receptor, Igf-1R, in the impairment of Igf-1 signaling during statin-induced myotoxicity. N-linked glycosylation is indeed crucial to form mature Igf-1R.² Statins could cause a lack of glycosylation by decreasing the amount of dolichol, an intermediate in the mevalonate pathway which is used as a membrane anchor for the formation of the oligosaccharides. From our data we assume that reduced synthesis of dolichol is not essential for myotubes survival. In fact, co-incubation of dolichol and simvastatin rescues myotubes only partially whilst preventing the upregulation of Mafbx expression to a limited extent. In contrast, Rap1 prenylation, which is impaired by statin treatment due to inhibition of the mevalonate pathway, is not restored by the addition of Igf-1.

Conclusion: Simvastatin impairs Igf-1 signaling and the addition of Igf-1 prevents simvastatin-induced cytotoxicity blocking the protein degradation and inducing protein synthesis. Impaired Igf-1 signaling associated with simvastatin is only partially explained by reduced glycosylation and Igf-1 does not act via Rap1.

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58. Gender and strain contributions to the variability of buprenorphine-related respiratory toxicity in mice

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Objective: While most deaths from asphyxia related to buprenorphine (BUP) overdose have been reported in males, higher plasma concentrations of BUP and its toxic metabolite norbuprenorphine (NBUP) have been observed in females. We previously demonstrated that P-glycoprotein (P-gp) modulation at the blood-brain barrier (BBB) contributes highly to BUP-related respiratory toxicity, by limiting NBUP entrance into the brain. In this work, we sought to investigate the role of P-gp-mediated transport at the BBB in gender and strain-related variability of BUP and NBUP-induced respiratory effects in mice.

Methods: Ventilation was studied using plethysmography, P-gp expression using western blot, and P-gp mediated transport at the BBB using *in situ* cerebral perfusion.

Results: In male Fvb and Swiss mice, BUP was responsible for ceiling respiratory effects. NBUP-related reduction in minute volume was dose-dependent but more marked in Fvb ($p < 0.01$ with 1 mg/kg NBUP and $p < 0.001$ with 3 and 9 mg/kg NBUP) than in Swiss mice ($p < 0.05$ with 9 mg/kg NBUP). Female Fvb mice were more susceptible than males to BUP with significantly increased inspiratory time ($p < 0.01$) and to NBUP with significantly increased expiratory time ($p < 0.05$). Following BUP administration, plasma BUP concentrations were significantly greater ($p < 0.01$) and plasma NBUP concentrations significantly lower ($p < 0.001$) in Fvb compared to Swiss mice. Plasma BUP concentrations were significantly greater ($p < 0.05$) and plasma NBUP concentrations significantly lower ($p < 0.01$) in male compared to female Fvb mice. In contrast, following NBUP administration, comparable plasma NBUP concentrations were observed in both genders and strains. No differences in P-gp expression or BUP and NBUP transport at the BBB were observed between male and female Fvb mice as well as between Swiss and Fvb mice.

Conclusion: Our results suggest that P-gp-mediated transport at the BBB does not play a key-role in gender and strain-related variability in BUP and N-BUP-induced respiratory toxicity in mice. Based on our findings, gender-related differences in metabolism of

BUP to NBUP and strain-related pharmacodynamic differences in respiratory vulnerability could be hypothesized.

59. Blindness following closantel poisoning: Report of three cases

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Objective: Closantel is a broad-spectrum antiparasitic agent used against several species and developmental stages of trematodes, nematodes and arthropods. The classical signs of closantel toxicity in animals include blindness, paresis and ultimately death.¹ In humans, except for eleven cases of women in Lithuania who temporarily lost their eyesight after using closantel (the drug was mistakenly given to treat endometritis)² no cases of blindness with closantel have been reported subsequently. We report three cases of accidental ingestion of this veterinary product leading to blindness with ophthalmic lesions.

Case series: A 3-year-old girl presented with sudden onset of blindness, 24 hours after accidental ingestion of an unknown amount of closantel. She had bilateral mydriasis with abolition of pupillary reflex. The fundal photograph showed severe papilloedema. The diagnosis of toxic optic neuropathy was established because of normal radiological investigations and biological exams. The Poison Control Centre of Morocco advised the administration of oral vitamins B1, B6 and B12, with a gradual improvement of blindness two months later. Two more patients aged 40 and 44 years presented with blindness one week after, accidental ingestion of closantel in the first case, and ingestion in order to treat intestinal parasitosis in the second case. The fundal photograph was normal. The visual field showed scotoma. Laboratory tests were normal. Another cause of blindness could not be eliminated in the absence of radiological investigations. The outcome of both patients was unknown since they were lost to follow-up.

Conclusion: This unusual toxic cause of optic neuropathy after ingestion of closantel must push the search for the mechanism of action of this poisoning in order to find an effective treatment. The goal should be to prevent such accidents, based on broad public education on the use of veterinary products.

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60. Amitraz acute toxic exposure: A retrospective case series

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Objective: To describe a retrospective case series of acute toxic exposures caused by amitraz followed-up by the Campinas Poison Control Center from 2006 to 2010.

Case series: Seventy-four cases were included, of which 54% were males. Age ranged from 1 to 76 years (median = 21 years; interquartile range (IQR) = 3 to 33 years). The main circumstances involved were non intentional (48%) and suicide attempts (46%); only one case was due to occupational exposure. Ingestion was the main route of exposure (93.2%), followed by cutaneous (5.4%). Regarding the total amount ingested (available information in 45 cases; product concentration not specified), the median was 20 mL (IQR = 10 to 40 mL). Most of the patients developed signs of neurological depression (39%), followed by miosis (15%), vomiting (10.8%), and restlessness (9.4%); bradycardia was reported in only 4 cases (5%). The median length of the hospital stay was 24 h (available information in 60 cases; IQR = 14 to 48 h). None of the patients developed sequelae.

Conclusion: Amitraz is a contact tick killer with a residual effect, chemically related to formamidines, commercially available in Brazil in 12.5%-20% emulsions diluted in xylene. It acts as a central (alpha-2) and a peripheral (alpha-1 and alpha-2) adrenergic receptor agonist, and can also inhibit monoamine oxidase (MAO) and prostaglandin E2 synthesis.¹ Toxic manifestations are associated principally with its alpha-2 agonist action, causing inhibition of cerebral sympathetic outflow, which may result in neurological and respiratory depression, bradycardia and hypotension, similar to that observed after acute toxic exposures caused by imidazoline derivatives (topical decongestants and clonidine). Xylene can also act synergistically, worsening the neurological and respiratory depression. Other clinical manifestations have been described, such as miosis/mydriasis, nystagmus, seizures, diarrhea, hyperglycemia, and hyper or hyponatremia. Similar features were observed in our case series. Considering the high frequency of use of amitraz in Brazil, a multicentre study should be carried out in the country.

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61. Dangers of 2,4-dinitrophenol as a weight loss agent: A case report

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Objectives: To highlight the resurgence of 2,4-dinitrophenol (DNP) as a weight loss agent and the mortality and morbidity associated with its use.

Case report: A 24 year old lady was admitted thrice in 12 months for DNP poisoning. She had bought DNP tablets over the Internet to aid with weight loss. She presented with breathlessness and diaphoresis and was tachypnoeic. Her blood gases showed metabolic and respiratory disturbances and she was admitted to the high dependency unit (HDU) on all 3 occasions. On her 2nd admission, she required continuous veno-venous hemofiltration and she had to be intubated in her last admission as her conscious level was decreasing. Soon after intubation, she suffered ventricular tachycardia and had generalized tonic-clonic seizures

before deteriorating into asystole collapse. She was given 14 mg of intravenous adrenaline but did not respond to resuscitation and died. Of note, the medical team who resuscitated her had difficulty ventilating her despite using a neuromuscular blockade agent.

Discussion: DNP induces a hyper-metabolic state (hyperthermia, tachycardia, tachypnoea and diaphoresis) by uncoupling oxidative phosphorylation.¹⁻³ It was popular as an anti-obesity drug but was subsequently banned due to its adverse effects (e.g. hepatic/renal failure, cataracts and death).⁴ Its illicit use as a weight loss agent has recently resurfaced as it is easily available over the Internet.^{2,4} Another point we would like to highlight is that early administration of dantrolene might be beneficial. DNP uncouples oxidative phosphorylation, leading to free intracellular calcium.¹ Dantrolene could have inhibited the calcium release from sarcoplasmic reticulum, thus reducing cytosolic concentration and helping prevent muscle rigidity and difficult ventilation as experienced by our patient.^{1,3,5}

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62. Ciprofloxacin-induced methaemoglobinaemia

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Objective: To report a case of acute methaemoglobinaemia in a patient treated with ciprofloxacin.

Case report: A 60 year old lady, with a history of hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease and penicillin allergy, presented to the emergency department with giddiness, breathlessness and chest pain. She was pale and cyanotic (oxygen saturation on room air was 91%). There were no identifiable causes for her symptoms except that she was started on ciprofloxacin by her family physician one day ago when she consulted him for possible inflammation around her perianal region. Arterial blood gas analysis showed no hypoxia and no retention of carbon dioxide. Her methaemoglobin level was 36.7%. She was not G6PD deficient. Intravenous methylene blue was initiated with improvement of her symptoms and reduction of her serum methaemoglobin level. She was discharged well with advice to avoid fluoroquinolones and had no recurrence of symptoms during her follow-up in the clinic. Ciprofloxacin is widely used as a broad-spectrum fluoroquinolone antibiotic. The widely-reported adverse outcomes associated with its use include tendinopathy/tendon rupture, QTc prolongation and central nervous system effects e.g. seizures.¹ There have been no published case reports of ciprofloxacin-induced methaemoglobinaemia though it has been listed as one of the possible adverse events in the post marketing surveillance reports.² In our patient, there were no identifiable causative factors beside the initiation

of ciprofloxacin. In view of the temporal sequence between commencement of ciprofloxacin and the manifestation of symptoms, it is likely that ciprofloxacin is the culprit in causing methaemoglobinaemia in our patient.

Conclusion: Ciprofloxacin (fluoroquinolones) can be associated with acute methaemoglobinaemia. Awareness of this information can help in prompt diagnosis and treatment (withdrawal of offending drug and initiation of methylene blue) which can potentially be life-saving.

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63. A case report of early levothyroxine toxicity in a young child

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Objective: This case report represents a sentinel case of early levothyroxine toxicity in a 23-month old girl and demonstrates a potential challenge to the theory that levothyroxine overdose causes symptoms days later.

Methods: We present a case in which toxicity was seen within 8 hours of ingestion, and included tachycardia, hypertension and hyperpyrexia. A 23 month old Caucasian female was brought to the emergency department by her mother after ingesting 1200-microgram of levothyroxine one hour prior to arrival. The patient had no significant past medical history, was not taking any medications and had no medication allergies. The mother indicated that the child was asymptomatic and at her baseline activity and mental status.

Results: Her initial vital signs were significant for a heart rate (HR) of 125, blood pressure (BP) of 106/54, respiratory rate (RR) of 22, and temperature of 36.8 C. The patient had an unremarkable exam. Five hours after the initial ingestion BP was 116/69, HR was 151, RR was 28, and temperature was 37 C; electrocardiogram (ECG) showed sinus tachycardia at 153 with normal intervals. Approximately 8 hours after ingestion she became febrile peaking at 39.5 C. Over the next two days, her heart rate and blood pressure fluctuated; peak HR was 180 s and peak systolic blood pressure was 128. Her mental status remained normal, and she did not require propranolol therapy. On day one of her hospital stay, her thyroid stimulating hormone (TSH) was 1.04 uIU/mL and free T4 was 5.17 ng/dL. On day two, she was found to have a TSH of 0.30 uIU/mL and free T4 of 4.56 ng/dL and total T4 of 17.02 micrograms/dL. The patient had no further progression of her thyrotoxicosis, and was discharged with close outpatient follow-up.

Conclusion: Levothyroxine is ubiquitous among the general population and has a relatively large therapeutic window.¹ Current theory suggests hyperthyroid symptoms do not develop until several days after overdose.^{2,3} Other studies have reported hyperthyroid symptoms within 12 to 48 hours after massive overdose.⁴

Our case is evidence that dose does not predict onset of symptoms. Further investigation is needed to determine a true timeline for levothyroxine-induced thyrotoxicosis in children.

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64. The role of a P-glycoprotein inhibitor in a fatal multidrug intoxication, simvastatin and colchicine

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Objective: To highlight the importance of P-glycoprotein inhibition by simvastatin in the context of a fatal intoxication with a moderate dose of colchicine and to create awareness of possible side effects or toxicity by other drugs such as antiarrhythmics and anticoagulants when combined with simvastatin.

Case report: A 49 year old woman with a history of hypercholesterolemia, fibromyalgia and a previous suicide attempt with benzodiazepines arrived at the emergency department (ED) with a chief complaint of diarrhea, 15 hours after ingesting 20 mg of colchicine and 120 mg of simvastatin. Clinical findings on examination were: systolic blood pressure of 70 mm Hg, heart rate of 80 b.p.m., Glasgow Coma Scale of 12, acrocyanosis, and oxygen saturation of 79% at room air. Laboratory investigations were: creatinine 5.04 mg/dL, creatine kinase 1448 IU/L, aspartate aminotransferase 1009 IU/L, prothrombin time 32 seconds, a pH below 6.8 and a pCO₂ of 27. The electrocardiogram was unremarkable. Despite intensive medical management, that included intravenous fluids, sodium bicarbonate and orotracheal intubation, the patient died after four hours in the ED due to an irreversible asystolic cardiac arrest.

Conclusion: P-glycoprotein is an efflux pump that plays an important role in the blood-organ barrier with the cytochrome p450 superfamily determining tissue availability of certain drugs.¹ While simvastatin has been proven to be a powerful P-glycoprotein inhibitor², there have been reports relating colchicine toxicity to other P-glycoprotein inhibiting drugs like cyclosporine³ but not with a fatal outcome that in our case is related to high doses of both drugs, which resulted in higher toxicity aided by efflux pump inhibition. Colchicine, like verapamil, diltiazem, digoxin, amiodarone and dabigatran are all substrates for P-glycoprotein, and its inhibition might lead to decreased metabolism and elimination by the liver and kidneys and toxicity.

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65. Hypoxic-ischemic encephalopathy from hydrogen sulfide poisoning treated with therapeutic hypothermia: A case report

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Introduction: Poisoning from hydrogen sulfide (H₂S) inhibits mitochondrial cytochrome c, thereby causing systemic toxicity that resembles hypoxia. This can result in hypoxic-ischemic encephalopathy (HIE). Therapeutic hypothermia seems capable of reducing the severity of HIE in cardiac arrest patients. Here we report a case who suffered from HIE consequent to H₂S poisoning and achieved nearly full neurologic recovery after receiving therapeutic hypothermia.

Case report: Two men working in a frozen food company collapsed in a two-meter-high tank for the steaming of dead pig bodies. The 34-year-old patient who collapsed first lay supinely. Coming to his rescue, the 28-year-old patient entered the tank but immediately fainted and fell to the floor, face down. Half an hour later they were both rescued, but the younger patient was found pulseless, and eventually succumbed despite resuscitation in our emergency department. The first patient still had slow and shallow breathing. Glasgow Coma Scale (GCS) was E₁M₃V₁. His carboxy-hemoglobin level was 0.9%, and the methemoglobin level was 7.2%. Brain computed tomography (CT) revealed indistinct gray-white matter junction suggestive of HIE. For suspected hydrogen sulfide poisoning, he was given amyl nitrite inhalation and sodium nitrite intravenous infusion. Therapeutic hypothermia to maintain his core temperature around 33°C for 24 hours was instituted at the 19th hour after the index event. During the course, the patient developed junctional rhythm and minor stress ulcer bleeding but was otherwise stable. After rewarming his consciousness progressively improved, and one month later he achieved nearly full neurologic recovery (Cerebral Performance Category 1).

Discussion: Carbon monoxide, cyanide and H₂S poisoning can all cause HIE through essentially the same mechanism. The standard treatment for carbon monoxide poisoning is hyperbaric oxygen, and for cyanide and H₂S poisoning, sodium nitrite. Therapeutic hypothermia may mitigate hypoxic injury to brain tissue, and in cardiac arrest patients it improves neurologic outcome. Whether therapeutic hypothermia can pose the same effect on patients with these kinds of poisoning remains to be confirmed. Nonetheless, our case has provided an experience that is encouraging.

66. “Waterproofing syndrome” after spreading a stain repellent with a trigger spray on dry-stone

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Objective: The fluoropolymer-induced pulmonary toxicity of waterproofing aerosols for clothing (propellant, organic solvents and fluoropolymer) is well known. Only three cases of acute pulmonary toxicity have been reported following occupational exposure to a floor stain protector spread with a trigger spray, which contained a low concentration of acrylate fluoropolymer (<1%) in alkane solvents and methoxy-2-propanol.¹ Our objective is to describe four recent cases of “waterproofing syndrome” after household exposure to stain repellents applied with a trigger spray on dry-stone floors or walls. These products contained only 2–3% of active compounds (acrylate fluoropolymer associated with tripropylene glycol or tert-butyl alcohol) in aqueous solution.

Case series: Four healthy men (3 active smokers), aged between 35 and 44 years, sprayed stone waterproofing products in small, poorly ventilated areas without any individual protection equipment. The product was spread with a trigger spray during 40 min to 2 h. Only one admitted going outside twice to smoke. One hour after stopping their activity, all 4 patients developed dry cough and dyspnoea. Two experienced flu-like symptoms without fever, one complained of chest pain and another one of throat burning. All patients required hospitalization. Hypoxemia and tachypnoea were evidenced in three. Chest radiography and thoracic computed tomography (CT) scan remained normal in one who developed severe restrictive ventilatory defect and decreased carbon monoxide diffusing capacity. In two others, X-ray showed bilateral pulmonary infiltrates. All patients recovered within 1 to 5 days with oxygen and corticosteroids.

Conclusion: Acrylate fluoropolymer, even at very low concentration (1.6%) in aqueous solution, induces pulmonary toxicity when inhaled in large amounts. The size of the aerosol particles is seemingly not a predominant factor since very little organic solvent is present and a trigger spray was used without any propellant. Inhalation of pyrolysis by-products of the fluoropolymer in contact with burning cigarettes is not a relevant hypothesis since three of these four patients denied any tobacco use during, or just after coating.

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67. Subcutaneous self-injection of tetrodotoxin and ouabain

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Background: Tetrodotoxin (TTX) is a significant non-protein quinazoline toxin.¹ A dose of 10 micrograms/kg may be fatal in humans.² We present a case report of subcutaneous self-injection of tetrodotoxin (TTX), ouabain and ryanodine treated by excision of the injection site.

Case report: A 20 year-old female with a history of depression presented to the emergency department with vomiting, paraesthesia of the mouth and tongue and occasional breathlessness after subcutaneous injection of a mixture that reportedly contained an unknown

concentration of TTX, 15 micrograms of ouabain and a small, but unknown amount of ryanodine, all obtained from a physiology laboratory. The patient had drawn these into a 10 mL syringe with distilled water and then injected approximately 0.1–0.2 mL of the solution into the anterior abdominal wall. She requested an ambulance soon after exposure. On arrival in hospital, clinical features included bradycardia (fluctuating 29–48 bpm), hypotension (blood pressure 108/48 mmHg), a normal conscious level (Glasgow Coma Scale 15), normal pupils and bilateral nystagmus. Laboratory evaluation showed hyperkalaemia (6.68 mmol/L), elevated lactate (4.0 mmol/L) and digoxin concentration <0.2 micrograms/L. The electrocardiogram (ECG) showed prolonged PR interval (280 ms) and widespread ST depression. On the day of presentation she underwent surgical excision of the injection site and was treated with intravenous (IV) fluids, 0.5 mg atropine IV and 10 mL of 10% calcium chloride IV. She was monitored in an intensive care unit for 48 hours post-operatively and discharged with no sequelae on the 3rd day of presentation.

Conclusion: This is the first report in the literature of use of surgical excision to treat tetrodotoxin poisoning. In this case, clinical features were consistent with TTX toxicity. Co-administration of ouabain may have contributed to the severe bradycardia, although the dose involved appears very low.

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68. Barium chloride poisoning: A case report with gastric, blood, serum and urine barium concentrations

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Objective: This is a report of a rare case of suicidal, oral barium chloride poisoning, confirmed by the determination of barium concentrations in gastric contents, blood, serum and urine using the ICP-MS (Inductively Coupled Plasma Mass Spectrometry) method. The concentrations were compared with the results obtained from a non-intoxicated person.

Case report: A 39-year-old female (64 kg) chemist was admitted to the Toxicology Department 3 hours after ingestion of 20 g of barium chloride (312.5 mg/kg body weight). At home she had vomited profusely and collapsed. On arrival, the patient was conscious but confused. She experienced general muscle weakness, resulting in respiratory failure which called for mechanical ventilation. Her blood pressure was 90/50 mmHg, heart rate - 150/min.

Gastric lavage was performed. Potassium infusions and a 6-hours hemodialysis were started immediately. During the dialysis procedure, a rapid improvement of the clinical condition was observed. After 25 hours of treatment, the patient was discharged from the hospital at her own request, without any complications. The blood tests performed on admission revealed profound hypokalemia (1.3 mmol/L), slightly elevated creatinine levels (1.24 mg/dL), metabolic acidosis (pH 7.19) with high lactate levels (7.5 mmol/L) and leucocytosis (29.3 G/L). An electrocardiogram (ECG) test revealed ventricular tachycardia 150/min. Three hours post ingestion, barium concentrations determined using the ICP-MS method were: 20.45 µg/mL in serum and 150 µg/mL in blood (compared to 12.07 µg/mL in serum and 7.15 µg/mL in blood in a non-intoxicated person). Elevated barium concentrations were detected - 10,500 µg/mL and 63,500 µg/mL in urine and gastric contents respectively (compared to 1.21 µg/mL in urine and 0.5 µg/mL in gastric contents in a non-intoxicated person). The accuracy of the analytical results was assessed with the use of Certified Reference Material (CRMs).

Conclusion: Barium chloride poisonings are very rare and little is known about their pathophysiology and treatment. In the case under consideration, acute poisoning was confirmed by the presence of elevated barium levels in the analyzed samples, compared with the results obtained from a non-intoxicated person. Despite the profuse vomiting at the initial stage of intoxication, 3 hours post ingestion, the barium level in gastric contents was still high, requiring aggressive decontamination and magnesium sulfate administration.

69. Berries that weren't that sweet after all... – A case of raspberry ketone intoxication

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Objective: Raspberry ketone (4-(4-hydroxyphenyl) butan-2-one; RK), one of the major aromatic compounds of red raspberry (*Rubus idaeus*), has gained popularity as a dietary supplement following its promotion by an American celebrity physician as a lipolytic. RK is purported to prevent obesity based on a small number of *in vitro* and animal studies.¹ To date, no human studies have been published to support its claims. Since RK is structurally similar to amphetamine, it carries many of the theoretical risks of this drug class.

Case report: A 43-year-old man with no significant past medical history presented to the emergency department with a three week history of insomnia, palpitations, and jitteriness. He was taking no licensed pharmaceuticals or drugs of abuse but was consuming RK tablets for weight loss for a month as a dietary supplement. He denied any recent changes in his life or psychosocial stressors. His vital signs were normal except for a heart rate of 125 beats/min. His electrocardiogram demonstrated sinus tachycardia with normal QRS and QT intervals. His tachycardia was unchanged following intravenous administration of two liters of normal saline. Laboratory analyses including a basic metabolic panel, complete blood cell count, D-dimer, thyroid stimulating hormone, and

cardiac enzymes were normal. He was observed in the hospital on a cardiac monitor with no events and gradual resolution of tachycardia over 24 hours.

Conclusion: RK prevents weight gain in mice by enhancing norepinephrine-induced lipolysis. RK also suppresses fat absorption by inhibiting triacylglycerol hydrolysis.¹ Currently the demand for RK supplements is high and manufacturers cannot maintain sufficient production. This case demonstrates the potential amphetamine-like adverse effects of RK in humans. It further illustrates the danger of promoting natural substances for medicinal use without adequate safety data.

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70. Acute levothyroxine overdose – unpredictable clinical outcome and late onset symptoms: A case series

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Objective: Levothyroxine (LT) overdose is often considered a benign disease. A severe outcome is most frequently reported in adults¹ or in children ingesting a large dose². In the present study we investigated the relation between ingested LT dose, symptoms and age. Also late onset symptoms and influence of multiple drug ingestion on clinical outcome were explored.

Methods: Between March 2007 and September 2012 all LT ingestions registered at the Danish Poison Information Centre (DPIC) were evaluated and the following parameters were recorded: age (children ≤ 15 years), dose, time from ingestion, multiple drug intake and symptoms. Follow up: Patient records from non-symptomatic subjects were subsequently reviewed and the patients were later contacted by telephone.

Results: 182 subjects were registered, 112 (62%) were children. Total LT dose ingested: 861 ± 1767 micrograms (mean ± SD). The time from ingestion to calling DPIC was 7.59 ± 52.6 hours (mean ± SD). Twenty-nine (16%) subjects were symptomatic at the time of registration. The two most common causes of intake were play (54%) and suicide attempt (25%). We did not find any difference in ingested LT dose between children and adults; neither in asymptomatic nor in symptomatic subjects ($P < 0.67$ and $P < 0.61$, respectively). Fifty-five subjects (30%) had ingested multiple drugs and they had more symptoms than subjects who had ingested only LT ($P < 0.0001$). Follow up: Of 21 evaluated subjects (≤ 15 years), 9 (43%) described tremor, diaphoresis, severe and mild hyperactivity, insomnia, restlessness, tachycardia, fever and headache. They had ingested LT (as a single drug) in the dose range 300–15,000 µg and their symptoms started within 24 hours. None of the cases resulted in readmissions.

Conclusion: The clinical outcome of LT overdose is often unpredictable. We were not able to demonstrate any correlation between ingested LT dose and risk of developing symptoms in either children or adults registered at the DPIC. However, during follow-up

we found a large number of patients describing late onset LT related symptoms, some of them potentially severe.

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71. Prolonged QTc and ventricular tachycardia after ibogaine ingestion

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Objective: We present a case of ventricular tachycardia (VT) and hallucinations associated with ibogaine ingestion.

Case report: Ibogaine is an alkaloid isolated from *Tabernanthe iboga*, a plant indigenous to West Africa. Ibogaine has hallucinogenic and oneirogenic effects; it is also used in the treatment of substance addiction¹. Despite its reported efficacy, safety concerns have led to its prohibition in many countries, including the United States. A 21-year old male with Marfan's Syndrome presented to the emergency department (ED) after ingesting 1.5 grams of ibogaine approximately one hour prior to presentation and a second 1.5 gram dose while in the ED waiting room. The patient took the substance to prevent the development of mental illness, though he denied any psychiatric symptoms. In the ED, the patient was initially asymptomatic, but subsequently developed visual hallucinations. An initial electrocardiogram (ECG), obtained approximately one hour after the reported ingestion, revealed a QTc interval of 459 milliseconds (ms) and QRS interval of 94 ms. Cardiac monitoring revealed intermittent runs of ventricular tachycardia (VT). A second ECG obtained one hour after the initial revealed a prolonged QTc of 621 ms. Two grams of intravenous magnesium sulfate were administered, followed by an intravenous bolus and infusion of lidocaine. No further VT was noted, though occasional premature ventricular contractions were present. The patient was admitted to the medical intensive care unit for further monitoring and continuous lidocaine infusion. The following morning, the patient's QTc interval had returned to baseline and the patient reported decreased visual hallucinations. He was discharged after psychiatric consultation with a normal ECG.

Conclusion: Ventricular tachyarrhythmias are a rarely reported complication of ibogaine ingestion, but a suggested mechanism for ibogaine-related sudden death². Our patient initially had a normal ECG but developed VT after ingesting ibogaine and was successfully managed with intravenous magnesium and lidocaine.

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72. Acute clenbuterol poisoning

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Objective: We report a case of a healthy 29 year old male who ingested forty tablets of clenbuterol 40 micrograms, easily bought on the Internet.

Case report: A 29 year old male presented to the emergency department shortly after ingesting 1.6 mg of clenbuterol in order to lose weight. He was anxious, sweaty, complaining of palpitations, chest pain and oppressive dyspnea. He had prolonged sinus tachycardia (150 bpm) with 2 mm ST segment depression in leads V4–6, with normal troponin levels. He presented biological abnormalities: hypokalemia (2.5 mEq/L), hyperglycemia (serum glucose: 260 mg/dL) and slight elevation of creatinine (1.21 mg/dL). All symptoms and biological abnormalities resolved within 24 hours after symptomatic treatment with intravenous metoprolol and potassium supplementation. Clenbuterol is an orally administered long-acting beta-2 adrenergic agonist used in veterinary medicine as a bronchodilator and tocolytic agent.¹ In some European countries, clenbuterol is registered as an anti-asthmatic agent for human use. The anabolic and lipolytic properties which provoke increase of lean muscle mass and decrease of fat mass lead to abuse of clenbuterol as a doping agent. More recently, its use for weight loss purposes has tended to increase.² Although the use of clenbuterol is prohibited in the United States and in some European countries, illicit networks are emerging, especially on the Internet, where this molecule can be easily ordered.³

Conclusion: Anabolic and lipolytic effects make clenbuterol very attractive and it is quite easy to obtain. Consumption should be suspected for all beta-adrenergic symptoms occurring in a young healthy person.

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73. Blindness caused by self-treatment with the veterinary drug closantel

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Objective: Fluciver Combi® (closantel 50 mg/mL and mebendazole 75 mg/mL) is a veterinary drug used as an oral or parenteral antihelminthic for cattle, sheep and goats. The recommended treatment is a single dose of 1 mL per 5 kg body weight (closantel 10 mg/kg and mebendazole 15 mg/kg). Mebendazole is used in human medicine too, but the salicylanilide-derived component closantel is only used in veterinary medicine. Overdoses of closantel

cause toxic effects in farm animals. The drug highly binds to albumin (99%), and is eliminated unmetabolized in faeces with a half-life of 2 to 3 weeks. The mechanism of mammalian toxic effects is unknown in detail. An antidote is not available at present.¹

Case report: A 59-year-old man ingested 36 mL Fluciver Combi® (closantel 30 mg/kg and mebendazole 45 mg/kg) over 3 days on purpose to treat himself. Within the next few days, scotomata developed in both fields of vision, the sight decreased below 40% on day 5 to complete loss at about day 10, accompanied by extinction of visually evoked potentials (VEP). The treatment was symptomatic. Additionally, plasmapheresis was performed more than one week after ingestion. To date (6 weeks after ingestion), 60% of vision has reappeared.

Conclusion: t Hoen E et al.² reported on the reversible blindness of 11 women that were treated accidentally with Fluciver® (closantel without mebendazole), but the authors did not communicate details. This is the first well-documented human poisoning caused by closantel. It indicates the remarkable risk in self-treatment with drugs not approved for human use.

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74. “Benzofury” poisoning that mimics meningoenphalitis/septicemia

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Objective: Benzofury is a new-recreational drug of abuse (NRDA) that may contain benzofurans, pipradrol derivatives (or its precursor) and caffeine. At present toxicological information is scarce; the main mechanism is considered similar to MDMA/MDA. We describe a case whose initial clinical presentation mimicked an infectious disease.

Case report: A 40 year-old man, with history of hypothyroidism and HIV infection was brought to the emergency department (ED) for severe psychomotor agitation, confusion and disorientation. At physical examination mydriasis, profuse sweating, tachycardia (167 beats/minutes), hyperthermia (39.2°C), diffuse clonus and severe agitation were observed. Laboratory analysis revealed leukocytosis (11.81 10³/μL), creatinine 1.61 mg/dL, total-bilirubin 4.82 mg/dL, α-amylases 318 U/L, lactate dehydrogenase (LDH) 505 U/L, creatine kinase (CK) 493 U/L, myoglobin 388 ng/mL. Electrocardiogram (EKG) revealed a supraventricular tachycardia; chest radiograph, contrastographic cranial-MRI as well as

cerebrospinal analysis were normal; cranial CT-scan showed aspecific and irregular widespread areas of hypodensity in cortical-subcortical left parieto-occipital, in right parietal and in the parasagittal vertex region. Meningoencephalitis/septicemia was initially suspected and the patient was treated with fluids, midazolam, propofol, ceftriaxone and acyclovir. The peak of LDH 532 U/L, CK 3961 U/L and myoglobin 2029 ng/mL were registered 12 hours after ED admission when the patient was awake, afebrile and mentioned the consumption (every weekend for 18 months) of a legal product named “benzofury” bought on the web. The patient needed 3 days treatment with benzodiazepines. Standard urine test was positive for MDMA and amphetamine. The analysis of the product used revealed the presence of (2-aminopropyl) benzofuran (APB)-isomers and 4-methylethcathinone (4-MEC). Only APB-isomers was detected in blood (302 ng/mL) and urine (14600 ng/mL) samples. At chromatographic confirmation amphetamine and MDMA were negative.

Conclusion: The NRDA represents a challenge for emergency physicians. The clinical picture of this case mimicked other diseases and only the false positivity for MDMA/amphetamines in urine allowed the suspicion of an intoxication by NRDA. The network between Pavia-PCC, toxicological laboratories and EDs inside the National Early Warning System plays a key role in the early identification, correct diagnosis and specific clinical management of severe cases of poisoning by NRDA.

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75. Gastric perforation after liquid nitrogen ingestion

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Objective: To raise awareness amongst European poisons agencies of the potential for this type of injury following liquid nitrogen ingestion. To alert public health bodies to the danger of liquid nitrogen when used inappropriately by the hospitality industry.

Case report: An 18 year old female drank an alcoholic drink containing liquid nitrogen. The extent of the resulting injury necessitated total gastrectomy. She complained of severe abdominal pain immediately after swallowing the drink and presented to the emergency department where she was noted to be peritonitic with abdominal distension. She had no comorbidities. Computerised tomography of the abdomen showed the free intra-abdominal fluid and a large quantity of gas consistent with visceral perforation. At laparotomy there was a perforation on the lesser curve of the stomach. Surrounding this was a large area of necrosis and haemorrhage. Oesophagogastroduodenoscopy did not show any thermal injury to the oesophagus. This injury could not be closed primarily and a total gastrectomy with Roux-en Y reconstruction was undertaken. She was discharged 15 days post operatively. She will need lifelong nutritional support.

Conclusion: Cases of ingestion resulting in gastric perforation are reported in the literature.^{1–4} The absence of injury to the oesophagus does not seem to support thermal injury as the cause of visceral perforation. Barotrauma to the stomach, resulting from the rapid

increase in volume on vaporisation of the liquid, appears to be the primary cause. We propose the need to consider regulatory action to restrict the use of liquid nitrogen this way to prevent any further morbidity or even mortality.

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76. Nefopam poisoning: A case report with analytical confirmation

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Background: Nefopam is a centrally-acting non-opioid analgesic drug that was developed in the 1960s. Its mechanisms of action are poorly understood but involve the inhibition of serotonin, dopamine and noradrenaline reuptake along with actions on histamine H3 receptors, glutamate receptors and the voltage-gated sodium channel. There are only nine non-fatal cases related to nefopam overdose in the published literature, of which only one was analytically confirmed and included nefopam concentrations.

Case report: A 21 year old male with previous self-harm was brought to the emergency department (ED) approximately one hour after ingestion of an unknown combination of tablets (thought to include nefopam, aspirin, zopiclone, dihydrocodeine and paracetamol). Prior to admission, he had a single self-terminating convulsion. On arrival in the ED he was alert but appeared pale and clammy, had a heart rate of 116 bpm, systolic blood pressure of 162 mmHg, temperature of 35.2; there were no signs suggestive of serotonin toxicity. His electrocardiography ECG showed a sinus tachycardia with QRS duration of 95 msec and QTc of 406 msec. In the four hours after presentation, he had four further self-terminating convulsions, following which he was intubated and ventilated due to a persisting ongoing decrease in level of consciousness. His salicylate concentration was negative on two occasions. Following intubation there were no further convulsions and he was managed supportively. He was difficult to wean from the ventilator due to agitation, which required treatment with clonidine, risperidone and haloperidol. He was discharged from hospital two weeks after admission with no ongoing sequelae. Toxicological screening: Urine and serum samples were obtained approximately 5–6 hours after ingestion and subsequently analysed by gas-chromatography mass-spectrometry. The urine sample was positive for nefopam, dihydrocodeine and lidocaine. Quantification of the serum sample demonstrated nefopam at a concentration of 0.59 mg/L.

Discussion: We describe here a non-fatal case of nefopam toxicity, analytical confirmation of nefopam use and a serum nefopam concentration of 0.59 mg/L. In the previous non-fatal overdose the serum concentration was 3.8 mg/L at 1 hour post-ingestion and 0.9 mg/L at 19 hours. Our reported case here adds to the literature on the acute toxicity related to the ingestion of nefopam.

77. Severe encephalopathy after poisoning with a degreasing mixture

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Objective: Degreasing solvent mixtures of white spirits and halogenated hydrocarbons are widely used. We present a case of poisoning with such a mixture with unusual sequelae such as cerebral lesions.

Case report: A 20 year old male was admitted 24 hours after drinking a beverage subsequently identified as a wagon degreasing liquid (containing n-hexane, benzene, trichloroethylene, methyl n-butyl ketone, diethyl ether). He had nausea, emesis and ocular troubles. The first acid-base analysis showed mild metabolic acidosis which resolved after initial therapy. After 48 hours, the neurologic status altered, and he became comatose needing ventilatory support. He was transferred 72 hours after ingestion to ICU II Toxicology. On admission: severe clinical condition, profound coma, miosis, ventilatory support, TA = 114/71 mmHg, AV = 90/min, normal diuresis. Laboratory values and blood gases were within normal limits. Toxicological testing for methanol was negative. Cerebral computed tomography: symmetric wide hypodense areas in basal nuclei bilaterally; cerebral edema. Ophthalmology consult: discolored papillae with blurred contour (papillary edema). Therapy was symptomatic and the patient was weaned from ventilator support in 48 hours. The magnetic resonance imaging (MRI) performed 7 days after poisoning showed subacute ischemic and haemorrhagic lesions on the level of lentiform nuclei. The patient remained conscious with periods of agitation, without motor sequelae, and with normal respiratory and hemodynamic functions; visual acuity could not be performed. He was referred to a neurologic recovery center.

Conclusion: We must be aware of cerebral lesions produced by ingestion of solvent mixtures, perhaps through a diffuse hypoxic-ischemic acute mechanism.

78. Poisonings due to transfer from digitoxin to digoxin in Norway

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Objective: To report poisonings during transfer from digitoxin to digoxin in a large patient population. Digitoxin has been the preferred digitalisglucoside in Norway. Due to shortage of raw material, digitoxin production was permanently stopped in mid 2011. This caused a shift from digitoxin treatment to digoxin treatment

in 23,000 patients. The first patients were initiated on digoxin at the end of 2011, and the shift to digoxin will be completed by the end of 2013.

Methods: Data were collected retrospectively. Data regarding inquiries to the Norwegian Poison Center (NPIC) were collected. Number of deaths was obtained from the adverse event registry at the Norwegian Medicines Agency.

Results: NPIC received twice as many calls regarding digitoxin/digoxin intoxication in 2012 compared to 2011. Two deaths were registered from simultaneous use of digitoxin and digoxin alone. Based on the inquiries to the NPIC there have been additional deaths caused by digitalis intoxication during the transition to digoxin, but the number has been hard to quantify. In the second and third quarter of 2012 there has been a shortage of digitalis antidote caused by the increased number of patients needing antidote treatment.

Conclusion: The number of digitalis intoxications has increased during the transition from digitoxin to digoxin. Retrospectively, several precautions should have been taken before switching to digoxin. Digitoxin concentration should have been monitored down before initiating digoxin therapy. Availability of digitalis antidote should have been ensured beforehand. Physicians should have been better informed about symptoms of digitalis intoxication, potential drug interactions and pharmacokinetics of digoxin. Better patient information regarding interactions, kidney function and signs of toxicity would probably have reduced the number and severity of digoxin intoxications.

79. Prophylactic management of QTc-prolongation in drug-poisoning: New guidelines from the Swedish Poison Centre

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Objective: Torsade de pointes (TdP) is a rare complication of drug-poisoning, while QTc-prolongation in this setting is a common finding. A recent case of poisoning complicated by sotalol-induced TdP is reported and suggestions for prophylactic management are presented.

Case report: A 40-year-old man ingested 100 sotalol tablets of 80 mg each. At presentation one hour later he was fully awake and displayed a normal electrocardiogram (ECG). Our poison centre was consulted and advised monitoring and treatment presented below (conclusion). After gastric lavage and administration of charcoal, the patient was referred to ICU for continuous cardiac monitoring. During the following ten hours his blood pressure slowly decreased and the ECG monitoring displayed sinus rhythm of 50–60 bpm with an increasing QTc-prolongation. For unclear reasons, the given advice was not followed. The patient was treated with intravenous fluids and noradrenaline only. Suddenly, he developed ventricular fibrillation and became unconscious. The patient was defibrillated twice after which sinus bradycardia was restored and he woke up. An amiodarone infusion was started and our centre was contacted again. We recommended the clinician to stop amiodarone immediately and instead administer isoproterenol and magnesium. The patient then had an uneventful hospital course. When checking the recorded ECG-tapes, it was evident that the QTc-time was over 700 ms during the hour before the cardiac arrest and that a long and typical TdP preceded the ventricular fibrillation.

Method: Our management suggestions, briefly summarized below, are based on a systematic literature review and consist of an assessment of risk factors such as type of ingested drug, extent of QTc-prolongation, heart rate and co-existing electrolyte disturbances.

Conclusion: If a patient has overdosed a pharmaceutical known to carry a risk of inducing TdP (www.qtdrugs.org) and the QTc-time is 450–500 ms, continuous ECG monitoring is imperative. S-potassium and s-calcium should be checked and corrected if low, S-potassium to 4.5–5.0 mmol/L. Further, the administration of magnesium, 10 mmol intravenously over 5 minutes, is recommended. If the QTc-time exceeds 500 ms, an infusion of magnesium, 4 mmol/h during six hours, should be added and treatment with isoproterenol be considered if the heart rate is below 60 bpm.

80. Lipid emulsion in treatment of cardiovascular collapse in acute poisoning

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Objective: To assess the efficacy and complications of intravenous lipid emulsion (ILE) antidotal use in acute human poisoning.

Methods: Prospective clinical study on ILE (Intralipid 20%) effects given as fast intravenous infusion in total dose of 500–1000 mL. The main criteria for administration were cardiocirculatory failure caused by liposoluble agents and poor response to vasopressors. Effects on blood pressure (BP), electrocardiogram (ECG), and central nervous system (CNS) depression were assessed. Pre- and post-lipid administration concentrations of drugs were obtained.

Results: A total of nine patients were treated with ILE. Poisonings were caused by glyphosate/polyethyloxyated tallowamine (POEA) herbicide (1 patient), verapamil and benzodiazepines (3 patients), propranolol combined with alcohol or psychoactive drugs (2 patients) and mixed ingestion of various drugs including carbamazepine, lamotrigine, sertraline, risperidone, amitriptyline, clozapine, haloperidol, valproic acid/valproate and chlorpromazine (3 patients). Significant increase of BP leading to vasopressor therapy reduction was noted in all patients after the initial dose of 500 mL, but in some cases this effect was transient and an additional dose of Intralipid was necessary. The most prominent effect was on wide complex tachycardia which developed in two patients (ingested glyphosate/POEA or propranolol/alcohol) as sinus rhythm was regained before the end of Intralipid infusion. ECG changes in others included slight widening of QRS or QT prolongation. There was no rapid normalisation that could be attributed to ILE. All patients were comatose (Glasgow Coma Scale (GCS) 3–5). Improvement in GCS was noted in all except the cases with predominant carbamazepine and valproate. There were no significant changes in drug concentrations in blood after lipid administration. In cases of verapamil toxicity, analysis after lipid removal by ultracentrifugation revealed a decrease in concentration. The only complication which may be connected with ILE treatment was acute respiratory distress syndrome (ARDS) in a case of severe verapamil intoxication.

Conclusion: Our results, though limited by the small number of patients, revealed that the most invariable effect of ILE was the increase of BP, and the most impressive was the fast reversal of wide complex tachycardia. Efficacy of ILE in case of poor response to other therapies indicated that the fear of adverse interactions with other conventional drugs for the treatment of cardiotoxicity may not be rational.

81. Increased in-hospital mortality in acutely poisoned patients with hypotension at triage

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Objective: The use of hypotension measured at triage in assessing the severity of poisoned patients lacks evidence. Some established models of scoring systems such as the APACHE scores have been used to predict in-hospital mortality but it is not performed easily in the emergency department.

Methods: From January 2005 to December 2008, 997 patients admitted to the emergency department with acute poisoning were retrospectively enrolled. Triage vital signs and clinical information were recorded. Primary outcome was in-hospital mortality. Statistical analysis was using Chi-square analysis or T test for univariate analysis, Kaplan-Meier curves for survival estimates, and receiver operating characteristics (ROC) curves for cut-off values analysis.

Results: Overall in-hospital mortality was 7% (70/997). Hypotension at the triage area has a relatively high positive likelihood ratio for in-hospital mortality. By ROC curve, the optimum cut-off value using systolic blood pressure (SBP) to predict in-hospital mortality was 100 mmHg. The Kaplan-Meier survival curves illustrate a trend toward increased mortality in patients exposure to triage hypotension (systolic blood pressure, SBP \leq 100 mmHg) compared with non-exposure groups (SBP > 100).

Conclusion: This study concluded that acute poisoning patients with measured SBP less than 100 mmHg at triage area are more likely to die during hospital admission. We believe that the report makes clinical decision judgements easier and simpler.

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82. Respiratory arrest, seizures and broad complex tachycardia due to propranolol overdose

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Objective: We report a case of severe propranolol overdose, a beta-receptor antagonist, presenting unusually with respiratory arrest, seizures and broad complex tachycardia.

Case report: A 21 year old man presented 40 minutes post ingestion of 1.7 g of propranolol. Toxic doses cause profound inotropic, moderate chronotropic cardiotoxicity, atrio-ventricular conduction disorders and dysrhythmias and less commonly neurological toxicity. Rarely does this lipophilic, sodium channel blocking beta-blocker act centrally to cause respiratory arrest.¹⁻³ On arrival, our patient had no respiratory effort, systolic blood pressure (BP) was 79, Glasgow Coma Scale was 3 and tonic clonic seizure activity was present. Electrocardiograph showed QTc (QT interval corrected for heart rate) of 620 ms and QRS of 191 ms. pH on the arterial blood gas was less than 6.80. Immediate respiratory support was given with rapid progression to intubation and mechanical ventilation. Standard resuscitation included fluids, diazepam, glucagon and sodium bicarbonate. He was admitted to the intensive care unit and was extubated 24 hours later with full neurological recovery.

Conclusion: Centrally induced respiratory arrest is rare in propranolol overdose but can happen rapidly and prompt recognition and management is critical in order to ensure a positive outcome.

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83. Initial emergency department cardiac troponin is highly predictive of mortality from drug overdose

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Background: Drug overdose is the leading cause of injury related mortality in the USA, but the prognostic utility of cardiac biomarkers is unknown. We hypothesized that serum cardiac troponin I (cTnI) would independently predict overdose mortality.

Methods: Prospective observational cohort at 2 university hospitals enrolled all adults with suspected acute drug overdoses in the emergency department (ED) over 3 years. Data included demographics, vital signs, prior coronary artery disease (CAD), urine cocaine metabolite, and results of cardiac biomarkers (CK, CKMB%, cTnI) drawn at the bedside as standard clinical care. The endpoint was in-hospital mortality, which was used to determine test characteristics of initial/peak cTnI using area under the curve (AUC) of receiver operating characteristics (ROC), odds ratios (OR), and 95% confidence intervals (CI). Assuming 5%

prevalence of elevated cTnI overall, we calculated the number needed to analyze as 435 subjects to show a 5% proportional difference between fatal and non-fatal overdoses with 80% power and 5% alpha.

Results: Out of 845 overdoses (mean age 38, 48% female), 438 (52%) had cTnI results available, with 20 (2.4%) deaths. Clinicians were more likely to order cTnI in patients with known prior CAD, however there were no other substantial differences in other clinical variables between groups. Abnormal vital signs (i.e. tachycardia, bradycardia, hypotension) were not substantially different in the groups with elevated cTnI or mortality. Mean initial cTnI was significantly higher in the mortality group (1.2 vs. 0.06 ng/mL, $p < 0.001$). The ROC curve revealed excellent cTnI prediction of mortality (AUC 0.87, CI 0.76–0.98). Elevated initial cTnI (> 0.09 ng/mL) significantly predicted mortality (OR 21.1, CI 6.2–71.4) as did peak cTnI (OR 25, CI 6.7–93.9). Test characteristics for initial cTnI (90% specificity, 99% negative predictive value) were better than peak cTnI (88.2% specificity, 99.2% negative predictive value), and initial cTnI was normal in only one death out of the entire cohort (1/438 or 0.2%).

Conclusion: Initial cTnI is an important and independent predictor of in-hospital mortality from acute drug overdose. Future research should focus on high-risk overdose features to optimize strategies for utilization of cTnI as part of the workup for acute drug overdose.

84. The increasing prevalence in New Zealand of exposures of children to nicotine replacement therapies

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Objective: A review of calls to the New Zealand National Poisons Centre to determine if there is an increased incidence of children ingesting oral nicotine replacement therapies (NRTs).

Methods: Call data was extracted from the National Poisons Centre calls database (NPCPhone) using the following parameters: Age = 0–16 years, date range = 1 January 2003 to 31 December 2011, substance name = nicotine, route of exposure = ingestion. To capture exposures by buccal absorption, calls where the product was chewed then discarded were also included. The data were then filtered to only include nicotine gum, lozenges and dissolvable microtabs. A total of 142 records were retrieved.

Results: Calls relating to children ingesting oral NRTs from 2003–2008 were low with an average of 6.6 calls per year. In 2009, there was a 122% increase in the number of calls from the previous year with calls dramatically increasing to a total of 45 in 2011. The age range of children ingesting NRTs was 6 months to 16 years. The highest recorded exposures were 15 pieces of gum and 20 lozenges. Since 2010, the New Zealand government has placed significant yearly tax increases on tobacco products, which has resulted in an increased uptake of subsidised nicotine replacement therapies to assist with smoking cessation. These products are provided by the government funded national stop-smoking support service 'Quitline'.

Conclusion: An increase in the number of consumers using NRTs creates a greater risk of nicotine exposures in children. Oral nicotine products can quickly produce toxicity in children with a rapid onset of symptoms which may include nausea, vomiting, abdominal pain, and diarrhoea. Tremor, sweating and salivation are also early signs of intoxication. Large exposures can produce more serious neurological and cardiovascular effects. Children are not able to visually differentiate between therapeutic gum and lozenges and confectionary gum and lozenges. Oral NRT products should be clearly labelled as medicines and consumers should be educated to keep them well out of the reach of children.

85. Three cases of attempted suicide by ingestion of nicotine liquid used in e-cigarettes

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Objective: We report three cases (in two persons) concerning deliberate ingestion in attempted suicide. The Poisons Information Center in Denmark is experiencing an increasing number of calls concerning intake of nicotine liquid used for electronic cigarettes. Most cases concern accidental intake in children.

Case series: Case 1. Woman, age 36, admitted to a psychiatric ward, who had ingested 20 mL of nicotine liquid labelled as containing 18 mg to commit suicide. The Poisons Information Center was contacted 10 minutes after intake. The patient presented no symptoms. The patient was admitted to the emergency ward for treatment with activated charcoal. Case 2. The same woman as in case 1 was admitted to the emergency ward after ingestion of 50 mL of nicotine liquid labelled as containing 30 mg of nicotine/mL, i.e. 1500 mg of nicotine in total, to commit suicide. Two hours after ingestion the symptoms present were abdominal pain, nausea, and voluminous vomiting, oxygen saturation 100%, blood pressure (BP) 103/69, pulse (P) 70, Glasgow Coma Scale (GCS) 15. Treatment: activated charcoal and observation for 6 hours. Case 3. Male, age 13, ingested 3 mL of nicotine liquid, no information about concentration, to commit suicide. Fifteen minutes after ingestion symptoms were nausea and shivering. He was treated with activated charcoal and 1 hour after ingestion symptoms were decreasing. BP 113/76, P 84.

Conclusion: Nicotine liquid for e-cigarettes is imported to Denmark via the Internet. The concentrations in the different products vary. Nicotine fluid products with concentrations up to 100 mg/mL nicotine are distributed in cans containing 5 litres! Symptoms develop shortly after ingestion (minutes). The symptoms after ingestion vary. In milder cases: nausea, vomiting, dizziness, headache, tremor, diaphoresis, tachycardia, pallor, and hypertension. In more severe cases: seizures, confusion, weakness, bradycardia, hypotension, and respiratory paralysis. The lethal dose in adults has been estimated: 40 to 60 mg. Treatment is symptomatic. In cases where the patient is not already vomiting activated charcoal can be considered. More similar cases are expected as the use of e-cigarettes increases.

86. Unintentional exposures to methylergometrine maleate in oral solution

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Objective: Methylergometrine maleate (Methergin[®]) is an ergot alkaloid used in obstetrics for prevention and treatment of post partum haemorrhage. In October 2011, the European manufacturer (Novartis) decided to withdraw the oral solution of the medicine from the market having been informed about a series of cases of adverse reactions due to medication errors in neonates identified in Italy. This case series included a 3-day-old child who developed life threatening complications as a consequence of repeated administration of the medicine due to being given another patient's medication. The present contribution is aimed at describing the main characteristics of cases accidentally exposed to Methergin[®] in Italy from January 1, 2005 to December 31, 2011.

Methods: The database of the National Poison Control Centre of Milan was searched retrospectively in order to identify all cases of interest. Data were analysed using STATA 11 Program.

Results: A total of 642 cases were identified. About 75% of patients were less than one year old, 13% 1–2 years old, and 9% 3–4 years old. About 44% of cases aged < 1 year were exposed in the first week of life, 23%, 17%, and 3% in the following three weeks of life, respectively. The vast majority of these patients were the victims of therapeutic error (89%), mainly due to being given the wrong medicine. About 14% (66) of these cases developed clinical effects. Severity of poisoning was minor in 45 cases, moderate in 11, and severe in one case. This last case was a 3-day-old male, who received for two days 0.1 mg/kg/day of the oral solution because of misunderstanding about the person to be treated. On the third day of treatment, the newborn baby developed metabolic acidosis, apnea, cardiac arrest, cyanosis, and coma. He was intubated for two days. By day 13 of life examination was entirely normal.

Conclusion: Most toxic exposures to Methergin[®] which occurred in Italy in 2005–2011 were caused by inadvertent oral administration of the medicine to newborn children. These types of incident were prevented by withdrawal from the market of the oral solution of this medicine.

87. Infants exposed to metformin: A case series

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Objective: The orally applicable antidiabetic metformin is the only biguanide approved for the treatment of type-II diabetes in Germany. It is the treatment of first choice for the young obese diabetic patient. As metformin is not approved for the use in children below ten years of age, there is only limited experience in accidental intoxications in this group. In adults, metformin can cause severe lactate acidosis accompanied with substantial mortality. To estimate the risk of lactate acidosis after accidental exposure to metformin in infants and children a retrospective case study was performed.

Methods: Criteria for enrolment in this study consisted of: age below 12 years, single intoxications, exposure definite or likely, minimum follow up interval: six hours.

Results: A total of 71 intoxications with metformin were analyzed retrospectively. Ages ranged from 10 months to 12 years with a median of 2 years and 6 months. The reported dose ingested ranged from 7.4 mg/kg to 250 mg/kg, with a median of 43 mg/kg. Clinical effects were observed in four of the 71 children (6%). The occurring symptoms were mild and consisted of gastrointestinal symptoms and fatigue. In 37 of the 71 children (52%) blood glucose was monitored, only three experienced mild hypoglycemia. Blood gas measurements were performed in 29 of the 71 children (41%). A mild acidosis was reported in four children. In 13 of the 71 children (18%) serum lactate concentrations were measured. Three of the 13 had a mild increase of plasma lactate, however all below 3 mmol/L. In 54% of all cases a maximum dose of 50 mg/kg body weight was ingested with 95% of these showing no symptoms. In 28 children the dose range was between 50 and 100 mg/kg with 75% experiencing no sequelae. In this group there was no correlation between dose and the probability of symptoms.

Conclusion: Metformin ingestions in children up to a dose 100 mg/kg caused no or only mild symptoms needing no treatment. In contrast, severe lactate acidosis after ingestion of large amounts of metformin in deliberate self-harm behavior is a common clinical feature in adults. Minor toxicity may be due to the lack of risk factors as well as to the relatively low dose of metformin accidentally ingested by children.

88. Methemoglobinemia secondary to rapid dose escalation of dapson

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Objective: Dapsone is a medication traditionally used for treating leprosy as well as for prophylaxis against *Pneumocystis pneumonia*. It is also used for its anti-inflammatory effects in the treatment of certain rheumatologic diseases.¹ We present a case of methemoglobinemia secondary to dapson used for the treatment of autoimmune lipoatrophic panniculitis (ALP) that is notable for the striking cyanosis of the patient in the absence of acute overdose or significant co-morbidity such as pneumonia or anemia.

Case report: A 17-year-old female was brought to our pediatric emergency department (ED) complaining of headache. She was recently started on 50 milligrams of dapson daily for the treatment of her ALP. The day prior, the dose had been increased to 100 milligrams daily. On presentation, the patient was hypertensive and tachycardic with marked central cyanosis but in no acute distress (blood pressure 140/67, heart rate (HR) 124). Blood co-oximetry

demonstrated a methemoglobin level of 23% and her hemoglobin was 12.7 mg/dL. The patient was treated with 60 milligrams of methylene blue intravenously (1 mg/kg). Within 10 minutes, her cyanosis resolved and her HR normalized to 90 beats-per-minutes. A repeat methemoglobin level was 2.9%. Ten hours later, the patient required another dose of methylene blue at 0.5 mg/kg due to recurrence of cyanosis with a new complaint of chest pain. Her methemoglobin level was found to have rebounded to 8.1%. Upon discharge from the hospital, the patient was restarted on 100 milligrams of dapson in conjunction with cimetidine.

Conclusion: Methemoglobinemia is a known adverse effect of dapson administration typically in the setting of overdose or co-morbidity such as pneumonia or anemia. The acute manifestation of methemoglobinemia that our patient presented with was most likely due to the rapid dose escalation of dapson. Physicians should be aware of this dose-related complication of dapson treatment and increase doses gradually. Clinicians should consider co-administration of cimetidine to inhibit the CYP450 pathway leading to production of the methemoglobin-inducing metabolite.²

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89. “Say NO to Poisons!” The development and evaluation of poison prevention resources for childcare practitioners to teach pre-school children about poison safety

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Objective: To develop poison prevention educational resources specifically for childcare practitioners to teach poisons safety to pre-school children.

Methods: The National Poisons Information Centre (NPIC) of Ireland collaborated with childcare and education experts to develop a poisons awareness programme for pre-school children. A storybook was developed as the principal learning tool. The “Say NO to Poisons!” title was chosen as a simple, effective catchphrase to help reinforce children’s comprehension of the material and facilitate learning. The language, key messages, and illustrations were scrutinised to ensure they were appropriate and reassuring for children. A pilot educational programme (Storybook, Learning Plan, Colouring-in page, Poison Search, Slide-show, Safety Signs) was delivered by 3 childcare practitioners to 3 groups of pre-school children following parental consent. The children were aged (i) 15–24 months (n = 5), (ii) 24–36 months (n = 6) and (iii) 3–4 years (n = 8). An education professional delivered an information session to the childcare practitioners and the children’s parents prior to the pilot study. After the pilot study, the practitioners completed an evaluation questionnaire on the clarity, appropriateness, effectiveness and interest of the programme to the children.

Results: Childcare practitioners rated the materials as clear, appropriate and effective. The most effective materials/activities for teaching purposes were the Learning Plan, Storybook, childcare centre tour with Safety Signs, Reflective Discussions and Activity Pages. The programme was most appropriate for 3–4 year olds and the children asked questions, engaged in discussion and repeated the catchphrase “Say NO to Poisons!” Following the pilot study, the older children had an enhanced knowledge of poison safety and knew to ask if something was safe to eat, drink or touch. The younger children did not understand the term “poison”, were easily distracted, but were interested in discussions about medicine safety. Following the pilot study, the educational resources were made available to download/order on-line. There are currently 6,000 registered childcare facilities in Ireland. In the initial 6-months since the launch, 3,600 books were ordered for registered childcare facilities and 238 books were downloaded.

Conclusion: This innovative collaboration facilitated the development of a poison prevention programme specifically for childcare practitioners to teach pre-school children about poison safety.

90. Unintentional injection of sodium hypochlorite instead of procaine for a dental nerve block

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Objective: To describe a medication administration error that occurred as a result of a common dental procedure with significant patient injury.

Case report: A 35 year old female presented to the dentist for a root canal on a right lower tooth. At completion of the root canal, the dentist then attempted to fill dental caries on the left side of her mouth. The dentist administered 5.4% sodium hypochlorite, used in root canal irrigation, into the patient’s inferior alveolar area instead of the intended procaine. The patient had immediate pain and discontinued the procedure. The patient presented to the emergency department one hour later with progressive pain and swelling to her left face extending down her lateral neck and sternum. It was at this time the medication error was recognized. Over the next several days, the patient developed massive facial swelling, and both hemorrhage and necrosis of her buccal mucosa. The patient received steroids, antibiotics, pain control, and over the course of a 15 day hospital stay had multiple surgical debridement procedures.

Conclusion: Sodium hypochlorite is a popular agent used by dentists, particularly in endodontics. Misuse can lead to significant alkaline caustic injury. Health care workers, dentists, and toxicologists need to be aware that such administration errors are possible and great care should be taken to prevent these occurrences as there is no established treatment for these injuries.

91. Veterinary product exposure inquiries to the New Zealand Poisons Information Centre, 2003 to 2011

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Objective: To describe the epidemiology of human exposures to veterinary products referred to the New Zealand Poisons Information Centre.

Methods: Telephone calls reporting human exposures to veterinary products for the period January 2003 to December 2011 were reviewed. Patient demographics, product names, active ingredients and classifications, exposure characteristics and treatment advice were collated.

Results: 2,473 exposures involved veterinary products; including 901 in children 12 years and younger, and 1,563 in adults; 1,374 in males, 1,063 in females with 36 unknown. Ninety-nine per cent of cases were acute, with parasiticide containing products in 46.9% of cases, vaccines (26.6%), and less frequently nutrients (8.8%) and chemotherapeutics (4.0%). Ingestions accounted for 47.8%, needlesticks 30.8%, and skin exposures for 12.6% of cases. Sixty-eight per cent of cases occurred in the home, 878 incidents in children, including 755 exploratory ingestions, with pyrantel, praziquantel and imidacloprid containing products involved in 164, 76 and 48 cases respectively. There were 788 adult cases including 323 ingestions of products containing imidacloprid in 23.8% of cases, pimobendan (12.7%) and pyrantel (9.3%) most prominent, and 220 needlestick cases mainly of products containing vaccines in 159 cases and/or an avermectin, moxidectin or levamisole in 32 cases. Adult exposures accounted for 98.8% of workplace exposures including 520 needlestick cases (75% in males) involving products containing vaccines in 385 cases and/or levamisole, an avermectin, or moxidectin in 54 cases. Self medication or self harm ingestions by adults occurred in 22 cases (10 males, 12 females). Referral for medical assessment, observation or substance related active treatment was recommended in 12.2% of child exploratory ingestions with self management in 38.5% of cases, whereas medical referral was recommended in 84.2% of adult workplace needlestick exposures, with self management in 11.2% of these cases.

Conclusion: Veterinary product exposures are reported uncommonly and intentional exposures rarely. Accidental ingestion of pyrantel or praziquantel anthelmintics and imidacloprid topical insecticides, and needlestick exposures account for the majority of cases. The relatively high proportion of patients referred for medical assessment is related to the high proportion of needlestick exposures where skin penetration occurred or tetanus immunization status was uncertain.

92. Risperidone: A cause of medication errors in children

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Objective: In France, the atypical antipsychotic drug risperidone can be used in children aged ≥ 5 years at the maximal daily dose of 0.75 mg in children less than 50 kg, and 1.5 mg in those above

50 kg. As its toxicity profile in children is not well described, our aim is to report the experience of the French network of poison control centres (PCC) on risperidone overdose in children ≤ 12 years.

Methods: To have an accurate ingested dose, the study was restricted to medication errors. Cases were included when the patients were symptomatic at the time of request, or if the delay between ingestion and the first request was at least 2 hours in asymptomatic patients. In addition, only those cases with an ingested dose above 2-fold the maximal daily recommended dose were examined, except for children < 5 years.

Results: According to these criteria, 153 cases (115 males) were analysed. The median age was 7.5 years and 31 children were ≤ 5 . The 1 mg/mL oral solution was involved in 73% of cases. This was the current treatment in 71% of children, including 10 of the 31 children of less than 5 years of age, and a 10-fold error or more was the most frequent (65%). The median ingested dose was 3.7-fold (range 2–40) the maximal recommended dose. Overall, 58 children had no symptoms, but complete follow-up (≥ 12 hours after the ingestion) was available for only 33 (57%) of them. In these patients, the median ingested dose was 0.09 ± 0.06 mg/kg ($n = 41$, range: 0.01–0.3 mg/kg). In the 95 symptomatic children, the ingested dose ranged from 0.75 to 30 mg (median: 3 mg), i.e. 0.14 ± 0.3 mg/kg ($n = 55$, range: 0.04–1.23 mg/kg). The most common symptom was drowsiness (49%). Overall, 18 (19%) of symptomatic patients experienced mild to moderate extrapyramidal disorders, 14 also had tachycardia and 3 had a minimal increase in QT interval.

Conclusion: The estimated toxic dose of risperidone in children is higher than 0.1 mg/kg and mostly associated with mild symptoms, which may require at-home observation only in the majority of cases.

93. Multicentre analysis of pediatric tizanidine exposures

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Objective: Tizanidine is a centrally acting myotonolytic agent licensed to treat spasticity of various origins. It is approved for adults, and the maximum recommended initial daily dose is 6 mg/d. Dose should not exceed 36 mg/d after slow increase. The aim of this analysis was to assess toxicity of tizanidine in case of pediatric exposure.

Methods: Multicentre retrospective analysis of well documented cases of acute pediatric tizanidine exposure reported to German, Austrian and Swiss Poison Centres from 1986 until July 2012. Inclusion criteria were patient age ≤ 6 years; absence of co-ingestants; confirmed or likely causal relationship between exposure and clinical effect, written feedback from the treating physician or follow-up by telephone (at least 4 hours post ingestion). Asymptomatic patients with high likelihood of exposure were also included. The severity of symptoms was graded in accordance with the Poisoning Severity Score.

Table 1. Summary of pediatric tizanidine exposures.

Clinical course	Total number of patients	Number of patients with known dose ingested	Dose range	Number of cases with decontamination (SDAC [n = 7] or Ipecac [n = 3])
Asymptomatic	5	2	2 – 4 mg	4
Minor	24	20	2 – 12 mg	6
Moderate	1	0	Max. 24 mg	0
Severe	1	0	Tizanidine serum concentration 20 ng/mL (time of determination unknown, but certainly > 1 h after ingestion)	0

Results: 31 cases met our inclusion criteria (Table 1). Patients were between 7 months and 6 years of age. Body weight was between 8 and 18 kg with a median of 12.5 kg. The following symptoms were observed: somnolence (n = 23), muscular hypotension (n = 6), coma (n = 1), ataxia and disorientation (n = 1), mild arterial hypotension (n = 4), mild bradycardia (n = 2), respiratory insufficiency (n = 2). No fatal cases were recorded.

Conclusion: Pediatric patients exposed to doses of up to 12 mg tizanidine remained asymptomatic or developed minor symptoms. Symptomatic patients should be monitored for central nervous system depression, but hemodynamic monitoring for arterial hypotension and bradycardia is also recommended.

94. Effect of safety update on quinine use in leg cramps on prescribing and toxicity in the UK

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Objective: We studied the effect of the June 2010 UK Medicines and Healthcare products Regulatory Agency's (MHRA) safety update for quinine use in leg cramps¹ on prescribing trends and toxicity of quinine following concerns about its benefit-risk balance for this indication.

Table 1. Characteristics of National Poisons Information Service telephone enquiries relating to quinine.

	2008/9	2009/10	2010/11	2011/12
Self-harm, n(%)	53 (39%)	63 (43%)	34 (32%)	46 (38%)
Cardiac toxicity, n(%)	18 (13%)	33 (22%)	29 (28%)	26 (21%)
Visual impairment, n(%)	17 (13%)	26 (18%)	16 (15%)	14 (11%)
Hearing impairment, n(%)	10 (7%)	6 (4%)	3 (3%)	13 (11%)
Cardiac, visual or hearing impairment (events), n(%)	45 (33%)	65 (44%)	48 (46%)	53 (43%)
Cardiac, visual or hearing impairment (Patients), n(%)	39 (29%)	39 (27%)	34 (32%)	31 (25%)
Total number of cases, (n)	136	147	105	122

Method: Quinine prescribing in England, together with data on telephone enquiries and accesses to TOXBASE[®] from the UK National Poisons Information Service (NPIS) relating to quinine toxicity from 2008/9 to 2011/12, were analysed using Pearson's correlation and joinpoint regression tests.

Results: Annual growth in quinine prescribing declined from 6.0% to -0.6% following the MHRA update (difference in slopes -0.0401 [95% CI -0.0672 to -0.0130], p = 0.0111). Targeted information to patients on the benefit-risk balance of quinine in leg cramps by one regional primary health care trust following the update resulted in a decline in prescriptions from 26.3 to 7.6 items/1000 patients (difference in slopes -0.6337 [95% CI -0.905 to -0.487], p = 0.0006), with limited changes in other trusts. Quarterly TOXBASE[®] quinine accesses, which correlated with corresponding quinine prescribing (R = 0.56; p = 0.0103), were increasing before the update but have since declined (difference in slopes -19.76 [95% CI -39.28 to -9.20]; p = 0.0575) with stabilisation of the number of moderate-severe cases of quinine toxicity. The annual incidences of deliberate self-harm and serious toxic features associated with quinine are shown in Table 1.

Conclusion: National efforts targeted at reducing quinine prescribing for leg cramps have led to a limited reduction in quinine prescribing and toxicity.

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95. Pediatric patients with exposures rarely need advanced life support prehospital care

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Objective: Pediatric exposures result in frequent calls to poison control centers and referrals to emergency departments. Despite the frequency, little is written in prehospital literature about the interventions performed on pediatric patients requiring Advanced Life Support (ALS) for toxic exposures. We sought to characterize the prevalence and types of interventions performed by ALS on pediatric patients with ingestions.

Methods: Setting: A large, suburban, two-tiered emergency medical service (EMS) system with approximately 27,000 Advanced

Life Support (ALS) requests per year. Design: Retrospective cohort study. Population: Consecutive patients less than 13 years-old for which ALS was requested for the dispatch categories of "Ingestion" or "Overdose" over a 66-month period. Calls primarily for allergic reactions that were misclassified were excluded. Initial Glasgow Coma Score (GCS), procedures performed, and medications given were recorded. Placement of an intravenous line (IV) was considered a procedure, but Normal Saline was not considered a medication. Descriptive data with percentages and 95% confidence intervals (CI) were calculated.

Results: Of 103,289 total ALS calls, 39 (0.04%) were for pediatric exposures. The average age of the patients was 3.0 years (CI: 2.4, 3.6). The average initial GCS was 14.6 (CI: 14.1, 15.1), with only 3 patients having a GCS less than 15. Ten per cent of patients (CI: 1, 20) had peripheral IVs attempted, and no other procedures were performed. No patients were given a medication. One patient, a 10-year old with a clonidine and guanfacine ingestion, had an IV and naloxone ordered, but naloxone was not given because the IV could not be established.

Conclusion: Despite the frequency of calls to poison control centers for pediatric exposures, very few, if any, require prehospital ALS interventions. This information may be useful in making dispatch decision.

96. Toxicological eye injuries: Physiopathology and management

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Introduction: The eyes occupy 0.1% of the total and 0.27% of the anterior body surface; the significance of their injury is magnified as vision is the most important sense. Loss of vision is likely to lead to loss of career, major lifestyle changes and disfigurement. Eye injuries usually occur in economically active individuals predominantly males (70%) with an average age of 39 years. Eye and orbital injuries are the commonest cause of extended hospitalization for ophthalmic patients. The home is now the commonest place for a serious injury to occur (30.2%), followed by the workplace (19.6%) and sports or leisure facilities (15.8%). Tools or machinery at home or at work are the most frequent cause of injury (approx 25%), followed by assault (approx 20%) and sports-related activities (12.5%). War related eye injuries have become more common over the past few years and are often from high explosive devices associated with injuries from the blast wave itself or secondary to debris from the explosion. Eye injuries come at a high cost to society and are largely avoidable.

Discussion: Ocular Burns: Thermal burns are usually from contact with hot liquids, gases or molten metals. Tissue damage is typically limited to the superficial epithelium, often with damage to the corneal limbal stem cells that retards re-epithelialisation. Thermal necrosis and ocular penetration can occur, especially in conjunction with intraocular foreign bodies (IOFB). Topical antibiotics are prescribed for epithelial defects and conjunctivitis. Initially, lid swelling may protect the corneal surface, but sloughing and contracture can lead to corneal exposure, requiring topical ocular lubricants. Chemical burns are blinding emergencies. Alkaline agents such as lye or cement penetrate cell membranes and cause

more damage than acidic agents. Acid burns are usually from battery acid explosions which precipitate on reaction with ocular proteins. Corneal epithelial defects range from superficial epitheliopathy to total epithelial loss. Limbal ischaemia is a whitened area without blood flow around the eye. The whiter the eye is, the worse the burn. Management of chemical burns is by immediate copious irrigation with Ringer's lactated solution for 30 min or an amphoteric solution such as Diphoterine (normal saline or even tap water are crude alternatives). The pH should be measured after 5 min on ceasing irrigation and irrigation continued until neutral (pH 7.0). For all severe burns, the conjunctival fornices are swept with a glass rod to remove retained debris and break conjunctival adhesions. Topical antibiotic ointment and cycloplegic drops are prescribed along with topical and oral ascorbic acid (vitamin C) to promote fibroblast activity. Oral tetracyclines are given to inhibit matrix metalloproteinase activity and corneal melting. Oral analgesia is used if required. Topical steroids are used cautiously as they may cause corneoscleral melting. Amniotic membrane grafts promote corneal surface healing and are especially useful in the management of severe burns.

Intraocular foreign bodies: These injuries cause approximately 15% of hospital admissions for eye injuries, 95% are male, with an average age of 37 years. They must be excluded if there is a history of high speed tool use or hammering. The final resting place of and damage caused by an IOFB depends on the size, the shape, and the momentum of the object at the time of impact, and the site of ocular penetration. Over 90% intraocular foreign bodies (IOFB) are metallic; 5% are multiple. Appropriate eye protection would virtually abolish all IOFB injuries. Hammering metal is the cause of 70% of cases. Increasing IOFB mass is associated with posterior segment injury, retinal impact, and poor vision. The frequency of globe penetration by an IOFB is determined by its shape; blade-shaped > disc-shaped > cylindrical > spherical. Secondary complications from IOFB occur in half of patients; including endophthalmitis, corneal scarring, elevated intraocular pressure, cataract, retinal detachment, and metallosis (e.g. chalcosis, siderosis). Siderosis occurs if a ferrous IOFB is left *in-situ*, iron dispersion throughout the globe causes retinal toxicity; IOFB removal is usually followed by visual and electroretinogram (ERG) recovery. Chalcosis occurs from IOFB that contain more than 85% copper, which is highly retinotoxic and causes profound visual loss associated with a greenish hue to the affected cornea. Diagnosis is by copper assay of an aqueous fluid sample.

War Injuries: Primary ocular blast injuries are from the transfer of kinetic energy from the explosive blast wave alone and occur in approximately 9% of war related eye injuries. They have a characteristic presentation of a profoundly hypotonic eye without evidence of globe rupture, often with traumatic cataracts that spontaneously resolve over 7–10 days. Secondary blast injuries are the most common blast injury (42% of cases). They occur when debris is blown into the coats of the eye or within the eye itself. Tertiary ocular blast injuries (1%) are caused by indirect damage to the eye when an individual is thrown by the blast wind. Quaternary blast injuries (3%) are those not caused by primary, secondary or tertiary blast and include thermal and chemical burns around the eye and adnexae. Quinary blast injuries describe a hyperinflammatory state occurring after an explosion, unrelated to the injury complexity and severity of trauma, particularly associated with hypercoagulability. They are thought to cause vascular occlusions after exposure to blast.

Recovery: The pattern of recovery following an eye injury can be divided into three main stages. The first stage is one of rapid recovery over the first 3–4 weeks. A poor initial visual acuity at this stage does not preclude recovery of vision. The second stage 1–3 months after the injury is one of specific syndromes including, glaucoma, retinal detachment and hypotony. A final visual acuity can usually be predicted at this time. The third stage ranges from three months to three years when the vision may improve further, but rarely deteriorates. The visual results from ocular trauma can be predicted using the Ocular Trauma Score. This grades the eye according to the presenting acuity and the main type of injury. If the retina remains attached and if the macula was not damaged, there is a good visual prognosis.

97. Halogenated pyrimidines: An unusual cause for skin burns

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Objective: Halogenated pyrimidines like 4,6-dichloropyrimidine, 2,4,6-trichloropyrimidine, 2,4,5,6-tetrachloropyrimidine or 4,6-dichloro-5-fluoropyrimidine are used as intermediates in the synthesis of reactive dyes, pharmaceuticals and crop protection products. They penetrate leather and many glove materials. Accidents occur very rarely in the chemical industry, but the local corrosive effect is aggravated in some cases by delayed dissemination of skin efflorescences reminiscent of chemical burns to areas not directly affected. A case series and the empiric treatment approach are described.

Case series: Over 20 years 7 cases have been seen and documented with photographs. One patient exposed to 4,5,6-tetrachloropyrimidine saw a doctor on day 3, had local skin symptoms only, but pain for 5 more days. Treatment consisted of parenteral prednisolone for 5 days followed by oral tapering, and local steroid cream. Four cases with 2,4,6-trichloropyrimidine were seen. One saw a doctor after 3 days with consecutive extension of severe blistering to adjacent initially unaffected skin areas requiring hospitalization. Treatment was with intravenous (IV) prednisolone and local steroid cream. The second case came to the infirmary immediately, was treated accordingly, but developed a skin lesion far from the initial contact with significant pain. The third patient came to the infirmary on the second day, needed initially only local steroids, but developed blisters on another, unaffected extremity on day 9, requiring IV steroids. Case 4 came on day 3 with a local burn, and developed urticaria responsive to antihistamines on day 12. Radioallergosorbent test (RAST) was negative. The other 3 cases had contact with 4,6-dichloro-5-fluoropyrimidine. Blistering set in very rapidly in all cases requiring hospital treatment with IV and local steroids. In one case skin lesions far from the contact area developed after 10 days.

Conclusion: Exposure to halogenated pyrimidines may go unnoticed initially causing delayed presentation to medical services. After 1 to 3 days rash and itching will develop, followed by brownish skin discoloration and blistering. A dissemination of these skin symptoms can occur after 5 to 10 days to initially unaffected skin areas. Empirically, treatment is carried out with IV prednisolone with oral tapering, and local steroid creams. Healing is slow; skin discoloration may persist for a long time.

98. The use of stem cells for improved wound healing of chemical-induced skin wounds

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Background: Dermal exposure to chemical substances can cause severe skin disorders resulting in slow or non-healing wounds. Conventional treatment includes symptomatic measures (bandages, cooling and analgesics) but due to the resistance of especially skin wounds caused by chemicals, debridement of the affected skin area, followed by skin graft is a common course. Wound healing is considered to be dependent on sequential biological processes (coagulation, inflammation, proliferation and maturation), in which formation of granulation tissue is an elementary requirement for effective wound healing. Thus, impairment of angio- and vasculogenesis which are decisive events for the formation of granulation tissue will therefore aggravate the problem of non-healing wounds.

There is growing evidence demonstrating the promising use of stem cells in the treatment of non-healing wounds. Bone-marrow derived mesenchymal stem cells (BM-MSC) and tissue specific adult stem cells (ASC) such as epidermal stem or progenitor cells (epiSC) are considered to play a substantial role in the regeneration of skin tissue and are the focus of current research. Nevertheless, many aspects especially about the interaction between these different entities of stem cells are still unknown. From the clinical point of view, treatment of acute and chronic wounds with stem cells is expected to result in accelerated wound closure with increased epithelialization, granulation tissue formation and angiogenesis. Although there is evidence for stem cell differentiation in the wound, most of the therapeutic effects are likely due to the release of soluble factors (from e.g. hMSC) that regulate local cellular responses to cutaneous injury.

Methods: Taking Sulfur Mustard (SM) as a model substance for alkylating chemical agents, we analyzed the effect of SM (causing erythema, blister formation and non-healing skin wounds) on the regulation of central signal transduction pathways in stem- and progenitor cells. Moreover, we elucidated the release of autocrine and paracrine factors from hMSC and its effect on proliferation, differentiation and migration of epidermal progenitor cells. To investigate the effect of SM on vasculo- and angiogenesis, murine embryonic stem cells were cultured in embryonic bodies (EBs), differentiated and exposed to SM. Endothelial tube formation as a parameter for angio- and vasculogenesis was determined by platelet/endothelial cell adhesion molecule 1 (PECAM-1) staining. In addition, we analyzed the effect of SM on early endothelial cells (PECAM-1 positive cells) isolated from EBs with special regard to migration capacity.

Results: Bone-marrow derived stem cells (both mesenchymal and haematopoietic) as well as epithelial stem cells have been shown to participate in the complex physiological process of wound healing. After exposure to toxic chemicals (e.g. alkylating agents) the tissue and BM-derived stem cells are affected. SM initiated markers of terminal differentiation in local epidermal stem cells (NHEK) which were accompanied by activation of MAP-kinase signaling (p38). Application of a synthetic MAPK-Inhibitor was able to counteract the SM induced maturation of NHEK

and ameliorate the migration capacity *in vitro*. Moreover, SM induced the release of cytokines (e.g. Wnt-signaling molecules) which are involved in the regulation of hMSC. With regard to angio- and vasculogenesis we were able to demonstrate that SM had a tremendous effect on endothelial tube formation in EBs. In relation to the differentiation level of the EBs virtually no intact endothelial tubes were formed. In addition, SM decreased migration activity of early endothelial cells.

Conclusion: Alkylating chemical substances such as Sulfur Mustard cause non-healing skin wounds. One reason is the impact of SM on the proliferation, migration and differentiation of stem, progenitor and early endothelial cells.¹⁻⁴ Our studies provide more insight into the molecular mechanisms in the pathophysiology of SM-induced impairment of wound healing, enabling the opportunity for the development of innovative therapeutic concepts.

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99. Incidence of carbon monoxide calls to a US poison center following Hurricane Sandy

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Objective: Carbon monoxide (CO) exposure following weather-related disasters remains a significant public health concern.¹ Hurricane Sandy's landfall on 29 October 2012 caused widespread damage to homes and utilities, which was further exacerbated by a 7 November nor'easter. We examined CO exposures following the storms.

Methods: A single Poison Center's electronic database was searched for exposures to CO from just prior to Sandy's landfall through 12 November, when 99% of the area regained power.² Abstracted data included date, exposure, context, age, gender, caller zip code, AAPCC outcome, duration of effect, and exposure source. Exposures were defined as possible (a), probable (b) or confirmed (c), depending on suggestive environmental circumstances (a), detection by environmental CO sampler (b), or clinical CO measurement (c). Poisoning was similarly defined based on appropriate signs or symptoms in the setting of (a), (b), or (c). Hospital-based cases were assessed for hyperbaric oxygen (HBO) recommendations and HBO accomplishment. Data were compared to identical dates from 2008–2011.

Results: 437 CO exposures were reported in the two weeks following Sandy (possible, 5.9%; probable, 77.3%; confirmed, 13.7%).

Three hundred and eleven of these occurred in a November 9th fire, pursuant to restoring power in a storm-damaged building. Excluding this fire, 47.6% were confirmed exposures. This dwarfed the number of cases for identical dates in 2008, 2009, 2010, and 2011 (which also experienced a nor'easter): 18, 13, 24, and 61, respectively. Excluding the fire, the most common CO sources were grilling indoors (26.2%) and generators (17.5%). HBO was recommended in 46.8% of confirmed poisonings and was accomplished in 46% of these. There were no fatalities.

Conclusion: CO remains a significant public health threat after catastrophic storms. A consequential number of patients received HBO. While our poison center undertook an outreach and educational campaign, further mitigation efforts before and after severe weather events are required to ensure public safety.

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100. The effectiveness of hyperbaric oxygen in carbon monoxide poisoning is time dependent: *in vitro* and *in vivo* studies

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Objective: Carbon monoxide (CO) poisoning results in neuronal and astrocytic necrosis and apoptosis which may cause delayed neurological symptoms. The usefulness of hyperbaric oxygen (HBO) in CO poisoning has never been confirmed since the analysis of normobaric oxygen (NBO) and HBO studies showed no clear differences. This could be the result of failure to comply with HBO time-dependency. The aim was to evaluate NBO and HBO efficacy in different time periods after CO exposure.

Methods: In the *in vitro* model primary rat astrocyte cultures were exposed to 3,000 ppm CO for 8 hours and NBO or HBO for 60 minutes 0–7 hours after CO exposure. Astrocytic viability was determined by measuring the metabolic activity and intracellular ATP level, astrocytic necrosis by lactic dehydrogenase activity and triggering of apoptosis by caspase-3/7 activity. In the *in vivo* model Wistar rats were exposed to 3,000 ppm CO for 60 minutes and HBO for 30 minutes 0–12 hours after CO exposure. The apoptosis was evaluated by immunohistochemical analysis with antibodies against activated caspase-3 and the percentage of caspase-3 positive neurons was reported. For statistical analysis we used the analysis of variance between groups with the Bonferroni correction method.

Results: In primary astrocyte cultures CO reduced metabolic activity and ATP concentration ($p = 0.01$) and caused caspase-3/7 activation ($p = 0.01$), but lactic dehydrogenase activity remained unchanged ($p > 0.05$). HBO did not have any effect on astrocytes after CO-exposure ($p > 0.05$), while HBO increased astrocytic viability (increase of metabolic activity and ATP levels; $p = 0.01$) and prevented astrocytic apoptosis by inhibition of caspase-3/7 activation ($p = 0.01$) with the highest efficacy at 1–5 hours after CO-exposure ($p = 0.01$). In rats CO poisoning resulted in neuronal apoptosis (32%) and HBO had a time-dependent protective effect on CO-induced neuronal apoptosis with the highest efficacy at 3–5 hours after CO poisoning ($p = 0.03$).

Conclusion: CO reduces brain cell viability and triggers their apoptosis. HBO has a time-dependent protective effect on CO-induced neuronal and astrocytic apoptosis with the highest efficacy at 3–5 hours after CO poisoning. The presented information could encourage further studies of HBO according to the time elapsed after CO exposure since immediate or late HBO might not be so effective.

101. Formate analysis as a simple methanol diagnostic approach: The cost-beneficial answer for evaluating metabolic acidosis

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Objectives: Methanol poisoning represents an under-reported global public health problem. Outbreaks are regularly occurring in both the developing and developed parts of the world. In spite of efficient treatment, morbidity and mortality remain high due to difficulties in obtaining the diagnosis. The clinical features often mimic other diseases, and many patients die in the community before hospital admission, without a diagnosis of methanol poisoning. Measuring methanol is not widely available: even in the developed world, the turn-around time is often very long (> 24 – 48 hours). The delay for analytical results in the developing part of the world is much longer and more uncertain. Given this difficulty in obtaining the correct diagnosis, the frequency of methanol poisoning is likely to be underestimated. A search through the medical literature and newspapers identifies a large number of outbreaks and deaths in recent years. This is likely to be only the "tip of the iceberg". Effective treatment exists, and the antidote fomepizole has recently been suggested for addition to the WHO Essential Medicines List. There is, however, limited value in improving treatment options if one does not know whom to treat, and so alternative diagnostic equipment is needed.

Results: Formic acid and its anion formate are the toxic metabolites of methanol. A well-defined method for measuring formate enzymatically has been used for years for scientific purposes.¹ This can easily be adapted to spectrophotometric analysers available in most laboratories. The method is very sensitive (0.1 mmol/L or 0.5 mg/dL) and specific, with a day-to-day coefficient of variation of 5%², being able to detect formate production several hours before the symptoms even appear³. Finally, the analysis is cheap, and it can be adapted to most spectrophotometers. In an extension of this laboratory method, an even simpler method is now being suggested: some glucose meters for measuring blood sugar use

glucose dehydrogenase (GDH) + nicotinamide adenine dinucleotide (NAD) as their enzymatic pathway. By exchanging GDH with formate dehydrogenase (FDH) on the paper strips used, the same glucose meters can be used to measure formate: both operate in a similar concentration range (mmol/L), and no calibration of the glucose meter would be necessary. This will greatly simplify the diagnostic process, making it independent of laboratory equipment. The distribution of paper strips would also be easier, as would the educational aspects.

Conclusion: This method would have a very important potential for saving lives in the developing world where diagnostic options are scarce, but it will also represent a very cost-beneficial way of verifying or excluding methanol as the reason for a metabolic acidosis of an unknown origin, which is frequently found in all hospitals worldwide.

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102. Prospective follow-up study on potential toxic methylphenidate exposures

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Objective: Methylphenidate is a pharmaceutical indicated for the treatment of attention deficiency hyperactivity disorder (ADHD) in patients > 6 yrs. In the US, methylphenidate is the most frequently dispensed pharmaceutical amongst children (12–17 yrs) and it is used by *circa* 2 million paediatric patients (< 18 yrs) that receive *circa* 25 million prescriptions annually.¹ In the Netherlands, the number of methylphenidate prescriptions increased from 70,000–200,000 from 2005 to 2011.² In this period, the number of information requests regarding potentially toxic methylphenidate exposures to the Dutch Poisons Information Center (DPIC) also increased. To expand our knowledge on these exposures (e.g. dose-response relationship), the DPIC is performing a prospective follow-up study on methylphenidate exposures.

Methods: All human cases concerning non-therapeutic methylphenidate exposures, on which the DPIC was consulted, were included in this follow-up study. We aimed to survey both the consulting physician, as well as the exposed patient (if < 16 yrs, the parents), by telephone within one week following the information request. Informed consent procedures included asking the physician for permission to participate in this study. In addition, patients were asked permission (if < 16 yrs, the parents) through their physician to remain anonymous and if agreed, the physician delivered patient contact information to the DPIC. The survey consisted of a standardized questionnaire tailored to physicians or patients, including questions on exposure circumstances, symptoms, treatment and the presence of co-exposures. Following the survey, data

was processed anonymously. This follow-up study was approved by the accredited Medical Research Ethics Committee of the University Medical Center Utrecht.

Results: The first 100 cases were included and surveyed from August–November 2012 and preliminary results are presented here.

Inclusion & follow-up: Of all cases, 5% were excluded because exposure had been therapeutic or had not occurred. Of the 95 included cases, 16% were lost to follow-up due to missing contact information or unwillingness to participate in the survey, e.g. due to lack of time or privacy considerations. Follow-up was conducted in 84% of all included cases.

Patient characteristics: In the majority of exposures, male patients were involved (64%). The age distribution revealed that most patients were adults (> 18 yrs: 48%, 13–17 yrs: 23%, 5–12 yrs: 19%, 0–4 yrs: 9%). The type of methylphenidate involved was Ritalin (37%), Concerta (extended release, 37%), generic methylphenidate (19%), Medikinet (4%) or a combination (3%). In 70% of all exposures, methylphenidate was obtained from the patients' own medication stock. In 65% of these cases, methylphenidate was prescribed to treat ADHD and in 20% to treat attention deficiency disorder (ADD). In 30% of all exposures, methylphenidate was not the patients' own medication. Of these cases, methylphenidate was obtained through a friend (23%) or relative (23%).

Presence of co-exposure: 50% of the cases involved methylphenidate as the sole substance (mono-exposure). In the multi-exposure cases, one or more other substance(s) was co-ingested; pharmaceuticals (50%), alcohol (16%), drugs (5%) or a combination of these (29%).

Symptoms: In 85% of the mono-exposure cases, the amount ingested and body weight were known. In these cases, the exposure could be classified for the seriousness of the intoxication based on DPIC guidelines: none (< 1 mg/kg, 15%), mild (1–2 mg/kg, 42%), moderate (2–5 mg/kg, 21%), severe (> 5 mg/kg, 21%). Symptoms were observed in ~80% of all mono-exposures; headache (43%), agitation (37%), sleepiness (~33%) and tachycardia (30%) were most frequently observed. Severe effects like hyperthermia (> 40°C), rhabdomyolysis, convulsions, cerebral haemorrhage, coma or cardiac arrest were not reported. Surprisingly, the percentage of patients with a mono-exposure that developed symptoms was hardly different between lower and higher exposure groups: 80% of patients classified as “no intoxication” developed symptoms versus 86% of patients classified as a “severe intoxication”. Furthermore, in different exposure groups the same observed symptoms occupy the top 4.

Treatment: In the mono-exposure cases, 5% of the patients were seen by a general practitioner (GP), 46% visited an emergency department (ED) and 44% were admitted to the hospital (average and median ~12 hrs). Of the patients who visited an ED or were admitted to the hospital (n = 20), 45% did not receive any treatment. In 50% of the (ED/admission) cases, laboratory testing was performed and in 40%, gastrointestinal decontamination (85% activated charcoal and 15% gastric lavage).

Intentional or accidental: Of all cases (mono- and multi-exposures) 40% were accidental, due to a dosing/intake error (63%) and young children that had mistaken methylphenidate tablets for candy (30%). Of the intentional exposures (60%), ~40% were due to a suicide attempt and 15% because of the desire to “feel better”. Other, less frequently reported reasons for intentional exposures included “to be more calm”, “to increase performance and/or concentration”, “to reduce stress” and “for fun”.

Conclusion: From these data, it is clear that patients exposed to potentially toxic doses of methylphenidate represent a group with diverse characteristics. Methylphenidate exposure varied from a classification in no- to severe intoxication, although clinical effects within these groups were comparable. Furthermore, although a large part of the patients developed at least one symptom, the severity of the symptoms appeared to be mild to moderate. Therefore, our current classification of the seriousness of the intoxication, based on the dose-response relationship, appears conservative. However, these are preliminary results and for many analysed subgroups, absolute numbers are too small to draw conclusions. Continuation of this follow-up study will result an increased number of observations in each subgroup, enabling development of new classifications values (dose-response relationship) and will further expand our knowledge.

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103. Cardiotoxicity of newer antipsychotics: Mechanisms, diagnosis and management

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Objective: To describe the mechanisms, diagnosis and management of cardiotoxicity associated with typical and atypical antipsychotic drugs, with particular emphasis on pro-arrhythmic effects after overdose.

Background: Antipsychotic drugs are widely prescribed and commonly taken in overdose. Over the last 2 decades there has been a change in the pattern of antipsychotic drug prescribing¹, with ‘atypical’ (second generation) agents more commonly encountered in overdose than first generation ‘typical’ agents. Antipsychotic overdose has been associated with a high mortality in some case series², with 50–80 cases of fatal poisoning recorded annually in the UK³.

Methods: Literature review with emphasis on publications since 2000.

Results: Features of poisoning with typical and atypical antipsychotic drugs usually appear within 4 h of ingestion. Non-cardiovascular features include reduced level of consciousness, agitation, delirium, hypersalivation, respiratory depression, extrapyramidal effects, seizures, and occasionally electrolyte and glucose abnormalities disturbances of thermoregulation.^{2, 4–7} Pulmonary oedema may occur as a result of acute lung injury. Cardiovascular toxicity may involve anticholinergic (especially clozapine, olanzapine, quetiapine) or alpha adrenergic antagonist effects resulting in hypotension and tachycardia, although bradycardias and hypertension are also recorded.^{2,7} Most patients with hypotension respond to intravenous fluids, although inotropic or pressor agents may occasionally be required. The most

frequently encountered electrophysiological effect is potassium channel inhibition, thought to be caused by blockade (or reduced expression) of the delayed rectifier channel IKr, coded by the gene KCNH2 (previously termed HERG). This causes ventricular repolarisation delay, resulting in QT interval prolongation on the ECG and a propensity to develop the ventricular arrhythmia torsade de pointes.⁸ Potency in this respect varies between agents and is related to dose. Although well described after overdose with some typical agents (e.g. thioridazine, droperidol, pimozide), QT prolongation is also reported with some atypical agents, including quetiapine⁷, amisulpride⁹, sertindole and ziprasidone, although torsade de pointes appears uncommon after overdose with these agents, with the probable exception of amisulpride⁹. Torsade de pointes or severe QT prolongation (e.g. QTc > 500 ms, especially with other risk factors for torsade e.g. female sex, bradycardia, frequent ventricular premature beats, electrolyte abnormalities, structural cardiac disease) should be managed by correction of hypoxia, acidosis and electrolyte disturbances and administration of intravenous magnesium sulphate. Overdrive cardiac pacing is occasionally needed in patients with bradycardia or pauses. Defibrillation is required for torsade associated with loss of cardiac output. Antipsychotics may also cause sodium channel blockade associated with QRS prolongation and if severe this may be associated with re-entrant (monomorphic) ventricular tachycardias. This effect has been reported for quetiapine, for example.¹⁰ VT associated with QRS prolongation should be treated with sodium bicarbonate in the first instance. PR interval prolongation may occur but seldom leads to more severe heart block and specific treatment is usually unnecessary. There are anecdotal reports of successful use of lipid rescue therapy in patients with severe antipsychotic poisoning.

Conclusion: Overdose with atypical antipsychotic drugs has increased in frequency and may be associated with significant toxicity. Differences exist in the clinical features of poisoning, including adverse cardiovascular effects, between individual antipsychotic drugs.

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104. Toxicology of high-dose olanzapine treatment in clinical settings

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Objective: In Denmark there is an ongoing debate about high-dose, off-label use of olanzapine in psychiatric patients with the aim of shortening treatment response and lowering the use of coercive measures and especially the use of bed-belts. The safety of olanzapine used in higher doses than the maximum recommended 40 mg as treatment for psychiatric patients in psychiatric wards has not previously been described. We aimed to describe the prevalence, symptomatology and the clinical observations in psychiatric patients treated with olanzapine in doses higher than the recommended 40 mg daily.

Methods: We searched data from EPM (electronic medication registration) concerning the use of olanzapine in the Capital Region of Denmark in the period between 01.01.2012 and 15.03.2012 and identified a total of 226 patients treated with > 40 mg olanzapine daily at least once during admission to a psychiatric ward. Relevant patient charts were selected for retrospective review based on predetermined risk factors believed indicative of olanzapine toxicity. The risk factors were death, treatment with olanzapine ≥ 100 mg, the need for somatic medical assessment and/or foreign social security number.

Results: The audit of 91 selected patient charts revealed that 43% of the patients had adverse effects most likely due to olanzapine. Ten per cent of the patients were reported not to experience any adverse effects. For the remaining 47% of patients there was no mention of adverse effects. Extrapyramidal symptoms (EPS) and central nervous system (CNS) depression were each reported in 25% of the patients and were the most common adverse effects. Hypotension, tachycardia and prolonged QT were other well known but less common adverse effects described in 2%, 2% and 1% of patients, respectively. Approximately 50% of the patients were concomitantly treated with other antipsychotics. Two patients experienced serious events (death and serious EPS, respectively) that could be related to the treatment with high-dose olanzapine. The doses of olanzapine in these two cases were 60 mg.

Conclusion: In our retrospective chart review, the use of olanzapine in doses higher than the recommended 40 mg daily led to well-known adverse effects in more than 40% of patients. However, death (1%) and serious EPS (1%) were also observed.

105. A ready to use kit for therapeutic drug monitoring in organophosphorus compound poisoned patients

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Background: The high number and variety of factors determining the clinical course of each single case of poisoning by organophosphorus compounds (OP) make a universal therapy difficult. Determinants of clinical development such as amount and type of

poison ingested, time to development of clinical signs and symptoms as well as time to first treatment frequently remain obscure during intensive care treatment. Therefore, therapeutic strategies are mainly directed at antagonizing life threatening features (e.g. atropine, supportive intensive care measures) without getting rid of the cause of these events. For a wide variety of cases, antidotes, namely oximes, are available which are able to remove the poison from its target thereby causally cutting the poisoning short. The concept of this strategy is based on the assumption that an oxime removes the inhibiting OP from the acetylcholinesterase (ACHE) which is thereby reactivated and able to cleave acetylcholine again. However, for clinical effectiveness, several preconditions have to be fulfilled. At first, the oxime has to be able to reactivate the respective OP-ACHE conjugate *per se*. This decisive prerequisite is dependent on the properties of the type of OP, type of oxime and finally the species. Second, even a well reactivatable OP-ACHE conjugate may undergo metabolism (aging) thereby being transformed into a non-reativable OP-ACHE complex. Here, for clinical practice, it is decisive, to know whether or with what velocity this process is progressing. Third, even when reactivation is achieved in a patient, the remaining poison may re-inhibit reactivated ACHE thereby preventing net-reativation. However, under such conditions, enhanced elimination of the poison and a delay in the aging process may be assumed.

Methods: Basing on the finding that red blood cell ACHE resembles synaptic ACHE within a single species, a laboratory test system, called the cholinesterase status, was established. It consists of determination of erythrocyte ACHE, butyrylcholinesterase, reactivatability of OP inhibited ACHE and presence of inhibitory material (equivalent of poison). In a clinical setting, it was shown that this system can be used to monitor the effects of the oxime obidoxime in OP-poisoned patients.¹ Moreover, it was shown that sufficient reactivation was accompanied by improvement of neuromuscular transmission indicating clinical benefit of oxime treatment.² However, until now, determination of parameters needed adequate sampling, storage and transport to an external laboratory where the parameters were then assessed according to time-dependent available resources. Therefore, its use for on-line therapeutic management of effective oxime treatment was rather limited. In order to overcome this shortcoming an easy to use laboratory system was developed that allows on-site determination of the complete cholinesterase status needing only very limited laboratory linkage (e.g. power supply, basic laboratory equipment).

Results: The portable laboratory system consists of a photometer with integrated incubation unit and a reagent kit for the incubation and analysis of blood samples. The system allows the determination of ACHE activity and reactivatability of ACHE in patient blood dilutions as well as the determination of butyrylcholinesterase and inhibitory activity in patient plasma samples. All incubation and analysis steps are menu-driven thus superseding extensive training. The laboratory system was validated by comparison to a DIN EN ISO 15189 accredited procedure for the determination of the cholinesterase status.

Conclusion: A ready to use laboratory system is available that allows on-site monitoring of therapeutic effectiveness of oximes thereby enabling optimized patient-oriented oxime treatment. This system provides a new tool for rational clinical assessment of indications and limitations as well as effectiveness of oxime therapy.

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106. Aspects of product safety which may facilitate the oral ingestion of cleaning and cosmetic products containing surfactant. Results from a prospective multicentre study in Germany

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Objective: Cleaning and cosmetic products containing anionic and non-ionic surfactants are a common cause of chemical exposure and of enquiries in poison centres. Since these products are considered to be of low toxicity their packages are commonly not specially designed to prevent children from access by child-resistant closures. One aim of this prospective study was to evaluate certain aspects of product safety, for instance attributes of the product and of the package, which may facilitate the exposure (ingestion), or transfer of the product to another container.

Method: Prospective observational study of acute ingestions of cosmetics (soaps, shampoos, bath additives) or cleaners (general purpose cleaners, laundry detergents, manual dishwashing detergents) from 3 German poison centres (PC) during a seven-month period. Additional data on circumstances of exposure and of product identification were collected by a structured telephone interview based on a detailed questionnaire.

Results: Exposures: 540 children, 42 adults, 23 seniors. Accidental exposures dominated (591). Cosmetics were more often ingested than cleaners because of their odour (14% vs. 7%), and cleaners more often than cosmetics because of their colour (19% vs. 11%, $p < 0.01$). Ingestions were mainly from the original package (427). Cosmetics were more often ingested from the original package than cleaners (79% vs. 64%, $p < 0.001$). Easy-to-open closures facilitated ingestion from the original container in 114 out of 427 cases. Push-pull closures similar to drinking bottles were reported to be the cause of the ingestion of manual dishwashing detergents (45) and liquid soap (1). Trial packages were risky especially for toddlers (19). Product identification by name was successful in 76%.

Conclusion: Cosmetics were more often ingested because of their attractive odour, cleaners because of their attractive colour. Cosmetics were more often ingested from the original package than cleaners. Ingestion of manual dishwashing detergents from the original container was facilitated by push-pull closures similar to drinking bottles. Product identification by name of household products was successful in 76% only, evidence of the need for the product information element. PC's data are an important source for product exposure risk assessment in selected populations (e.g. consumers, children) and can contribute substantially to improve product safety.

107. EAPCCT survey of European poisons centres: Services provided

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Objective: To survey the services provided by European poisons centres (PC).

Methods: A SurveyMonkey® questionnaire with 66 questions was sent to all European PCs (n = 77) by e-mail in June 2012.

Results: By 1 Nov 2012 responses had been received from 32 PCs in 21 different countries (response rate 41.6%), with 23 completing all questions. All countries except one had 24 h availability of advice from at least one PC. Eighteen PCs could provide advice in more than one language on a 24/7 basis and a further 8 during usual office hours. In 10 countries more than one language was commonly spoken. All centres provided information by telephone, with 25% having a toll-free number and no centre using a premium rate (high cost) number. Information was also available by e-mail (84.4%), fax (71.9%), website (53.1%), personal attendance at the centre (34.4%) or Facebook® (1 centre). While 87.5% of responding PCs had websites, only one had a presence on social media. For services see Table 1. Of 23 PCs responding to questions on publications, all produced an annual report and 20 had an active research programme (median 7.5 papers/year; range 2–180). Other publications included handbooks/chapters in textbooks (8), public leaflets/posters (6), anti-

Table 1. European poisons centres - services provided.

Options	Count	Percentage
Telephone poisons information service to medical/health professionals	32	100.0%
Telephone poisons information service to the general public	27	84.4%
Telephone poisons information service to veterinarians	24	75.0%
Telephone drug (i.e. pharmaceuticals) information service to medical/health care professionals	19	59.4%
Telephone drug (i.e. pharmaceuticals) information service to the general public	17	53.1%
Internet information (home page) for all (public)	19	59.4%
Internet information (home page) for health personnel only	11	34.4%
Information about acute and chronic poisoning	26	81.3%
Information about acute poisoning only	6	18.8%
Guidelines and advice to health personnel on antidotes/antivenoms	28	87.5%
Holding and dispatch centre for antidotes/antivenoms	13	40.6%
National guidelines/recommendations for treatment of poisonings	24	75.0%
Written or e-mail enquiries answered	24	75.0%
Treatment facilities for poisoned patients, involving admission to a ward	15	46.9%
Laboratory toxicological analyses	12	37.5%
Other, e.g. disaster preparedness, teratology information, teaching	12	37.5%
Outpatient treatment facility for patients	12	37.5%
Telephone consumer health advice line on behalf of a commercial organisation	9	28.1%

dote lists/handbooks (5) and poisons information monographs (4).

Conclusion: Most European PCs provide a range of services and have active research programmes. The survey is limited by the low response rate, especially for some questions. Online questionnaires can be administered using SurveyMonkey® but the number of questions should be limited to encourage a higher response rate.

108. ToxIndex – a tool to compare population poisoning risks for toxic agents

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Objective: Poisons centres (PC) play an increasing role in toxicosurveillance, i.e. the detection of new poisoning risks and trends. If a signal indicating a new poisoning risk is detected there is often need for quantitative evaluation. A simple algorithm was developed and applied to describe and compare poisoning risks of products based on PC exposure data.

Methods: All human exposure cases in the GIZ-Nord database in 2011 were classified for poisoning severity according to the Poisoning Severity Score. All agents related to these cases were categorised based on their intended uses according to the Toxikologischer Dokumentations- und Informationsverbund (TDI) agent category system.¹ ToxIndex was defined as the sum of all cases classified as lethal, severe or moderate divided by the number of all exposure cases. Subsets of cases selected by product category and patient age were analysed.

Results: In total, 31,154 exposure cases were included. The ToxIndex for all exposures was calculated to be 13%. ToxIndex for selected product groups are listed in Table 1. Drugs of abuse are the most risky product group, while exposures to homeopathic drugs very rarely lead to more than minor symptoms.

Conclusion: ToxIndex, i.e. the proportion of more than minor-grade poisoning cases of all exposures, is a simple tool to identify and compare poisoning risks in product groups. Based on ToxIndex for wider product groups (as presented here) the poisoning risk for selected subgroups or single products can also be evaluated: ToxIndex for liquid laundry detergent capsules was 13% compared to 3% for all laundry detergents.

Table 1. ToxIndex calculated for selected exposures reported to GIZ-Nord Poisons Centre in 2011.

Agent category	Total number of exposures	ToxIndex for 0–17 year old patients	ToxIndex for patients older than 17 years	Overall ToxIndex
All agents	31154	27%	3%	13%
Drugs of abuse	459	51%	39%	48%
All medical drugs	11746	35%	5%	23%
Animals	280	28%	7%	19%
Biocides including pesticides	938	16%	3%	9%
Plants	3399	14%	2%	3%
Cosmetic products	1721	6%	1%	2%
Homeopathic drugs	224	6%	1%	1%

Reference

1. <http://www.klinische-toxikologie.de/142.0.html> [accessed 28/11/12] [Website in German].

109. Quality guidelines for poison centers: A systematic review

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Objective: To review available Poison Center (PC) operation and quality guidelines.

Methods: We performed a systematic review to identify the guidelines. Three reviewers assessed the retrieved studies for eligibility and extracted the data from selected documents. All guideline items were listed to assess their similarities and disparities.

Results: A total of 2,002 non-duplicated records were retrieved, but only three guidelines met eligibility criteria: American Association of Poison Control Centers (AAPCC) criteria for certification of PCs¹, the European Association of Poison Centres and Clinical Toxicologists (EAPCCT) self-assessment checklist for PCs², and the World Health Organization (WHO) Guidelines for PCs³. Only the AAPCC guideline is mandatory. All guidelines were unanimous in recommending that PCs should offer 24/7 phone assistance for poisoning management and local treatment capabilities. PCs have to be readily available to anyone (public and health care professional) via a toll-free or low cost number. PCs must have an adequate telecommunication system. All cases should be recorded in a secure electronic medical record system. Information resources about commercial and natural products, textbooks, and primary resources must be available. At a minimum, PCs should staff specialists in poison information 24 hours a day (nurse, pharmacist or physician), medical director for toxicological supervision and managing director. Some guidelines recommended a direct connection between PCs and emergency services^{2,3}, ability to respond in all languages spoken in the region^{1,2} and provide service to hearing impaired individuals¹. Two guidelines suggested that one PC can serve a maximum population of 10 million inhabitants^{1,3}, and should be located in a safe, dedicated, and well-designed area, ideally located in or very close to a hospital that cares for poisoned patients^{2,3}.

Conclusion: There was little difference in the criteria between guidelines authored by three diverse organizations. This summary may assist with setting PC quality standards in localities where regional quality guidelines are lacking.

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3. WHO. Guidelines for poison control. Available at http://www.who.int/ipcs/publications/training_poisons/guidelines_poison_control/en/index.html [accessed 29/11/12].

110. Pregnant and lactating women's fear of teratogenic risk and the impact of counselling

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Objective: Almost every day, the Norwegian Poison Information (PIC) receives calls from the public where the risk of the foetus or breastfed infant has to be considered. Studies have shown that pregnant and lactating women often have an unrealistic fear of drug and chemical exposures. The fear of teratogenicity could lead to unnecessary anxiety, discontinuing drug therapy and the terminating of an otherwise wanted pregnancy. For the poison information specialists some questions are easy to answer, other enquiries are challenging, primarily due to vague literature and anxious callers. Very few studies have examined how the professional counselling affects the woman's risk perception. The aim of the study is to assess the impact of the PIC's counselling on the risk perceptions of pregnant and lactating women.

Methods: All pregnant and lactating women who consulted the PIC were asked to participate in the study. The women used numeric rating scale ranging from 0 (no risk to the foetus or infant) to 10 (very high risk for endangering the foetus or infant) to evaluate their own perceptions of the teratogenic risk both before and after counselling. The «before» and «after scores» were compared. Further information was collected during a structured telephone interview and by Internet questionnaire.

Results: In the period May to October 2012, 120 women (87 pregnant and 33 lactating women) have been enrolled in the study. In 83 per cent of enquiries the poison information specialists considered the exposure to involve no risk at all. Before counselling, 39 per cent of the women perceived that the risk was ≥ 5 . After counselling this fraction was reduced to 8 per cent. The total risk reductions were respectively 68 per cent among the pregnant and 57 per cent among the lactating women.

Conclusion: Our results show that pregnant and lactating women overestimated the teratogenic risk. The data reveal that professional tailor-made counselling by poison information specialists significantly reduces the women's fear. It also reveals that it is sometime challenging to get the women to accept that the exposure involves no risk at all.

111. Cases of human exposure to cosmetic products 1995–2011: Risk assessment by product groups using the new Cosmetic Products Notification Portal (CPNP) categories

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Objective: According to Regulation (EC) No 1223/2009 on Cosmetic Products the European Commission (EC) developed a new database for cosmetic products Cosmetic Products Notification Portal (CPNP). Design and development of the database was

carried out by a joint venture of the EC, industry associations, governmental authorities and poisons centres (PC). Product categorization is important for PCs. Therefore harmonized categories were developed on the basis of the German Toxikologischer Dokumentations- und Informationsverbund (TDI) categorization system. The aim of this study is to show the relevance of product categorisation for risk assessment of human exposures to cosmetic products.

Methods: A retrospective explorative analysis of data from a regional PC (1995–2011). Standardized documentation of phone calls and written follow up. Grouping of cases was according to the TDI Categorisation System containing 403 CPNP categories on 4 levels.

Results: Among 378,898 human cases 16,502 cases (4.4%) with cosmetic products were found. For final analysis 15,749 monoin-toxications (95%) were considered. Median age was 2 years, 49.6% were female, written follow up could be achieved in 6,131 cases (39%). Case numbers of main categories, distribution of maximum Poisoning Severity Score (PSS) within each product group: Skin Products: 10,166 (65%) no symptoms (n) 71.5%, minor (m) 27.2%, moderate (o) 1.2%, severe (s) 0.1%; Hair and Scalp Products: 2,564 (16%) n 67%, m 30.8%, o 1.9%, s 0.3%; Nail and Cuticle Products 1864 (12%) n 67.8%, m 31.0%, o 1.1%, s 0.1%; Oral Hygiene Products 950 (6%) n 69.6%, m 28.1%, o 2.2%, s 0%. Cosmetic Products - not classified 165 (1%). The product group with the highest severity grading was identified as "Hair Bleaching and Dye Remover Products". Six fatal cases were found, 4 cases within "Bath / Shower Products" and 2 cases within "Soap Products"; median age 78 y (65–89), in 4 cases dementia was mentioned, cause of death was in all cases aspiration pneumonia.

Conclusion: For the first time severity grading of human exposures to cosmetics according to the new CPNP categories has been realised. Only 1.5% of cases showed moderate or severe courses with no variability within the 4 main categories. Nevertheless subgroups revealed significant differences in PSS. Using the CPNP categories prospectively will help the performance of multicentre studies.

112. Trained nurses in poisons information: An approach to increase effectiveness in poisons information

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Objective: In the modern poisons information service an increasing workload of inquiries comes into conflict with restricted funding for personnel resources.

Methods: Two clinically experienced nurses were trained, following a special curriculum focused on low level inquiries from non-professional inbound callers. At all times a physician was immediately available to accept those calls that the nurses judged to be beyond the scope of their training. To evaluate the effectiveness of this participation in the provision of advice to people calling the Berlin poisons information center several parameters were studied. Non-professionals consisted of ordinary people, employees at homes for seniors, handicapped people, pharmacists; health care professionals were physicians, paramedics and nurses.

Results: A three month time interval was examined for the following parameters: a total number of 10,986 of inbound calls were counted with 3,463 (31.5%) received by nurses. From these, 2,045 calls were initiated by non-professionals and 1,301 by health care professionals i.e. 37.6%. In 39 cases of the 2,045 the call was handed over to a physician because of the unexpected complexity or other medical problems. In contrast 703 calls from health care professionals had to be managed by a physician. To analyze the throughput of calls their duration was measured yielding a median of 2:41 [min:sec]. In comparison, toxicological advice by physicians had a median duration of 3:03 [min:sec]. 1,468 from 2,045 (71.8%) calls by non-professionals did not need any therapeutic advice; in 280 cases simple treatment (e.g. defoaming agent) was requested; in 240 cases admission to a hospital was advised.

Conclusion: Trained nurses following a pre-defined pathway of interviewing and advice are a valuable alternative in managing non-complex inbound calls received by poison information centers. With a physician present at all times the quality of toxicological advice is maintained.

113. Establishing real-time communications with TOXBASE® users via TOXBASE® on-line and the TOXBASE® app, when agents of interest are accessed: A report on behalf of the National Poisons Information Service

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Objective: The UK National Poisons Information Service (NPIS) previously reported plans to establish real-time communications with UK healthcare professionals when agents of interest are accessed via TOXBASE®, the UK's primary poisons information database.¹ The Urgent-Alerting system has now been operational for over six-months and a retrospective analysis of data has been conducted to demonstrate system utility.

Methods: Within five-minutes of a tagged TOXBASE® entry being accessed an email alert is automatically generated detailing which TOXBASE® user accessed which agent. NPIS Units in Birmingham, Cardiff, Edinburgh and Newcastle monitor all alerts 24/7 and act immediately when required. Currently over 140 TOXBASE® entries are tagged as being of interest; the alerting tag is not visible to the user. Data collected between the 1/04/2012 – 30/09/2012 has been analysed.

Results: 5359 alerts were received; 951 alerts were patient-related, 188 users provided contact details and 124 (66%) were followed-up successfully. Reasons for an unsuccessful follow-up include failed contact attempts or user had already contacted NPIS directly. NPIS identified 264 clusters of potentially related alerts (defined as five or more alerts to the same agent on the same day) and followed-up 71 of these. Seventy-five per cent of successfully followed-up alerts originated from hospital A&E departments. Agents most commonly accessed in association with patient-related exposures were carbon monoxide (21%), chlorine (21%) and ammonia (7%).

The most common types of exposure were accidental (68%) inhalations (54%) that occurred at home (42%).

Conclusion: It is likely that the number of patient-related TOXBASE® accesses is under-reported by TOXBASE® users. However, this does not impact on the ability of the alerting system to act as a surveillance system. NPIS can act immediately when clusters of alerts are identified and thereby consider patients presenting with specific poisonings across different regions of the UK as a whole. The alerting system will soon include Trending-Alerts, which means NPIS will be notified when access levels to agents of interest exceed a relevant threshold, allowing NPIS to monitor accesses to a considerably larger number of TOXBASE® entries and respond accordingly.

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114. Enquiries to UK national poisons information service centres from ambulance services

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Objective: To review contacts to UK poisons centres originating from ambulance service personnel.

Methods: Retrospective analysis of poisons centre data for enquiries to the four UK poisons centres from 1st April 2007 to 31st March 2012 inclusive. Enquiries where the enquirer type was recorded as “Emergency Services” or “Ambulance” compared with overall call load. Analysis included basic demographic patient details, agent(s) involved and severity of poisoning as assessed by poisoning severity score (PSS), a measure of the patient's symptoms as assessed at the time of the enquiry to the National Poisons Information Service (NPIS).

Results: 250,170 enquiries were made to the UK NPIS over this period, of which 22,741 (9.1%) overall were classified as originating from “Emergency Services” or “Ambulance”. Yearly percentages were: 2006/7: 6.7%; 2008/9: 8.9%; 2009/10: 10.1%; 2010/11: 9.6%; 2011/12: 10.0%. Comparison of PSS breakdown for ambulance calls versus overall call load (broken down by year) shows a similar pattern between the two groups: (ambulance calls/all calls PSS0 (60.0% 34.5–65.7%)/61.2% (38.4–67.3%); PSS1 26.0% (15.5%–29.6%)/23.3% (15.4%–25.7%); PSS2 1.8% (0.8%–2.5%)/3.3% (2.1%–4.1%); PSS3 0.2% (0.1%–0.3%)/1.5% (1.0%–3.3%).

Discussion: Calls to the UK NPIS from ambulance services consist of calls from crews responding to a poisoning episode and calls from support personnel who feed clinical information through to ambulance crews. The proportion of the NPIS call load which relates to ambulance service enquiries, when expressed as a percentage, is reasonably static year-on-year, despite fluctuations in overall enquiry numbers. Broad comparison of ambulance service enquiries with our overall enquiry load, focusing on PSS as a comparator, do not reveal marked differences between the two groups.

Conclusion: Enquiries from ambulance service personnel continue to represent a significant proportion of the overall NPIS workload, indicating it may be mutually beneficial to identify agents

commonly seen in enquiries from ambulance crews and provide entries tailored to ambulance crew needs. Ambulance services and other front-line responders are expected to benefit from using the new TOXBASE application which can be used offline with portable devices such as mobile telephones, allowing ambulance crews to access a poisons database directly while ‘on-scene’ with patients.

115. Human exposures to veterinary medicines reported to the Poisons Information Centre Erfurt from 2002–2011

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Objective: The aim of the study was to obtain recent information on important characteristics of all human exposures to veterinary medicines (HEVM) reported to the Poisons Information Centre (PIC) Erfurt over a ten year period.

Methods: In a retrospective study we analysed the development of frequencies, circumstances of exposure, symptom severity, age groups, and substances involved in all HEVM-related inquiries to the PIC Erfurt from the beginning of 2002 to the end of 2011.

Results: In total, 379 cases of HEVM with 398 veterinary medicines were registered. In 350 cases of HEVM, only one veterinary medicine was involved. Although cases of HEVM increased almost twofold from 28 in 2002 to 46 in 2011 their relative frequency compared with all cases of exposure remained almost constant at 0.30% (0.28–0.32%) over the same period. Age groups involved in HEVM were more often children 54.7% (toddlers 45.1%) and less frequently adults 44.8% than in all exposures (children: 49.6% (toddlers 34.5%); adults 49.4%). The portion of accidental exposures was higher in HEVM (83.2%) than in all exposures (58.9%), whereas the portion of suicidal exposures was lower (HEVM: 6.7%, all exposures: 23.7%). Most frequent veterinary medicines in HEVM were antiparasitic products (124/398) such as insecticides and repellents (32/398), other ectoparasiticides for topical use (15/398), and pyrethrins and pyrethroids (11/398) followed by antiseptics and disinfectants (68/398) and anti-infectives for systemic use (27/398). HEVM mostly resulted in no symptoms to mild symptoms (82.4%) and rarely in moderate (8/379, 2.1%) or even severe symptoms (3/379, 0.8%). All cases of HEVM with severe symptoms occurred in suicidal exposures to products for animal euthanasia (2/379) or methadone (1/379) taken by veterinary surgeons.

Conclusion: In comparison to other human exposures, HEVM are rare. Most accidental HEVM in laymen result only in either no symptoms or mild symptoms. If veterinary surgeons, however, swallow or inject products for animal euthanasia or opioids with suicidal intention, severe symptoms can be expected.

116. The greater proportion of the inquiries to the Norwegian Poisons Centre is due to self-inflicted exposures

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Objective: Our objective is to investigate the attributes of inquiries to the poisons information centre.

Methods: Annual reports from 1984–1995 and 2 separate inquiry-databases for the period 1996–2011 were searched for data regarding self-inflicted incidents or incidents related to abuse (hereafter called self-inflicted incidents).

Results: The overall number of inquiries per year had risen from approximately 2500 in the mid-80s to 41,000 in 2008, but there has been a reduction over the last 3 years. This reduction is likely due to more readily accessible information on the Internet. In the 1980s/1990s the majority of calls involved small children: approximately 60% of the patients were younger than 4 years of age. In 2011 only 42% were less than 5 years old. The percentage of acute exposures due to home accidents has dropped from 90% in 1990 to 68% in 2011, meanwhile the percentage that are self-inflicted has risen from 6% in the late 1980s to 21% in 2011. In the same period the proportion of acute exposures to pharmaceuticals that were self-inflicted increased from 31% to 40%. Numbers for 2011: where sex is identified, women and men are responsible for 61% and 39% of the self-inflicted incidents, respectively. Sixty-six per cent of self-inflicted pharmaceutical exposures involved women, while men were involved in 62% of other self-inflicted exposures (illegal drugs, gasses, household products etc). In 2011 drugs in the ATC-group N were the main agents in 80% of the inquiries regarding self-inflicted exposures to pharmaceuticals.

Conclusion: The proportion of acute incidents that are self-inflicted has risen four-fold over the last 25 years to a record high of 21%. The proportion is now similar to that found in USA which was 20% in 2010.¹

Reference

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117. Changes in referral rates for acute toothpaste ingestions reported to the NPIS

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Objective: In June 2010, the management advice on TOXBASE® (the UK poisons database) for toothpaste ingestion changed, from advising medical assessment in patients developing anything other than minor gastrointestinal symptoms to advising observation in patients ingesting over 5 mg/kg fluoride, and further management in those ingesting over 10 mg/kg fluoride. We investigated the amounts ingested, features present, and advice given in cases of acute toothpaste ingestion reported to the UK National Poisons Information Service (NPIS) before and after this change.

Methods: Using data extracted from UKPID, a centralised NPIS telephone enquiry database, we reviewed cases involving toothpaste

ingestion from 21/06/2007 to 20/06/2012. Data from the three years prior to TOXBASE® advice changing, and the following two years were compared.

Results: The NPIS received 355 calls regarding acute toothpaste ingestion over the 5 years: 158 in 2007–2010, and 197 in 2010–2012; an 86.9% increase in annual calls. Over the same period, total calls received by NPIS fell by 8.8%. The number of calls from NHS Direct/NHS24 (public access services) increased from 47 (29.7% of all toothpaste calls) in 2007–2010 to 89 (45.2%) in 2010–2012; a 183% increase in annual calls. 299/355 (84.2%) patients were aged under 4 years. 256/355 patients (72.1%) had remained asymptomatic since ingestion (117/158 [74.1%] in 2007–2010; 139/197 [70.6%] in 2010–2012). 83/355 (23.4%) had minor symptoms, most commonly vomiting (31/83 [37.3%]) and abdominal pain (21/83 [25.3%]). 7/83 patients (8.4%) had persistent vomiting, constituting moderate severity. The mean reported volume of toothpaste ingested was 35.4 mL in 2007–2010, and 38.4 mL in 2010–2012. The mean fluoride dose in asymptomatic and symptomatic patients was 3.89 mg/kg and 4.78 mg/kg respectively. The lowest dose associated with symptoms was 1.6 mg/kg. 38/355 patients (10.7%) were referred for medical assessment; 5/158 (3.2%) in 2007–2010, 33/197 (16.8%) in 2010–2012. The mean reported fluoride dose in referred patients was 6.96 mg/kg in 2007–2010 and 6.95 mg/kg in 2010–2012.

Conclusion: Changes to TOXBASE® management advice for toothpaste accurately reflected the potential for moderate symptoms to occur following ingestion. Similar amounts of toothpaste/fluoride were ingested before and after June 2010; however more than 5 times as many patients were referred after management advice changed.

118. Implementing the first step of the article 45 CLP-regulation: Notification of “dangerous mixtures” under the new § 16e Chemicals Law in Germany

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Objective: Since 20 January 2009, the EU-CLP Regulation (EC) No. 1272/2008 (Classification, labelling and packaging of substances and mixtures) has been in effect. Article 45 stipulates compulsory reporting of formulations of mixtures by industry for emergency health services. For adaptation of the CLP Regulation on a national level, the German government implemented Art. 45 CLP-Regulation into the § 16e (Chemicals Law - Chemikaliengesetz). For a transition period (9th November 2011 limited to the 1st July 2014) German industry can already start to use “Art. 45-Electronic Product Notification” via an adapted BfR-Electronic Product Notification Portal.

Methods: Since 2007, notification of formulations of detergents and cleaning agents has been performed by file transfer in XML-format. This procedure was developed by the BfR and had been well adopted by industry. This format was refined by the BfR to ensure that data on all notifiable products and data reported on a voluntary basis can be transmitted in XML-format. This prototype and the procedures have been practice-tested in cooperation

with a major enterprise (Henkel, Düsseldorf). After final testing the BfR-database has been adapted to the new requirements of the CLP-Regulation on e.g. labelling and all important data, including clear identifiers (e.g. product identification element) which can be exchanged in the new format.

Results: The § 16e (new) has been successfully adapted to the CLP Regulation (EC) No. 1272/2008: 1) governed by public law with a transition period in awaiting the EU-harmonisation dataset for product notifications and 2) technical in having an adapted BfR-XML Electronic Notification Portal which carries all the requirements for the rapid adaptation to the future EU standard data set. With the new § 16e the notification of dangerous mixtures is considerably extended. Products with all hazard identifiers – commercial/non-commercial – have to be notified. The increase is already visible in 2012. From January to October 38,735 dangerous mixtures (excluding biocides) had been notified. This represents a 25-fold increase compared to 2011.

Conclusion: A universal electronic notification procedure for industry will enable BfR to considerably increase the number of product notifications received, processed and communicated to German PCCs.

119. A European Chemical Emergency Network: Developing capabilities for responding to cross border chemical health threats [20121101]

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Background: Across the EU there is a significant difference in Member States response capability to serious chemical health threats, particularly transboundary events.¹ For serious events affecting public health, there are a number of legal requirements that have been put in place to notify others (e.g. WHO through International Health Regulations²). A European notification system to promote a rapid response to a chemical event (RAS-CHEM) has been successfully developed.³ A set of standard operating procedures (SOPs) and guidelines has been developed to govern the implementation and management of RAS-CHEM. However there is still a need to strengthen and streamline a harmonised approach to dealing with chemical incidents of cross border significance.

Discussion: European Chemical Emergency Network (ECHEMNET) will: 1. further develop an EU-level network of Member State representatives for 'ad-hoc' expert advice pertaining to emerging chemical emergencies; 2. further develop the SOPs and guidelines for the assessment and management of transboundary events; 3. engage with experts, end-users and stakeholders; 4. test technical outputs with 'developed' and 'live' incidents.

The ECHEMNET project aims to encourage interest in the work within the poisons centres community. ECHEMNET welcomes interest from attendees in joining the project as a collaborative partner.

Conclusion: The project will ensure that a pilot network of expert risk assessors is formed, tested and functioning to aid in the co-ordinated response to serious transboundary chemical health threats.

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120. National Poison Data System environmental encounters: Pesticides and carbon monoxide over time and Geographic Information System

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Objective: We examined 3 subsets of US National Poison Data System (NPDS) encounters from 2000–2012: all pesticides (Pesticides), pyrethrins/pyrethroids (Pyrethrins), carbon monoxide (CO), and all exposures (All).

Methods: Geographic data and change over time (COT), in particular changes within the year (seasonality), and differences among NPDS population-adjusted exposures based on by-state linear regression from 1-Jan-2000 through 3-Nov-2012, and geographic relationships for seasonality based on mean temperature data by state by month were analyzed. Raw data plots versus time, descriptive statistics, and multivariate modeling using SAS JMP 9.0.0 were used. Analysis included state, zip, day, week, month, season, and year. Results were judged highly statistically significant (HSS) where p-value (2 sided) was < 0.0001.

Results: Variation among states was greater for CO versus the other 3 (Table 1). Seasonality showed a spring-summer decrease for CO and the converse for all other groups. Seasonal variation and temperature relatedness were greatest for Pyrethrins and least for All exposures. Anomalies were most frequent for CO and least frequent for All exposures. Population adjusted Geographic Information System (GIS) differences, seasonality, and temperature dependence were HSS for all 3 toxins. COT was HSS and increasing for Pyrethrins and decreasing for CO.

Conclusion: Understanding toxin-specific seasonality and COT trends can: 1) help focus research, public and professional

Table 1. NPDS data for pesticides and CO over time.

Measure/Model Parameter, N	Carbon Monoxide	All Pesticides	Pyrethrins	All Exposures
Exposures/year, US, mean (2000–2012), N = 13	15,283	91,323	24,153	2,337,594
Exposures/day, US, mean (2000–2012) [95% CI], N = 13	42.2 [39.6, 44.9]	253 [245, 261]	67.2 [57.8, 76.6]	6473 [6285, 6661]
Exposures/day, US, 2012/2000 = ratio, N = 2	32.2 / 45.4 = 0.708	253 / 230 = 1.10	90.9 / 38.5 = 2.36	6269/5710 = 1.10
Exposures/day/mil-pop by state, median (min, max), N = 48	0.168 (0.0511, 0.407)	0.908 (0.501, 1.54)	0.240 (0.124, 0.445)	22.9 (15.1, 44.4)
Seasonality, US (% of mean) winter/spring/summer/fall, N = 52	49.4/–37.3 /–43.4 /31.2	–46.4/34.1/48/–35.7	–52.5/22/66.5/–36.1	–3.16/3.51/4.96/–5.30
Contribution of Temperature by state by month, Coefficient, % of mean per year [95% CI], N = 7082	–3.76 [–4.38, –3.15]%	2.55 [2.31, 2.79]%	0.555 [0.24, 0.871]%	–0.061 [–0.185, 0.0637]%
Linear Change over Time, Slope, % of mean per year [95% CI], N = 7082	–2.56 [–3.02, –2.1]%	–0.432 [–0.617, –0.248]%	5.1 [4.87, 5.34]%	0.232 [0.131, 0.334]%
Anomalies in residuals from multivariate model, Anomalies with $Z > 2$ of states x months, N = 7082	228 of 7082	169 of 7403	209 of 7194	69 of 7440

education, and intervention programs; 2) form the basis of an adaptive threshold for real-time surveillance of poisoning anomalies.

121. Initial reception of the TOXBASE® app, a poisons information resource for mobile devices

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Objective: To assess the initial response from users of the TOXBASE® app for mobile devices.

Background: TOXBASE®, the UK Internet poisons information database, has been available to NHS healthcare units since 1999. Currently, 2580 (37.1%) registered units are hospital-based, 2669 (37.3%) are general practices, and 363 (5.2%) are ambulance services. Responding to advancing technology and user feedback, a TOXBASE® app has been developed for use by individual healthcare professionals, allowing greater user mobility and off-line availability.

Methods: Pre-development, all registered TOXBASE® users were invited to provide their thoughts on the proposed development by completing an electronic questionnaire. TOXBASE® app data for the first 6 weeks following launch (1/10/2012–11/11/2012) were analysed to ascertain user type and database usage, and compared to data from online TOXBASE® during the same period.

Results: 157 pre-development questionnaire responses were received. One hundred and four (66.3%) responded they would consider using such an app. Reasons provided by those who would not included satisfaction with the existing online database, unavailability of suitable devices, and infrequent need for poisons information. Respondents indicated they anticipated using the app for multiple reasons: “managing patients” 93 (89.4%), “maintaining local protocols” 40 (38.5%), “personal education” 72 (69.2%),

and “teaching others” 5 (4.8%). Of those who indicated they would use an app, 56 (53.8%) worked in hospitals, 27 (26.0%) in general practice, and 18 (17.5%) within ambulance services. Six weeks after app launch, 134 individuals had subscribed. Sixty-one (45.5%) were hospital-based, 15 (11.2%) worked in general practice, and 46 (34.3%) within ambulance services. Paracetamol was the top substance accessed by both online (12,101[9.4%]) and app (72[7.4%]) users. The online top-20 contained one drug of abuse (786[0.6% accesses]) and 6 antidepressants (10,538[8.2%]). The app top-20 contained only 2 antidepressants (26[2.7%]) and featured 7 drugs of abuse (75[7.7%]).

Conclusion: Six weeks from the app launch subscriber numbers are still building. However, evaluation before and after introduction suggests: 1. users perceive the TOXBASE® app as primarily useful for managing patients but also potentially of benefit for personal educational development; 2. compared to online registrations, a higher proportion of hospital and ambulance users have subscribed; 3. compared to online database usage a higher user interest in drugs of abuse is evident.

122. Enquiries to the National Toxicological Information Centre from the general public

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Objective: The National Toxicological Information Centre (NTIC) in Bratislava was founded in 1968. It has been providing information to the general public since 2001 which now accounts for a significant proportion (23%) of enquiries to the NTIC. This study was performed to describe enquiries from the general public and to determine how many were related to non-toxic exposures.

Methods: All telephone enquiries to the NTIC from the general public about human cases of poisoning between 1 January 2001 and 31 December 2011 were retrospectively reviewed. Data was

Table 1. Advantages and disadvantages of the Cloud system.

Advantages	Disadvantages
No loss of NPIS services due to third party human error.	Development of a complex system requires thorough user testing prior to implementation.
Co-operative working practices allowing greater integration of geographically distinct units.	Contractual limitations on the number of agents logged onto the Cloud, with financial penalties should the limits be exceeded.
Increased functionality: agents can transfer calls to other agents, set up conference calls with NPIS Consultants etc.	Considerable time required to train staff to use the new system.
Greater resilience (calls can be routed to other locations easily).	Fault location can be difficult when a problem occurs.
Potential for allowing greater staff resource during periods of increased demand, including remote access.	Main services rely on Internet connection (although users can revert to 'phone only' when Internet access is lost).
Reporting tools (Real Time and Historic).	
Provides secure recording facilities.	

collated on patient age, circumstances and location of the poisoning incident, agents, poisoning severity score and treatment advice.

Results: The general public made 5687 enquiries about human poisoning during the study period. Three thousand, five hundred and four (61.6%) patients were children, mostly under the age of 5; 2183 (38.4%) were adults. Most exposures (97.8%, n = 5561) were accidental and 86.8% (n = 4930) of all exposures occurred in the home or a domestic environment. Household products (39.1%) and drugs (26.2%) were the most common agents. Four thousand, four hundred and six (77.5%) patients were asymptomatic at the time of the call, 743 (13.1%) had mild features and 79 (1.4%) had moderate features. Symptoms were not known or were unrelated to poisoning in 454 cases (8.0%). Five adults had severe features following intentional overdose. Two thousand, nine hundred and eleven patients (51.2%) required no treatment and a further 671 (11.7%) could be managed at home with advice to seek medical attention if symptoms developed. Eight hundred and thirty-one patients (14.6%) were immediately referred to a hospital.

Conclusion: The majority of the enquiries from the general public were about accidental, non-toxic exposures in children. Most of these patients required no treatment or could be managed at home. The number of these consultations increases every year. In these cases a consultation with a toxicological centre significantly reduces the necessity of a medical facility visit and saves the costs of health care.

123. Advantages and disadvantages of using Cloud technology to provide telephone services to the National Poisons Information Service

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Objective: To discuss the implications of using Cloud technology to deliver telephone services to the National Poisons Information Service (NPIS).

Methods: An assessment of Cloud implementation from an NPIS perspective, specifically the preparation, implementation and post-implementation phases.

Results: Before 2005 NPIS centres were independent units. Since 2005 a number of ground-breaking measures have been taken to integrate the service. These include establishing a three-centre national enquiry answering rota and developing a shared

enquiry-logging database (UKPID). Previously, telephone calls were delivered to NPIS centres via a system known as inbound architect. Telephone enquiries were delivered according to a 24 hour rota but the system was prone to third party human error which on occasion had an impact on NPIS services. The transfer to Cloud involved establishing user requirements, testing the bespoke system prior to implementation and training of NPIS staff to use the new system. NPIS were supported by the telecommunications company BT throughout. The following advantages and disadvantages of the Cloud system have been identified in Table 1.

Conclusion: Cloud technology has helped to integrate the NPIS, facilitating co-operative working practices and conferring a number of operational advantages. However as with any technologically complex system there are impacts in terms of staff training and dealing with faults.

124. EAPCCT survey of European poisons centres: Staff profile

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Objective: To survey staffing levels and training in European poisons centres (PC).

Methods: A SurveyMonkey® questionnaire with 66 questions was sent out to all European PCs by e-mail in June 2012.

Results: By 1 Nov 2012 responses had been received from 32 PCs in 21 different countries (response rate 41.6%); 31 centres answered most of the questions relating to staffing. Twenty-seven (87.0%) centres had a medically qualified director, 3 directors were pharmacists and another had an MSc in chemistry/biology. Twenty-four (77.4%) centres were staffed by dedicated information staff throughout opening hours; six partially and in one case there were no dedicated staff. Staff dealing with poisons enquiries included physicians (25 centres), scientists/specialists in poisons information (SPIs) (16), pharmacists (10), nurses (7), medical students (1), veterinarians (1). All centres except one (non-graduate nurses) required staff to have at least a university degree. In 23 centres physicians also treated poisoned patients, with the proportion of working time spent on this averaging 32% (range 3–100%; median 20). Access to a medical toxicology specialist was available 24/7

in 25/30 responding centres, with <24 hour access in 3 and no access in 2. Specific training was provided for new SPIs in 24/30 responding centres, usually organised by the director, manager and senior staff and lasting from 1 day to 1 year; 18 centres had written guidelines for new staff. No formal assessment of new staff was made in 7 centres, in the other 23 who replied some combination of observational assessment (23), oral (7) and written (4) examination occurred. Eighteen of 30 centres had a programme of continuing professional development for staff. The median number of professional staff in the 27 responding centres was 14 (range 1–36).

Conclusion: Conclusions that can be drawn from this survey are limited by the low response rate, especially for some questions. Although most centres had appropriate 24 h medical toxicology support, specific training for new scientific staff with formal assessment on completion and a programme of professional development, these were not always available.

125. Abuse of energy drinks among young people: Experience of the Pavia Poison Control Center

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Objective: Abuse of energy drinks among young people, often in combination with alcohol or other substances, is a worrying and growing concern in Europe and the United States. The energy drinks, generally non alcoholic, contain mainly caffeine (80–200 mg) and other substances such as taurine, guarana, ginseng, yerba mate, ginkgo biloba, creatine, L-carnitine, glucuronolactone, sugars, antioxidants, vitamins. Consumers are often unaware of the potential health hazards. The aim of the study was to describe all cases of energy drink abuse referred to the Pavia Poison Control Center (PPC) and the clinical effects presented in these intoxications.

Methods: A retrospective analysis of all cases of acute poisoning related to ingestion of energy drinks in the period between 1 January 2007 and 30 June 2012 referred to the PPC was performed. Age, medical history, any co-consumed substances and the clinical picture were evaluated.

Results: Twenty-four cases were included (20 male; mean age 26.5 years). In 12 cases, the energy drink was ingested for the purpose of abuse, in combination with alcohol (7/12) and other drugs of abuse (4/12). In 6 other cases the energy drink has been used with a stimulant aim; in 4 cases for the purpose of suicide (together with medications) and accidentally in 2 cases (children aged 6 and 7 years). The symptoms most frequently present on admission were: psychomotor agitation (46%), tachycardia (33%), vomiting (25%), palpitations (21%) and gastric pain (17%). Other reported signs of intoxication were mydriasis, confusion, drowsiness, hallucinations, delirium, fainting, high blood pressure, nausea, tremors, dyspnea, fever, flushing, headache, malaise, rhabdomyolysis, myoclonus, diaphoresis and motor incoordination. All patients fully recovered in a few hours with the exception of a young woman who died,

after developing acute heart failure, and who was suspected to have taken slimming products, caffeine in large amounts and beta blockers.

Conclusion: The abuse of energy drinks should be suspected in patients, especially young people, who present to the emergency department with agitation and tachycardia. The ingestion may be associated with the abuse of alcohol and drugs of abuse.

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126. Caustic effects due to sodium hypochlorite ingestion: Toxicological properties, clinical manifestations and esophago-gastro-duodenoscopy

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Objective: Medical literature lacks data concerning specific management of sodium hypochlorite ingestion.¹ We describe the clinical manifestations and Zargar classified esophago-gastro-duodenoscopy (EGDS)² of a retrospective case series of sodium hypochlorite ingestions from Pavia Poison Centre experience.

Case series: 109 cases of 1–5% sodium hypochlorite (household bleach) confirmed ingestions have been retrospectively evaluated during a 20 month period (Jan 2011 – Aug 2012). Deliberate ingestion was registered in 31/109 (28%) patients, while 78/109 (72%) accidentally ingested hypochlorite. All patients presented clinical manifestations characterized by abdominal pain (69/109; 63%) and spontaneous vomiting (54/109; 49%); no fatal cases were registered. Deliberate ingestion of 100–200 mL (estimated) occurred in 19/31 (61%) cases and more than 200 mL in 12/31 (39%) cases. The largest number of deliberate ingestions occurred in adult patients (27/31 aged 18–75) and a minority in younger patients (4/31 aged 14–18). Among deliberate ingestions 25 patients underwent EGDS and 13/25 (52%) presented moderate to severe esophageal-gastric lesions (9 grade 2A; 2 grade 2B and 2 grade 3). Among accidental ingestions 48/78 (61%) patients were under 18 years of age and 30/76 (39%) were 18–73. Nineteen (25%) accidental ingestions underwent EGDS that showed moderate gastric-esophageal lesions (grade 2A) in 10/19 (52%) patients. Three patients (2 accidental, 1 deliberate) presented a clinical worsening of esophageal and gastric lesions during the 12–24 hours following sodium hypochlorite ingestion.

Conclusion: Hypochlorite ingestion may represent a medical emergency. However clinical and toxicological evaluation may be complex and related to multiple critical aspects (e.g. hypochlorite concentration, pH solution, amount ingested) which are not always assessable. Thus, the diagnosis and the therapeutic approach can be difficult, and not standardized in the medical literature. Considering our case series, more than half of the symptomatic accidental ingestions ('one swallow') of 1–5% hypochlorite solution may present with moderate-severe esophageal-gastric lesions. EGDS should be performed within 12–24 hours from ingestion. In deliberate massive ingestions it would be reasonable to perform a prompt EGDS in the emergency setting followed by a second-look

EGDS within 12–24 hours aimed to evaluate a potential clinical worsening of gastric-esophageal lesions.

References

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2. Zargar SA, Kochhar R, Mehta S, et al. The role of fiberoptic endoscopy in the management of corrosive ingestion and modified endoscopic classification of burns. *Gastrointest Endosc* 1991; 37:165–9.

127. Severe respiratory and esophageal effects resulting from ingestion of unit dose liquid laundry detergents: A case report

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Objective: Unit dose liquid laundry detergents (UDLDs) are water soluble capsules containing 15/32 mL of highly concentrated cleaning agents. The risk of corneal damage and severe respiratory effects due to accidental exposure of young children had been initially documented in a few European Countries^{1–3} where these products were introduced in the market in 2001. In Italy, UDLDs were marketed for the first time in July 2010. Between July 29, 2010 and October 31, 2012, the National Poison Control Center in Milan handled 1,162 cases of exposure to UDLDs. Among them, 94% were <5 years old, 74% were exposed by ingestion (862/1162) and 23% reported at least one sign/symptom possibly related to the exposure. The present contribution is aimed at describing a case with prolonged respiratory clinical effects and esophageal lesions due to ingestion of a UDLD.

Case report: A 13-month-old, 10.5 kg, girl experienced breathing difficulties, repeated episodes of apnea, and vomiting immediately after ingestion of a UDLD. On arrival at hospital, minutes after ingestion, the child was breathing normally. However, she was noted to be irritable. Oral examination showed inflamed pharynx and increased bronchial secretions. Five hours later she began coughing and wheezing and was treated with methylprednisolone (2 mg/kg). Laryngoscopy revealed epiglottic, arytenoids and hypopharynx oedema. Gastroscopy found longitudinal and circumferential esophageal lesions and the lower middle third of the stomach contained bloody contents. Bilateral lung opacities and esophageal lesions were demonstrated by thoracic ultrasounds. Chest x-ray showed perihilar bronchial wall thickening. The child needed endotracheal intubation and mechanical ventilation for 11 days. She was extubated on the 12th day after ingestion. Full respiratory recovery followed over the next four days. Forty days after exposure gastroscopy was normal.

Conclusion: Ingestion of UDLDs poses a relevant public health issue since these products can cause severe injuries in children. With particular reference to exposure by ingestion, patients may present with severe respiratory prolonged effects and gastroenteric lesions.

References

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128. Ocular toxicity of unit dose liquid laundry detergents: A case report

Anna Celentano, Fabrizio Sesana, Giovanni Milanesi, Antonella Pirina, Francesca Assisi, Maurizio Bissoli, Rossana Borghini, Tiziana Della Puppa, Valeria Dimasi, Marcello Ferruzzi, Paola Moro, Iliaria Rebutti, Angelo Travaglia, Franca Davanzo

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Objective: Between 1 August 1 2010 and 31 October 2012 the Milan Poison Control Center collected 1,162 cases of exposure to unit dose liquid laundry detergents. One hundred and fifty-eight cases (14%) were ocular contact. We describe an ocular exposure with prolonged clinical effects.

Case report: A 40 year old female attempted to separate two unit dose liquid laundry detergents from their container. One of the units broke and the contents splashed into her right eye. Ocular pain developed immediately. She rinsed the eye thoroughly with water, presenting to the hospital emergency department (ED) about 1 hour after exposure. In the ED, she was in obvious distress. Examination showed localized periorbital edema, lacrimation, ocular hyperaemia, photophobia, ptosis and reduction in visual acuity. Fluorescein examination revealed corneal abrasion. Treatment included ocular irrigation, antibiotic ointment, and eye patch for 4 days. Treatment continued with tobramycin-dexamethasone drops for two weeks. Symptoms attenuated within twenty days. Ocular healing was complete after a month with no residual effects.

Conclusion: Corneal lesions due to ocular exposures to unit dose liquid laundry detergents are described and the clinical effects may be disabling for many weeks.

Reference

1. Fayers T, Munneke R, Strouthidis NG. Detergent capsules causing ocular injuries in children. *J Pediatr Ophthalmol Strabismus* 2006; 43:250–1.

129. Skin injuries resulting from accidental exposure to unit dose liquid laundry detergents: A case report

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Objective: Unit dose liquid laundry detergents (UDLDs) are water soluble capsules containing 15/32 mL of highly concentrated cleaning agents. In Italy, UDLDs were introduced in the market in July 2010. Between July 29, 2010 and October 31, 2012, the National Poison Control Center in Milan handled 1,162 cases of exposure to UDLDs. Among them, 94% were <5 years old, 9% (n = 94) were by skin exposure. The present contribution is aimed at describing a case presenting with skin injuries due to exposure to the content of an UDLD.

Case report: A 28-year-old female was exposed via skin contact alone to the content of a UDLD. The incident was caused by accidental breakage of the capsule. The involved body area was lower abdomen and inguinal. The woman immediately rinsed the exposed area with plenty of cold water. The skin appeared hyperemic, edematous and excoriated. Two days after exposure, the woman referred to a first aid service where she was prescribed a steroid ointment and an oral antibiotic. She applied the ointment three times a day. In the following days dark spots were present in the exposed area. The lesions were completely healed five months after exposure.

Conclusion: Exposure by skin contact to UDLDs content can cause skin effects.¹ Since the capsules contain concentrated surfactants, the mechanism of action could be related to skin barrier impairment and damage of stratum corneum. Individual hypersensitivity can worsen chemical effects and lead to long lasting damages.

Reference

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130. Market withdrawal of a caustic product due to infraction of the Belgian pesticide regulation and misleading labeling

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Objective: Potassium hydroxide (KOH) is a strong base with numerous applications. Misuse and underestimation of the dangers can lead to severe caustic burns. We describe the process leading to the withdrawal of a product containing a caustic concentration of KOH due to inappropriate labeling.

Results: Since 2010, we stumbled upon cases of caustic burns with a product called “Destructeur Total – Totaalbestrijder”, containing up to 10% KOH. It was *de facto* presented as an “ecological” herbicide. The herbicide action was suggested by the suggestive trade name and by the label showing a man applying the product on weeds using a backpack sprayer, without any protective clothing. The label mentioned the words “ecologic”, “without pesticides”, “under plantations” and showed a ladybird. The product had not been authorized as a herbicide. The competent federal ministry was informed and the product was withdrawn from the market for infraction of the pesticide regulation. The manufacturer reintroduced virtually the same product on the market as a cleaning agent for stone terraces under the name of “Total Clean”, fulfilling all legal obligations. The label was virtually unchanged. We kept on identifying

cases and advocated taking action against the product for two reasons: 1° although complying with the regulation, the front label suggests an innocuous product; 2° application of a caustic by backpack spraying poses unacceptable risks through mist drift and through manipulation risks, e.g. leakage or tube failure. Finally, in November 2012, there was a Ministerial Decree in preparation aiming to remove the product from the market. From January 2010 till November 2012 we detected 7 incidents. This resulted in some cases with 3rd degree caustic skin burns on the back (2), the leg (1) and the fingers (1). The remaining cases had significant ocular (2) or dermal (1) exposure, but were lost to follow-up.

Conclusion: The toxicovigilance of the Belgian Poison Centre led to the withdrawal of a caustic product due to inappropriate labeling. We advocate against the use of caustics as cleaning agents. We warn that caustic products can be presented as innocuous even if they comply with the regulations.

131. A case of corneal lesion after use of anti-fog for swimming goggles

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Objective: We present a case of corneal lesions after inappropriate use of an anti-fog product on swimming goggles.

Case report: A man experienced bilateral corneal lesions after 1 hour’s accidental exposure to a diluted anti-fog product. The day before taking part in an Ironman (long distance triathlon with 3.8 km swim), a 51 year old man sprayed his swimming goggles with an anti-fog agent. Instead of rinsing the goggles after the product had been sprayed, as stated in the instructions for use, he let it dry. The day after, during the swimming part of the race, water entered into the goggles. No pain but a pressing need to keep the eyes closed was felt while swimming. Once out of the water, a severe painful burning sensation quickly developed in both eyes and it was progressively almost impossible to keep the eyes open. The athlete was referred to the hospital. The ophthalmologist diagnosed a profound corneal abrasion on 50% of the surface of the left eye and middle corneal abrasion on 70% of the right eye. After symptomatic treatment, the patient fully recovered within 9 days.

Discussion: The following ingredients are mentioned on the product data sheet: <5% anionic and non-ionic surfactants (1–3% docosate sodium and <1% non ionic surfactant ethoxylate), 0.1–0.2% formaldehyde solution and 4–6% propan-2-ol, all classified as eye irritants. As the product was allowed to dry during 15 hours, we assume that isopropyl alcohol and formaldehyde evaporated and that only the surfactants, made soluble in water, came in contact with the eyes for about 55 minutes. The final product is not classified according to the old dangerous preparation directive and does not carry any warning label. According to the new Classification, Labelling and Packaging of substances and mixtures regulation (CLP), the product should at least be classified as an eye irritant and carry a hazard pictogram.

Conclusion: The absence of a hazard symbol does not exclude disabling eye damage after exposure to a surfactant based mixture. The instructions for use should carry a user warning. Labeling according to the new CLP regulation will improve users’ information.

132. A case of immediate and delayed skin reaction after oral contact with cashew seed shell

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Objective: We present a case of immediate and delayed skin reaction after ingestion of cashew apple and oral contact with the soft shell of the cashew seed.

Case report: During a journey in Brazil, a 17 year old Belgian woman, with no known allergy, tasted a mouthful of a raw cashew apple. She was unfamiliar with the fruit and bit on the inedible soft shell of the cashew seed (better known as cashew nut in the culinary language). She experienced a burning sensation in her mouth. Within minutes, she developed a tickling rash on the forehead (2.5 cm x 0.5 cm) and the abdomen (5 x 7 cm). The tickling quickly resolved. Eight days later, the rash increased in size, evolving towards hives. In addition, 5–6 new itchy lesions, similar in aspect, appeared on both sides of the abdomen. She was treated during 5 days with oral antihistamine and topical corticosteroids with no improvement of the rash but relief of the itching. Lesions progressively attenuated and completely resolved over 4 to 5 weeks. The oil produced by the cashew nut tree (*Anacardium occidentale*) is irritating and can induce skin sensitization. The soft shell of the seed produces a highly irritating oily juice used in some areas to treat warts. It contains anacardic acid, chemically related to urushiol and causes allergic contact dermatitis. Eczema can develop in children playing with fresh cashew nuts. Professionals harvesting nuts can be affected. Imported toys or jewels made out of nut shell can induce a contact dermatitis. Roasted cashew seeds are edible and commonly sold as cashew nuts. Cashew nuts are known as a food allergen and are responsible for anaphylaxis and systemic contact dermatitis after ingestion. The patient however had previously eaten roasted cashew nuts without reactions.

Conclusion: Cashew apple is unknown in Europe. When invited to taste local fruit, travellers should be informed which part is edible. Limited contact with the shell of the cashew seed resulted in this patient in immediate and delayed long lasting dermatitis.

133. Bone scintigraphy images in a case of 70% hydrofluoric acid burns treated with intra-arterial calcium gluconate

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Objective: To report a case of 70% hydrofluoric acid (HF) digital burns treated with intra-arterial calcium gluconate, and investigated with bone scintigraphy.

Case report: A 28 y male worker from a plastic bottle recycling plant had touched a supposed empty bottle of 70% HF without gloves. Severe progressive pain started after 20 minutes. He was seen at the emergency department (ED) nearby and the lesions were wrongly interpreted as strong acid burns, and treated only with analgesics. He was kept under observation for 36 hours and sent to our ED when HF burn was clinically diagnosed. At admission he was complaining of excruciating pain (PAS = 10), presenting both anterior parts of his thumbs with epidermal whitish discoloration and no ulceration. Considering the digital localization, the degree of pain, and the high HF concentration, intra-arterial 2% calcium gluconate solution was established in an infusion pump in his two radial arteries.¹ Due to the late start of the procedure no significant improvement was seen in pain, as expected in the first hours, and the infusion was maintained for 36–48 hours. After that the pain started to subside and necrotic tissue appeared in the center of the lesion. MDP-99mTc bone scintigraphy performed 48 hours after the accident, showed only areas of bone remodeling in both thumbs. Despite the thorough deep tissue debridement performed after 10 days no skin graft was necessary, and a nice scar covered the entire area.

Conclusion: HF acid is a weak acid with low dissociation rate, which allows the fluorine to reach deep soft tissues due to its affinity to Ca and Mg ions. Bone lesions, tissue necrosis, and even loss of digital endings, are very common. The specific antidote is calcium gluconate, given intravenously, sub-cutaneously, intramuscularly around the lesion, or intra-arterial in the case of digital injuries¹. Given the bone scintigraphy results and the outcome of this case, we assume it can probably be used as a prognostic predictor in such cases.

Reference

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134. A retrospective analysis of caustic ingestions in Slovakia

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Objective: The ingestion of caustic substances can represent a serious medical problem. The aim of this retrospective analysis was to study the caustic effects of chemicals in patients hospitalized in the Children's Faculty Hospital in Bratislava and other Slovak hospitals, whose medical reports were involved in the analysis after consultation with the National Toxicological Information Centre.

Methods: We reviewed the medical reports registered from January 1998 to December 2010. The following data were analysed: age, sex, intent of exposure, ingested substances and clinical severity. The corrosive burns were defined according to Zargar's classification.¹

Results: We analysed 328 patients who were hospitalized with caustic substance ingestion, but only 189 (58%–98 children, 91

adults) had complete urgent endoscopic findings at hospital admission. Half of the cases (52%) were children aged three years on average. Caustic exposures in males were more prevalent (65%). Accidental poisonings were more common (84%) than suicidal ones (16%). Spontaneous vomiting and abdominal pain were among the most common clinical symptoms at admission. Most of the patients (148/189, 78%) showed positive endoscopic findings, out of which children represented 42%. Grade I was present in 70 patients (37%), grade IIa in 40 (21%), grade IIb in 6 (3%), grade IIIa in 15 (8%) and grade IIIb was found in 3 cases (2%). Negative endoscopic findings were indicated in 41 of the patients (22%), and 14 adults (7%) died (grade IV). Eleven patients died after ingestion of strong acids; the majority of the patients ingested hydrochloric acid (55%). One patient died after ingestion of strong alkali and two after paraquat.

Conclusion: Edema and hyperemia (grade 1) were the most frequent finding in the children as well as in the adults. Ingestion of concentrated strong acid, mainly hydrochloric acid, was very serious, resulting in death.

Reference

- Zargar AS, Kochlar R, Mehta S. The role of fiberoptic endoscopy in the management of corrosive ingestion and modified endoscopic classification of burns. *Gastrointest Endosc* 1991; 37:165–9.

135. Pepper spray (capsaicin) exposure: Decontamination with amphoteric, chelating and hypertonic solution

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Objective: Pepper spray contains 1–15% of capsaicin. Capsaicin interacts with muco-cutaneous sensory nerve receptors and causes severe facial pain with reflex blepharospasm and lacrimation. The aim of this study was to evaluate an amphoteric, chelating and hypertonic decontamination solution¹ in capsaicin exposure.

Methods: In the prospective study we evaluated patients sprayed in the faces by capsaicin who were admitted to the emergency department (ED) in 2012. Facial pain, blepharospasm, lacrimation and skin redness were self-reported by the patients and clinically assessed by the emergency physicians on arrival and after decontamination with the amphoteric, chelating and hypertonic solution¹ which was sprayed over their faces immediately on arrival. Emergency physicians reported complete, partial or no clinical improvement after decontamination.

Results: A total of 15 capsaicin exposed patients were enrolled with a mean age of 34 years. All patients had their faces deliberately exposed to capsaicin and 4 of them were decontaminated with tap water before arrival, but without significant effects. The average time to presentation was 24 minutes after capsaicin exposure. On arrival the patients had facial pain, blepharospasm, lacrimation and skin redness in 100%, 33%, 53% and 80% of cases, respectively. After decontamination facial pain, blepharospasm and lacrimation completely disappeared or became clinically insignificant in all patients, while skin redness

remained unaffected by the decontamination. Facial pain reappeared in 2 patients (13%), but permanently disappeared after a second spraying with the amphoteric, chelating and hypertonic solution. Two patients (13%) were urgently admitted to the ophthalmologist due to conjunctivitis and blepharitis, but the rest were discharged home within half an hour after arrival at the ED.

Conclusion: Delayed capsaicin decontamination with the amphoteric, chelating and hypertonic solution at the ED effectively reduces facial pain with reflex blepharospasm and lacrimation. The limitation of this study is the lack of control and measurement of clinical symptoms.

Reference

- Goldich Y, Barkana Y, Zadok D, et al. Use of amphoteric rinsing solution for treatment of ocular tissues exposed to nitrogen mustard. *Acta Ophthalmol* 2013; 91:e35–40.

136. Toxic coma in children - nine year retrospective study

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Objective: To study the characteristics of toxic coma in children admitted to a pediatric poisoning department.

Methods: We have performed a retrospective study of children with the diagnosis of coma at the moment of presentation to the emergency department (ED), between 1 January 2003–31 December 2011. The following criteria were taken into consideration: the age, gender, etiology, grade of coma, evolution.

Results: Out of a total of 750 children with coma presenting to the ED during the mentioned period, 445 (59.33%) had toxic etiology resulting from the history and toxicological analysis. The number of patients with toxic coma represented 7.72% out of the total of 5761 cases with poisoning registered in this period. Regarding age we noted two peaks of incidence: 2–3 years (which overlaps the peak of incidence of accidental poisonings) and 14–16 years (the peak of suicidal attempts). Using the REED scale to measure the severity of coma, the following groups were observed: grade 1–185 (41.5%), grade 2–199 (44.7%), grade 3–52 cases (11.6%) and grade 4–9 cases (2%). The main etiology of toxic coma was acute ethanol poisoning and drugs of abuse: 213 patients; followed by neurological medication: 67; unknown: 57; other substances: 47; two or more medicines: 35; Dentocalmin (dental local anesthetic containing lidocaine, menthol and phenol): 21; and isoniazid: 5 patients. Death was noted in 23 patients representing 5.1% out of the total of cases with toxic coma. The involved substances were the following: cholinesterase inhibitor insecticides: 9 cases, sodium hydroxide: 6 cases; hydrocarbons, carbamazepine, heroin, and Dentocalmin: 1 case each; remainder unknown.

Conclusion: Although the presence of coma implies increased severity of poisoning, in children the evolution was favorable (3.06% deaths). The main etiology of toxic coma in children was ethanol with a peak of incidence 14–16 years old.

137. Neuroleptic malignant syndrome toxidrome mimic: A case report

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Objective: Describe a presentation of Herpes Simplex encephalitis (HSE) with clinical similarities to Neuroleptic Malignant Syndrome (NMS).

Case report: A 71-year-old female with a 3-year-history of Parkinson Disease presented to the emergency department (ED) after being found unresponsive. She had abruptly discontinued carbidopa-levodopa 24 hours prior to presentation. Vital signs: temperature 40.3°C, blood pressure 100/60 mm Hg, heart rate 139 beats/minute, oxygen saturation 100% on room air. On physical exam, she had generalized rigidity with decreased reflexes throughout and withdrew to painful stimuli. Due to her rigidity, paralysis was required to facilitate lumbar puncture. Initial laboratory studies were significant for: white blood cells (WBC) 7.0 (61% lymphocytes, 35% neutrophils), bicarbonate 17 mEq/L, blood urea nitrogen 20 mg/dL, creatinine 1.6 mg/dL, glucose 173 mg/dL, AST 100 IU/L, ALT 46 IU/L, lactate 3.7 mMol/L, troponin 1.07 ng/mL, creatine phosphokinase 213 IU/L. Arterial blood gas: pH 7.32, pCO₂ 32 mmHg, and pO₂ 401 mmHg. Lumbar puncture results: tube 1 and 4 were clear with white blood cells 27 and 0; red blood cells 6766 and 508, respectively. Bacterial cultures were negative in blood and cerebrospinal fluid (CSF). Brain magnetic resonance imaging was normal and electroencephalogram showed no focal slowing or epileptiform discharges. Vancomycin, ceftriaxone, acyclovir, bromocriptine, and carbidopa-levodopa were started empirically. On hospital day (HD) 5, Herpes Simplex Virus (HSV) cerebrospinal fluid (CSF) polymerase chain reaction (PCR) resulted positive and bromocriptine was discontinued. Her rigidity resolved and she was discharged to inpatient rehabilitation on acyclovir and carbidopa-levodopa.

Conclusion: NMS is characterized by fever, mental status changes, muscle rigidity, and autonomic dysfunction. Symptoms may occur abruptly and mimic several other life-threatening conditions. While NMS is most commonly associated with medications that block postsynaptic dopamine receptors, it may also be seen with cessation of dopamine precursors. Herpes simplex encephalitis (HSE) has an incidence of 1 in 250,000 individuals per year, and mortality approaches 70% in untreated infections. Clinical manifestations include fever, altered mental status, behavioral changes, headache, neck stiffness, focal neurological deficits, or seizures. HSE presenting with generalized rigidity has not been previously reported; though, this patient's underlying Parkinson's disease and recent discontinuation of levodopa likely influenced this unusual presentation. This case serves to illustrate that NMS must be a diagnosis of exclusion.

138. Valproic acid poisonings: An old and new concern

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Objective: Poisonings involving valproic acid have increased in number and severity in the last year.

Methods: We performed an analysis of valproic acid poisonings admitted to ICU Toxicology of the Emergency Hospital Bucharest from October 2011-October 2012. Data collected included: age, gender, severity score, laboratory values, length of hospital stay, and medical outcome. We made a special follow-up of valproic acid serum concentrations, ammonia, pancreatic enzymes, thrombocytopenia in severe cases.

Results: During the study period there were 133 cases of valproic acid poisoning, 12% of the total number of intoxications (previous years' average 2–3%). All the cases were suicide attempts. Poisonings involving valproic acid as a single agent were 43% of the total. One hundred and one patients had serum valproic acid concentrations greater than 100 mg/L; peak serum valproic acid concentrations ranged from 89–2500 mg/L. Multiple drug exposures involved ethanol, antidepressants and other anticonvulsants. Sex distribution: 59% female, 41% male. Age range was 16–78 years. The poisoning severity score was 1 in 41 cases, 2 in 49 cases, 3 in 38 cases, 4 in 5 cases. Symptoms included altered mental status (71), coma (62), tachycardia (47), metabolic acidosis (15), and hypotension (23). Hyperammonemia was present in 20% of patients, increased pancreatic enzymes in 2%, thrombocytopenia in 10 patients. The mean hospital stay was 52 ± 42.3 hours.

Conclusion: Valproic acid poisonings as suicide attempts have become a real toxicological problem due to the increasing severity of the cases. A peak valproic acid concentration above 500 mg/L correlates with coma, ventilatory support, altered acid-base status, and even multiple organ and system failure.

139. Clinical features and severity of clozapine poisoning

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Objective: The aim of the study was to analyse clinical features and severity of clozapine poisoning cases reported to the Poisons Information Centre (PIC Erfurt) over a ten year period. Additionally, we demonstrate a typical course after ingestion of a potentially lethal dose.

Case series: The PIC Erfurt recorded 97 cases (10 children–10.3%, 87 adults – 89.7%) with a single acute clozapine overdose from the beginning of 2001 to the end of 2011. Suicide attempts represented the greatest proportion of all cases (49%). Other causes were accidental ingestions (33%), adverse effects (4%), and unknown (14%). Doses ranged from 0.4 to 285 mg/kg and 0.1 to 67-fold defined daily dose (DDD) respectively. Symptoms were severe in 8.3%, moderate in 13.4%, and minor in 60.8% of all cases, while 17.5% of patients remained without symptoms. The most common symptoms were somnolence (33.0%), tachycardia (25.8%), and drowsiness (11.4%), followed by coma (8.2%), agitation (7.2%), respiratory insufficiency (7.2%), dysarthria (6.2%), general slowing down (6.2%), hypersalivation (5.2%), hypotension (4.1%) and dizziness (4.1%).

Case report: A 14-year-old female ingested 3000 mg clozapine (approx. 62.5 mg/kg) in the evening before admission. Next morning, she showed increasing loss of consciousness and agitation. She

Table 1. Hospitalizations related to gabapentin or pregabalin abuse.

Age/Gender	Agent (other agents in parenthesis)	Presenting symptoms
55 year-old F	Gabapentin (lorazepam)	Somnolence to coma, tremor, hyperreflexia
28 year-old M	Gabapentin	Headache, myoclonus, hyperreflexia, ataxia, blurry vision
53 year-old M	Gabapentin (methadone)	Coma and respiratory failure due to accidental OD with methadone and gabapentin (hypoxic to 80%)
48 year-old F	Gabapentin (hydrocodone, diazepam)	Somnolence, dry mouth, urinary retention
32 year-old F	Gabapentin (methadone) (sertraline, tramadol)	Serotonin syndrome, fall with trauma (<i>ankle injury</i>), myoclonus, possible seizure, elevated CK, tachycardia
60 year-old F	Gabapentin (zolpidem, diphenhydramine, dextromethorphan, alcohol)	Delirium, hyponatremia, ataxia,
51 year-old F	Gabapentin (alcohol, cocaine)	Delirium, somnolence, ataxia, developed w/d (alcohol/sedative)
33 year-old F	Gabapentin	Somnolence, ataxia, tremor, hyperreflexia (<i>sent from PCP for assessment after abuse ID'd</i>)
20 year-old M	Gabapentin (alcohol, cocaine, oxycodone)	Somnolence to coma, mild hypotension, myoclonus and hyperreflexia
46 year-old F	Gabapentin (methadone)	Coma and respiratory failure, myoclonus, tremor
44 year-old F	Pregabalin (alcohol, possible cocaine)	Seizure, delirium, tachycardia, mild rhabdomyolysis, myoclonus, tremor
31 year-old F	Pregabalin (alcohol, possible cocaine)	Somnolence, disinhibition, slurred speech (<i>sent from addiction specialist for assessment</i>), ataxia
15 year-old F	Pregabalin (tramadol)	Mydriasis, seizure (x 2), ataxia, hyperreflexia
33 year-old F	Pregabalin (alprazolam)	Somnolence, later developed w/d

was comatose with respiratory depression and recurrent seizures 18 to 20 hours after ingestion at admission to the emergency room. Initial heart rate was 140 to 155 beats per minute with normal blood pressure. Clozapine plasma level was 2.9 mg/L, still highly toxic on day 3, correlating with persistent cerebral depression and tachycardia. The further course was complicated by aspiration pneumonia, high fever, pancreatitis, and rhabdomyolysis with transient renal failure. All therapeutic measures were supportive. The plasma level reached the upper therapeutic limit on day 5. The patient was transferred for psychiatric treatment on day 9.

Conclusion: Symptoms and severity of clozapine poisoning cases in our study confirmed the results of a 13-year retrospective study in Switzerland.¹ A minor exceeding of the therapeutic dose can induce severe symptoms, especially in non-adapted individuals.

Reference

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140. Recreational abuse of gabapentin and pregabalin are under-recognized causes of hospitalization related to these prescription drugs

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Objective: Pregabalin and gabapentin are structurally related chemicals and gamma-amino butyric acid (GABA) analogues used for the treatment of pain (i.e. fibromyalgia and neuropathy) and certain anxiety and seizure disorders. There is also abundant off-label use in patients with drug abuse and dependence as primary treatments (i.e. for marijuana or cocaine dependence), as adjunctive agents for pain in this population as well as increasing interest

for the treatment of alcohol withdrawal syndrome. There is very little previous literature describing abuse of these agents. We present a series of patients in which recreational abuse of these drugs contributed to or directly caused hospitalization.

Methods: Retrospective review of a Toxicology Service records from January 1, 2011 to November 15, 2012 for hospitalizations related to gabapentin and/or pregabalin. Cases were included if recreational abuse was identified as the primary reason for use of gabapentin or pregabalin and if abuse contributed to hospitalization.

Results: 14/51 hospitalized cases identified involving gabapentin (10) or pregabalin (4) were due to abuse. Concomitant abuse of other substances occurred frequently (i.e. alcohol, opioids, sedatives and stimulants). Basic information, including presenting symptoms, for the 14 cases is included in Table 1.

Conclusion: Recreational abuse of gabapentin and pregabalin is an underappreciated cause of hospitalization related to these substances. Females appear to abuse these substances more commonly than males. Additional information regarding abuse and dependence of these substances is important due to the increasing frequency at which these agents are being prescribed in particularly vulnerable populations.

141. A case of perphenazine decanoate poisoning

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Background: Perphenazine decanoate (PD) is an antipsychotic depot formulation used in the long-term maintenance treatment of psychotic diseases. We report a case of a 26-year-old woman with a diagnosis of schizophrenia, who took an accidental overdose of PD. To our knowledge it is the first report in the literature of a PD overdose.

Case report: The patient was admitted to the psychiatric emergency department with symptoms of acute psychosis. Initially she was treated with olanzapine but after ensuring that oral per-

phenazine was tolerated well, it was decided to switch to PD. The patient was supposed to have a dose of 54 mg PD administered intramuscularly but by a mistake she was given as a 10-fold dose (540 mg). The recommended therapeutic dose of PD is 50–200 mg/week, which means that the she was given a dose that was 2.7 times higher than the maximum recommended dose. Plasma-perphenazine-levels were followed for 30 days and varied from 7–18 nmol/L with a peak on Day 5. Subsequently a decline was seen until day 10, when a secondary rise in the plasma-levels was observed. After 5 days the patient experienced muscle stiffness. At this point plasma-perphenazine was 18 nmol/L, which turned out to be the peak value. At Day 8 the patient suffered from severe extrapyramidal side effects – tiredness, drowsiness, slow and impaired movements. The side effects slowly subsided and at Day 14 the patient had neither any symptoms related to PD side effects nor psychotic behaviour.

Discussion: In theory a large intramuscular depot of PD may have resulted in massive systemic influx of perphenazine and severe poisoning with very few specific treatment options. We have demonstrated a more prolonged systemic uptake with a late peak and more moderate side effects related to the plasma-concentration.

Conclusion: Poisoning with a large intramuscular depot of PD does not result in a hyper acute poisoning but rather a more sustained moderate poisoning.

142. Evaluation of quetiapine abuse and misuse reported to poison centers

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Objective: There are case reports and one poison center's study of quetiapine abuse¹, but data on toxicity and outcomes are limited. The purpose of this study is to evaluate national poison center data on misuse/abuse of quetiapine.

Methods: A retrospective study of American Association of Poison Control Centers National Poison Data System data on single substance quetiapine exposures was performed. The study included cases from 2005–2011 coded as intentional misuse or abuse. Data were evaluated for age, dispositions and coded final outcomes.

Table 1. Disposition in cases of misuse and abuse of quetiapine.

Disposition	MISUSE (%)	ABUSE (%)	TOTAL (%)
On-Site Non HCF	776 (23.9)	197 (11.7)	973 (19.8)
Managed in HCF			
Treated/Released ED	1,160 (35.8)	723 (42.9)	1,883 (38.2)
Admit Critical Care	243 (7.5)	185 (11.0)	428 (8.7)
Admit Non-Critical Care	207 (6.4)	103 (6.1)	310 (6.3)
Admitted to Psych	208 (6.4)	118 (7.0)	326 (6.6)
Lost to follow-up/left	369 (11.4)	189 (11.2)	558 (11.3)
AMA			
Refused referral	197 (6.1)	130 (7.7)	327 (6.6)
Other	54 (1.7)	24 (1.4)	78 (1.6)
Unknown	27 (0.8)	16 (0.1)	43 (0.9)
Disposition Total	3,241(100)	1,685 (100)	4,926

HCF = health care facility, ED = emergency department, AMA = against medical advice.

Results: There were 4,926 cases meeting inclusion criteria; reason was misuse in 3,241 and abuse in 1,685. Excluding the 52 cases with unknown age, the age breakdowns for misuse and abuse respectively were 10 and 0 cases <6 years; 98 and 45 cases between 6 and 12 years; 878 and 942 cases between 13 and 19 years; and 2,221 and 680 cases >19 years. There was one abuse-related death. Moderate or major toxicity occurred in 14.3% and 18.8% of misuse and abuse cases, respectively. Disposition is displayed in Table 1.

Conclusion: Misuse was more common than abuse, except in adolescents for whom abuse was more frequent. Although outcomes were generally good, significant toxicity occurred in 16% of cases and 53% of patients were treated in the emergency department and/or required medical admission. The consequences of misuse or abuse of quetiapine are serious in some patients.

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143. Gastroscopic bezoar removal in acute quetiapine poisoning

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Objective: Acute poisoning with sustained release preparations of quetiapine (SR) may lead to a prolonged clinical course of the poisoning due to pharmacobezoars. We report two cases with gastric pharmacobezoars, removed by water jet lavage under endoscopic control.

Case series: 1. After an overdose with unknown amounts of quetiapine (SR), sertraline, lorazepam, and lithium carbonate a 32 year old male required mechanical ventilation and circulatory support with catecholamines. Suspecting bezoar formation, endoscopy was initiated 25.5 hours after admission (h25.5). A white mass adhering to the gastric mucosa was not removable by mechanical efforts. Water-jet lavage through the endoscope with a roller pump (Endowasher) was initiated. A total of 4.8 g quetiapine were recovered with the lavage-fluid. After endoscopy the patient received multiple dose activated charcoal (MDAC) (two administrations of 50 g). Due to the additional ingestion of lithium, hemodiafiltration (HDF) was performed twice. On day 4 the patient was extubated and recovered completely. On admission quetiapine in serum (Qs) was 1800 µg/L. Peak conc. was 5950 (h16) and fell to 3895 µg/L (h19). During gastroscopic lavage at h25.5 it re-increased to 5500 µg/L. From h25.5 to h41 Qs fell with t1/2 13 h. HDF at h33.5 and h42 eliminated 17 mg and 24 mg respectively. 2. A 45-year-old female was intubated and mechanically ventilated in deep coma after ingestion of 18 g quetiapine (SR), zopiclone and lorazepam. One hour after arrival at the hospital single dose activated charcoal (SDAC) was administered. At h12 a bezoar of viscous

texture adhering to the big curvature was completely removed by gastroscopic jet lavage. 4.5 g quetiapine were eliminated with 11 L lavage-fluid. The patient recovered completely. Qs peaked at 4750 µg/L on admission and fell to 1458 µg/L before gastroscopy and rose again to 4420 µg/L with jet lavage. Afterwards Qs fell with $t_{1/2} = 6.7$ h.

Conclusion: Pharmacobezoars of quetiapine (SR) can adhere at the gastric mucosa and resist mechanical efforts to remove them. They can be removed by gastroscopically performed jet lavage with water. However this procedure may give cause to a sharp but only short lasting rise in Qs. HDF is not effective in quetiapine elimination.

144. Poisoning due to tramadol in New Zealand: An emerging hazard

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Objective: A 26 year-old female is one of two patients this year presenting with suspected serotonin syndrome to one emergency department following the intentional overdose of tramadol. Fourteen hours following the ingestion of tramadol (600 mg) and citalopram (240 mg), her vital signs were: blood pressure 126/78, heart rate 110, temperature 37.1, Glasgow Coma Scale 13 (E3,V4,M6). Exam was positive for a mild tremor, diaphoresis and 6-beat inducible clonus. Based on the Boyer/Shannon criteria¹, a diagnosis of serotonin syndrome was made. Tramadol has been subsidized in New Zealand (NZ) since 2010; it is hypothesized that subsidization has led to an increase in prescriptions with a subsequent increase in poisonings. The objective of this study is to investigate the epidemiology of tramadol poisoning in NZ over the last 9 years, based on calls received by the NZ National Poisons Centre (NZNPC).

Methods: Call data from the NZNPC telephone collection database regarding exposures to tramadol between 2003 and 2011 were analysed retrospectively.

Results: The NZNPC received 449 calls associated with tramadol over the study period. Between 2003 and 2009 the rate was steady, averaging 38 calls per year. In 2010 this increased to 81, and 104 calls in 2011. Adult exposures were most common with 379 exposures (84%). The majority of poisonings in adults were intentional (52%), with the remainder being accidental (40%), abuse (2%) and unknown (6%). Age ranged from 10 months to 85 years; the mean and median were 25.9 years (standard deviation 19.7) and 23 years, respectively. There were 249 cases of sole ingestion and 200 cases with co-ingestants. Medical attention was advised in 83% of cases.

Conclusion: Retrospective analysis has shown a recent increase in exposures to tramadol in NZ, likely due to subsidization leading to increased prescriptions. The association between serotonin syndrome and tramadol is well described. Those prescribing tramadol and those treating overdoses need to consider tramadol's serotonergic properties and its potential for contributing to serotonin syndrome. This trend of increasing calls is concerning;

awareness and poison prevention strategies need to be implemented to minimize these exposures.

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145. “Sleep well!” – epidemiological and clinical findings in zopiclone/zolpidem poisoning

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Objective: The daily practice of physicians considering prescription of GABAergic agents such as zopiclone and zolpidem has changed during the last decades leading to a broader use. At the same time poisons centres have observed an increasing number of intoxications regarding zopiclone and zolpidem. This study aims to show the epidemiology of these intoxications and the clinical complications ensuing.

Methods: Retrospective analysis of data from a regional poisons centre from Jan 1995 until June 2012; selection of cases with either zopiclone or zolpidem as single substance intoxication and further analysis including epidemiology, clinical presentation and outcome.

Results: Zopiclone: 1830 cases were identified (follow up rate (FUP) = 31.7%). In particular 150 patients (8.2%) showed moderate or severe symptoms (according to the Poisoning Severity Score (PSS)); 3 of these patients died (0.16%). Zolpidem: 1550 patients (FUP = 33.7%); 199 with moderate or severe symptoms (12.8%); one patient died (0.06%). In both groups 69% of the patients were women. In 87%/85% (zopiclone/zolpidem) there was suicidal intention. The median age was 48/44 years. Major symptoms in patients with severe intoxications (PSS = 2 or 3) were coma (14.8%/18.2%), cardiovascular symptoms such as hyper-/hypotension, tachy-/bradycardia (3.7%/8.8%) and respiratory insufficiency (2.9%/2.1%). In 2 patients causes of death were connected to underlying conditions and directly affected by the intoxication. Two other patients died under unknown circumstances; therefore no causality to intoxication can be stated.

Conclusion: Zolpidem and zopiclone have widespread use in Germany. Although they have a high potential for intoxication symptoms are mostly mild and even in cases with more severe clinical presentation outcome tends to be benign under conditions of critical care treatment.^{1,2}

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146. Prolonged delirium and abnormal movements in paediatric lamotrigine ingestion

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Objective: Lamotrigine is a new generation broad spectrum anti-epileptic medication. Unintentional paediatric ingestion in the majority of cases has no or minimal symptoms.¹ Reported symptoms of overdose include ataxia, dizziness and tachycardia. There have also been reports of more serious clinical effects in overdose including coma, seizure and respiratory depression. We report two paediatric cases of accidental lamotrigine ingestion, where both children had prolonged agitation, altered sensorium and abnormal movements.

Case series: Case 1: An 18 month old healthy girl (9 kg) presented with acute behavioural changes. Examination revealed an altered sensorium, increased tone and intermittent jerking and choreathetoid movements. These abnormal “thrashing” movements were symmetrical, not rhythmic and not purposeful each episode lasted approximately 20 minutes. She had been found playing with her mother’s 100 mg lamotrigine tablets earlier that day. A lamotrigine level taken on presentation was 118.2 micromol/L (reference range 3.9–15.6 micromol/L), repeat level 8 hours later was 116 micromol/L. Her symptoms resolved by 72 hours and she was discharged with no deficit. Case 2: The second case involved a 20 month old healthy boy (11 kg) who had been found playing with his mother’s tablets and had possibly ingested lamotrigine (100 mg), paroxetine and bupropion the previous evening. On waking the next morning he was flushed and agitated. On presentation to hospital he was anxious, had altered sensorium, jittery and had dilated pupils. Twenty-four hours post ingestion he was noted to have abnormal limb movements of all 4 limbs lasting minutes; they were not associated with any post-ictal period. He had increased tone and reflexes. A lamotrigine level taken 16 hours post ingestion was 20.4 micromol/L. His symptoms resolved by 48 hours and he was discharged with no deficit.

Conclusion: There have been paediatric case reports of tonic clonic seizures, drowsiness and confusion following lamotrigine ingestion.² We report two cases of paediatric lamotrigine ingestion with documented elevated lamotrigine levels that developed agitation, altered sensorium and abnormal movements which persisted for over 48 hours.

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147. Misuse of prescription benzodiazepines and non-prescription sedative hypnotics (‘Z drugs’) in the United Kingdom

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Background: There is increasing concern in the United Kingdom (UK) about the potential misuse of benzodiazepines and non-benzodiazepine sedative hypnotics (often referred to as the ‘Z Drugs’). However, there is no UK data available on the frequency of misuse of these classes of drugs.

Methods: Using a market research company we undertook an Internet questionnaire survey of an existing consumer survey panel. For validity of the data set, lifetime prevalence of cannabis, powder cocaine and MDMA (‘ecstasy’) use in our participants was compared to data from the 2011/2012 British Crime Survey. Those who agreed to participate were asked for basic demographic data (age and sex) and whether they had ever used the following for non-medical reasons: benzodiazepines: nitrazepam, diazepam, alprazolam, lorazepam, oxazepam, phenazepam; non-benzodiazepine sedative hypnotics (‘Z’ drugs): zolpidem, zopiclone and zaleplon.

Results: The survey was completed by 1,500 individuals, of whom 737 (49.1%) were male and 763 (50.9%) female. 9.1%, 40.5%, 21.1% and 29.3% were aged 16–20, 21–39, 40–49 and 50–59 respectively. Life-time prevalence of use of cannabis (31.0%-vs-28.1%), cocaine 9.5%-8.1% and MDMA (‘ecstasy’) 8.6%-vs-8.2% were similar to the 2011/12 British Crime Survey. Life-time prevalence rates, in decreasing order, for the misuse of benzodiazepines and non-benzodiazepine sedative hypnotics (‘Z Drugs’) were: benzodiazepines: diazepam 4.3%; lorazepam 1.8%; alprazolam 1.3%; nitrazepam 0.8%; oxazepam 0.9%; and phenazepam 0.5%. Non-benzodiazepine sedative hypnotics (‘Z Drugs’): zopiclone 1.9%; zaleplon 0.8%; and zolpidem 0.4%.

Conclusion: This Internet consumer survey has demonstrated a low but potentially significant misuse of both benzodiazepines and non-benzodiazepine sedative hypnotics in a population with recreational drug use similar to that in the British Crime Survey. Further work is needed to understand the true extent of the misuse of benzodiazepines and non-benzodiazepine sedative hypnotics in the UK, and explore other factors including the reasons for misuse and the routes of supply.

148. Delayed presentation of serotonin syndrome after co-ingestion of serotonergic agents and benzodiazepines

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Objective: Serotonin syndrome is a potentially life-threatening condition that needs prompt recognition and management. The majority of cases present within 24 hours, and most within 6 hours after the ingestion.¹ We report a case of serotonin syndrome with a delayed onset of myoclonus, developing 24 hours after a mixed drugs overdose.

Case report: A 30-year-old male attempted suicide at midnight by ingesting a massive quantity of hypnotics and antidepressants (venlafaxine, zolpidem, diazepam, trazodone and moclobemide). Finding him unresponsive in the morning, his family brought him to a local hospital. Because of sustained consciousness disturbance, he was then transferred to our emergency department. Twenty hours after his poisoning, we received an unconscious

male with a Glasgow Coma Scale of E1V2M5. Initial vital signs were: blood pressure 89/64 mmHg; heart rate 115 beats/min; respiratory rate 17 breaths/min; temperature 35.3°C. His pupil sizes were estimated at 4 mm bilaterally with adequate light reflex. Neither myoclonus nor rigidity of extremities was noted. Bilateral Babinski's signs were negative. Laboratory studies revealed acute kidney injury, hyperkalemia, (serum creatinine 2.92 mg/dL, K 7.5 meq/L) metabolic acidosis (lactate 47.2 mg/dL, pH 7.18, pCO₂ 45 mmHg, bicarbonate 16.2 mm/L) and rhabdomyolysis (creatinine kinase: 75600 U/L). We gave him sufficient intravenous fluid, started a sodium bicarbonate infusion, and admitted him to the intensive care unit. About 24 hours after poisoning, myoclonus and hyperreflexia developed. On suspicion of serotonin syndrome (based on Hunter's criteria), we intubated this patient, prescribed lorazepam intravenously, and gave him cyproheptadine via nasogastric tube. The myoclonus subsided on the second day, so we tapered lorazepam and then extubated this patient when fully conscious. We also arranged intermittent hemodialysis for his anuria. His urine output improved gradually in 2 weeks after admission, and his serum creatinine improved to 1.33 mg/dL on the day of discharge.

Conclusion: Co-ingestion of serotonergic agents and benzodiazepines possibly delays the presentation of serotonin syndrome. Proper recognition of patients at risk for serotonin syndrome, even without typical presentations within the first few hours, prevents physicians from inadvertently precipitating serotonin syndrome by administering serotonergic agents.

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149. A case of pregabalin abuse

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Objective: Pregabalin is a gamma amino butyric acid (GABA) analogue used in the treatment of generalized anxiety disorder, epilepsy and neuropathic pain. During recent years increasing evidence indicates a considerable abuse potential.¹

Case report: A 38-year old man was referred to the psychiatric department due to auditory hallucinations, suicidal ideation and a large daily intake of 8.4 g pregabalin. He also suffered from alcohol (drinking approximately 70 cl of vodka daily in the weeks prior to admission), and opioid dependency (approximately 130 mg methadone and 50 mg ketobemidone daily). The Danish national medication register showed that the patient had bought pregabalin 21 times within the last two months, a total of 487.2 g pregabalin. At admission (approximately 36 hours after the last intake of 8.4 g pregabalin) the patient was fully conscious but had both auditory and visual hallucinations, and suicidal ideation. He was sweating, appeared tense and complained about anxiety and inner turmoil. Apart from tachycardia (115 bpm) he was cardiovascularly stable with a normal ECG. All

blood samples were within the normal range except for gamma glutamyltransferase (93 U/L). Unfortunately, it was not possible to obtain a blood sample from the patient for a concentration determination. During his hospital stay, pregabalin intake was continued at therapeutic doses (600 mg daily) and the patient was treated with chlordiazepoxide and quetiapine. Withdrawal symptoms disappeared within 48 hours, psychotic experiences and the suicidal ideations faded during the next couple of weeks.

Conclusion: High doses of pregabalin are tolerated with surprisingly few toxicological consequences, though lethal cases have been described.¹ Pregabalin abuse, however, can lead to dependency and subsequent withdrawal symptoms and health care professionals should be attentive towards excessive requests for this drug.

Reference

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150. Oral chloroform poisoning

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Objective: To describe retrospectively the clinical findings, treatment and outcome of an accidental ingestion of liquid chloroform by a 90-year old man.

Case report: The Poison Information Centre (PIC) received a call from a 90-year old man's relative. The patient had ingested mistakenly 10 minutes previously a sip of chloroform. Chloroform acts mainly as a central nervous system (CNS) and cardiac depressant. Through active metabolites, delayed hepatic and renal toxicity may occur. Ingestion of small amounts (e.g. 10 mL) can prove fatal due to CNS depression. Treatment with N-acetylcysteine (NAC) has been proposed to prevent liver injury. Drowsiness began shortly after ingestion, coma developed in 10 minutes; bradycardia was detected in the ambulance approximately on the 45th minute. The patient was admitted to hospital comatose (Glasgow Coma Scale 3p, SpO₂ 68%, respiratory rate 80/50 mmHg, wide QRS-complex 46x/min) on the 80th minute. Prior to arrival the emergency department was informed by the PIC about the potential health effects of chloroform and hepatotoxicity prevention options. Administration of NAC in loading dose (150 mg/kg) was initiated within one hour of admission. The patient was intubated and ventilated with 100% oxygen, diuresis was forced by furosemide, haemodynamics stabilised with infusion of vasopressors. The patient was transferred after 4 hours and 15 minutes from ingestion to the intensive care unit. Within the next 24-hours his general condition stabilised with supportive care. The patient was extubated. Initially the patient remained oxygen dependent and needed small doses of vasopressors. Slight hepatorenal damage developed (maximal values of AST 87U/l, ALT 46 U/l, creatinine 240 µmol). The patient was transferred to the nursing department on the 16th day after ingestion with satisfactory status, laboratory abnormalities

improving, with need for assistance in everyday life due to previous comorbidities.

Conclusion: We report the case of an elderly man who accidentally ingested chloroform and recovered after supportive treatment with NAC.

151. Blood cyanide concentrations in fire smoke poisoning

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Objective: Traditionally, fire smoke exposure was generally considered as carbon monoxide poisoning. Recently, the contribution of hydrogen cyanide and the necessity of appropriate antidotal treatment are under discussion.^{1,2}

Methods: Whole blood samples were drawn immediately after onset of emergency medical care, cooled and promptly transferred to the laboratory. Cyanide concentrations were determined using headspace gas chromatography with NP-sensitive detector. Hemoglobin derivatives were measured by a blood gas analyzer (IL GEMPremier4000).

Results: 49 blood samples from fire smoke exposures were analyzed (29 minor, 20 moderate or severe symptoms). In minor intoxications, cyanide concentrations ranged from <0.1 to 0.3 mg/L (median: <0.1 mg/L) and carboxyhemoglobin (CO-Hb) concentrations from 1.8 to 56.3% (median: 6.6%), in moderate or severe intoxications <0.1 to 4.1 mg/L (median: 0.7 mg/L) and 3.5 to 55.4% (median: 29.5%), respectively. Moderate and severe intoxications, where samples could be drawn within 30 minutes, are shown in Table 1. No patient had severe burns; patients #2 and #11 received hydroxocobalamin (7 h and 1 h after admission).

Conclusion: In minor poisonings, no clinically relevant internal cyanide exposure was found. In some moderate or severe poisonings, potentially toxic (> 1 mg/L) or even lethal (> 3 mg/L) cyanide concentrations were detected, but only weakly correlated with poisoning severity. Cyanide concentrations > 10 mg/L¹ or even > 20 mg/L² as reported recently were not observed.

Table 1. Moderate to severe fire smoke poisonings.

#	Age	Initial State	Outcome	Cyanide [mg/L]	CO-Hb [%]	Met-Hb [%]
1	81	somnolence	death (3 h)	4.1	20.3	0.2
2	4	somnolence	survival	3.4	22.2	0.8
3	53	coma	survival	3.1	51.3	0.0
4	64	coma	survival	1.8	20.5	0.2
5	69	cardiac arrest	death (1 h)	1.3	44.1	0.0
6	21	cardiac arrest	survival	0.7	43.2	0.3
7	76	coma	survival	0.7	44.4	0.0
8	50	dizziness	survival	0.6	55.4	0.0
9	70	dizziness	survival	0.4	34.5	0.5
10	48	coma	survival	0.1	23.8	0.7
11	54	coma	survival	<0.1	54.4	0.0
12	91	coma	death (2 d)	<0.1	3.7	0.4
13	28	dizziness	survival	<0.1	12.5	0.7
14	80	dizziness	survival	<0.1	55.3	0.2

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152. Smoke inhalation – decontamination study of toxic substances on an *in vitro* model of human airway epithelium

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Objective: Smoke inhalation (SI) is nowadays the major cause of morbidity and mortality in burn patients. The inhalation of toxic or corrosive gaseous molecules with smoke particles is at the origin of cellular damage and an inflammatory cascade that often lead to acute respiratory distress syndrome (ARDS) and potential death in patients exposed to SI. The toxicological impact of such corrosive or toxic agents contained in smoke needs to be quantified. Only then, can some polyvalent decontaminants be rationally designed.

Methods: A 3D *in vitro* model of the Human Airway Epithelium was used to assess the toxicity of three representative contaminants occurring in smoke: an acidic corrosive (hydrochloric acid), an alkaline corrosive (ammonia) and an electrophilic toxic molecule (acrolein). Their toxicity was assessed from the measurement of trans-epithelial electric resistance (TEER), lactate dehydrogenase (LDH) activity in basal cells, cell viability as well as cilia beating frequency.

Results: Toxicity of the two corrosive agents (hydrochloric acid and ammonia) was shown to be extremely concentration-dependent, with a critical threshold at 25 mM, beyond which the epithelium completely loses its barrier function in less than 10 minutes, without reversibility. Below this critical threshold, in case of a prolonged contact, the two corrosive agents also induced some detrimental effects on the epithelium. The evaluation of some decontaminating solutions is now under investigation. Compared to these corrosive substances, electrophilic acrolein was shown to have a much higher toxicity (loss of barrier function if its concentration exceeds 0.25 mM), but its effect is more delayed. The evaluation of decontaminating solutions has been performed after a 20 minutes contact with acrolein. A reduction in the degree of cytotoxicity of acrolein was observed, as quantified by the LDH released from epithelial cells.

Conclusion: It is clear that pulmonary corrosive or toxic compounds present in smoke may contribute to the airway damage of fire victims as soon as a critical threshold is reached. This knowledge adds essential information to optimize the design of an efficient pulmonary decontamination protocol.

153. Google trends analysis of carbon monoxide searches in the wake of Hurricane Sandy

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Introduction: The Centers for Disease Control released a report in November 2012 describing an outbreak of carbon monoxide poisoning following post-tropical cyclone Sandy in the Northeastern US.¹ Carbon monoxide poisoning from inappropriate use of portable petroleum-powered generators and heating devices is commonly increased after major weather events involving power outages. We sought to determine whether this increase was mirrored in Google Trends analysis of Internet searches, which has demonstrated utility as a biosurveillance tool.² We investigated searches in the New York and New Jersey area after the storm, and whether this appeared to be influenced by average daily temperatures.

Methods: We conducted a Google Trends search³ with the string “carbon monoxide” in New Jersey and New York from October 29, 2012 (the day of the storm) until November 13, 2012. We compared the search frequency to average daily temperatures at Newark International Airport⁴ to evaluate whether the search frequency corresponded with the onset of the storm and also with lower temperatures.

Results: Google searches for carbon monoxide began to increase from a baseline index number of 17/100 to 35/100 on October 29, and peaked at 100 on November 1. This peak occurred when the average daily temperature dropped below 50 °F (10 °C). Searches decreased thereafter, dropping below 30/100 after 12 days.

Conclusion: Interest in carbon monoxide in the New York and New Jersey area, which suffered the greatest brunt of Hurricane Sandy with extensive power outages and flooding, peaked significantly 2 days after storm landfall when average daily temperature dropped below 50 °F. Thereafter a decrease in searches occurred, which may reflect the gradual restoration of power to the region. This demonstrates the importance of Internet resources in public health surveillance.

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154. Carbon monoxide exposures presenting to Northeast US emergency departments from 1996–2010

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Introduction: Carbon monoxide poisoning is the number one cause of accidental poisoning deaths in the United States. However, the epidemiology of carbon monoxide presentations to US emergency departments (EDs) is poorly studied. There have been few attempts to investigate the epidemiological link between smoke inhalation and carbon monoxide poisoning.

Objective: To characterize carbon monoxide exposures presenting to New Jersey and New York emergency departments.

Methods: Design: A multi-center retrospective emergency department (ED) cohort. Study setting: 34 New Jersey and New York EDs. Subjects: Consecutive patients with the ED diagnosis of “toxic effect of carbon monoxide” (ICD9 code = 986) as well as patients with a narrative diagnosis of “smoke inhalation” were identified from January 1, 1996 to December 31, 2010.

Results: Out of 9,488,847 consecutive patients, 2869 patients were diagnosed with “toxic effect of carbon monoxide” (0.03% of all ED patients) with 278 admitted to the hospital (9.7% admission rate). Only 2387 patients had completed charts for review. The patient demographics were as follows: mean age = 31.1 years (range: 0.0–102 years) and gender = 52.7% female. Carbon monoxide exposures were more frequent during winter months (December–February) = 35.6%. During the same time period, 2390 patients were diagnosed with “smoke inhalation” with only 37 diagnosed with “toxic effect of carbon monoxide”, ICD9 code = 986.

Conclusion: Carbon monoxide poisoning is a rare presentation to Northeast US emergency departments. ED presentations were more frequent during winter months. Hospitalization following exposure appears to be infrequent. Most recorded cases were not associated with significant smoke inhalation.

155. A case of “mud bogging” resulting in carbon monoxide toxicity

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Objective: To describe the first case of carbon monoxide toxicity from mud bogging.

Case report: “Mud bogging” is a form of off-road motorsport popular in the United States. The goal of this sport is to successfully drive a vehicle through a pit of mud. A healthy 19-year-old man was transferred to our tertiary care center after being found unconscious in a motor vehicle by paramedics. He had been mud bogging with three other individuals in a 1993 sport utility vehicle (SUV) when the vehicle became stuck in the mud. The driver repeatedly revved the engine until the exhaust reversed flow into the cabin through the air vents. The patient was in the back seat and remained in the cabin for an unspecified period of time. Paramedics extricated him after the SUV was removed from the mud. Upon presentation to the emergency department, the patient was agitated and complained of loss of vision. Vital signs: 36.3 degrees Celsius, heart rate 80 bpm, respiratory rate 18 rpm, blood pressure 120/72 mmHg, oxygen saturations 100% on 100% oxygen by non-rebreather. His laboratory evaluation measured sodium 143 mEq/L, potassium 2.8 mEq/L, chloride 101 mEq/L, bicarbonate 27 mEq/L, blood urea nitrogen 19 mg/dL, creatinine 1.39 mg/dL, glucose 181 mg/dL. His white blood cell count measured $17.3 \times 10^9/L$, hemoglobin 16.1 g/dL and platelets $264 \times 10^9/L$. His carboxyhemoglobin level was 47.5%. The patient received three hyperbaric oxygen treatments at 2 atmospheres without complications. The patient was discharged without symptoms twenty four hours after admission.

Conclusion: Mud bogging is becoming increasingly popular in the United States and Canada. Therefore, physicians should be aware that mud bogging is a potential cause of carbon monoxide toxicity.

156. Carbon monoxide exposure following Hurricane Sandy

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Introduction: Carbon monoxide (CO) poisoning is a potentially lethal disorder that is commonly overlooked and with noteworthy immediate and delayed complications. It is speculated that cooler months have amplified occurrence due to the increased utilization of carbon monoxide producing devices. A byproduct of incomplete combustion, it is suspected that during periods of power outages, the utilization of portable generators would lead to an increased rate of emergency department (ED) visits from this ailment.

Objective: To determine if an increase number of patients were seen in the ED in the month following Hurricane Sandy.

Methods: A retrospective study of consecutive patients presenting to one suburban emergency department with an annual census of 75,000, and which is also a teaching hospital. Data was obtained using an electronic charting system, extracting the charts with a final diagnosis of carbon monoxide poisoning. All charts were manually reviewed for specific predetermined data points and to confirm the exposure. Data was entered onto a closed-ended questionnaire. Patients seen in the 11 months prior to the Hurricane were compared to the two weeks following the hurricane. Statistics: Mann-Whitney, with a significant alpha of 0.5, two-tailed. This study was approved by our institutional review board.

Results: 34 patients were seen during that time period. Female gender comprised 50% (N = 17). Mean age was 34.7 years (Interquartile range 11–63). Admission to the hospital occurred in 6% (N = 2). Monthly totals: Dec (N = 1), Jan (N = 1), Feb (N = 3), Mar (N = 1), Apr (N = 2), May (N = 1), June (N = 0), July (N = 1), Aug (N = 3), Sept (N = 1), Oct (N = 4), Nov (1st 2 wks) (N = 15). Mean CO level for those presenting in November 2012 was 9.47, compared to an overall average of 2.76 (p < 0.001). Six patients in the 11 months preceding Hurricane Sandy had a CO level of 0, while none in the two weeks following did.

Conclusion: An increased number of patients presented to the emergency department in the weeks following hurricane Sandy, and they had a significantly higher carbon monoxide level.

157. Carbon monoxide exposure during pregnancy, a five year review

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Introduction: Data is conflicting regarding the management of carbon monoxide (CO) poisoned patients. This data becomes even more controversial/limited in pregnant patients. With fetal hemoglobin's higher affinity for carbon monoxide, would evaluation and treatment be different in those who are gravid?

Objective: To determine the management practices of emergency department (ED) physicians in regard to patients presenting with CO exposure while pregnant.

Methods: Design: A multi-center retrospective ED cohort study. Setting: 23 New York/New Jersey EDs comprising academic, non-academic, urban, and suburban hospitals. Subjects: Consecutive patients with the ICD-9 primary diagnosis of "toxic effects CO", from Jan. 2001 to Dec. 2006. A manual chart review was performed for specific data points. Severe exposure was reported if: CO level > 15, syncope, LOC, abnormal cardiac, or neurological exam. Statistics: Mann-Whitney was utilized for statistical significance with a preset alpha of 0.05.

Results: "Toxic effects CO" was diagnosed in 1136 patients, 1073 charts were available for analysis and 20 (2%) met inclusion criteria as pregnant. Mean age was 29 years (Interquartile range 24–32). Arterial draws were reported in 15% (N = 3) of patients. No patients died. Oxygen therapy was initiated in 70% (N = 14). Intubations occurred in 0 patients. Admission occurred in 10% (N = 2) of patients. Mean CO level in those who were pregnant was 2.9%, compared to an overall level of 7 (p < 0.001). Repeat CO levels were drawn in 0 pts. Of all patients, 40% had electrocardiograms (EKG) and 30% cardiac markers. With regard to symptoms frequency: headache 40%, cough 30%, dizziness 20%, nausea 15%, chest pain 10% and no symptoms 35%. Five per cent (N = 1) of patients received hyperbaric oxygen (HBO). No patients were considered to have a severe exposure.

Conclusion: The majority of patients who are exposed to carbon monoxide while pregnant have mild symptoms and were discharged home.

158. Impact of drug screening on the management of severely poisoned patients

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Objective: Urine drug screens are commonly requested in overdosed patients in the belief that it will assist in patient management. Controversies continue to exist regarding the value of comprehensive urine drug screening in the clinical setting.

Methods: This study evaluated the clinical usefulness of the information obtained from comprehensive urine drug screens in the management of patients with severe drug overdose requiring intensive care unit (ICU) care when the history and clinical information may be limited. Urine samples were collected from 54 patients with a diagnosis of severe poisoning admitted to the Prince of Wales Hospital, a tertiary teaching hospital in the New Territories Region of Hong Kong, and requiring ICU care from January 2007 to June 2012.

Results: The mean age of patients was 44 years (range: 1 month – 88 years) and 56% were female. All except two patients

recovered after standard investigations and management, which did not include knowledge of urinary drug screen results. One hundred and twenty compounds were detected in the 54 urine samples. Ten patients had no drug detected in their urine, while 33 patients had more than one drug detected, with a median 2 drugs per patient. Twenty-three drugs, in 12 patients, were identified that the patients did not report taking. Of these, ketamine ($n = 4$) and methamphetamine ($n = 3$) were the most common. In general, the agents causing poisoning were correctly identified based on history, clinical features, basic and specific investigations. Even if the results of urine screening had been immediately available, the management of these patients would not have been changed. However, the results of targeted urine drug screen helped to confirm two cases of unexplained hypoglycemia due to presence of glibenclamide in erectile dysfunction products which had saved the need of further investigations and led to subsequent control of the outbreak in Hong Kong.

Conclusion: The use of comprehensive drug screen is unlikely to affect the immediate management of severely poisoned patients. However, judicious use of the tests, taking into account of the clinical condition of the patients, may help to confirm the diagnosis and identification of the culprit poison.

159. Detection of paracetamol indicates phenacetin-induced methemoglobinemia in a bodypacker

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Objective: To report an unusual case of methemoglobinemia in a bodypacker.

Case report: A 46 year old male presented to us with a self-reported history of swallowing drug containers containing cocaine of unknown number, weight and concentration. At presentation, physical examination revealed no pathologies, the patient was slightly anxious and agitated, laboratory values were in normal ranges except a positive finding for cocaine in a urinary specimen. Besides standard intensive care unit (ICU) monitoring we provided oral charcoal in repeated doses (15 g every 4 to 6 hours) to prevent resorption of the drug as well as prokinetic medication. A multi-slice computed tomography (CT) scan of the abdomen showed a significant number of drug containers located in the stomach. The poor quality of the packaging (remainder of one container in the faeces consisted of the finger part of a rubber glove and self-adhesive tape) necessitated prolonged ICU monitoring and charcoal-medication. In the following days the patient repeatedly developed signs of substantial mental distress with tachycardia, panic and delirium, lacking other signs of cocaine toxicity, all controlled by administration of diazepam. A coincidentally performed blood gas analysis showed a significant amount of methemoglobinemia (20%), a finding not known as cocaine- but benzocaine- or phenacetin-related toxidrome. Phenacetin is used in drug-trafficking as a diluent to maximise economic benefit. In the absence of signs of benzocaine-toxicity and lacking the ability to directly detect phenacetin we measured its metabolite paracetamol; positive values indicated the presence of phenacetin as culprit agent for the methemoglobinemia. The blood levels for methemoglobin

normalised spontaneously after a few hours; the patient suffered from at least 5 of the described episodes, partly correlated to radiologic findings of disintegration of the drug containers.

Conclusion: Phenacetin is a rarely described cause of methemoglobinemia in drug-trafficking; the observed toxicity mimicked cocaine-toxicity, potentially leading to misdiagnosis. Laboratory test kits for paracetamol will be more readily available in many hospitals compared to those for phenacetin, so the detection of paracetamol as surrogate for phenacetin might be helpful in this situation.

160. The use of pharmacogenomic testing in overdose – what role does it have?

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Objective: We aim to highlight the potential role of pharmacogenetic testing in the setting of drug overdose.

Discussion: Databases have been established to provide clinicians with pharmacogenetic data relevant to adverse drug reactions, attempting to identify genetic variants that predispose a patient to poor outcomes. A literature search resulted in only two case reports that described utilization of pharmacogenetic testing in this setting. One describes a *post-mortem* study of a 5 year old child who had died from an overdose of hydrocodone and was found to be a rapid metabolizer of codeine via CYP 2D6.¹ In the second, the authors describe a case of coumarin overdose in a 19 year old.² In the second case, knowledge of the patient's genetic polymorphism of CYP 2C9 and subsequent slow metabolism of coumarin, helped guide successful reversal of her anti-coagulation to a safe level. In both cases, pharmacogenetic testing aided in the management of the overdose. We compiled the list of the top ten agents resulting in fatality from overdose published in the National Poison Data System Annual Report of 2010.³ Five of these agents have identified pharmacogenetic markers with demonstrated significance. They include oxycodone (marker: CYP 2D6), amitriptyline (marker: CYP 2D6), methamphetamine (markers: DTNBPI and PICK1), morphine (marker: OPRM1), and amlodipine (markers: CLCN6, NPPA, and NPPA-AS1). Identification of patients with polymorphisms at these markers may assist clinicians in the diagnosis and management of the acute overdose. Clinical grade pharmacogenetic testing is advancing, with both cost and turnaround times decreasing rapidly, creating an environment in which this information will be readily attainable.

Conclusion: With further development, pharmacogenetic testing will become another tool to facilitate the clinical care of the poisoned patient.

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161. Does routine CYP2D6 and CYP2C19 genotyping reduce the risk of adverse events related to antipsychotic drug treatment?

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Objective: To evaluate whether routine genotyping of CYP4502D6 and CYP4502C19 reduces the risk of adverse events (AEs) related to antipsychotic drug (AD) treatment.

Methods: A prospective randomized study with three arms, each including 100 patients within the schizophrenic spectrum of whom 20 were genetically predicted poor or ultrarapid metabolizers for CYP2D6 or CYP2C19 (Total N = 300). In study arm 1 the genotype information was given to the physician in charge and could be used to direct the pharmacological treatment. In study arm 2 the patient's primary contact person systematically registered treatment effect, AEs and patient's attitude towards medication. In Study arm 3 treatment followed usual local practice. In both study arms 2 and 3 medical treatment was adjusted according to clinical observation, the genotype information was not revealed. All patients were followed for one year. Primary outcome was time to discontinuation of treatment (TTD) as an overall measure for AD tolerability. Secondary outcome were AEs (48 AE items divided in 4 categories; psychiatric, neurological, autonomic and other AEs). TTD was analysed by a time-to-event-analysis. Differences in AEs between study arms were analysed, by a general linear model, as the sum of differences between follow-up and baseline using study arm allocation as primary variable.

Results: We found no differences in mean TTD between study arms (198, 214 and 187 days; $p = 0.68$) and no differences regarding the sum of differences between AEs at follow-up and baseline ($p > 0.05$). However, there was a borderline significant difference ($p = 0.0628$) regarding neurological AEs and a pair wise analysis showed a significant difference between study arm 2 and 1 in favour of study arm 2 (0.85, StdErr 0.36, $p = 0.019$).

Conclusion: Routine genotyping of CYP450 2D6 and 2C19 does not improve drug persistence or reduce the risk of AEs related to ADs.

162. Validation of an acetaminophen immunoassay for unconventional matrices

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Objective: Our academic hospital-based laboratory has been receiving an increasing number of requests from clinicians to analyze different biological fluids for diverse analytes. One recent example was a request from the medical toxicology service to measure the acetaminophen concentrations in urine and dialysate for a

patient treated for an acute intoxication by hemodialysis. As the automated method that we employ (Beckman turbidometric assay on a Synchron LXi725) has only been validated for serum and plasma, we performed a series of studies to validate the method for both urine and dialysate.

Methods: Recovery studies were done by adding increasing amounts of acetaminophen to biological fluids free of the analyte and comparing the expected with the measured final concentrations. In order to confirm our fluid results, we fortified serum (acetaminophen free) with either urine or dialysate containing acetaminophen and compared the results to measurements made on the fluids.

Results: Dialysate yielded recoveries of 87% to 103% for acetaminophen concentrations ranging from 151–870 $\mu\text{mol/L}$. Urine yielded recoveries of 98% to 114% for concentrations ranging from 159–1262 $\mu\text{mol/L}$. Fortifying serum with dialysate resulted in an average difference of $13.9\% \pm 5\%$. Similarly, fortifying serum with urine resulted in an average difference of $1.4\% \pm 3\%$. In addition, we were able to demonstrate that for all fluids tested (serum, urine and dialysate), the samples were stable at 4–8°C for a minimum of 15 days (retained concentrations of $96.7\% \pm 5.3\%$).

Conclusion: Based on the results of our validation studies, we were reassured that we can provide meaningful analyses for acetaminophen concentrations in unconventional matrices. We are planning to perform similar studies with other xenobiotics amenable to extracorporeal removal. We suggest that prior to reporting xenobiotic concentrations in unconventional matrices, the analytical methodologies be validated for these purposes.

163. Drugs highly associated with infusion reactions enhance nitric oxide signaling

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Objective: Infusion reactions (IRs) can be a serious life threatening adverse event associated with N-acetylcysteine (NAC) administration. Additionally, many drug and biologic Food and Drug Administration (FDA) labels contain warnings about infusion reactions. Enhanced nitric oxide (NO) signaling may be a mechanism.

Methods: The US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) was data mined for drugs highly associated with the preferred term infusion reaction. Drugs were ranked by Empirical Bayesian Geometric Mean (EBGM) score where $N > 30$. The top 20 drugs by EBGM score were analyzed by searching PubMed to determine if the drugs or biologics increased NO signaling.

Results: Table 1 contains 9 representative drugs. Iron infusion products represent the drug class with 3 of the 4 highest EBGM scores. The biologics include many antibodies and enzymes that contain cysteine thiol groups that may undergo S-transnitrosylation. Some drugs (amphotericin B, paclitaxel) increase NO production, while oxaliplatin binds NO and nitrosylates proteins. Vancomycin reactions may involve histamine release that promotes NO production. The other proteins not in the Table by decreasing EBGM score are gemtuzumab, α -glucosidase, cetuximab, immunoglobulin, β -galactosidase, laronidase, rituximab, panitumumab, and antithyocyte immunoglobulin.

Table 1. Representative drugs for drug classes highly associated with infusion reactions.

Drug	Class	N	EBGM	Action	PMID
Fe Dextran/Sucrose/Na	Iron	177	48/38/27	Binds NO and Emits NO	22449080
Idursulfase	Enzyme	86	33.6	Transnitrosylation	22657837
Ca, Na, K, Cl, Lactate	Electrolytes	34	27.0	Calcium Cofactor in NO signaling	9480877
Alpha-1-Antitrypsin	Proteinase	35	24.6	Transnitrosylation	22657837
Infliximab	Antibody	3858	23.2	Transnitrosylation	22657837
Amphotericin B	Antibiotic	59	7.3	Increases NO production	14692429
Vancomycin	Glycopeptide	110	7.1	Histamine release	9743397
Paclitaxel	Taxane	239	5.5	Increases NO production	9285245
Oxaliplatin	Platinum	149	4.6	Binds NO and transnitrosylation	19328230

Conclusion: Data mining AERS supports the hypothesis that infusion reactions are mediated by nitric oxide signaling. Future research should measure the production of nitric oxide, nitrites, nitrates and nitrosylation during variable administration rates of drugs and biologics highly associated with infusion reactions. If this nitric oxide hypothesis is correct, a NO scavenger such as methylene blue might be beneficial for life threatening infusion reactions.

164. Serum perfluorooctanoic acid concentration is associated with clinical renal disease but not clinical cardiovascular disease

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Objective: Previous analyses of National Health and Nutrition Examination Survey (NHANES) data have reported that serum perfluorooctanoic acid (PFOA) concentrations correlate with decreased glomerular filtration rate, hypertension, and elevated homocysteine levels raising the concern that PFOA may increase the risk of clinical renal or cardiovascular disease.^{1,2} We analyzed the same NHANES data to determine if serum PFOA concentrations are associated with clinical renal or cardiovascular disease.

Table 1. Association between serum PFOA concentrations and clinical renal and cardiovascular disease.

Outcome	Uncontrolled for age, gender, and race/ethnicity		Controlled for age, gender, and race/ethnicity	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Kidney disease	1.13 (1.04, 1.22)	0.001*	1.15 (1.07, 1.25)	<0.001*
Hemodialysis within last 12 months	1.78 (1.13, 2.79)	0.011	1.88 (1.18, 2.97)	0.006*
Congestive heart failure	0.99 (0.95, 1.02)	0.36	1.00 (0.96, 1.05)	0.90
Coronary heart disease	0.98 (0.95, 1.01)	0.15	1.00 (0.96, 1.03)	0.81
Angina pectoris	0.98 (0.95, 1.01)	0.19	0.99 (0.95, 1.03)	0.67
Heart attack	0.98 (0.96, 1.01)	0.24	1.00 (0.97, 1.04)	0.86
Stroke	0.98 (0.95, 1.01)	0.19	0.99 (0.96, 1.03)	0.73

*Statistically significant (alpha = 0.007).

Methods: We performed a cross-sectional study of 6305 adults who participated in the 2003–2008 NHANES survey and in whom a serum PFOA concentration was obtained. Outcome measures included kidney disease, hemodialysis within the last 12 months, congestive heart failure, coronary heart disease, angina pectoris, heart attack, and stroke. We performed logistic regression to determine if serum PFOA concentrations were associated with the outcome measures both without and with controlling for confounders of age, gender and race/ethnicity. We applied a Bonferroni correction due to multiple statistical analyses (alpha = 0.007).

Results: Serum PFOA concentrations at or above the detection limit were found in 6294 out of 6305 adults. Logistic regression results are listed in Table 1. No relationship was seen between cardiovascular disease and serum PFOA concentrations. Serum PFOA concentrations were associated with both clinical renal disease and hemodialysis within the last twelve months and the association was strengthened by controlling for age, gender, and race/ethnicity.

Conclusion: Serum PFOA concentrations are associated with an increased risk of clinical renal disease but are unrelated to clinical cardiovascular disease.

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165. Delayed bullae formation after sulfur mustard exposure

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Objective: We present a case of delayed bullae formation in a patient with cutaneous sulfur mustard (bis(2-chloroethyl) sulfide) exposure.

Case report: A 28 year-old crab fisherman handled artillery shells that were inadvertently raised from the seafloor in his crab traps. The shells were significantly corroded and, while throwing the munitions overboard, fluid from inside the shells splashed onto his arms and legs. Despite wearing protective clothing, including gloves, boots, and oilskins, the patient experienced the onset of burning pain to his right forearm and left leg approximately six

hours after exposure to the shells. Over the next six hours, the patient developed erythema, bullae, and increasing pain in the same distribution. The patient presented to an acute care facility twelve hours after exposure where, based on his history and physical examination findings, he was diagnosed with sulfur mustard exposure. Six days after exposure, new bullae formed on his right forearm and left knee.

Conclusion: Sulfur mustard exposure has been previously reported in fisherman handling munitions that have been discarded at sea. Sulfur mustard is well known for its vesicant properties. The mechanism by which sulfur mustard causes cellular death and cutaneous chemical injury is by alkylation of macromolecules such as DNA and proteins. As with other chemical injuries, progression of the burn usually is complete within 24–48 hours. The case we present is unusual in that our patient developed new bullae 6 days after his sulfur mustard exposure. Delayed bullae formation is an unusual complication of sulfur mustard exposure. In a series of 535 persons exposed to sulfur mustard, delayed bullae formation was reported in 33 persons (6%).¹ The mechanism for delayed bullae formation has not been elucidated.

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166. Nosocomial poisoning risk in sodium azide ingestion: Analysis of an exposure

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Objective: External decontamination is important in chemical exposures to prevent secondary contamination of health care and other emergency service workers. The place of a hazmat response in an oral ingestion with minimal external contamination is less clear and the requirement for staff to wear personal protective equipment (PPE) that might impair their ability to deliver patient care is controversial. We undertook a follow up contact to ascertain any major physical effects on emergency services professionals involved in the care of a patient with a fatal ingestion of sodium azide. The patient presented to an urban emergency department (ED) without pre hospital decontamination and despite a hazmat assessment 100 minutes after presentation, a decision was reached that staff did not require PPE beyond standard measures. The patient died 3 hours after arrival in ED.

Methods: A record of clinical staff directly involved with the case was obtained from ED administrative staff and contact made by phone or in person a minimum of 3 months after the incident. Additionally 2 ambulance personnel and one police officer, all of whom had close contact with the patient and who subsequently presented to the ED for a medical assessment, were also contacted. Data collected were age, sex, time in contact with the patient, time off work as a result of the incident and details of this.

Results: Ten individuals were deemed to have had close contact with the case. Two cases were unable to be contacted, however

communication from respective department heads confirmed both were still functioning normally. Of the 8 cases contacted, 4 were male and median age was 43 (Interquartile range 38–50). Four individuals described being in close contact for greater than 60 minutes, 2 estimated being in contact for 15–60 minutes and 2 for 5–15 minutes. Absence from work occurred in 2 cases for 1 day and several weeks. Both of these cases were ambulance personnel and neither of these absences was due to physical effects of exposure.

Conclusion: Our data does not support sodium azide ingestion as a high risk situation in causing significant nosocomial poisoning in emergency service workers.

167. Symptoms associated with accidental and intentional ingestions of acetone-containing nail polish remover

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Objective: Severe acetone toxicity is rarely reported but significant central nervous system (CNS) depression may occur from >2–3 mL/kg.¹ Ingestion of nail polish removers containing up to 90% acetone is relatively common in Ireland but severe toxicity is uncommon. We reviewed all cases reported to the National Poisons Information Centre in Dublin over a 10 year period to assess severity of symptoms.

Methods: We retrospectively reviewed cases of exposure to nail polish remover from January 2001 to December 2011 inclusive. Cases of inhalation, dermal exposure, and eye exposure were excluded from the study. Cases of ingestion of products containing acetone were reviewed and data on patient demographics, circumstances and clinical features was collated.

Results: We received 570 enquiries about acetone-containing nail polish removers over the 10 year period; 501 cases met our inclusion criteria. Ninety-four per cent of cases were accidental (n = 469) with the majority involving children under 5 years of age (n = 413). The volume ingested can rarely be confirmed in these cases but the average estimated dose was 33 mL. Most enquiries were received within 2 hours of ingestion (median time 20 mins). Mild vomiting was the most common feature (n = 61) followed by local mucosal irritation (n = 10). Seven patients developed transient drowsiness. Seventy-nine per cent of patients remained asymptomatic. There were 30 cases of intentional ingestion; an estimated dose was provided in 22 cases and the average amount was 150 mL (median 100 mL, range 5–400 mL). Fifty-six per cent of patients remained asymptomatic (n = 17). Two patients became mildly drowsy, 4 patients complained of nausea or abdominal pain and 2 patients had superficial local mucosal irritation. One patient intentionally ingested 200–400 mL on 3 separate occasions; she developed coma, respiratory depression and acidosis on each occasion and required intubation and ventilation. Severe hypotension requiring high-dose inotropes developed on one occasion but was not reported during subsequent presentations.

Conclusion: Severe toxicity following ingestion of acetone-containing nail polish removers was rare during our study period and was only seen following intentional ingestion of large volumes. Accidental ingestions by children were not associated with significant symptoms.

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168. Achieving access to apartments of migrants in Berlin to assess risks for their children concerning chemical consumer products

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Background: In 2009, in a joint cooperation, the Federal Institute for Risk Assessment (BfR) carried out an investigation concerning the poisoning situation of children, but with indifferent results for the poisoning risks in migrants. Between 2010 and 2011 some scientific assumptions were published in Germany that migrants could carry a higher risk of childhood poisoning. A feasibility study in Berlin, however, evaluated the options for achieving access to families with a migrant background in order to develop a framework for further, enlarged and systematically established scientific studies.

Method: Existing data on migration background were evaluated regarding risks of chemical consumer products being responsible for childhood household poisoning accidents. The main instrument was a semi-standardised questionnaire for parents. Subject matter was focused on poisoning accidents which had occurred; knowledge about chemical products; attitudes towards the use of those products, their household storage and safety aspects and an important item "looking through the keyhole". This means that if respondents agreed an expert would make a home-visit to evaluate real household product knowledge together with poisoning risks for children.

Results: Regarding the cases of childhood poisoning accidents, the study did not support the assumption of a higher rate of relevant accidents in families with a migrant background - on the contrary, accidents occurred mainly in families with minor chemical use. There was no obvious correlation between age of the parents, family status, job, dwelling, knowledge about the products or their possible risks and causes of poisonings. In three-quarters of the cases, the affected children were the eldest. Possible impacts to be evaluated are e.g. the knowledge which might well have its origin in a specific cultural setting - about handling and risks of chemical products and the level of knowledge of the German language. Furthermore, more than half of the respondents agreed to an expert's visit to their home.

Conclusion: In order to develop adequate means of prevention in childhood poisoning, the focus has to be taken to special target groups and the evaluation of specific instruction materials. It is of nationwide importance to get personal access to the migrants. A combination of legal and educationally oriented measures seems promising.

169. Aerotoxic Syndrome: Five cases in Germany

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Background: German physicians have to document cases of poisoning (§16 Chemicals Law) to the Federal Institute for Risk Assessment (BfR). Based on good cooperation with physicians, hospitals, Poison- and Environmental Centres, the BfR also receives data on rare or extraordinary cases, such as the case reports of "Aerotoxic Syndrome" (AS). AS is not an officially recognized health impairment entity in aviation medicine. The syndrome describes alleged short-term and long-term ill-health effects that are attributed to exposure to contaminated cabin air in relation to fume events in which the ingredients of engine-oils such as tricresyl phosphate (TCP) could possibly be toxic to humans. In particular in the mass media, radio and television spectacular AS-stories (e.g. near air crashes) have been published.

Methods: The German AS-cases were investigated and documented at the BfR. Individual reports as well as cases reported so far under §16e were analysed, evaluated and recorded in the form of standardised case reports. The existing data were evaluated and assessed regarding possible risks for fume events associated with TCP-contaminated cabin air. The categorisation of the health impairment followed the Poison Severity Score (PSS). The causality (exposure vs. symptoms/signs) was assessed by the BfR-standard "Three-Level-Model".

Results: Between 2009 and 2012 the BfR documented 5 cases of AS. All were adults and flying personnel of different airlines (three stewardesses/two pilots). All claimed smell events but no real fume events. The stewardesses especially had symptoms and signs which Prof. Michael Bagshaw (UK, 2008) described in a paper as similar to those known as Chronic Fatigue syndrome, Gulf War syndrome, Lyme disease, chronic stress and chronic hyperventilation. On the other hand, the two pilots developed symptoms and signs which could not be clearly classified (extreme fatigue, prickling, tingling, numbness etc). Both pilots landed the aircraft with an oxygen mask being afraid of an air-crash. In all cases the analysis of cabin-air contaminants (incl. TCP) was negative.

Conclusion: The BfR-assessment of the 5 cases could not find causality between possible inhalational exposure and the health impairment that occurred. TCP poisoning is unlikely.

170. A case of methanol toxicity from huffing paint lacquer

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Objective: To describe an occult source of methanol exposure in an unexplained anion gap acidosis.

Case report: A healthy 55 year old man was transferred to our tertiary care center after being found to have altered mental status and a high anion gap acidosis of unknown etiology. The patient is a mechanic who claimed to have been working in a pool of anti-freeze, but denied any ingestion. Vital signs: 36.6 degrees C, heart rate 80 bpm, respiratory rate 18 rpm, blood pressure 131/76 mm Hg, oxygen sat 100% on room air. His laboratory evaluation measured sodium 137 mEq/L, potassium 3.7 mEq/L, chloride 104 mEq/L, bicarbonate 9 mEq/L, blood urea nitrogen 28 mg/dL, creatinine 0.8 mg/dL, glucose 146 mg/dL. His white blood cell count measured $17.3 \times 10^9/L$, hemoglobin 16.1 g/dL, and platelets $264 \times 10^9/L$. Serum osmolality measured 282 mmol/kg. Venous blood gas measured pH

7.20, pCO₂ 17 mmHg, pO₂ 37 mmHg, bicarbonate 7 mEq/L. The patient was empirically treated with fomepizole (15 mg/kg) and a bicarbonate infusion. Subsequently, a toxic alcohol panel demonstrated undetectable ethylene glycol, ethanol, propylene glycol, and acetone levels. The methanol level was 48 mg/dL. The patient was treated with hemodialysis and folinic acid (50 mg every four hours). At the time of discharge, the patient's brother-in-law produced an empty can of paint lacquer that he found in the patient's bedroom. He confronted the patient who confessed to huffing the paint lacquer in an attempt to become intoxicated.

Conclusion: Patients that huff organic solvents may not be forthcoming in admitting the source of their intoxicants making the diagnosis of toxic alcohols problematic.

171. The last dinner: Fatality from 2-chloroethanol intoxication

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Background: 2-Chloroethanol is a toxic solvent with an LD50 of 58 mg/kg orally in rats. Grape farmers in Taiwan apply it on grapevines to hasten sprouting and can land themselves in potentially lethal conditions. Severe intoxication presenting with hypotension, respiratory failure, seizure, coma or mortality can occur in 24 hours even after only skin or inhalational exposure. It is hard to make the correct diagnosis in cases of unknown contamination history due to lack of specific clinical signs/symptoms or availability of routine laboratory tests.

Case series: In July 2011, two couples (2 males and 2 females, 40–58 years old) suffered from nausea, vomiting, shortness of breath, consciousness change and suspected convulsions 6–12 hours after eating dinner and drinking together. One case was noted to be dead on arrival in the emergency room, and the other three rapidly progressed to coma, hypotension and cardiac arrest in 1–3 hours. The most important laboratory finding was metabolic acidosis with blood pH value 7.223 to 7.291. This outbreak caused disquiet in the public with respect to food and drink. The grape sprouting agent, 2-chloroethanol was proved to be the killer after Poison Center consultation and clinical investigations about 2 weeks later. High concentrations of 2-chloroethanol and its metabolite were detected in the patients' blood samples and tissues by gas chromatography–mass spectrometry.

Conclusion: The toxic mechanism of 2-chloroethanol is not well known. In case of deliberate poisoning with 2-chloroethanol Poison Centers may play a critical role in early diagnosis and in alleviating public panic.

172. Thirty-nine cases of acute respiratory distress following one single exposure event for a surface coating product

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Objective: Pulmonary toxicity following exposure to aerosols of surface coating products has been reported worldwide, but most reports include few cases per exposure event. We report one incident involving 39 subjects after extensive spreading of a floor-sealing product containing poly-fluorinated silicones.

Case series: During the renovation of a 600 m² big supermarket in Maniitsoq, Greenland 2 craftsmen sprayed an area of about 50 m² of floor with 30 liters of a floor-sealing product with the use of compressed air sprayers. The ventilation system was out of order due to renovation. In a period of minutes to 3 hours later 39 subjects were admitted at the local hospital with respiratory and flu-like symptoms in varying degrees. Seven patients had acute radiological changes on chest X-ray and 10 patients presented low blood oxygen saturation. Nine of the hospitalized subjects worked or shopped on the level above the sprayed area or were briefly exposed. All patients were discharged after 3 days. At a clinical follow-up 2 months later 21 patients still mentioned dyspnoea during heavy physical activity. They all had, however, normal clinical examination, lung function, chest X-ray and blood oxygen saturation during exercise. Lung diffusion test was normal in the one patient where it was measured.

Conclusion: Poly-fluorinated silicones are potent chemicals able to produce pulmonary toxicity even at low-intensive exposure levels with a potential risk of extensive spreading of its aerosols. The use of such products requires, therefore, adequate protection measures for both the subjects in direct contact with the product and for bystanders.

173. Mustard gas poisoning - an unusual occupational injury

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Introduction: Mustard gas or S-Lost is a chemical warfare agent that was used during World War I and in the 1980s in the war between Iran and Iraq. At that time a number of mustard gas victims were treated in European hospitals. Nevertheless clinical experience in the diagnosis and treatment of this intoxication is very limited throughout Europe. Yet chemically related Lost-derivatives are frequently used in oncology. We present two cases with occupational exposure.

Case series: 1. A 45-year-old warfare expert sought medical treatment eleven days after he had been exposed to mustard gas while cleaning some decontamination equipment from World War I. At the time of exposure he wore dungarees, rubber gloves, and protective boots. A small quantity of liquid dropped on the trouser leg of his right shank. Some days later an erythema at the right groin and the genital region occurred. Moreover, there was a painless ulcer on the right shank. The lesions were treated conservatively; no systemic symptoms developed. The patient recovered completely and left hospital after one week. 2. A 27-year-old chemical technician sought medical advice shortly after being wetted on the ventral trunk with a small amount of S-Lost at his workplace. After decontamination the patient was

referred to hospital the following day because of aggravation of the dermal lesions (erythema and blister formation). The typical skin findings of the ventral trunk were demarcated as 1% of body surface. The lesions were treated surgically with necrosectomy and reconstructed with a split skin graft. Systemic symptoms of mustard gas intoxication were not observed.

Conclusion: Mustard gas (S-Lost) is an alkylating, cytotoxic substance. After dermal exposure the following symptoms can emerge: blisters, melanoderma, conjunctivitis and ulceration, especially in very thin and moist areas of the skin like axilla, groin and genital regions. Systemic intoxication is characterised by gastrointestinal symptoms, bone-marrow damage, immune deficiency and fatigue. The treatment is symptomatic and no specific antidote has been discovered so far.

174. Cutaneous cyclohexylamine exposure resulting in significant dermal burns without systemic toxicity

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Objective: Cyclohexylamine is a common aliphatic amine used as a corrosive inhibitor and chemical intermediate in the manufacturing of insecticides, plasticizers, and emulsifying agents. There are no reports of significant human cutaneous exposure published. The objective of this abstract is to report a case of significant partial thickness dermal burns that developed no systemic toxicity following extensive cutaneous exposure to the liquid corrosive cyclohexylamine.

Case report: A previously healthy 50 year-old male was transferring liquid cyclohexylamine between two containers at work. While transferring, he wore a full-face respirator, short-sleeved shirt, and pants. Overfilling the container caused cyclohexylamine to splash across his upper body and face causing an immediate burning sensation. Decontamination was performed for 30 seconds, during which time he reported tasting the chemical. On physical examination, he was noted to have 14% partial thickness burns with diffuse erythema, hyperpigmentation, blistering, and desquamation located bilaterally across the upper extremities, face, and chest. Sites of exposure were painful to touch and blanching. There were no signs of throat irritation, hoarseness, respiratory distress, chest discomfort, eye irritation, or altered mental status. A complete metabolic profile and complete blood count were normal. Chest radiograph was clear. He was treated with intravenous fluids, morphine for pain control, and was admitted for observation to a burn center with typical burn wound treatment. He was discharged the following day with the diagnosis of cyclohexylamine-induced partial thickness chemical burns. At one week follow-up, his pain had improved and partial re-epithelialization of burned areas was noted without signs of infection or soft tissue loss. At no time during his medical course were there signs of central nervous system depression or other neurologic sequelae following this exposure.

Conclusion: Cutaneous exposure to cyclohexylamine liquid can cause significant dermal burns without the development of systemic toxicity.

175. Gasoline exposures following Hurricane Sandy

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Objective: Hurricane Sandy made landfall on October 29th 2012 and caused severe infrastructure damage in heavily-populated areas. The prolonged electrical outage and damage to oil refineries caused a gasoline shortage and rationing unseen in the USA since the 1970s. We report an acute surge in gasoline exposures in NY following Hurricane Sandy.

Methods: The Poison Center's electronic medical record database, Toxicall[®], was systematically searched for gasoline exposures (American Association of Poison Control Centers - AAPCC code 039502) from October 29, 2012 at 19:00, prior to Sandy's landfall, through November 12, 2012 when electricity returned to >99% of the households that lost power. Gasoline exposure data was extracted for the same time period for the previous four years for comparison. Descriptive data analysis was performed using SPSS version 19 (IBM, Chicago, IL, USA). The primary outcome was the trend in gasoline exposures during the acute gasoline shortage. Secondary outcomes included exposure type, severity of clinical outcome based upon AAPCC definitions, and hospital referral rate.

Results: A total of 288 gasoline exposure cases were reported to the Poison Center during the study period. Exposures increase by 18-, 288-, 72-, and 96-fold compared to 2011, 2010, 2009, and 2008, respectively. The majority of exposures involved men (83.3%), and siphoning was the leading exposure reason (52.1%). Unintentional ingestions accounted for an additional 28.5%, (likely associated with undisclosed siphoning); inhalational, dermal, and ophthalmologic exposures were 16%, 2.4%, and 1%, respectively. Based on AAPCC's definitions, 66% of the exposure cases were not followed, as they were judged as either nontoxic or minor toxic exposures. Minor and moderate toxic effects were noted in 12.5% and 3.5%, respectively. Moderate toxic effects were primarily pulmonary, gastrointestinal, and CNS in nature (cough, vomiting, and dizziness). Overall, the majority of the cases were managed at home (87.8%), and of these cases, 71.9% were judged as nontoxic or minor toxic exposures.

Conclusion: An acute gasoline shortage markedly increased human gasoline exposures by siphoning. Although the majority of the exposures were deemed nontoxic and managed at home, a small number of the cases resulted in moderately toxic effects. Public health messaging was created to help promote safe gasoline handling.

176. Indoor environmental exposure to polychlorinated biphenyls

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Objective: Polychlorinated biphenyls (PCBs) are environmentally persistent chemicals with long-term health effects. About 90% of human exposure is assumed to derive from dietary exposure. Recent studies indicate additional exposure from building materials.^{1,2} We investigated PCB-exposure of people working in a building with PCB-containing sealants.

Methods: The study population included 15 exposed and 44 unexposed people. Data on sex, age and duration of exposure were obtained by questionnaire. Plasma concentration of 27 PCB congeners was analyzed by isotope dilution gas chromatography–mass spectrometry (GC-MS) method. Comparisons were evaluated by Mann-Whitney U test.

Results: Significantly higher plasma PCB concentrations were found for the sum of all 27 analyzed congeners, PCBs substituted with 3–4 and 5 chlorine atoms and for non-dioxin like congeners in exposed. No significant difference was found for the sum of 6 indicator PCBs, the group 6–7 chlorine atoms or for the dioxin like PCB congeners.

Conclusion: In people working in an indoor environment contaminated by PCB from sealants plasma levels of the sum of 27 PCB congeners were 40% higher than in unexposed. The lowest chlorinated and most volatile PCBs especially contributed to the exposure. The health consequences of this exposure are at present unsettled.

References

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177. Container incidents, a serious problem or a media hype

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Background: Yearly 2–3 million containers enter Dutch ports, 10–20% of these containing fumigants like methyl bromide, phosphine, 1,2-dichloroethane, toluene, benzene and formaldehyde. Over the years, the risk of exposure to these gases, has received increasing media attention, suggesting serious health risks for employees and consumers. In 2006 news items on container incidents were published on 3 individual days in the year but by 2009 this had increased to 31 days. In this period, the annual number (*circa* 9) of the consultations to the Poisons Information Center, did not change. Poisons centers in Germany and Switzerland reported comparative numbers, although this was considered to be an underestimation. The apparent discrepancy between the scope of these incidents in the media and the consultations at our poisons center warranted further research towards the extent and severity of container related incidents.

Methods: In close cooperation with Dutch labour organizations active in the field of transport and shipping containers, announcements were regularly placed on their websites and in their newsletters, encouraging employees to contact the poisons center in case of (presumed) exposure to container gases. From January 2011–October 2012 all consecutive cases were followed-up by telephone, using a standardized questionnaire for clinical symptoms and exposure conditions.

Results: The poisons center recorded 14 incidents; 24 of 33 involved employees were interviewed. The main reasons for exposure were lack of procedures before opening the containers, and lacking information about fumigation. The reported health effects were minor (upper-airway irritation, nausea, vomiting, headache, dizziness); in addition there was concern about long-term effects. In this period media coverage decreased to a few items annually.

Conclusion: Drawing attention to this project very likely increased workers' awareness of the risks of handling containers, however to our knowledge this did not result in a change in working procedures. The annual number and severity of incidents reported to the poisons center did not change compared to previous years. Therefore, although underestimation is common in occupational settings, we believe this study shows there is not a significant medical problem associated with exposure to container gases. In the study period the media coverage dropped, most likely indicating a media-hype in previous years.

178. Fire eater's lung: Analysis of 123 cases reported to a national poison centre

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Objective: Fire eater's lung (FEL) is a distinct form of acute chemical toxic pneumonitis, which is caused by aspiration of flammable petrochemical derivatives, like petroleum or its distillate, used by street performers for "fire eating". To date, the largest case series evaluating patients with FEL includes 17 cases, and the optimal management of this condition has not yet been determined. The aim of this study was to investigate patient characteristics, clinical features, treatment, and outcome of FEL.

Methods: Single-centre retrospective review of consecutive cases of FEL in children and adults reported to a national poison centre (STIC) between 1995–2012. Data were analyzed by chi-square test or Fisher's exact test.

Results: 123 cases (83.7% males, mean age 21.9 years) were included. The most frequently reported offending fuel was a petroleum distillate (95%). Among 36 cases in which detailed information on clinical features and follow-up data was available, 19.4% showed mild, 69.4% moderate, and 11.1% severe symptoms (Poisoning Severity Score (PSS)). The most frequently reported symptom was cough (50.4%), followed by chest pain (45.5%), and fever (35.8%). Dyspnea was reported by 23.6%. Cough ($p = 0.002$) and chest pain ($p = 0.026$) were significantly more prevalent in subjects reporting to have aspirated the fuel compared to those

who had swallowed it or who did not perceive poison exposure. A pulmonary infiltrate was detected in 83% of the cases in which chest x-ray was performed. Overall, 22% were treated with an antibiotic agent for a mean duration of 10.4 days. Corticosteroids were administered in 4.9%, and in most cases they were combined with antibiotics. Of the 24 patients in whom information on hospitalization was available, 75% were hospitalized due to FEL for a mean duration of 5.1 days. All showed complete recovery irrespective of therapeutic management.

Conclusion: FEL is mainly observed in young adults with a clear male predominance. The combination of intense pleuritic chest pain, cough, dyspnea, and fever, or any of these symptoms after "fire eating" or erroneous swallowing of petroleum should alert the clinician to the diagnosis of FEL. Early antibiotic treatment of severe cases seems justified, considered that clinical, laboratory, and radiologic findings of FEL are overlapping with bacterial superinfection.

179. Influential factors of impact of chemical, biological, radiation, and nuclear personal protective equipment on the performance of emergency airway management in the emergency medicine setting

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Objective: Airway management is an important step in resuscitation. Personal protection equipment (PPE) is recommended for use during airway management of chemical, biological, radiation, and nuclear (CBRN) victims. The authors evaluated whether wearing PPE made any impact in emergency physician performance of airway control with either an endotracheal tube (ETT) or a laryngeal mask airway (LMA). The purpose of this study is to answer the above questions from the point of view of rapid sequence intubation (RSI) in the emergency medicine setting.

Methods: Forty emergency physicians with 1–4 years of residency participated in this study. Each participant intubated the manikin and inserted the LMA into it with and without PPE in a random, crossover sequence. We assessed the intubation time by preassembling the intubation aids and the incidence of misplacement. A questionnaire was administered to examine participants' subjective experiences and comment on airway management with PPE.

Results: The mean times to successful ETT intubation without and with PPE were similar (17.01 ± 7.28 and 17.08 ± 5.70 seconds, respectively; $p = 0.93$). There were also no statistically significant differences between the time required to place the LMA without and with PPE (9.65 ± 3.29 and 10.19 ± 3.79 seconds, respectively; $p = 0.29$). The time to place the LMA was significantly faster than the placement of the endotracheal tube with protective equipment (10.19 ± 3.79 seconds and 17.08 ± 5.70 , respectively; $p < 0.0001$). There were 4 intubation failures in the junior group (1 ETT without PPE, 2 ETT with PPE and 1 LMA with PPE), but no intubation failure in the senior group. In choosing devices during airway management of CBRN victims, the senior residents preferred ETT rather than LMA; while the junior residents preferred LMA.

Conclusion: Although loss of dexterity may be associated with wearing butyl gloves, we can diminish its effect by preassembling the intubation aids. A well prepared CBRN set which includes preassembled intubation aids, prefilled medication syringe would be of great help in treating patients who are under respiratory distress under the circumstances of CBRN affairs.

180. Medication poisoning in Morocco: Retrospective study from 1980 to 2009

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Objective: Medication poisoning is an important source of activity in emergency and intensive care departments and in Poison Control Centres around the world. The aim of our study was to describe the epidemiological features of human medication poisoning identified by the Moroccan Poison Control Centre (CAPM) between 1980 and 2009, and to analyze risk factors for this phenomenon.

Methods: We conducted a retrospective study including all cases of medication poisoning reported to CAPM from 1 January 1980 to 31 December 2009. Adverse effects and poisonings in the fetus and the newborn of an intoxicated mother were excluded from this study. Statistical analysis was based on tests of association.

Results: The CAPM has collected 20,796 medication poisoning cases (20% of all types of intoxications). Poisonings were of urban origin in 92% of cases. Emergency departments notified more than 90% of the medication poisonings. The average age was $18.51 \text{ years} \pm 12.82$. Sex-ratio (M/F) was 0.57. The drugs implicated in the largest number of poisoning cases were nervous system drugs (58.49% of cases) followed by respiratory system drugs (9.21% of cases). Poisonings were intentional in 52.3% of cases. The dominating clinical signs were gastrointestinal signs (52.14% of cases) and neurological signs (29.03% of cases). The mortality rate was 0.55% of cases (77 deaths). Male intentional poisoning, age greater than 15 years, cardiovascular and musculoskeletal system drugs were risk factors for death.

Conclusion: In Morocco, the frequency of medication poisoning remains underestimated. Etiological studies should be conducted to help establishing a program for prevention of these poisonings.

181. Self-induced abortion in Mali

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Objective: Every year, about 5.5 million unwanted pregnancies are terminated by induced abortion in Africa. Because most abortions are illegal, these procedures are performed under clandestine

conditions. As a result, different regions face a serious public health problem that threatens women's lives and endangers their reproductive health. The aim of this study is to determine the profile of women hospitalized for complications of clandestine abortion as a result of self-poisoning in Mali.

Methods: A retrospective analysis of self-induced abortion cases, recorded between 2000 and 2010 in Malian hospitals, was performed.

Results: During the period of study, a total of 253 voluntary poisoning cases have been identified, constituting 23 cases on average per year. The average age of women experiencing induced abortion is 20 years. Most victims are adolescents and young adults aged 15–24 years (78.4%), 85.3% of whom are unmarried. According to data available, drugs are widely used by victims to terminate pregnancy (97.2% of cases), particularly chloroquine (87.8%). The poisoning symptoms are varied, depending on involved toxins, the ingested quantity and the delay before treatment. Among the 252 cases for whom the evolution is known, 14 died from complications caused by unsafe abortion. For other cases, the outcome was favorable with or without sequelae.

Conclusion: To reduce the need for abortion, it is important for family planning programs to include women who are young and unmarried in their outreach efforts.

182. Pattern of acute poisoning in Mali

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Objective: Voluntary poisoning is a major medical and social problem in developing countries and the most common method of attempted suicide. The aim of this study is to describe the main characteristics of self-poisoning in Mali.

Methods: A descriptive retrospective analysis of voluntary poisoning cases, recorded between 2000 and 2010, in the medical records and the consultation register at 15 hospitals in Mali, was performed.

Results: During the period of study, 884 self-poisoning cases (233 male and 651 female) were identified, constituting 28% of poisoning cases notified during this period. The average age of the victims was 23 years. According to data available, suicide attempts and self-induced abortion by voluntary ingestion of toxic products were the most common forms of self-poisoning (respectively 62.8% and 29% of cases). Drugs are the primary means employed by victims (74.5%), particularly chloroquine (65%), followed by industrial products (9.1%). The most used industrial products were hydrochloric acid (26.7%), sodium hypochlorite (bleach) (22.2%) and sulphuric acid (15.6%). Poisoning symptoms varied, depending on involved toxins, the ingested quantity and the delay before treatment. Among the 877 cases for whom the evolution is known, 86 of them died.

Conclusion: The real number of voluntary poisonings is probably underestimated, because of undiagnosed and unreported cases.

183. Epidemiology of toxic exposures reported by military personnel to a National Poison Center

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Objective: To evaluate the characteristics of toxic exposures reported by military personnel to the Israel Poison Information Center (IPIC).

Methods: A retrospective chart review from January 2007 to December 2011.

Results: 412 records of calls made by military personnel to the IPIC during the study period were retrieved. All the calls reported toxic exposures in adults serving in the army. Most of the exposed individuals were in the ages of 18 to 21 years (n = 293, 71.1%); 269 (65.3%) were male. The majority of callers were military physicians (n = 345, 83.7%). Two hundred and twenty-six (54.8%) calls were received up to one hour post exposure. There was a relatively equal distribution of exposures throughout the study years and seasons. Exposure was through ingestion in 214 (52%) cases and through inhalation in another 54 (13.1%) cases. Chemicals were the most frequent toxic group reported (n = 187, 45.3%), with hydrocarbons being the most frequent chemical agents (n = 36, 8.7%). Exposure to pharmaceuticals was reported in 140 (34.9%) cases; approximately half of these exposures were to analgesics (n = 73, 17.7%). In 48 (11.6%) cases the exposure was to a biological agent; 13 reports were on scorpion bites and 10 cases on centipede bites. Two hundred and two (49%) exposures were due to an accident or misuse; 90 (21.8%) exposures were a result of a suicide attempt. In 181 (43.9%) cases no clinical manifestations were reported. Gastrointestinal complaints were reported in 70 (17%) cases. Eye and mucous irritation was recorded in 49 (11.9%) cases. Dermal manifestations were reported in 22 (5.3%) cases. In 174 (42.2%) cases the IPIC recommended ambulatory observation; emergency department referral was recommended in another 158 (38.3%) cases. In 361 (87.6%) cases the severity of exposure was defined as no effect or minor. There were no severe or fatal exposures.

Conclusion: Toxic exposures in the army have distinct epidemiology following the unique characteristics of military service. In the reported study a higher prevalence of chemical exposures was recorded with more cases related to accidents or suicide and a relatively large share of emergency department referrals. Consultation with a poison center may improve case management and outcome.

184. Analysis of self-poisoning cases among schoolchildren and adolescents in four different years reported to a regional poison center

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Objective: To analyze the nature, frequency and trend of inquiries regarding self-poisoning cases among schoolchildren and adolescents reported to a regional poisons center in Mainz, Germany.

Methods: Retrospective study of inquiries made by telephone calls to the Poison Center pertaining to self-poisoning among school children and adolescents (≥ 6 years and < 18 years), in the years 1995, 2000, 2005, and 2010. Factors analyzed included age, gender, time and location of poisoning, nature of poison, route of exposure, amount taken, number of poisons encountered, information about the callers, degree of severity of poisoning. All data were analyzed using Statistical Package for Social Sciences 19 (SPSS 19).

Results: A total of 1654 inquiries regarding self-poisoning cases (25% of 6735 poisoning cases in these age groups) were retrieved from the database. The percentage of self-poisonings in these age groups were 35.3%, 27.5%, 23.0% and 16.7% in the years 1995, 2000, 2005 and 2010 respectively. The average age of the cases was 15.5 ± 0.04 years, without any change over the years. Most cases were females (1384; 83.7%), with a significant decrease over the years. Analysis revealed that 1513 (91.5%) of the cases were teenagers (14–17 years old). Most inquiries regarding suicide were received during the evening (6 pm till midnight) in all the years investigated, followed by early morning (midnight till 6 am). Almost all cases (1653; 99.9%) committed self-poisoning by oral ingestion of a pharmaceutical or a chemical substance. Most inquiries were made by clinical doctors (1434; 86.7%). Most of the self-poisoning incidents happened in domestic surroundings (1578; 96.4%) and the majority (945; 57.1%) took only one substance. The most common substance reported in self-poisoning incidents was acetaminophen followed by ibuprofen, aspirin, diclofenac sodium, and diphenhydramine.

Conclusion: Self-poisoning among adolescents is still a problem throughout the years of the study. The number of cases and the rate of self-poisonings are decreasing over the years. There is no trend in mean age, but an increasing rate of male patients. Support groups and other methods are needed to continue the decrease of self-poisoning incidence among future generations.

185. Gender, dose escalation and mortality during opioid therapy

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Objective: Millions of North Americans receive opioids for chronic non-cancer pain each year, and more than 17,000 people now die annually of opioid-related causes. Whether a patient's gender influences the likelihood of opioid dose escalation or opioid-related mortality is unknown.

Methods: We performed a population-based cohort study in Ontario, Canada from 1997 to 2011, linking prescription data on all provincial residents aged 15 to 64 who receive publicly-funded insurance to cause-specific mortality records from the Chief Coroner for Ontario.

Results: During the 14-year study period, we identified 290,174 patients with no history of cancer or palliative care services who

commenced treatment with an opioid, as well as 24,772 with evidence of long-term (> 3 months) use of opioids. Overall, 833 subjects (459 men and 374 women) escalated to high-dose opioid therapy (defined as > 200 mg morphine or equivalent per day), and 50 (32 men and 18 women) died of opioid-related causes. After using Cox proportional hazards regression to adjust for differences in demographics, comorbidity, physician service utilization and medication use at baseline, male sex was associated with a 55% increased likelihood of escalation to high-dose opioid therapy (adjusted hazard ratio 1.55, 95% confidence interval 1.35 to 1.79), as well as a markedly increased risk of opioid-related death (adjusted hazard ratio 2.44, 95% confidence interval 1.33 to 4.45).

Conclusion: Men prescribed opioids for non-cancer pain are more likely than women to escalate to high-dose therapy and far more likely to die of opioid-related causes.

186. Repetition of deliberate self-poisoning: A population-based cohort study

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Objective: Little is known about repetition of deliberate self-poisoning (DSP) because most studies rely on short-term follow-up or data from a single institution. We sought to characterize recidivism and mortality after a first episode of DSP in a population of approximately 13 million people.

Methods: We performed a population-based cohort study from April 2002 to March 2011 in Ontario, Canada. We studied all patients discharged from a hospital or an emergency department (ED) after a first episode of DSP, defined as no such presentation in the preceding 10 years.

Results: We identified 68,071 with an ED visit or hospital admission for a first DSP episode, including 537 (0.8%) who died prior to discharge. Acetaminophen, benzodiazepines and antidepressants were the most commonly implicated ingestions, and multiple drugs were involved in 25.5% of cases. Following discharge, 11,308 patients (16.7%) were readmitted for DSP, including 3,591 patients with multiple repeat episodes. The median time to repeat DSP was 274 days (interquartile range: 60 to 764 days). Roughly 1 in 6 of all repeat DSP episodes ($n = 1830$; 16.2%) occurred after a delay of 3 years or longer following the initial event. Female sex, rural residence, low income, diagnosis of depression, psychiatric care, and evidence of alcohol dependence were factors associated with recidivism. Patients with an initial episode of DSP were four times more likely than population-based controls to die from any cause, most commonly injuries (including suicide) ($n = 810$), cardiovascular disease ($n = 316$) or cancer ($n = 256$).

Conclusion: Repeat DSP is common, but many cases occur long after the initial event. Several factors including female sex, lower income quintile, psychiatric care and an alcohol use disorder are

associated with recidivism. Patients discharged from hospital following an index DSP event are four times more likely than matched controls to die, most often from injuries including suicide. Understanding the long-term prognosis of DSP has broad implications for harm prevention.

187. A randomised controlled study on the efficacy of prophylactic antibiotics in the management of kerosene-associated pneumonitis at a tertiary children's hospital in South Africa

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Objective: Kerosene ingestion is a major cause of childhood poisoning in South Africa.¹ The subsequent inflammatory pneumonitis has potential for secondary infection, but clinical manifestations may be indistinguishable. As secondary infection is rare, the role of early antibiotic intervention is debatable.²⁻⁴

Methods: A double-blind placebo-controlled trial of prophylactic amoxicillin in the management of kerosene-associated pneumonitis following ingestion was performed at Red Cross War Memorial Children's Hospital, Cape Town South Africa, from July 2010 to September 2011. Each child was followed-up at Day 3 and 5 post-ingestion. The primary outcome was the number of treatment failures in each group, defined as any child deteriorating at any time necessitating a change to the treatment regimen.

Results: Seventy-four patients were enrolled; 35 (47%) received placebo and 39 (53%) amoxicillin. In the placebo group, there were 32 treatment successes (32/35, 91%; 95% CI, 78 to 97) and three treatment failures (3/35, 9%; 95% CI, 3 to 22). In the amoxicillin group, there were 37 treatment successes (37/39, 95%; 95% CI, 83 to 99) and two treatment failures (2/39, 5%; 95% confidence interval (CI), 1 to 17). There was no significant difference between groups in treatment failures (RR, 0.60; 95% CI, 0.11 to 3.37). The median length of hospital stay for placebo (0.5 days; interquartile range (IQR), 0 to 1.0) and amoxicillin (0.5 days; IQR, 0.5 to 1.0) groups was identical. The assessment of symptoms and signs at Days 3 and 5 post-ingestion was similar.

Conclusion: Secondary infection of kerosene-associated pneumonitis following ingestion in children is rare and prophylactic antibiotics do not improve outcome.

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188. Poisoning due to metformin accumulation in diabetic patients on chronic therapy: Analysis of 66 patients with lactic acidosis and high plasma metformin levels

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Objective: To study the relationship between metformin therapy and lactate increase in all patients with metformin accumulation referred to the Pavia Poison Control Centre (PPC).

Methods: All cases of lactic acidosis (pH \leq 7.35; arterial lactate \geq 5 mmol/L) related to metformin accumulation (plasma level \geq 4 micrograms/mL) referred to PPC from 2007 to 2011 were retrospectively reviewed. Medical history, epidemiological, clinical and analytical data were evaluated either in all patients or in MILA (Metformin-Induced Lactic Acidosis) and MALA (Metformin-Associated Lactic Acidosis) subgroups (classified according to the presence of risk factors for lactic acidosis other than metformin accumulation). A correlation between metformin plasma levels and lactic acidosis has been evaluated.

Results: Sixty-six patients (76% female, age 68.35 ± 10.17 years) were included. Thirty-five patients had no contraindications to metformin therapy: among these, 57% were treated with ACE-inhibitors or NSAIDs. Mild gastrointestinal manifestations were the most frequent prodromal symptoms. All patients showed severe lactic acidosis (pH 6.91 ± 0.18 , lactate 14.36 ± 4.90 mmol/L) and acute renal failure (creatinine 7.24 ± 3.29 mg/dL). The mean metformin plasma concentration was 40.68 ± 27.70 micrograms/mL (range 4.6-117) and showed a correlation with creatinine (p = 0.002, R = 0.37) and plasma lactate levels (p = 0.001, R = 0.41). Sixty-two patients (94%) underwent dialysis. Hospitalization in the intensive care unit (ICU) lasted for a median of 5 days and mortality before discharge from ICU was 26%. The mean level of creatinine was 7.91 ± 3.10 mg/dL in survivors and 5.30 ± 3.15 in patients who died (p = 0.011). Among the included patients, 55% were attributed to the MILA group and 45% to the MALA group. Despite a more severe lactic acidosis (p = 0.01), the higher creatinine (p = 0.004) and metformin plasma levels (p < 0.0001), MILA and MALA patients showed similar mortality rates.

Conclusion: Metformin accumulation should be suspected in diabetic patients with metabolic acidosis, acute renal failure and a history of gastrointestinal manifestations. Mortality does not present any correlation with serum creatinine, metformin and lactate levels: therefore the role of concomitant risk factors in determining the outcome should be highlighted. Metformin accumulation may develop also in patients without contraindications to therapy or risk factors for lactic acidosis, suggesting a potential primary role of metformin in determining lactic acidosis.

189. Hepatic toxicity of dronedarone in mice: role of mitochondrial beta-oxidation

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Objective: Dronedarone is a new amiodarone-like antiarrhythmic drug which became implicated in causing severe liver injury. We previously reported that dronedarone is an uncoupler and inhibitor of the mitochondrial respiratory chain and beta-oxidation *in vitro*.¹ We hypothesized that mitochondrial toxicity may explain hepatotoxicity of dronedarone *in vivo*.

Methods: We studied hepatotoxicity and effects on liver mitochondrial function of dronedarone (200 mg/kg daily for 2 weeks or 400 mg/kg daily for 1 week by intragastric gavage) in heterozygous juvenile visceral steatosis (JVS+/-) and wild-type mice. JVS+/- mice have reduced carnitine stores and are sensitive for inhibitors of mitochondrial beta-oxidation.²

Results: 200 mg dronedarone daily had no effect on body weight, serum transaminases and bilirubin, and hepatic mitochondrial function in both wild-type and JVS+/- mice. In contrast, 400 mg dronedarone per day was associated with a 10 to 15% drop in body weight and a 4 to 6-fold increase in serum transaminases and bilirubin in both JVS+/- and wild-type mice. *In vivo* hepatic beta-oxidation (metabolism of intraperitoneal ¹⁴C-palmitate) was significantly slower in JVS+/- mice treated with dronedarone (increased T_{max}) as compared to the other groups. This was also reflected by low serum beta-hydroxybutyrate concentrations during starvation. Impaired beta-oxidation was also found in isolated mitochondria *in vitro*. A likely explanation for these findings was a reduced activity of carnitinepalmitoyl transferase 1. In contrast, treatment with dronedarone did not affect the activity of the respiratory chain in isolated liver mitochondria.

Conclusion: Dronedarone inhibits mitochondrial beta-oxidation *in vivo*, but not the mitochondrial respiratory chain. JVS+/- mice appear to be more sensitive to the effects of dronedarone on mitochondrial beta-oxidation than wild-type mice. The results suggest that inhibition of mitochondrial beta-oxidation is an important mechanism of hepatotoxicity associated with dronedarone.

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190. Risk factors for cardiovascular events in emergency department patients with drug overdose

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Objective: We recently demonstrated that adverse cardiovascular events (ACVE) complicate a high proportion of emergency department (ED) patients with acute drug overdose.¹ It remains unclear which patients require intensive care unit admission or telemetry monitoring to assess for in-hospital ACVE. This study derived clinical risk factors for ACVE in ED patients with acute drug overdose.

Methods: This prospective cohort study was conducted at 2 urban university tertiary care hospitals. Patients > 18 years with acute drug overdose were enrolled from the ED over 3 years. Excluded were patients with alternate diagnoses, anaphylaxis, chronic drug toxicity, and missing outcome data. ED clinical data included demographics, exposure intent, ECG intervals, vital signs, laboratory chemistries, altered mental status (Glasgow Coma Scale < 15 or coma/agitation/delirium), and prior cardiac disease (coronary disease or congestive heart failure). In-hospital ACVE was defined as any of: 1) myocardial necrosis (elevated troponin), 2) shock (hypotension requiring vasopressors), 3) ventricular tachycardia or fibrillation (VT/VF), 4) cardiac arrest (no pulses or chest compressions). Analysis included univariate factor analysis and multivariable logistic regression with test characteristics of the derived model.

Results: There were 1,557 patients meeting inclusion/exclusion criteria with mean age 41.8 years, female 46%, suicidal 38%, median drug exposures = 2. ACVE occurred in 82 (5.7%) patients including: myocardial necrosis, 61; shock, 37; VT/VF, 23; and 22 cardiac arrests with 18 (1.2%) deaths. On univariate analysis, ACVE risk increased with age, lower serum bicarbonate, prolonged QTc, prior cardiac disease, and altered mental status. In a multivariable model adjusting for these factors as well as gender and ED site, independent predictors included: QTc > 500 msec (OR 2.6, CI 1.6–4.4), bicarbonate < 20 mmol/L (OR 4.8, CI 2.4–9.6), and prior cardiac disease (OR 12.5, CI 6.7–23.4). Absence of all 3 factors had 97.6% (CI 96.7–98.4) negative predictive value for ACVE.

Conclusion: We derived clinical risk factors for ACVE in ED patients with acute drug overdose that include prolonged QTc, serum bicarbonate, and prior cardiac disease. Future studies will validate these criteria in a new patient population.

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191. Current trends in the epidemiological profile of acute ethanol overdoses and alcoholism

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Background: Alcohol is the most used and abused substance worldwide. A standard alcohol drink is 14 gm ethanol, contained in the average 360 mL beer, 150 mL wine, 45 mL 80 proof liquor. In the past year, the percentage of Americans who had at least one

drink - 59.6% of women, 71.8% of men; of the drinkers, on a drinking day, 21.9% of women and 42.3% of men have 3 or more drinks. The percentage of lifetime abstainers - women 22.5%; men 11.6%.

Discussion: Moderate or "low-risk" drinking is defined as no more than 4 drinks on any single day AND no more than 14 drinks per week for men; for women: no more than 3 drinks on any single day AND no more than 7 drinks per week. Heavy or "at-risk" drinking is defined as having more than the single-day or the weekly amounts listed above. About 1 in 4 people who drink above these levels already has an alcohol use disorder. Binge drinking, which is defined as consuming enough alcohol within about 2 hours, such that blood alcohol content (BAC) ≥ 0.08 g/dL, occurs > 4 drinks in the average woman, and after > 5 for men. Binge drinking poses increased health and safety risks (motor vehicle accident (MVA), falls, drowning, etc). In the USA, 28.8% of women and 43.1% of men are binge drinkers.

Alcohol use disorders are medical conditions diagnosed when a patient's drinking causes distress or harm. In the USA, about 18 million people have an alcohol use disorder, classified as either alcohol dependence - aka alcoholism - or alcohol abuse. While the alcohol abuser is not physically dependent, they have a serious disorder, are a "problem drinker", and their drinking affects life at home, work, or school; causing risky behaviors such as driving while intoxicated, risky sexual behaviors, legal or social problems.

Alcoholism is a disease where affected patients' lives essentially revolve around alcohol. They spend a great deal of time drinking, making sure they can get alcohol, and recovering from alcohol's effects, often at the expense of other activities and responsibilities. Symptoms include: Craving—A strong need, or urge, to drink; Loss of control—Unable to stop drinking once started; Physical dependence—Physical withdrawal symptoms - the avoidance of which leads to daily drinking; and Tolerance—Greater amounts of alcohol required for same effect.

The 12-month prevalence of alcohol dependence is 3.81% in the USA, and is more common among men than among women. The prevalence peaks early in life, and declines rapidly after the age of 26. The disease course may be different for individuals who develop alcohol dependence earlier in life, since younger patients are less likely to seek treatment¹.

The amount of alcohol consumed per day affects the risk of morbidity and mortality, with a "J-shaped" curve: increased risk among abstainers, highest among heavy drinkers, lowest among light drinkers. Mortality rates increase after about 4 drinks per day.² This is important, since alcohol use is #3 cause of death in USA (85,000 US deaths per year) behind only tobacco use and obesity (deaths due directly and indirectly to alcohol, including MVA fatalities). If deaths due to alcohol in individuals who no longer drink are included, attributable mortality would rise to 140,000 deaths per year. The harmful use of alcohol results in 2.5 million deaths each year worldwide; most tragically, 320,000 young people between the age of 15 and 29 die from alcohol-related causes, resulting in 9% of all deaths in that age group³.

Alcohol use increases through the teen years, peaks in the early 20s, and then declines; males are more likely than females to report drinking alcohol in the previous month. In fact, 2.3% of 12-year-olds drink, which rises to about 70% of individuals ages 20–29, and drops to 33% of those aged > 65 years.

Alcohol use affects all types of accidents and injuries. The risk of an MVA increases as BAC increases. Compared with sober drivers, risk of a single-vehicle fatal crash for drivers with BAC's between 0.02 and 0.04 percent is estimated to be 1.4 times higher;

for BAC's between 0.05 and 0.09 percent, 11.1 times higher; for drivers with BAC's between 0.10 and 0.14 percent, 48 times higher; and for those with BAC's at or above 0.15 percent, the risk is estimated to be 380 times higher.⁴ Regarding falls, binge drinking leads to unintentional injuries and falls, especially in middle-aged and elderly adults, among other effects.⁵ Impulsivity and aggression are strongly implicated in suicidal behavior, and with acute alcohol use. Suicide completers have high rates of positive blood alcohol. Intoxicated people are more likely to attempt suicide using more lethal methods. Alcohol intoxication may be important in suicides among individuals with no previous psychiatric history.⁶ Alcohol is detected in the blood in 30%–70% of persons who drown while involved in aquatic recreation. Persons with a blood alcohol level of 0.10 g/100 mL have about 10 times the risk of death associated with recreational boating compared with persons who have not been drinking, but even small amounts of alcohol can increase this risk.⁷

While many references quote a BAC of 0.450 g% as the lethal level, the BACs in deaths attributed to acute alcohol poisoning (no other drugs present), the mean and median concentrations were similar, namely 0.36 g%. In 95% of these victims, the BAC at autopsy ranged from 0.22 g% to 0.50 g%.^{8,9}

Conclusion: Alcohol use is ubiquitous in western cultures; binge drinking is associated with increased morbidity; its use and abuse affects all aspects of life; and increases the risks of suicide, accidents, diseases. The all-cause mortality increases after > 4 drinks/day.

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192. Adverse drug effects from chelants used to treat metals poisoning

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Background: ‘Chelate’ is derived from the Greek word “chele” meaning claw. Like a claw, chelating agents have > 2 bonds with a polydentate ligand, usually an organic chemical, and a single central atom. As a medical therapeutic strategy, chelation of a toxic agent in the blood can potentially reverse toxicity by binding to the toxic agent in this chemical moiety, removing it from its target site of toxicity and facilitating its elimination. There is a role for the use of chelants in some clinical situations involving acute or chronic toxic exposures due to different metals. Dimercapto-succinic acid (DMSA), disodium calcium edetate (CaNa₂EDTA; versenate), and dimercaprol (BAL; British Anti-Lewisite) have all been employed to treat acute and chronic metals poisoning. In such cases, the practicing toxicologist must weigh carefully the potential benefits of using a chelating agent versus its known toxicities. Some adverse events are predictable and can be anticipated and averted. Others, such as allergic rashes and anaphylaxis, are idiosyncratic and unpredictable.

Discussion: The published literature on chelating drugs describes the toxicities of each.¹⁻⁷ Treatment with CaNa₂EDTA infusion, for example, has been associated with a risk of nephrotoxicity. As a result, the use of CaNa₂EDTA may be contraindicated in patients with underlying chronic renal failure. CaNa₂EDTA can also reportedly cause cerebral edema and worsening encephalopathy when used as the sole initial agent in the treatment of severe lead poisoning. DMSA can cause gastrointestinal symptoms, neurologic and neurobehavioral effects, bone marrow depression, rashes and transaminase elevations. Mechanisms underlying such toxicities are diverse and can be described in many cases. For example, there are concerns that some chelants would concomitantly eliminate essential trace minerals, such as zinc and copper, leading to clinically important deficiencies. Such knowledge can be used to anticipate and avoid chelant-related toxicity, optimizing the likelihood of benefit. Use of the correct salt of CaNa₂EDTA will avoid instances of life-threatening hypocalcemia. Supplemental iron, zinc, and other minerals after completion of a course of chelation can repair any associated nutritional deficits of essential minerals.

Conclusion: Adverse effects from chelating medicines used in the treatment of metals poisoning are usually mild and self-limited. However uncommonly side-effects from chelants such as dimercaptosuccinic acid or CaNa₂EDTA may be severe and can result in poor clinical outcomes. Prevention strategies and adequate vigilance during patient management can minimize the likelihood of these adverse effects.

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193. Pathology, treatment, and consequences of the alcohol hangover

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Objective: To give an overview of the causes, consequences, and treatment of the alcohol hangover.

Methods: A literature search was conducted (PubMed, Embase) to identify studies on alcohol hangovers.

Results: A series of studies have examined the socioeconomic, health and behavioral effects of the alcohol hangover. The studies showed that several aspects of cognitive functioning, psychomotor performance and memory are impaired during a hangover. This can have a negative impact on daily activities such as job performance and driving a car. A limited number of studies examined the pathology of the alcohol hangover. They revealed that the pathology of an alcohol hangover is unclear, but that it is likely that the immune system plays a role in the pathogenesis of the alcohol hangover. Given the limited knowledge on the pathology of the alcohol hangover, it is understandable that no effective hangover treatment has been developed.

Conclusion: The alcohol hangover has serious socioeconomic, health and behavioral consequences that are often underestimated. Much of the pathology of the alcohol hangover is unclear. As a result, currently no effective hangover treatments are available.

194. Ethanol metabolism in infants under 6 months of age

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Objective: There is a paucity of published data on the metabolism of ethanol in infants. This case series describes ethanol metabolism in two infants less than six months of age.

Methods: Two infants admitted for ethanol toxicity had serial ethanol levels measured and correlated to rate of metabolism.

Case series: Case 1. A 5-month old infant was unintentionally given ethanol in a piña colada mix. His parents noticed his significant altered mental status and decreased responsiveness. His presenting ethanol level was 288 mg/dL. Serial ethanol levels demonstrated an average metabolism rate of 16.51 mg/dL/hr. Case 2. A 9-week old infant female was inadvertently fed a mixture of formula and vodka. The discovery was made after her parents noted fussiness during feeding. Her presenting ethanol level was 188 mg/dL and rate of metabolism was 16.43 mg/dL/hr. Both children were monitored and recovered uneventfully.

Conclusion: Ethanol metabolism follows zero order kinetics in adults at an average of 20 mg/dL/hr. Teenagers metabolize ethanol

at the same rate as adults, but prior reports suggest that younger children metabolize ethanol as rapidly as twice that of adults.¹ However, one study reported an infant under 12 months whose metabolic rate of ethanol was 26.3 mg/dL/hr; this was not significantly different from older children in the study.² Our case series suggests that ethanol metabolism in infants follows zero order kinetics at a rate similar to adults. These findings correlate with known ontogenic information about the developmental activity of CYP 2E1 in the infant.³

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195. Unintentional pediatric opioid exposures as reported to the Global Toxicosurveillance Network (GTNet) from 2008–2010

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Australia; ⁵Swiss Toxicological Information Centre, Associated Institute of the University of Zurich, Switzerland; ⁶National Poisons Information Centre, Utrecht, The Netherlands; ⁷National Poisons Information Service, UK

Background: Lack of awareness regarding the public health hazard of children under age 6 years being unintentionally exposed to prescription opioid medications currently exists. This study examines the occurrence of these exposures reported to poison centres in Australia, Germany, Italy, the Netherlands, Switzerland, the United Kingdom, and the United States (US).

Methods: Pediatric exposures (< age 6 years) to oxycodone, buprenorphine, and methadone reported to poison centres from 2008–2010 were obtained using a standardized tool. All participating centres manage calls from health care providers. Australia, Italy, Germany, Switzerland and the US also manage calls from the public. Rates are expressed as percentages of the total number of unintentional exposure calls with confirmed patient age received by each poison centre for the opioid of interest.

Results: Unintentional opioid pediatric exposures increased from 2008–2010 (Table 1). Within Australia, US, Switzerland, and Italy, the percent of exposure calls concerning buprenorphine was disproportionately high relative to the number of exposure calls overall. In the Netherlands and Switzerland a similar pattern was observed for methadone.

Conclusion: There have been significant increases in unintentional pediatric exposures to various opioids reported to poison centres in Europe, Australia, and US. These accidental ingestions in children to the drugs studied are extremely dangerous. Heightened awareness of this issue is critical as opioid availability/prescriptions increases so efforts can be made to minimize the risk of exposure to children. Although the number of these poisonings outside the US is small, a relative increase is noticed as well for most drugs in most countries.

Table 1. Unintentional pediatric opioid exposures as reported to the Global Toxicosurveillance Network from 2008–2010.

Drug Class	Country	2008	2009	2010	Total	% change in proportion from 2008–2010
Buprenorphine	Australia	9 (12%)	10 (12%)	22 (28%)	50	132%
	Germany	0 (0%)	0 (0%)	0 (0%)	0	***
	Italy	3 (10%)	3 (16%)	4 (29%)	13	176%
	Netherlands	1 (17%)	1 (25%)	3 (38%)	5	***
	Switzerland	2 (29%)	3 (20%)	1 (6%)	8	–78%
	USA	689 (39%)	1007 (42%)	1173 (43%)	3198	10%
	UK	3 (6%)	8 (15%)	6 (13%)	17	104%
Methadone	Australia	10 (12%)	7 (8%)	9 (12%)	38	–3%
	Germany	1 (3%)	0 (0%)	1 (2%)	3	–35%
	Italy	4 (6%)	5 (9%)	7 (10%)	25	62%
	Netherlands	4 (5%)	5 (7%)	7 (9%)	17	73%
	Switzerland	2 (4%)	5 (7%)	5 (7%)	14	86%
	USA	247 (8%)	307 (9%)	274 (8%)	1082	1%
	UK	14 (18%)	8 (12%)	11 (15%)	33	–16%
Oxycodone	Australia	32 (8%)	44 (8%)	33 (6%)	144	–25%
	Germany	3 (8%)	1 (3%)	2 (5%)	7	–41%
	Italy	0 (0%)	1 (13%)	1 (11%)	2	***
	Netherlands	2 (5%)	3 (9%)	9 (14%)	17	170%
	Switzerland	2 (11%)	0 (0%)	1 (3%)	3	***
	USA	1381 (12%)	1579 (12%)	1562 (11%)	5581	–7%
	UK	4 (11%)	2 (3%)	1 (2%)	7	–81%

***There are too few cases to draw an accurate percentage change in proportion of exposures.

196. The pattern of methylphenidate exposures in Denmark

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Objective: The use of methylphenidate (MPH) for adult attention deficit hyperactivity disorder (ADHD) has increased in Denmark during recent years. In 2011, about 20,000 adults were treated with MPH.¹ However, the pattern of adult MPH abuse has not been described previously.

Methods: Using a retrospective observational design, all adult (> 18 years) MPH exposures reported to the Danish Poison and Information Centre from January 2006 to June 2012 were analysed. Furthermore, the trends in prescription and MPH exposures were compared (2007–2011).

Results: A total of 394 exposures were included. Demography: The median age was 27 years (Interquartile range (IQR) 20–35) and 57% of cases were males (95% confidence interval (CI) 52–62%). MPH status: In at least 163 cases (41%), MPH was prescribed by the doctor at the time of exposure. Reason for exposure: Unintentional: 21 (5%), recreational: 149 (38%), suicidal attempts/emotional strain: 202 (51%), other: 3 (1%), unknown: 19 (5%). Toxicology: The median dose was 300 milligrams (IQR 135–600 milligrams) and in 353 cases (90%), the entire dose was administered orally. In the remaining cases, injection, para-nasal route or a combination of oral and para-nasal route was used. Ritalin and Ritalin Uno constituted 63% of all exposures. Concurrent exposure was reported in 228 (58%) cases. One hundred and forty-three (36%) were exposed to medications, 93 (24%) to alcohol, 70 (18%) to recreational drugs and one (0.3%) to other substances. Symptoms: 323 (82%) had symptoms, 51 (13%) were asymptomatic while information about symptoms was insufficient in 20 (5%) cases. The most common symptoms were central nervous system (CNS)/constitutional symptoms, which were reported in 263 (67%) cases. Cardiovascular symptoms were reported in 227 (58%) cases. Exposure compared to prescription showed a linear relationship with 8 exposures per 1000 defined daily dose (DDD). For Ritalin and Ritalin Uno, this relationship was even stronger.

Conclusion: MPH abuse was most common among young male adults and the exposure rate follows the prescription rate (particular Ritalin and Ritalin Uno). Most exposures were intentional and caused by suicide attempts/reaction to emotional stress or recreational use. At least 82% of cases were symptomatic, most commonly CNS/constitutional and cardiovascular symptoms.

Reference

1. <http://medstat.dk/en>

197. Intoxications by synthetic cannabinoids – current trends

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Objective: More than 30 compounds with agonistic activity on the CB₁-receptor have been identified in herbal products.¹ We report 21 emergency department (ED) patients with analytically verified consumption of synthetic cannabinoids, who were hospitalised between 11/2011 and 10/2012.

Case series: Serum samples of 25 ED patients were analysed by LC-ESI-MS/MS after consumption of synthetic cannabinoids, as described before.¹ The intake of cannabimimetics was confirmed in serum samples of 21 patients (18 male, 3 female, 13–30 years old). JWH 210 (13), JWH 122 (7), AM-2201 (6), JWH-018 (6), JWH-019 (2), JWH-081 (2), JWH-200 (1), MAM-2201 (3) UR-144 (3), JWH-307 (1), RCS-4 (1), MAM-122 (1) were identified. In 65% of the cases more than 1 compound was present. MAM-2201 was found for the first time in March, UR-144 in July 2012, AM-2201 increasingly from January 2012 on. Most frequent clinical symptoms were tachycardia (12), nausea/vomiting (11), somnolence (9) and hyperglycaemia (9). Less frequent were hypokalaemia (4), syncope (4), dyspnoea (3), aggressive behaviour (3), amnesia (2), diplopia (2) and seizures (2). Acute psychosis lasted for 5 days in one patient (JWH-019 still found in the blood on day 4). Chest-pain, ECG-changes (negative t-wave, ST-elevation) and increase of CK/CK-MB were reported twice, but troponin was negative in both cases. One patient with diabetes mellitus developed pronounced hyperglycaemia (320 mg/dL).

Conclusion: Synthetic cannabinoids which are currently not banned in Germany such as AM-2201 and MAM-2201 are increasingly found in 2012 – together with the banned cannabinoids JWH-018 and JWH-122. The CB₁ receptor affinity of AM-2201 is similar to that of JWH-122; affinities of MAM-2201 and MAM-122 are unknown. We found more than one compound in most serum samples, at maximum 8 different compounds. This development is worrying, especially because of the high frequency of syncope (20%), diplopia, seizures and amnesia (each 10%). Besides a summation of effects of the different compounds, interaction effects should be taken into consideration also. Intoxications by MAM-122 and MAM-2201 had not been reported yet.

Reference

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198. Detection of use of novel psychoactive substances by attendees at a music festival in the North West of England

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Table 1 Frequency of detection of potential novel psychoactive substances from the two urinals within the festival.

Compound detected	Urinal 1	Urinal 2
1,4 methoxy phenyl piperazine	Detected	Detected
1,4-trifluoromethylphenylpiperazine	Detected	Detected
4-ethylmethcathinone	Detected	Detected
4-methylmethcathinone	Detected	Detected
4-fluorophedrine	Detected	Detected
4-fluoronorephedrine	Detected	Not detected
5-(2-aminopropyl)benzofuran (5-APB)	Detected	Detected
Hordenine	Detected	Detected
Methiopropamine	Detected	Detected
Methylhexanamine	Not detected	Detected

Objective: The pattern of use of novel psychoactive substances (NPS) in the night-time economy differs from that at music festivals. Previous studies analysing anonymous pooled urine have used city-centre street “pissiors” (urinals) to detect NPS. We used the same methodology to analyse samples from urinals at a festival in the North West of England, described as offering “pioneering contemporary music and art alongside traditional rural entertainment.”

Methods: Anonymous pooled urine samples were collected from two stand-alone urinals from different locations within the festival in July 2012. Samples were subsequently analysed using full-scan accurate mass high resolution liquid-chromatography coupled to tandem mass-spectrometry, processed against compound databases containing >1700 drug compounds/metabolites.

Results: A total of ten possible NPS were detected in the urine samples; the NPS detected in the urinals and their frequency of detection is shown in Table 1. The hordenine detected may relate to use of psychedelic cacti, however it is more likely that it is due to the ingestion of beer, since no mescaline was detected.

Conclusion: This study shows it is possible to extend the use of analysis of anonymous pooled urine samples to music festivals and confirms use of a range of NPS at this festival. There is the potential to compare the pattern of detection of NPS over time and across different festival events, to determine whether there are trends associated with the type of festival and/or musical genre at the festival. This will allow more

accurate characterisation of NPS actually being used in these environments.

199. Misuse of opioid containing prescription and over the counter medications in the United Kingdom

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Background: There is increasing evidence of misuse of prescription and over-the-counter (OTC) opioid containing products in the USA. Currently there is no data on the frequency and pattern of opioid misuse in the UK.

Methods: We undertook an Internet questionnaire survey using an existing market research consumer survey panel; only those aged 16–59 were asked to participate so that data could be compared to recreational drug use prevalence in the British Crime Survey. Basic demographic data (age and sex) were collected together with data on the prevalence of misuse of opioids available in the UK. For those individuals who indicated that they had misused opioids, data was collected on the reasons for this using pre-defined criteria (they were able to state more than one reason where appropriate).

Results: The survey was completed by 1,500 individuals, of whom 737 (49.1%) were male and 763 (50.9%) female. 9.1%, 40.5%, 21.1% and 29.3% were aged 16–20, 21–39, 40–49 and 50–59 respectively. The life-time prevalence of misuse of each group of opioid containing medications and the reasons for misuse is shown in Table 1. Life-time prevalence of use of recreational drugs was comparable to national data from the 2011/12 British Crime Survey (8.1%-vs-9.5% for cocaine, 8.2%-vs-8.6% for MDMA and 1.7%-vs-0.8% for heroin).

Conclusion: This study suggests that there is potentially significant misuse of opioid containing OTC and prescription medications in the UK. Further studies are needed to further explore this issue to inform the design of appropriate primary and secondary prevention initiatives.

Table 1. The life-time prevalence of misuse of each group of opioid containing medications and the reasons for misuse.

	Opioid containing medication group					
	Codeine, codeine - paracetamol	Dihydrocodeine - paracetamol	Dihydrocodeine	Oxycodone	Morphine	Tramadol
Lifetime prevalence of misuse (% of total survey population)	157 (10.5%)	38 (2.5%)	28 (1.9%)	21 (1.4%)	14 (0.9%)	39 (2.6%)
Reasons for misuse (% of those who reported misuse)						
For enjoyment / to get high	7 (4.5%)	5 (13.2%)	7 (25.0%)	4 (19.0%)	4 (28.5%)	7 (17.9%)
For social reasons / to fit in	3 (1.9%)	3 (7.9%)	8 (28.6%)	4 (19.0%)	4 (28.5%)	4 (10.3%)
Out of curiosity	8 (5.1%)	2 (5.3%)	4 (14.3%)	2 (9.5%)	0 (0%)	4 (10.3%)
Safer than street/illegal drugs	5 (3.2%)	2 (5.3%)	1 (3.6%)	2 (9.5%)	3 (21.4%)	5 (12.8%)
Help with come-down of other drugs	2 (1.3%)	1 (2.6%)	0 (0%)	1 (4.8%)	2 (9.5%)	3 (7.7%)
Help me cope with stress	17 (10.8%)	6 (15.8%)	4 (14.3%)	3 (14.3%)	4 (28.6%)	13 (33.3%)

200. Reduction in the availability and price of alpha-methyltryptamine from Internet suppliers over time

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Background: The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has developed an Internet snapshot methodology which allows assessment of trends in availability and price of novel psychoactive substances (NPS). This study used this methodology to assess changes in the availability and/or price of the NPS alpha-methyltryptamine (AMT) over time.

Methods: Using the same methodology as a snapshot undertaken in March 2012, "google.co.uk" was searched in October 2012, to allow comparison over time.¹ The cost of AMT was converted into cost per gram for powder or cost per pellet to allow comparison across different purchase quantities.

Results: There was a fall in the number of Internet sites selling AMT from March to October 2012 in all forms: powder (30 vs 25 sites), pellets (10 vs 6 sites), capsules (4 vs 0 sites). Of the 30 sites selling powder in March 2012, only 9 were still selling in October 2012 with 16 new sellers. A similar pattern was seen for sites selling pellets (1 of 10 sites still selling in October 2012, with 5 new sites). The cost per gram for powder fell across all purchase quantities: 100 mg purchase £125.95 ± £47.40 March 2012 to £83.11 ± £22.99 October 2012; 1 g purchase £42.82 ± £14.19 to £28.40 ± £8.24; 10 g purchase £25.61 ± £8.10 to £17.94 ± £4.49; 100 g £10.60 ± £2.69 to £9.52 ± £2.23. The cost per pellet also fell: 1 pellet purchase £6.50 ± £0 to £5.50 ± £0.91; 10 pellets £4.17 ± £0.76 to £3.75 ± £0.50; 100 pellets £3.33 ± £0.65 to £2.58 ± £0.49; 1000 pellets £2.50 ± £0.87 to £1.85 ± £0.77.

Discussion: This study showed that the number of Internet sites selling AMT fell between March 2012 and October 2012. There was poor continuity in sites that sold powder and pellets over time. No sites sold capsules in October 2012, this may reflect increasing awareness that capsules represent products being sold for human consumption. Despite this there was an overall reduction in price of both powder and pellet AMT over this time period.

Reference

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201. Awareness and use of 4-methylamphetamine is significantly lower than amphetamine in a high-drug using population

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Background: There has been concern across Europe regarding deaths related to the recreational use of 4-methylamphetamine in the UK and elsewhere in Europe. This has prompted a risk assessment by the European Monitoring Centre for Drug Addiction (EMCDDA). Data from the analysis of police and border seizures suggests that 4-methylamphetamine is found together with amphetamine and caffeine and typically sold to users as amphetamine ("speed"). There is limited data available on the prevalence of use of 4-methylamphetamine. The aim of this study was to determine the awareness and prevalence of use of 4-methylamphetamine.

Methods: This study was undertaken in three gay-friendly night-clubs in South London, UK on four separate nights in July 2012. Previous studies in this population have shown much higher drug use than in the general UK population.¹ Verbal consent was obtained and the study participants were asked basic demographic questions (age, sex and self-identified sexual orientation) and about their knowledge and frequency of use of amphetamine ("speed") and 4-methylamphetamine. The study was approved by Lancaster University Research Ethics Committee.

Results: 330 individuals completed the survey, 92% were male and the mean age was 31.5 years. Eighty-five per cent self-identified themselves as gay, 9% as straight and 6% as bisexual. A significantly greater proportion had heard of amphetamine (97.0%) than 4-methylamphetamine (16.2%), $p < 0.0001$. Amphetamine use was significantly greater than 4-methylamphetamine: life-time use (43.9% vs 5.8%, $p < 0.0001$), last year use (16.5% vs 4.0%, $p < 0.0001$) and last month use (5.5% vs 1.5%, $p < 0.001$).

Conclusion: This study shows that there is limited awareness of 4-methylamphetamine compared to amphetamine in this high drug using group. Although there is lower use of 4-methylamphetamine than amphetamine, this is likely to be of significance given the number of UK and European deaths related to 4-methylamphetamine.

Reference

1. Moore K, Wood DM, Dargan PI, et al. The Rise in Legal Highs: Prevalence and patterns of illegal drug and 'legal high' use in south London gay dance clubs. *J Subst Use* 2011; 16:263–72.

202. Acute neurotoxicity associated with recreational use of methylmethaqualone confirmed by liquid chromatography tandem mass spectrometry

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Objective: Methylmethaqualone (MMQ), 3-(2,4-dimethylphenyl)-2-methylquinazolin-4(3H)-one, is a sedative designer drug created by adding a methyl group to the 3-phenyl ring of methaqualone, and is at present not subject to restrictive regulation in many countries. No case of MMQ abuse has been published to date. The only

sources of information are users' reports on Web discussion forums and data from preclinical animal studies. A search of the US-based National Poison Database System between 2009–2010 retrieved no mentions of MMQ.

Case report: A 24-year-old previously healthy Caucasian male was admitted to the emergency department (ED) after ingestion of two 500 mg MMQ tablets for recreational purposes. One hour before admission, the patient was found at home in a somnolent state which suddenly switched to severe psychomotor agitation with generalized clonic muscle contractions, urinary incontinence and confusion. Agitation improved after administration of 10 mg midazolam intravenously by paramedics. On arrival to the ED, the patient was intermittently confused but his agitation had resolved. Except for a mild tachycardia (115 bpm), vital signs were normal. Clinical examination revealed a mild generalized resting tremor of upper and lower limbs and mydriatic pupils. The rest of the neurological and physical examination was unremarkable. The electrocardiogram (ECG) was normal, except for mild sinus tachycardia; there was no prolongation of the QT interval. Laboratory analysis: creatine kinase 368 U/L, alanine-aminotransferase 90 U/L; other parameters were within normal limits. Arterial blood gas analysis (ABGA): pH 7.418, pO₂ 11.5 kPa, pCO₂ 5.07 kPa, SatO₂ 97%, bicarbonate 24.1 mmol/L, and lactate 2.0 mmol/L. Blood alcohol concentration was 0.32 g/L. Urine toxicology screen was negative for benzodiazepines, cocaine, amphetamine, tetra-hydrocannabinol, opioids, barbiturates, methadone, tricyclic antidepressants, MDMA, and methamphetamines. MMQ was identified in a serum sample collected on admission by a LC-MS toxicological screening method. No other substances besides midazolam were detected. The subsequent clinical course was uneventful and the patient was discharged home on the following day. Ten days later the patient presented identical symptoms after a repeated ingestion of the same amount of MMQ.

Conclusion: MMQ appears to have a similar acute toxicity profile to methaqualone, with marked psychomotor stimulation, and a comparable addictive potential. Symptoms of acute toxicity can be expected to resolve within hours with supportive care.

203. Toxicity associated with recreational use of nitrous oxide in the United Kingdom. A report from the UK National Poisons Information Service

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Objective: Nitrous oxide has been inhaled for its euphoric and dissociative effects since soon after its discovery in 1772. This study was performed to establish the current frequency and patterns of clinical toxicity associated with recreational use of nitrous oxide in the United Kingdom using data collected by UK National Poisons Information Service (NPIS) Units in Birmingham, Cardiff, Edinburgh and Newcastle.

Methods: The UK Poisons Information Database (UKPID) was searched for enquiries relating to nitrous oxide and synonyms for the period January 2004 to October 2012. UKPID has stored records of enquiries to some NPIS Units since 2004 and all Units since 2007. Accesses to the NPIS poisons information database TOXBASE were quantified for the same period.

Results: Of 44 telephone enquiries received relating to nitrous oxide, 25 concerned apparent recreational users, 17 males and 8 females, with a median age of 23 years (range 16–34). Exposure was classified as chronic or took place over 1 day or longer in 6 cases. The mode of use was often not well documented, but use of Entonox[®], a 50:50 mixture of nitrous oxide and oxygen (2 patients), canisters for production of whipping cream (6 patients) and inhalation from balloons (3 patients) were recorded. No significant changes in annual telephone enquiry rates were observed over the period 2008–2012, when all UK poisons enquiries were available for analysis. Access numbers for TOXBASE also did not change significantly between 2005 (n = 111) and 2011 (n = 106). Nine (36%) patients were asymptomatic. Neurological features were recorded in 4 patients including paraesthesiae/neuropathy (2 patients), which was associated with choreoathetoid movements in one, abnormal gait (1) and tinnitus with hyperacusis. Other recorded clinical features included gastrointestinal symptoms (2 patients), tachycardia/palpitations (2), dyspnoea (2), stomatitis (2), chest pain, convulsion/syncope, dizziness, dry mouth, fever, rash, myalgia and anxiety (1 patient each). One patient had a cold-induced burn from handling a gas canister. Two of the patients with neurological features were treated with hydroxocobalamin.

Conclusion: Enquiries to the UK NPIS concerning the recreational use of nitrous oxide are uncommon, but toxic effects similar to those recorded after therapeutic use are occasionally encountered, with neurological effects present in some patients. No recent change in the frequency of presentation has been detected.

204. Variability in recreational drugs and novel psychoactive substances detected in anonymous pooled urine samples from street pissoirs (street urinals) over time: A technique to monitor trends in drugs use

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Objective: Previous studies have shown that it is feasible to collect anonymous pooled urine samples from street "pissoirs" (urinals) to detect use of classical recreational drugs and novel psychoactive substances (NPS). This study aimed to determine variability in compounds detected from the same street urinals over consecutive weekends.

Methods: Anonymous pooled urine samples were collected on two consecutive Saturday nights in central London (July 2012) using twelve stand-alone four-person urinals. Samples were analysed using full-scan accurate mass high-resolution liquid chromatography coupled to tandem mass spectrometry, processed against compound databases containing more than 1700 drug compounds/metabolites.

Table 1. Frequency of detection of classical recreational drugs and novel psychoactive substances in anonymous pooled urine samples from street urinals over two consecutive weekends.

Group	Drug	Collection 1	Collection 2	Uncontrolled (UK)
NPS	Hordenine	12	12	+
	Cathine	12	9	
	4-methylmethcathinone	5	11	
	Methylhexaneamine	3	9	+
	Methcathinone*	5	6	
	Ethylmethcathinone	3	1	
	Methiopropamine	1	3	+
	Pipradrol	1	3	
	Cathinone	3	0	
	Methoxetamine	0	2	temporary class order
	5-(2-aminopropyl)benzofuran	1	1	
	Methylone	0	2	
	1,4-Trifluoromethylphenylpiperazine	0	1	
	Classical	Cocaine*	12	12
Morphine		12	11	
MDMA*		9	12	
Amphetamine*		7	11	
Ketamine*		5	11	
Methadone		5	10	
3,4-methylenedioxymphetamine		3	12	
Cannabis*		8	4	
Methamphetamine		4	4	

*metabolite(s) of this parent compound also detected.

Results: The frequency of detection of recreational drugs and NPS is shown in Table 1. There was consistency in detection of classical recreational drugs - the same 9 were detected in both sampling periods. With respect to NPS, a total of 10 were detected in the urinals in week 1 and 12 in week 2. There was consistency between the sampling periods for 9 of the NPS; cathinone was detected only in week 1; methoxetamine, methylone and 1,4-trifluoromethylphenylpiperazine were detected only in week 2.

Conclusion: This study has shown there is stability in classical recreational drug detection, but potential variability in the detection of NPS over time. The stability of detection of classical recreational drugs provides validity for this sampling methodology for monitoring drug use. This small pilot study suggests that there is the potential to utilise this technique to monitor for trends in the use of NPS within a geographical area/region over time.

205. Telephone enquiries to the UK National Poisons Information Service relating to poisoning with recreational volatile nitrites and the frequency of use of methylthioninium chloride (methylene blue) for the treatment of methaemoglobinaemia

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Objective: To analyse calls to the four UK National Poisons Information Service (NPIS) Units between January 2008 and 31 October 2012 involving poisoning with volatile nitrites used as recreational drugs.

Methods: The NPIS records telephone enquiry data on the UK Poisons Information Database (UKPID). This database was searched for exposure to agents containing organic nitrites, amyl nitrite and for slang terms: 'liquid aroma'; 'liquid gold'; 'liquid incense'; 'locker room'; 'poppers' and 'rush'. Data were taken from January 2008 to the end of October 2012. Once extracted, the call data was reviewed to remove calls not relating to recreational nitrites but extracted using the slang terms.

Results: Results are summarised in Table 1. The number of calls involving recreational organic nitrites fell from 115 in 2008 to 53 in 2009 and then changed little in subsequent years. The proportion relating to skin exposure fell from 24% in 2008 to 11% in 2009. The proportion of cases requiring treatment for methaemoglobinemia with methylthioninium chloride was between 11% and 19% in 2008 to 2011 and then increased to 30% in the 10 months to the end of October in 2012.

Conclusion: These results show that although the numbers of calls the NPIS are receiving involving amyl nitrate have remained relatively static since 2009, the number of cases where methylthioninium chloride is required has increased in 2012.

Table 1. Enquiries to NPIS involving recreational organic nitrites from January 2008 to October 2012.

Year	2008	2009	2010	2011	2012 (10 months)
Total enquiries involving organic nitrites	115	53	58	53	44
Inhalation	29 (25%)	17 (32%)	22 (38%)	19 (36%)	16 (31%)
Ingestion	55 (48%)	29 (55%)	28 (48%)	29 (55%)	28 (49%)
Skin exposure	28 (24%)	6 (11%)	1 (2%)	5 (9%)	1 (2%)
Other	3 (3%)	1 (2%)		7 (13%)	1 (2%)
Methylthioninium chloride required	13 (11%)	6 (11%)	11 (19%)	7 (13%)	13 (30%)

206. A case series of acute intoxication with new psychoactive drugs in Japan: A vicious spiral of “Law” and “Market”

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Background: Recently, the number of people who take new psychoactive drugs such as the “Spice” series is increasing in Japan. Most of the drugs contained synthetic cannabinoids like JWH-018, though, at present, only 23 synthetic cannabinoids are regulated by the Pharmaceutical Affairs Law of Japan.

Methods: We have reviewed clinical records of patients who had taken the new psychoactive drugs and were admitted to our emergency department between January 1st 2011 and October 31st 2012. Their age, sex, route of intake, results of drug abuse, symptoms, complications, and outcomes were studied.

Results: Twenty patients (16 males and 4 females) are included in this study. Median age of patients: 24.9 years. Route of intake: inhalation (17 patients), ingestion (2 patients), and inhalation and intravenous injection and recto-anal injection (1 patient). Results of the screening test for drugs of abuse: negative (16 patients), tetrahydrocannabinol (2), benzodiazepines (3), barbiturates (1), tricyclic antidepressants (1). Main symptoms: disturbance of consciousness (10 patients), mydriasis (11 patients), tachycardia (10 patients), tachypnea (4 patients), hypertension (6 patients), seizure (1 patient), hallucination (5 patients), facial myoclonus (1 patient). Complications: rhabdomyolysis (2 patients). Outcomes: full recovery (19 patients); prolonged hallucinations with transfer to a psychiatric hospital (1 patient). The herbal blends, in one case, were analyzed using the gas chromatography-mass spectrometric method. As the result of a library search, the following synthetic cannabinoids were identified: JWH-122, JWH-203, JWH-210, AM-694, AM-2201.

Conclusion: In acute intoxications with the new psychoactive drugs in Japan, main symptoms were sympathomimetic with short disturbance of consciousness, which were consistent with those of the previously reported cases of synthetic cannabinoid intoxication. The Japanese government is now considering a regulation that would regulate collectively a group of compounds on the basis of common chemical structure. It will become necessary to regulate drug abuse by laws applied commonly all over the world.

207. What’s on the ‘Spice’ rack? Synthetic cannabinoid receptor agonist toxicity reported to the UK National Poisons Information Service

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Objective: To describe the features of synthetic cannabinoid receptor agonist (SCRA) toxicity as reported to the UK National Poisons Information Service (NPIS)

Table 1. Clinical characteristics of patients (n = 53) reported to NPIS as having synthetic cannabinoid receptor agonist toxicity by healthcare professionals.

Clinical feature	number	%
Drowsiness or low GCS	12	22.6
Tachycardia	11	20.8
Agitation	10	18.9
Confusion	10	18.9
Collapse	10	18.9
Dizziness	8	15.1
Nausea or vomiting	6	11.3
Palpitations	5	9.43
Hallucination	5	9.43
Anxiety	5	9.43

Methods: User sessions related to SCRA on TOXBASE®, the NPIS on-line information resource were quantified from 1st January 2010 to 30th June 2012. NPIS telephone enquiries from healthcare professionals were reviewed from 1st January 2011 to 30th June 2012.

Results: Monthly TOXBASE accesses for SCRA increased over the study period. Of a total of 532 TOXBASE sessions 334 (63%) were for ‘Black Mamba’, a product containing the newer SCRA AM-2201¹. There were 53 telephone enquiries to NPIS related to SCRA, (39 males, 13 females, 1 not recorded), median age 20 (range 13–52). Fifty-one calls related to ‘products,’ including ‘Black-Mamba’ (n = 28), ‘Herbal-Haze’ (n = 9). Of these 43 were from hospitals, 4 from ambulance services and 6 from primary care. Smoking was the route of exposure in 41 cases (77%). Median time from exposure to NPIS enquiry was 3 hours, suggesting early symptom onset. Nine enquiries involved the use of other substances. The most common reported clinical features are shown in Table 1. There was one death, in a patient who had reportedly jumped from a balcony following use of a SCRA product called ‘heavy haze incense’

Conclusion: NPIS data can be used to describe patterns of presentation and reported clinical toxicity for emerging psychoactive including new products (e.g. black mamba) and chemicals.

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208. Methoxetamine toxicity reported to the National Poisons Information Service: Clinical characteristics and the effect of the UK’s first Temporary Class Drug Order

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Objective: 1). To report the demographic and clinical characteristics of cases of methoxetamine toxicity reported to UK National Poisons Information Service by healthcare professionals. 2). To

Table 1. Clinical features reported in telephone enquiries related to suspected methoxetamine exposure.

Feature group	Reported terms	Number of cases	% of total (95% CI)
Stimulant	tachycardia, hypertension, mydriasis, palpitation, increased sweating	17	36 (24, 50)
Acute mental health disturbance	agitation, confusion, euphoria, aggression, hallucination, paranoia, hysteria, manic reaction, psychosis	20	43 (30, 57)
Dissociative	catatonia, dystonia, hypertonia, tetany	5	11 (5, 23)
Cerebellar	nystagmus, tremor	3	6 (2, 17)
Reduced consciousness	reduced conscious level, stupor, somnolence, coma	8	17 (9, 30)
Seizures	seizures	1	2.1 (0, 11)

assess the impact of the UK's first Temporary Class Drug Order (TCDO)¹ on enquiries from health professionals to the UK National Poisons Information Service (NPIS) related to methoxetamine.

Methods: All telephone enquiries and user sessions of TOXBASE[®], the NPIS on-line information resource, related to methoxetamine (and synonyms 'MXE', 'mkt' and '2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone') were reviewed from 1st April 2010 to 1st August 2012. Numbers were compared for the 3 months before and after the TCDO.

Results: There were 47 telephone enquiries and 298 TOXBASE[®] sessions regarding methoxetamine during the period of study. Comparing the 3 months before and after the TCDO, TOXBASE[®] sessions for methoxetamine fell by 79% from 151 to 32 and telephone enquiries fell by 80% from 15 to 3. Clinical features reported by enquirers were consistent with case reports^{2,3,4} of analytically confirmed methoxetamine toxicity and typical toxidromes are shown in Table 1.

Conclusion: Structured NPIS data may reveal trends in drugs of abuse use and toxicity when interpreted within their limitations. The TCDO for methoxetamine introduced in April 2012 has resulted in fewer enquiries to NPIS from clinicians, indicating reduced presentations with suspected methoxetamine toxicity.

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209. Chasing the wrong dragon: Acute respiratory distress from inhaling the contents of a fentanyl patch

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Objective: To describe the acute pulmonary effects of inhaling the vapor produced from heating a matrix fentanyl patch on aluminum foil.

Case report: A 38 year-old man with oxymorphone dependence presented to the emergency department (ED) 24 hours after "smoking" a fentanyl patch for recreational purposes. The matrix fentanyl patch was placed on aluminum foil and heated from below by a lighter. The vapor was inhaled in a method similar to "chasing the dragon" described for heroin. He developed dyspnea and fevers to 38.3°C within two hours. Vital signs were: blood pressure, 135/82 mmHg; pulse, 107/min; respirations, 28/min; oxygen saturation, 88% on room air. Physical examination revealed an awake, ill-appearing man with bilateral coarse, breath sounds with rhonchi. Initially, he was treated symptomatically with inhaled albuterol and ipratropium, intravenous methylprednisolone, and oxygen therapy via non-rebreather mask. He was placed on noninvasive ventilation via BiPAP overnight due to worsening hypoxia and confusion. Chest radiograph showed bibasilar patchy opacities, for which antibiotics were initiated. He was admitted to the medical intensive care unit for close monitoring and management of his hypoxemia and respiratory distress. A chest computed tomography revealed bilateral patchy, ground-glass opacities consistent with pneumonitis. By day 2, the patient tolerated the discontinuation of oxygen therapy and was discharged home. Further history obtained from the patient revealed a similar but less severe pulmonary reaction after similar use of a fentanyl patch once before.

Discussion: Inhalation of fentanyl vapor following heating has been reported online and in a case report. The case report discusses development of alveolar proteinosis in a patient known to smoke fentanyl patches daily for several months.¹ There are no case reports of acute pulmonary toxicity. Methods of smoking fentanyl from transdermal patches are described online, usually after extraction of fentanyl gel from reservoir patches. Given that the matrix patch is constructed of a synthetic polymer (polyolefin, with an adhesive backing), our patient's symptoms may represent polymer fume fever.

Conclusion: Acute pneumonitis can occur after smoking a matrix fentanyl patch in a method similar to "chasing the dragon."

Reference

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210. "Synthetic co-caine" as legal cocaine hides synthetic cannabinoids

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Objective: Synthecaine is a slang term that seems to originate from “Synthe-tic” and “Co-caine” and is available from on-line markets as legal cocaine. Web-sources describe synthecaine as a mixture of dimethocaine/camfetamine; the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) report notified dimethocaine and 3-(p-fluorobenzoyloxy)tropane (pFBT). We describe a case of abuse of synthecaine (containing synthetic cannabinoids) identified through the Italian N.E.W.S. of Department for Antidrug Policies - Presidency of the Council of Ministers.

Case report: A 20 year-old man, with a history of cannabis and cocaine abuse, was admitted to the emergency department (ED) about 6 hours after sniffing an unknown amount of a whitish powder named “synthecaine”, bought on the web as “legal cocaine”. On admission the patient presented excitement, xerostomia, chest pain, dyspnoea, tachycardia (150 beats/minutes) and hypertension (160/80 mmHg). Blood glucose (160 mg/dL) and creatine kinase (860 U/L) were elevated. Body temperature, oxygen saturation on room air, complete blood count, serum electrolytes, cardiac enzymes, EKG and coagulation parameters were normal. The patient was successfully treated with intravenous fluids and diazepam 10 mg and discharged asymptomatic 12 hours later. Gas chromatography–mass spectrometry (GC-MS) of the purchased substance identified benzocaine, MAM-2201 and sugars. Toxicological analysis of biological samples revealed the presence of MAM-2201 (11 ng/mL) and benzoylecgonine (137 ng/mL) in blood and cocaine and benzoylecgonine in urine (using GC-MS); opiates, methadone, amphetamines, MDMA, tetrahydrocannabinol, ethanol and benzocaine were negative.

Conclusion: Our experience revealed that synthecaine may contain mainly MAM-2201 and benzocaine. MAM-2201 is an analog of AM-2201 a potent synthetic cannabinoid which binds the CB1 and CB2 receptors with high affinity ($K_i = 1.0$ and 2.6 nM, respectively). MAM-2201 has never been identified in Italy. Actually, no human pharmacotoxicological data are available for MAM-2201 but the toxic effect should be related to AM-2201 (under law control in Italy from May 2011). On the basis of these cases and the increasing evidence of the availability of synthecaine on the Internet, clinicians should be made aware of the potential severe toxicity of synthetic cannabinoids mixed with benzocaine in patients presenting to the ED.

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211. The dangers of buying “research chemicals” online, bromo-dragonfly mislabelled as 2C-B Fly: A confirmed case report, and its follow up in “research chemical” specific social media

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Objective: To create awareness among emergency department (ED) physicians on the possibility of mislabeled drugs being sold through the Internet, its implications and reaction by users over the Internet.

Case report: A 23 year old male, with no prior medical history, arrived at the ED after ingesting 2C-B Fly that was bought over the

Internet, with a chief complaint of diaphoresis, anxiety and blurred vision. Upon arrival blood pressure 138/75 mm Hg, heart rate 100 bpm, saturation of 100% at room air, temperature 36°C. Physical exam was unremarkable except for profuse diaphoresis. His blood work revealed no alterations, the patient was administered benzodiazepines and kept under observation and was discharged 6 hours later. The patient provided us with a sample of the drug for us to test; it was later identified as Bromo-Dragon Fly. After extensive online research our team found an Internet blog where our patient describes his experience in full detail, in an attempt to create awareness in the community (www.erowid.org/experiences/exp.php?ID=81677).

Conclusion: Phenethylamines are potent hallucinogenic serotonin receptor agonists¹, 2C-B’s presence remains constant in the Spanish illegal drug market², and bromo-dragonfly being more potent, has been linked to at least one death³. In this case our patient realized the possibility of a mislabeled drug by searching in drug specific Internet forums, and was then advised to seek medical attention. The continuous development of new compounds makes it difficult for toxicologists to keep up; the possibility of mislabeling drugs by resellers puts users at great risk, thus making “Research Chemical” specific social media a great tool for physicians, providing us with user testimony on experiences, trends and warnings as in this case.

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212. Complications from ultra rapid opioid detoxification at a single detoxification center

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Background: Opioid replacement therapy is the mainstay of treatment for opioid dependence in the U.S. However, Ultra Rapid Opioid Detoxification (UROD) is performed in select detoxification centers. We report three UROD complications that occurred in a 3-month period from a single opioid detoxification center.

Case series: Case 1: A 30 year-old man presented to the emergency department (ED) with altered mental status after undergoing UROD. He had received propofol, midazolam, and isoflurane for general anesthesia, and naloxone (80 mg) and naltrexone (100 mg) during his 4-hour detoxification. In the ED, he was alert but non-interactive with respirations of 40 breaths/min and O₂sat of 94% on 10 L oxygen via facemask. Endotracheal intubation was performed due to worsening respiratory distress. Chest X-ray showed pulmonary edema and the computed tomography scan of the

chest showed pneumomediastinum without pulmonary embolus. The patient was extubated 2 days later with normal mental status. Case 2: A 51 year-old man presented to the ED after ventricular fibrillation after UROD. He had received clonidine, propofol and sevoflurane, followed by naloxone. He developed ventricular fibrillation approximately 12 hours post-procedure. Return of spontaneous circulation (ROSC) was achieved after defibrillation, epinephrine (3 mg), and vasopressin (40 units). Laboratory results were notable for hypokalemia (2.6 mmol/L). After resuscitation he became agitated, hypertensive (200/90 mmHg) and tachycardic (120 beats/min), and received benzodiazepine, propofol, and intravenous phentolamine. He developed anoxic encephalopathy and expired on hospital day 8. Case 3: A 26 year-old man presented to the ED after pulseless electrical activity (PEA) following UROD. He received clonidine (0.2 mg), propofol (100 mg), nitrous oxide, and an inhaled anesthetic, followed by naloxone (30 mg), prior to his PEA arrest. ROSC returned after chest compression, epinephrine (6 mg), and vasopressin (40 units). In the ED, the patient experienced a second PEA arrest requiring additional resuscitative efforts with ROSC. The patient was extubated one day later with normal mental status. His hospital course was complicated by necrotizing fasciitis of the upper extremity.

Conclusion: Many societies on addiction, including the American Society of Addiction Medicine, do not recommend UROD because limited data are available on its safety and efficacy. These cases highlight some of the potential complications of UROD

213. First report of misuse with PecFent® (fentanyl nasal spray) inducing life threatening features

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Objective: To report a case of misuse of fentanyl nasal spray.

Case report: A 24 year Caucasian female was found comatose with bradypnea, h + 45 minutes after a suicide attempt with alcohol and opioids (morphine sulphate and fentanyl spray). Clinical examination showed coma Glasgow Coma Scale 3/15, miosis, apnoea with cyanosis of lips and extremities. Blood pressure was 80/58 mmHg, heart rate 130 bpm, SpO₂ less than 50%. Dextrose was 6.1 mmol/L. Temperature was 35.8 C. She was intubated with mechanical ventilation. Blood pressure was normalised with 1000 mL crystalloids and ephedrine (27 mg) boluses. First arterial blood gases (corrected) showed pH 7.36, PO₂ 258 mmHg, PCO₂ 33.3 mmHg, HCO₃ 18.8 mmol/L, lactate 4.9 mmol/L. Hepatic, cardiac, and renal biology were unremarkable. On h + 6 hours she was extubated with

low respiratory rate needing an infusion of naloxone (0.16 mg/h) for 8 hours. On h + 10 she was awake with an outcome without sequelae the next day. Forensic samples were drawn at H + 3. Sample analyses were performed with two reference methods: GC-MS and UPLC-MS/MS. Results showed morphine and fentanyl in blood and urine. Fentanyl blood level was 3.6 µg/L which is reported as toxic.^{1,2} Morphine blood level was 98 µg/L. Ethanol level was 0.89 mg/dL.

Discussion: Painkillers for cancer are well used with an additive effect of the drugs e.g. acetaminophen plus morphine or fentanyl patch, sprays. PecFent® is a fentanyl nasal spray (100 or 400 micrograms per dose) used as a complement for hyperalgesic times. Fentanyl toxicokinetic simulation (volume distribution = 88 L, half-life = 2.4 h, absorption rate = 10 h⁻¹ and bioavailability = 0.6) shows, in this case, that the toxic level of fentanyl is the result of three doses (400 micrograms) self-administered.

Conclusion: Misuse of opioids has to be known and quickly reported to Health Agencies, especially with new formulations. Indeed, non-compliance with the interval between doses recommended by the summary of product characteristics (4 h) can cause intoxication. The nasal route is not safer than other routes of administration. A European follow-up for PecFent® has been carried on since 2011.

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214. Accuracy of on-site urine drug tests – an experimental study

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Objective: On-site drug tests (ODTs) are frequently used in hospitals to screen the urine of patients admitted for suspected poisoning. The purpose of this study is to evaluate the accuracy of such tests used in emergency departments in Sweden.

Methods: Two brands, ColibriCheck™ and Concateno™, were tested for detecting amphetamine, benzodiazepines, opiates and tetrahydrocannabinol (THC) in urine. The results were compared with laboratory screening (CEDIA) and confirmation method (GC-MS). The study was conducted from December 2011 to March 2012 using samples from drug dependence clinics; 400 positive (100 in each drug group) and 200 negative (applied to all drug groups).

Results: High specificity (Table 1) implies that most true negative samples are detected, but the risk of missing a true positive sample is high (6–26%). The incidence of false positive test results

Table 1. Sensitivity¹ (percentage of true positive samples detected) and specificity² (percentage of true negative samples detected) of two drug tests.

	Amphetamine		Benzodiazepines		Opiates		THC	
	n = 100	n = 200	n = 100	n = 200	n = 100	n = 200	n = 100	n = 200
	Sens ¹	Spec ²	Sens ¹	Spec ²	Sens ¹	Spec ²	Sens ¹	Spec ²
ColibriCheck™	82%	99%	92%	99.5%	90%	100%	74%	99.5%
Concateno™	94%	99%	91%	99.5%	88%	100%	76%	99.5%

was low ($\leq 1\%$). Limitations: inadequate blinding of the analysing procedure, emergency department samples were not included and GC-MS was performed on positive but not negative samples.

Conclusion: The implications of this study are that positive ODTs are fairly reliable whereas negative ODTs neglect 6–26% of true drug presence. Consequently patients might be overlooked if treatment depended on the test result. ODTs' intrinsic problems e.g. cross-reactivity and limited spectrum of analytes¹, that are not addressed in our study, could further influence the reliability of test results.

Reference

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215. Characteristics of Twitter conversations on illicit drug use

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Objective: To determine whether social networks could be useful for toxicovigilance, we investigated whether people share tweets about drug usage on Twitter in patterns that resemble those of small-world networks, the predominant form of spontaneous social network organization.

Methods: We queried Twitter for publicly available tweets that mentioned cocaine, marijuana, or LSD and traced how those tweets were shared among users. We quantified the distribution of retweets among users by measuring the graph's local clustering coefficient and degree of distribution. We developed an automated classification system for tweets that indicated immediate drug use, based on adjudication by a medical toxicologist and emergency physician. We compared the distributions of retweets across categories using the Kolmogorov-Smirnov test.

Results: We found that the clustering coefficients for all three drug networks (cocaine, marijuana, and LSD) were higher than would occur by chance ($p = 0.001$), indicating that those networks have more structure than a random network. Drug networks also had higher clustering coefficients than networks discussing coffee or beer ($p = 0.01$), indicating that drug networks have structure beyond typical social networks. The LSD distribution had a higher clustering coefficient than either the cocaine or marijuana graph ($p = 0.01$). Confirming these results, the distribution of degrees for all three drugs follow a stretched exponential rather than a power function, ($p < 0.01$ for all drugs). For cocaine, marijuana and LSD, respectively, the confidence intervals of the exponents of the stretched exponential overlapped, (0.25 ± 0.05 , 0.26 ± 0.05 , and 0.25 ± 0.08). However, the rate parameters were significantly different (0.13 ± 0.01 , 0.45 ± 0.05 , and 0.3 ± 0.05).

Conclusion: Discussions of drug use on Twitter have a structure that can be quantified, and exhibit different characteristics from typical small-world networks. Analysis of Twitter queries may add to the armamentarium for toxicovigilance to identify social characteristics of new and emerging drugs of abuse.

216. A case of life-threatening opioid withdrawal syndrome precipitated by buprenorphine abuse in 61 year-old methadone dependent patient

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Objective: Buprenorphine, an opioid agonist with partial affinity for the mu receptor, is used primarily for the treatment of opioid dependence. At low doses it functions similarly to full agonists but at high doses it functions more like mixed agonist/antagonists. Suboxone™ is the commercially available product with buprenorphine/naloxone in a 4/1 ratio. Naloxone has a very low bioavailability when ingested orally or sublingually and is only present in order to deter intravenous abuse. A small number of controlled studies have confirmed that buprenorphine is capable of precipitating withdrawal if administered in opioid-dependent patients. As there are few reports of buprenorphine-precipitated withdrawal in the medical literature we present a case of severe withdrawal in a methadone dependent patient.

Case report: A sixty-one year-old methadone-dependent male purchased Suboxone™ illicitly to supplement his methadone. He did not have previous experience with Suboxone™ and ingested several 8/2 mg tabs. Shortly after ingestion he yelled for his wife stating, "Something is terribly wrong, call 911!" The patient was incontinent of stool and urine and had recurrent vomiting during transport to the hospital. He was tachycardic (120–140 beats/minute) and hypertensive (160–230/92–120 mmHg) in the emergency department. The patient required restraints for agitation and delirium and was intubated for airway protection after intravenous fentanyl in 200 microgram increments and 20 mg lorazepam did not improve his clinical status. He spent three days in the intensive care unit requiring propofol (up to 60 micrograms/kg/minute), fentanyl 200 micrograms/hr, and clonidine at 0.2 mg/NGT/4hrs, and had severe hyperglycemia (glucose 600's despite insulin administration) acidosis, rhabdomyolysis, aspiration pneumonia and acute lung injury. Urine buprenorphine and metabolite levels were substantially elevated (total buprenorphine/creatinine 208 ng/mg creatinine and norbuprenorphine/Cr 174 ng/mg creatinine). Methadone was confirmed as well.

Conclusion: This patient was heavily dependent upon methadone, ingested a large amount of buprenorphine, was older with multiple medical co-morbidities and had a very long (> 30 years) history of opioid dependence. These factors have all been suggested to lead to higher risk for severe outcome in this clinical situation. This case report confirms that buprenorphine is capable of precipitating withdrawal in opioid dependent patients.

217. A cathinone of a different color – two cases of bupropion abuse presenting with seizures and serotonin syndrome

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Objective: Cathinone is a naturally occurring beta-keto amphetamine analogue found in the leaves of the Khat (*Catha edulis*) plant. Cathinone derivatives were first synthesized in the 1920s and

several agents were explored for medicinal use but abandoned due to side effect profiles including abuse and dependence. In recent years cathinones have become frequently encountered drugs of abuse (i.e. sold as Bath salts, over the Internet as research chemicals or misrepresented as “Ecstasy” or “Molly”). Bupropion, the par-chloro, N-tert-butyl derivative of cathinone is the only cathinone currently available therapeutically. It is used for smoking cessation and for the treatment of depression. Despite Internet drug forums including discussion regarding abuse of bupropion there are no cases in the medical literature describing bupropion abuse. Two cases of bupropion abuse causing hospitalization are discussed and presenting signs and symptoms of toxicity are reviewed.

Case series: A 27 year-old male with history of methylphenidate abuse “ran out” of methylphenidate tablets and, after reading on the Internet that bupropion gave a similar high, crushed and snorted several 300 mg SR tablets. Shortly after insufflation he developed chest pain, anxiety, blurry vision, ‘jerking movements’ and experienced a seizure. He was brought to the emergency department (ED) altered, tachycardic, hypertensive, tremulous, hallucinating and incontinent of urine. The second patient was a 51 year-old male with history of poly-substance abuse. He was found by a significant other altered and hallucinating with tremors and “spasms”. He had “crushed and snorted some pills” later identified as bupropion. In the ED he was tachycardic, diaphoretic, and had mydriasis, hyperreflexia and myoclonus. He later admitted to occasionally “binging” on his bupropion. He described prior episodes of seizures and hospitalization related to this practice but that he was “addicted” to the euphoria he got from it.

Conclusion: Drug users may abuse bupropion for stimulant effects similar to amphetamines or cathinones. Some individuals (i.e. previous stimulant abuse), may be particularly at risk for abusing this drug. Bupropion abusers may develop severe medical consequences including seizures and serotonin syndrome due to the narrow toxic-therapeutic index identified for this agent.

218. Parental cannabis abuse and accidental childhood exposure: Complementary and essential actions

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Objective: The most common illicit drug used in France among young adults is cannabis, inducing an increase in pediatric poisonings. The abuse of drugs has been clearly linked to the perpetration of child maltreatment, including child neglect as well as physical, emotional, and sexual abuse. The aim of this study was to highlight how pediatricians have to deal with legal duties, in such intoxications in France.

Methods: The medical records of children aged 0–16 years who were hospitalised for cannabis poisoning at the pediatric emergency department of the Children’s Hospital in Toulouse, France, from January 2007 to March 2012, were retrospectively evaluated. Dose ingested was revealed from the parents’ declarations.

Results: 12 children (4 boys and 8 girls) were included. One hundred per cent were younger than 3 years. Cannabis resin belonged

to one of the parents or a household member. In almost all cases, the poisoning took place at the child’s home. Eight children experienced drowsiness, hypotonia, mydriasis, or seizures. Urine toxicology for cannabinoids was measured in 7 children. All of them had a favourable outcome. Seventy-five per cent were discharged home with pediatric and community services follow-up. No child had clinical signs of physical abuse.

Conclusion: Although cannabis is currently an illegal drug, doctors are under no obligation to report possession by parents in such cases to the police or the prosecutor¹, especially in cases of accidental poisoning. Indeed, they would be breaching confidentiality. Nonetheless, physicians have to inform Social Services of such findings for further investigations, because parents with impaired judgment secondary to substance use may expose children to the risk of unintentional poisonings. Child abuse is strongly related to parental substance², including cannabis, abuse but fear of incurring legal sanctions may lead to nondisclosure. This latter observation underlines the need for systematic intervention of social workers and child protective services in all cases of accidental intoxication to help the detection of neglect behavior situations.

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219. Third party payor status of drug abuse and dependence patients in a large emergency department database

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Background: Medical toxicologists looking to start a toxicology service in their home institution are often concerned about the financial feasibility of such an endeavor. This is largely influenced by the third-party payor status of patients. In particular, patients with drug abuse and dependence may be more likely uninsured. We sought to determine the third-party payor in patients presenting to the emergency department (ED) with drug abuse and dependence.

Methods: Retrospective database review of 20 EDs in varied socio-demographic areas. 1,590,248 visits total over a 33 month period. We selected patients with International Classification of Disease (ICD-9) codes for drug abuse and dependence and evaluated the payor status in three categories: Self-pay (SP), Medicaid (MCaid), and Private Insurance (PrIns).

Results: There were a total of 8,405 patients, 68% male. Of these, 3,429 (41%) were designated “self-pay” or uninsured, 1386 (16%) were Medicaid, and the remainder were either Medicare or Private Insurance. In patients whose diagnosis code was for dependence (n = 447, 5% of total), 187 (42%) were SP and 67 (15%) MCaid. Patients coded as opioid abuse (n = 1399, 17%), 608 (44%) SP, 238 (17%) MCaid, and cocaine abuse (n = 614, 7%) 212 (35%) SP, 87 (14%) MCaid.

Conclusion: Over 50% of patients in this database were either uninsured or insured under Medicaid. This was especially true of

patients with dependence, opioid abuse and cocaine abuse. The concern regarding reasonable reimbursement for toxicology consultation services is valid given the large percentage of patients in this database who were uninsured. Although this stands to change with the advent of new healthcare legislation, the impact of this on health economics is not predictable. Medical toxicology inpatient consultants often need and will likely continue to need other sources of funding support to provide these valuable services to patients.

220. The characteristics of acute ethanol poisoning in adolescents - five year study

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Objective: To study the characteristics of acute ethanol poisoning in adolescents admitted to a pediatric poisoning department.¹

Methods: We have performed a retrospective study of ethanol poisonings admitted to our department between 1 January 2007 and 31 December 2011. The following criteria were taken into consideration: presence of coma, the association with other substances, clinical manifestations, hospitalization duration.

Results: 311 adolescents with acute ethanol poisoning were registered during the mentioned period. Coma was noted in 181 (58.19%). Regarding the grade of coma 152 patients were in Reed Coma Scale grade 1 coma, 24 patients Reed 2 and 5 cases Reed 3 coma. In 46 (14.79%) patients, out of the total of 311, the combination of ethanol with other substances (in 28 cases medicines and in 18 cases substances of abuse) was registered. The following medicines were identified: barbiturates 8 cases, benzodiazepines 6 cases, dextromethorphan 4 cases, paracetamol 2 cases, disulfiram 1 case, carbamazepine 1 case, metronidazole 1 case, rifampicin 1 case, nifedipine 1 case, doxepin 1 case, dextromethorphan and diazepam 1 case. The substances of abuse registered were: ethnobotanical substances in 14 cases, marijuana in 3 cases, cocaine in 1 case. The combination of ethanol with substances of abuse, disulfiram, carbamazepine and dextromethorphan caused the most severe cases. The median length of hospitalization was 2.4 days in poisoning with ethanol combined with other substances compared to 1 day in poisoning with ethanol alone. In 210 (67.52%) patients, out of the total of 311, chronic consumption was noted.

Conclusion: The use of medicines or substances of abuse in combination with ethanol in acute poisoning in adolescents has become a reality in the past years, the new association being the ethnobotanical substances. The combination of ethanol with these substances increases the severity of poisoning and consequently the length of hospitalization. A concerning fact is the chronic consumption noted in the majority of adolescents with acute ethanol poisoning.

Reference

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221. Severe diethylene glycol intoxication from smoke fluid ingestion

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Objective: Smoke fluid ingestion is rare. Four cases were reported to the Dutch National Poisons Information Center from 2006–2011. However, this number is increasing, with eight exposures reported in 2012. Smoke fluid is used to generate smoke with a smoke machine. It may contain various compounds, e.g. glycerol or polyglycols. We describe a case of smoke fluid ingestion resulting in acute renal failure and serious neurotoxicity.

Case report: A 48-year old man accidentally used smoke fluid (unknown composition) to make coffee. He took three sips (approximately 75 mL) on day 1. He developed nausea on day 3. On day 7 he sought medical advice for fever, vomiting, diarrhoea, back pain, and oliguria. On day 9 he was hospitalized with acute renal insufficiency. Abnormal lab results included C-reactive protein (CRP) 122 mg/L, leukocytes 12.7/nL, urea 29.8 mmol/L, creatinine 1590 micromol/L, glomerular filtration rate (GFR) using modification of diet in renal disease (MDRD) 2.8 mL/min, parathormone 12.2 pmol/L, sodium 127 mmol/L, potassium 5.4 mmol/L, phosphate 2.37 mmol/L. Blood pressure was 150/78 mmHg, pulse 49/min, temperature 36.7°C. Ultrasound revealed echodense areas in the right kidney. Kidney biopsy indicated interstitial nephritis with eosinophilia, and focal toxic damage to tubular epithelium. Hemodialysis was started. During admission he developed interstitial lung edema, blurred vision, hearing impairment, left-sided facial paralysis and convulsions. Magnetic resonance imaging (MRI) of the brain on day 14 showed symmetrical cortical and subcortical abnormalities, particularly in the posterior flow area and watershed locations. MRI on day 25 showed clear improvement, with only residual white matter changes. Blurred vision and hearing impairment were not fully resolved and dialysis was still necessary upon discharge on day 34. The composition of the smoke fluid was initially unknown. Analysis of the product by the hospital pharmacist showed trace amounts of propylene glycol and a large, unidentified peak. Only weeks later the producer admitted that the smoke fluid contained 60% diethylene glycol (DEG).

Conclusion: Ingestion of DEG-containing smoke fluid can result in life-threatening intoxication. However, the composition of smoke fluid is often unknown. Since producers tend to be secretive about the exact composition of smoke fluid and since DEG is not included in most standard laboratory analyses, the diagnosis of DEG-poisoning may be missed or delayed, increasing the risk of severe intoxication.

222. Alcoholic ketoacidosis: Highest reported serum lactate level

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Objective: To describe the highest reported lactate level associated with alcoholic ketoacidosis (AKA).

Case report: A 47 year old man with past medical history of alcoholism was transported to the emergency department for evaluation of altered mental status. The patient had been drinking alcohol continuously since his release from jail three days prior to presentation, and was found lying on the ground in a hotel room. Patient adamantly denied ingesting any other medications or substances. He denied any visual disturbance. Vital signs: temperature 36.8°C, heart rate 130 bpm, respiratory rate 18 rpm, blood pressure 129/86 mm Hg, room air oxygen saturation of 97%. Serum electrolytes measured: sodium 137 mEq/L, potassium 6.1 mEq/L, chloride 96 mEq/L, bicarbonate undetectable, blood urea nitrogen 41 g/dL, creatinine 2.9 mg/dL, and glucose 98 mg/dL. Arterial blood gases measured: pH 7.07, PaCO₂ 18 mmHg, PaO₂ 149 mmHg, bicarbonate 5 mEq/L, base deficit 24 mEq/L, lactate 22 mMol/L. Urinalysis measured: small ketones and no crystals. The urine did not fluoresce. Measured serum osmolality and ethanol were 363 mOsm/kg and 178 mg/dL, respectively. The osmolal gap was 31 mOsm/kg. The patient empirically received intravenous fomepizole, sodium bicarbonate, thiamine, folate and pyridoxine. The patient was also administered 5% dextrose 0.9 normal saline infusion. Over the course of 11 hours, the patient's metabolic derangements improved to normal acid base status, renal function, and serum lactate. Toxic alcohol screen levels were unmeasurable. Serum acetoacetate and B-hydroxy butyrate level measured 130 micrograms/L and >2 mMol/L, respectively. The patient returned to baseline health status during his hospitalization.

Conclusion: The patient's medical history and initial laboratory findings were concerning for toxic alcohol poisoning, a diagnosis that warrants prompt hemodialysis in the setting of profound acidemia. However, the fact that the patient maintained a clear sensorium, demonstrated no crystals or fluorescence on urinalysis despite an elevated serum Cr (likely ketone induced assay interference) were early bedside clues pointing to the diagnosis of severe AKA. Marked elevation of serum B-hydroxy butyrate levels confirmed the diagnosis and prevented unnecessary costly antidotal therapy and potentially hemodialysis. This case is extremely unusual in regard to his marked initial hyperlactemia which cleared promptly. The initial lactate level of 22 mMol/L is the highest reported level in the literature.

223. Prognostic factors in acute paraquat poisoning

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Background: Paraquat is a widely used herbicide that is highly toxic to humans. The aim of this study is to investigate the prognostic factors affecting survival in patients with paraquat poisoning.

Methods: This study included 790 paraquat poisoned patients who were diagnosed by checking plasma paraquat concentrations from January 2005 till August 2012. We divided these patients into two groups (survivors vs non-survivors), compared clinical characteristics, and analyzed the predictors of survival.

Results: The mean age of the included patients was 57 years (range, 14–95). The patients included 507 (64%) men and 283 (36%) women. Comparing clinical characteristics between the survivor group (n = 151, 19%) and the non-survivor group (n = 639, 81%), survivors were younger (47 ± 14 vs 59 ± 16) and had lower plasma paraquat concentrations (1.44 ± 8.77 vs 80.33 ± 123.15 µg/mL). On admission, serum creatinine of the survivor group was lower than that of the non-survivor group (0.95 ± 0.91 mg/dl vs 1.88 ± 1.27 mg/dL). The levels of pancreatic enzymes in the survivor group were also lower than those of the non-survivor group (amylase 86 ± 71 vs 207 ± 382 IU/L, lipase 50 ± 64 vs 115 ± 200 IU/L). In multiple logistic regression analysis to assess the predictors of survival, survival was associated with better initial renal function, lower amylase level, lower plasma paraquat concentration and weaker urine paraquat test results.

Conclusion: Low plasma paraquat level, good renal function on admission and favorable urine paraquat test are good prognostic factors of survival after acute paraquat poisoning.

224. Type II pyrethroids were associated with higher toxicity than type I pyrethroids in human exposures: A poison center based study in Taiwan

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Objective: Pyrethroids are commonly used insecticides worldwide. Individual pyrethroids are typically grouped into two general classes, namely type I and type II pyrethroids, based on a combination of toxicological and physical properties. Although type II pyrethroids have been shown to be associated with higher toxicity in animals, it is unclear whether a similar difference exists in human exposures.

Methods: We first identified patients with pyrethroid exposure reported to the Taiwan National Poison Control Center (PCC-Taiwan) from 1986 through 2010 by searching the PCC-Taiwan computerized database. We then manually reviewed all case records to identify eligible cases for final analysis. The relation between baseline/clinical characteristics and the severity of poisoning exposure was analyzed by employing multivariate logistic regression analyses.

Results: From 1986 through 2010, a total of 3,379 patients with pyrethroid exposure, including 145 (4.3%) patients with severe/fatal effects, were reported to the PCC-Taiwan. Most patients were males, aged ≥ 60 years, attempted suicide, and were exposed through the oral pathway. In multivariate logistic regression analyses, increasing age, attempted suicide, oral ingestion, exposure to type II pyrethroids (adjusted OR 1.6, 95% CI 1.1–2.3), and concomitant exposure to other pesticides or solvents were found to be associated with severe/fatal effects. When limiting the analysis to patients with oral ingestion only (n = 2,782), increasing age, larger doses of exposure, and exposure to type II pyrethroids were associated with the severity of poisoning.

Conclusion: Type II pyrethroids seem to be associated with higher toxicity than type I pyrethroids in human exposures. While such a finding is consistent with that observed in animal studies, future prospective studies that include a more complete list of prognostic predictors are needed to confirm such an association and to better delineate its underlying mechanisms.

225. The NPIS Pesticide Surveillance Project - neonicotinoids: Comparison of toxicity against other insecticide classes

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Objective: Neonicotinoids are a relatively new class of insecticide about which there is limited information on human toxicity in Europe. We describe neonicotinoid exposures during 8 years of the National Poisons Information Service (NPIS) Pesticide Surveillance Project and compare poisoning severity against other more established insecticides in use in the UK.

Methods: The NPIS monitors and follows up pesticide exposures following Internet (TOXBASE[®]) or telephone enquiry. Poisoning severity scores (PSS) for neonicotinoids were compared against other insecticides in similar categories of use. Categories of use: professional/amateur, agriculture, veterinary, fly-killer, ant-killer, other insecticide.

Results: 105 unintentional neonicotinoid exposures were reported. Seventy-four imidacloprid (28 in combination with moxidectin, 19 methiocarb, 7 permethrin, 1 beta-cyfluthrin); 24 nitenpyram; 4 acetamprid; 3 thiacloprid. Fifty-three adults and 52 children; 55 female, 50 male. Most exposures (103) were acute. Route: ingestion (61); inhalation (11); skin contact (11); eye contact (5); multiple routes (16); NK (1). Thirty-one exposures occurred during patient use, 11 by another person, 21 after application, 21 unsatisfactory storage. Volumes involved are likely to be small, data is limited. Common symptoms: nausea/vomiting (7); eye irritation (6); skin irritation (5); diarrhoea (4); mouth/throat irritation (4); mouth paraesthesia (3); skin paraesthesia (3); dyspnoea (3). Neonicotinoids were reported mainly in two categories: veterinary domestic use (71) and amateur "other insecticide" (28). Amateur "other insecticide" PSS - Neonicotinoids: none 18 (64.3%); minor 10 (35.7%); moderate 0; uncertain 0. Pyrethroids: none 98 (37.8%); minor 139 (53.7%); moderate 15 (5.8%); uncertain 7 (2.7%). Carbamates: none 12 (48.0%); minor 11 (44.0%); moderate 1 (4.0%); uncertain (4.0%). Other (not OP): minor 13 (40.6%); moderate 17 (53.1%); moderate 2 (6.3%); uncertain 0. (P = 0.046). Veterinary domestic PSS - Neonicotinoids: none 48 (67.6%); minor 22 (31.0%); moderate 1 (1.4%); uncertain 0. Pyrethroids: none 64 (57.1%); minor 47 (41.9%); moderate 0; uncertain 1 (0.9%). Other (not OP): none 39 (56.5%); minor 26 (37.7%); 4 moderate (5.8%); uncertain 0. (P = 0.285).

Conclusion: In the UK unintentional domestic exposures to neonicotinoids are of low toxicity. For amateur home/garden insecticides severity was significantly lower than other agent classes (P = 0.046). Toxicity may differ in other parts of the world or self-harm where larger volumes are involved.

226. The NPIS Pesticide Surveillance Project – eye contact with pesticides: Circumstances of exposure and toxicity

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Objective: To examine pesticide exposures involving eye contact during 8 years of the National Poisons Information Service (NPIS) Pesticide Surveillance Project with the aim of highlighting common causes of toxicity.

Methods: The NPIS monitors and follows up pesticide exposures following Internet (TOXBASE[®]) or telephone enquiry. All patient related enquires involving pesticides between 1/4/2004 and 1/4/2012 were examined.

Results: 6036 unintentional pesticide exposures were reported during the period; 673 (11.1%) of these cases involved eye contact. In 475 of these exposures eye contact was the only route of exposure. Five hundred and sixty-six (84.1%) exposures involved adults; 103 children; 4 ages unknown. In 246 (36.6%) exposures no symptoms were reported; 379 (56.3%) reported eye irritation; 52 conjunctivitis; 45 eye burn; 34 abnormal vision; 35 lacrimation. The most common agent classes involved were: herbicides (265); insecticides (212); wood preservatives (83); sheep dip (37); fungicide (28); surface biocide (20); rodenticide (18); fumigant (4) and anti-fouling products (4). In 430 (63.9%) exposures the pesticide was in use by the patient; 52 by another person; 59 exposures occurred after application; 64 due to unsatisfactory storage. One hundred and fifty-three exposures were occupational. Of the 566 adults: 62 (11%) patients reported being exposed during windy conditions; 42 (7.4%) reported hand-to-eye contamination; 13 reported using no eye protection. Five were exposed despite use of eye protection. Of the 475 where only eye contact occurred it is possible to assess the poisoning severity score (PSS): 97 were graded PSS "none"; 300 "minor"; 57 "moderate"; 21 "uncertain". For exposures graded "moderate" the most common agents were: cresol/phenol (7); glyphosate (5); paraquat (5); tetramethrin (4); diquat (4); 2,4-D (4). For exposures graded "minor" the most common agents were: glyphosate (49); cresol/phenol (25); cypermethrin (24); permethrin (14); diquat (12); deltamethrin (9). Treatments reported were: eye irrigation (183), antibiotic (28) and referral to ophthalmology (21).

Conclusion: Eye contact with pesticides is a common route of pesticide exposure (11.1%). Exposures frequently occur during patient use (63.9%) and may result in moderate symptoms such as corneal burns (57, 12%). We are uniquely able to highlight areas of concern for safety such as use in windy conditions (11%) and hand-to-eye contamination (7.4%).

227. A life-threatening dichlorophen poisoning case: Clinical features and kinetics study

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Objective: Human dichlorophen poisoning is rare. We aim to report a case of dichlorophen poisoning resulting in complete recovery despite life-threatening multiorgan failure and huge serum dichlorophen concentrations.

Methods: Description of features and management in one dichlorophen-poisoned patient. After liquid-liquid extraction, dichlorophen concentrations were measured using liquid chromatography-heated electrospray ionisation-tandem mass spectrometry.

Results: A 74-year-old female self-ingested an anti-moss dichlorophen solution (360 g/L). She rapidly developed caustic esophageal and gastric mucosal injuries, confusion, profuse diarrhea, and electrolyte disturbances. Initial elevation in serum aminotransferase and γ -glutamyltransferase rapidly improved. Serum dichlorophen concentration was 708.1 μ g/L on admission and decreased in parallel with aminotransferase. Dichlorophen elimination was prolonged (serum half-life: 35.5 hours), peaking in urine on day 2. Mild elevation in serum creatine phosphokinase (peaking 48 hours post-ingestion) and acute renal failure (requiring hemodialysis on day 8) occurred. Final outcome was favorable with supportive management.

Conclusion: Dichlorophen ingestion results in life-threatening multiorgan injuries including rapid onset of caustic digestive lesions, diarrhea, liver enzyme disturbances as well as delayed renal impairment and rhabdomyolysis. Recovery can be complete if prompt supportive management is provided.

228. Severe toxicity from accidental glyphosate ingestion in a child

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Objective: Glyphosate is a broad-spectrum systemic herbicide. Severe toxicity is rare.

Case report: A 2.5 year-old boy ingested unknown amounts of concentrated glyphosate (Round-Up), decanted into a soda bottle. Immediately after ingestion the boy was crying, experienced excessive salivation, vomited several times, spontaneous and provoked. Fifteen minutes after ingestion the National Poison Center was contacted, and advised immediate emergency ward contact. The Poison Center alerted the hospital staff about the patient and treatment plan including activated charcoal and examination of oral and gastrointestinal mucosa. On emergency ward arrival the child was awake, crying, reacted adequately, was warm and dry, respiratory

frequency (RF) 19/min, oxygen saturation 100%, heart rate 164 beats/min and blood pressure 104/71 mmHg. Activated charcoal 1 g/kg (body weight 14.5 kg) was dosed 1 hour after ingestion. Corrosive injury was suspected because of hypersalivation and red marks in the mouth and throat. Gastroscopy 3 hours after ingestion showed Grade 1b ulceration in the esophagus, pylorus and gastric mucosa. Antibiotic treatment (cefuroxime and metronidazole), with antiemetic (dexamethasone), and analgesics (diclofenac and paracetamol), was initiated. A gastric tube was placed for observation. Hemorrhage was not observed. Coagulation parameter deterioration with elevated international normalized ratio (INR 1.4) and decreased activated partial thromboplastin time (APTT 25 sec), was observed from 3 hours after ingestion and persisted to day 4. All other biochemical parameters were within normal range, and there was no sign of acute kidney injury. Three days after ingestion soft diet was initiated and the following day the patient was well and discharged.

Conclusion: Typical symptoms from glyphosate ingestion include nausea, vomiting, abdominal pain, mouth and throat pain. In severe cases gastrointestinal ulceration and bleeding, renal and hepatic deterioration, and circulatory effects might be observed. There have been deaths after rapid onset of respiratory and circulatory collapse. In this case the ingested amount is unknown but is supposed to be a limited minor amount of a highly concentrated product. Immediate development of symptoms and gastric mucosa ulceration confirmed by gastroscopy support the suspicion of concentrated glyphosate ingestion. Unfortunately it was not possible to get a product sample for chemical analysis. The effect on coagulation parameters was unexpected and calls for increased attention in future glyphosate poisonings.

229. Prospective outcomes following acute exposure to pyrethroid insecticides in pregnancy

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Objective: Pyrethroid insecticides are widely used in both domestic and agricultural settings. Environmental exposure to pesticides in general has been associated in some studies with an increased risk of adverse pregnancy outcome. Experience of acute pyrethroid exposure, or poisoning in pregnancy is however limited.^{1,2} Here we present data from an ongoing prospective case series of fetal outcomes following acute pyrethroid exposure in pregnancy.

Methods: Using standardised procedures, the UK Teratology Information Service (UKTIS) has provided fetal risk assessment and collected outcome data on a prospective case series of 70 women exposed to pyrethroid insecticides in pregnancy (cypermethrin n = 12, deltamethrin n = 6, permethrin n = 40, tetramethrin n = 8, pyrethroid not specified n = 4).

Results: Exposure occurred via inhalation in 51 women, topical exposure in two and ingestion in one. Route of exposure was not reported in the 16 remaining women. Maternal toxicity after pyrethroid exposure was reported in 12 women, 22 women were asymptomatic and details were not available for 36. The most

commonly reported symptoms of toxicity were headache (41.6%), dizziness (16.6%) and cough (16.6%). There were four miscarriages and one elective termination. No major congenital anomalies were observed among the 65 live-born infants exposed *in utero* to pyrethroid insecticides (0/65, 0%; 95% CI 0% to 6.9%), including 24 first trimester exposures. Four infants were reported to have minor congenital anomalies (6%; 95% CI 1.9% to 15.8%). These were positional talipes ($n = 2$), accessory auricle of the left ear and strabismus of the right eye ($n = 1$), and inguinal hernia ($n = 1$).

Conclusion: The overall rate of major or minor congenital anomalies was not significantly higher than the background population rates and no specific pattern of anomalies was observed, however these data are too limited to exclude an increase in risk and further data collection is needed.

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230. Prospective outcome data after acute exposure to carbamate insecticides in pregnancy

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Objective: Carbamate insecticides are widely used as pesticides both in a domestic and agricultural setting. The published data on carbamate poisoning are limited to a single case series and case reports, most of which involved carbamate ingestion, with pregnancy loss or fetal demise reported in several cases.^{1–4} Here we describe an ongoing prospective case series of fetomaternal outcome following acute carbamate insecticide exposure in pregnancy.

Methods: Using standardised procedures, the UK Teratology Information Service (UKTIS) provided fetal risk assessments and collected outcome data for 37 women acutely exposed to carbamate insecticides during pregnancy.

Results: Of the 37 pregnancies, 19 were not exposed to other chemicals or therapeutic agents. Exposure in the majority of the cases was by inhalation (70.2%). Maternal toxicity was reported in seven cases, nine women were asymptomatic following exposure, and details regarding toxicity were not available in 21 cases. Sixteen exposures (43%) occurred in the first trimester. There were three miscarriages and one elective termination. No major congenital anomalies were reported in the 33 live-born infants, of which 13 were first trimester exposures. The major malformation rate in this limited cohort (0/33, 0%, 95% CI 0% to 12.9%) was therefore not significantly higher than the expected background rate of 2–3% in the general population.

Conclusion: These data do not demonstrate an increased risk of congenital anomalies or fetal demise following acute carbamate exposure but are insufficient to exclude an increase in risk. More data, including details of maternal dose and toxicity, are required

for accurate assessment of fetal risk after maternal carbamate exposure.

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231. Atropine: Antidote or killer in chlormequat poisoning?

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Objective: Chlormequat poisoning clinically resembles that seen with anticholinesterase insecticides but the administration of atropine increases mortality.

Case series: We report four cases of lethal chlormequat poisoning. Case 1. A 46 year old man voluntarily ingested 150 mL of a chlormequat solution. He presented cardiac arrest at home. After resuscitation by the Urgent Mobile Service (SMUR), he was admitted to the intensive care unit. He developed multiorgan failure and died 19 hours later. Case 2. A 46 year old man voluntarily ingested an unknown quantity of Contreverse, containing 460 g/L of chlormequat chloride. Thirty minutes later, he presented a sudden cardiac arrest. He was treated by mechanical ventilation and intravenous infusion of adrenaline; because he presented important bronchorrhea, 2 mg of atropine were administered when sudden ventricular fibrillation appeared, treated by external electric shock. He died one hour later. Case 3. A 59 year old man voluntarily ingested 2 mouthfuls of Cycocel containing 460 g/L of chlormequat chloride and 320 g/L of choline chloride. Symptoms started 20 minutes later with diaphoresis and increased salivation. Thirty minutes after ingestion, asystolic cardiac arrest required external cardiac massage, intravenous adrenaline and atropine administration. Case 4. A 39 year old farmer accidentally inhaled Cycocel. Twelve hours later an acute pulmonary edema appeared followed by a respiratory and asystolic cardiac arrest which required external cardiac massage by the SMUR. He was intubated, and atropine and adrenaline were administered but he died at home.

Conclusion: All patients developed the characteristic cholinergic signs characteristic of chlormequat ingestion. However, if chlormequat poisoning clinically resembles organophosphate intoxication, it is not an acetylcholinesterase inhibitor and using atropine may increase toxicity and decrease survival time as it does in animal experimentation. Treatment is symptomatic with cardiovascular and respiratory support; there is no specific antidote. The laboratory can help the physician, by showing normal cholinesterases (AChE and BChE). Measuring chlormequat blood levels was not

useful for routine clinical management of suicide cases. This case series confirms the extreme gravity of chlomequat poisoning with with a risk of death in the hour post ingestion. The identification of the product by the poison centre is important to avoid atropine administration.

232. Bendiocarb and clopyralid: A toxicovigilance study based upon 8 years of NPIS Pesticide Project data

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Objective: Pesticide regulation is enforced regionally by agencies such as the Environmental Protection Agency in the USA and the Health and Safety Executive in the UK. The objective of this analysis is to evaluate the safety of two pesticides where a disparity exists between regulatory body recommendations using National Poison Information Service (NPIS) data. Bendiocarb, a potent acetylcholinesterase inhibitor, is currently banned in the USA while clopyralid, an herbicide with the potential to cause severe eye damage, is subject to strict regulations in several US states. Both are authorised for use in the UK.

Method: Since April 2004, the NPIS has monitored pesticide exposures as part of a pesticide surveillance study. Between April 2004 and April 2012 the NPIS collected information on 6689 pesticide exposures, of which 175 (2.6%) were to bendiocarb and 30 (0.4%) to clopyralid. Poisoning severity was assessed using the Poisoning Severity Score.¹

Results: Of the 175 bendiocarb exposures reported, 17 (9.7%) were graded as 2 (Moderate). No grade 3 (Severe) or 4 (Fatal) cases occurred. Of the remaining 158, 70 (40%) were graded as 2 (Minor), 84 (48%) as 0 (None) and four (2.3%) were unclassified. Regarding product class, 103 (58.9%) and 43 (24.6%) exposures were to amateur or professional products, respectively (3 (1.7%) were unknown and 26 (14.9%) other). Of the 43 exposures to professional products, 27 occurred following their use in the home. Of the 30 clopyralid exposures, two (6.7%) were graded 2 (Moderate). No exposures were graded 3 (Severe) or 4 (Fatal). Of the others, 19 (63.3%) were graded 1 (Minor), 8 (26.7%) 0 (None) and one (3.33%) was unclassified. Four eye exposures occurred but all were graded 1 (Minor).

Conclusion: Overall, exposure incidence and severity was low for both pesticides. Despite safety concerns, all eye exposures to clopyralid were minor. However, the data highlights a potential area of concern regarding exposures to professional bendiocarb products being used in the home.

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233. Comparison of current recommended regimens of atropinization in organophosphate poisoning

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Objective: Atropine is the mainstay of therapy in organophosphate (OP) toxicity, though consensus on dosing is lacking. In 2004, Eddleston et al¹ noted significant variation in recommended regimens. We repeated Eddleston's work with current references, to determine if the variability in atropine recommendations persists and compare newer resources.

Methods: Updated editions from Eddleston's work were reviewed for atropine dosing recommendations. Major texts of Internal and Emergency Medicine, Emergency Medicine study guides, and electronic resources were also accessed. For comparison, recommendations were assessed using the same mean dose (23.4 mg) and the highest dose (75 mg) of atropine as used in Eddleston's original paper.

Results: Fifteen of the original recommendations were updated and eight additional references were added giving a convenience sample of 23. Twenty provided sufficient dosing information to calculate time to effective dose. Compared to 2004, current recommendations have greatly increased the speed of atropinization. Eighteen of 20 (90%) recommendations reached the mean atropine requirement within an hour as compared with only 61% (22/36) in 2004. Similarly, in 2004, there were 13 regimens where the maximum time to reach 75 mg was greater than 18 hours, whereas now, there are only 2. For the slowest recommendations 18/20 can reach the average atropine requirement within 3 hours and the highest requirement within 9.3 hours. Of the recommendations in Eddleston's paper that were revised since 2004, 8 of 15 current works now include doubling the dose for faster escalation which was present in only one in 2004.

Conclusion: In 2004, Eddleston called for an evidence-based guideline for the treatment of OP poisoning that could be disseminated worldwide. While the WHO recommendations lag in terms of the time to appropriate dosing for the average patient with OP poisoning and more significantly for those with the highest requirements, other authorities have come closer to a consensus and updated recommendations can treat patients within one hour.

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234. Carbamate poisoning mixed with methanol intoxication - misfortunes never come singly: Case report

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Objective: Pesticide poisoning is a common occurrence in Taiwan, due to agriculture being one of the main occupations. Carbamate

is the fifth cause of pesticide poisoning according to epidemiology in Taiwan, but is third in mortality. Intentional ingestion is the most common reason for carbamate intoxication. Symptoms of carbamate intoxication are similar to organophosphate intoxication, including muscarinic and nicotinic toxidromes. Metabolic acidosis can be seen in cases of carbamate intoxication, but not very frequently.

Case series: Here we report two cases of carbamate intoxication with severe metabolic acidosis, which was proven to result from methanol intoxication. Although hemodialysis was arranged immediately, both patients died in 3–5 days. One case, a 59-year-old woman, was sent to the emergency department (ED) due to collapse on the road, and was found to be in cardiac arrest when the emergency medical technician (EMT) arrived. Cardiopulmonary resuscitation (CPCR) was carried out successfully in ED, and pinpoint pupils, bronchorrhea, sweating and bradycardia were noted. Organophosphate or carbamate intoxication was highly suspected. Blood tests disclosed low cholinesterase level, mixed respiratory and metabolic acidosis and elevated anion gap. Elevated methanol level was confirmed later by laboratory examination. Her family mentioned that she took a bottle of pesticide in a suicide attempt and the pesticide contained 30% methomyl (carbamate), 26% methanol and 16% ethylene glycol as emulsifiable concentrate. Hemodialysis was performed immediately, but the patient died 5 days later. The other, an 85-year-old woman, drank a bottle of carbamate (methomyl and alpha-cypermethrin mix) to commit suicide. Cardiac arrest was found in ED, and there was return of spontaneous circulation after CPCR. Like the first case, blood tests revealed severe metabolic acidosis, elevated anion gap and elevated methanol level. The patient died 3 days later although hemodialysis was arranged.

Conclusion: For patients with pesticide poisoning, most clinicians may put emphasis on the main component of the intoxication such as the organophosphate or carbamate. However, hidden toxic solvents such as methanol can be the cause of death for these patients.

235. Adult lead poisoning from ingested bullets

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Objective: Patients with retained soft tissue lead may have elevated blood lead levels and toxicity. We present a case in which a woman ingested 26 lead bullets and developed toxic lead concentrations.

Case report: A 65 year-old woman (wt. 69.6 kg) presented to the emergency department (ED) after ingesting bullets in a suicide attempt. She ingested 20–30 bullets individually and then notified her son who brought her to the ED 5 hours post-ingestion. On presentation she had normal vital signs and was asymptomatic with no abdominal pain, nausea, vomiting or diarrhea. An abdominal radiograph showed the bullets clumped together in the right upper quadrant (RUQ). The serum/urine toxicology screen was positive only for benzodiazepines, and the initial blood lead level was 9.7 micrograms/dL. The patient

was extremely agitated in the ED and had to be restrained physically and sedated chemically. Whole bowel irrigation was not started due to concerns of aspiration. The patient was admitted to the psychiatric ward. A repeat blood lead level was 25.7 micrograms/dL 31 hours post-ingestion. At that point her mental status had improved and polyethylene glycol solution was started orally at 1 L/hour for 6 hours. During that time the patient had multiple bowel movements, however a repeat abdominal radiograph showed the bullets were still in the same location in the RUQ and whole bowel irrigation was discontinued. The surgery consultant elected not to intervene due to risk of detonation from electrocautery. An upper GI endoscopy was performed and twenty-six .22 caliber bullets were removed from the gastric fundus. The fundus had folded over itself, thus trapping the bullets in the stomach. She was discharged home later that morning. A repeat blood lead level prior to discharge was 40.5 micrograms/dL 114 hours post-ingestion. Subsequent blood lead levels were 29.3 micrograms/dL and 17.2 micrograms/dL on days 24 and 60 post-ingestion, respectively. She remained asymptomatic with a normal complete blood count, serum creatinine and did not receive chelation therapy.

Conclusion: Retained gastric lead bullets can result in rapid lead absorption and toxic blood lead levels. Prompt removal of gastric lead bullets is indicated.

236. Plain film as a quick investigation tool for acute arsenic poisoning

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Objective: We present a patient with acute oral arsenic poisoning and the initial plain film showed radio-opaque lesions in the stomach. This image finding facilitated the early recognition of acute heavy metal poisoning and chelating agent usage.

Case report: A 58-year-old male presented to hospital due to self reported intentional arsenic trioxide ingestion minutes before arrival without clinical symptoms. Routine blood and biochemical exam, blood arsenic level, chest and abdomen plain films were obtained. The initial blood and biochemical exam were unremarkable. The chest and abdomen plain films disclosed radio-opaque lesions in the stomach. Persistent nausea, vomiting, abdominal pain, and bloody stools occurred one hour after arrival. Dimercaprol was prescribed for highly suspected acute oral arsenic poisoning based on history, clinical symptoms and the image finding on plain films. Eight hours after arrival, refractory hypotension occurred. The follow up blood exam disclosed creatinine 3.68 mg/dL, troponin-I 20.958 ng/mL. The arterial blood gas analysis showed pH 7.150, pCO₂ 34.0 mmHg, HCO₃ 11.6 mm/L. This patient died 12 hours after arrival due to multiple organ failure. The initial blood arsenic, reported 5 days after hospital arrival was 730 ug/L. The diagnosis of arsenic poisoning was confirmed.

Conclusion: Acute arsenic poisoning may lead to severe complications in multiple organ systems and can be lethal. Early recognition of poisoning is the key to subsequent decontamination, chelating agent prescription and disposition. The definite

diagnosis of acute arsenic poisoning depends on the arsenic level in blood or urine sample.^{1,2} In clinical practice, the laboratory result may not be available in a timely manner and in every hospital before the initiation of chelating agent use. An alternative investigation tool is critical. The radio-opaque lesion on the plain film combined with compatible clinical symptoms may help clinical physicians recognize acute arsenic poisoning at an early stage.

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237. Case report: Poisoning with elemental (metallic) arsenic

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Background: From literature nothing is known about the acute effects after ingestion of elemental arsenic, As(0). With its virtual insolubility in non oxidizing aqueous media one should expect only minor adverse effects after a single ingestion.

Case report: A 56 y male chemistry teacher ingested > 5 g elemental As(0) deliberately at h0. Twelve hours later, (h12) he went to a hospital reporting diarrhoea and respiratory distress. Anticipating a severe intoxication with As₂O₃ he was intubated, mechanically ventilated and transferred to our hospital. At h14 he received DMPS iv, 500 mg bolus, 83 mg/h continuously. Abdominal computed tomography (CT) scan revealed densities throughout the GI-tract, predominantly in the stomach and duodenum. Gastroscopic lavage with 4 litres of water retrieved 2.2 g metallic-black grains of As(0). At h205 a further 3 g As(0) were recovered by colonoscopic lavage. Serum-creatinine at h12 was 3.3 mg/dL and normalized after fluid replacement. No toxic organ failure was seen. However, extubation at h106 failed due to extreme agitation with delirium requiring deep sedation and re-intubation. A ventilator-associated pneumonia necessitated further mechanical ventilation. After extubation at h205 the patient was still delirious and complained about pain throughout the body without objective findings. The patient recovered within one further week and was transferred to psychiatry without any sequelae of the intoxication at h516.

Results: Arsenic concentration in blood [AsB] at h12 was 454 µg/L, at h14: 420 µg/L. With gastroscopic lavage (h16) [AsB] rose to 550 µg/L. From h18-h41 [AsB] declined to 76 µg/L with a half-life of 9.3 h. From h65 to h270 [AsB] fell to 3.6 µg/L with half-life 73 h. Arsenic concentration in urine [AsU] at h12 was 16 mg/L, with DMPS at h29 45 mg/L. [AsU] was 0.9 mg/L when DMPS was stopped at h132. Readministration of DMPS did not increase As-elimination: at h206: [AsU] was 0.2 mg/L. Total arsenic excretion in urine was ≥ 113 mg.

Conclusion: Ingestion of elemental, metallic arsenic(0) causes an intoxication less severe than would be expected with the same amount of As₂O₃. DMPS enhances As elimination in the first few days without further increase after 5 days.

238. Criminal thallium poisoning: A case series

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Objective: Acute thallium poisoning is rare and usually the result of a criminal act. Late onset of non-specific symptoms and lack of sufficient information lead to misdiagnosis and delay the start of specific treatment.

Case series: We present two cases of criminal thallium poisoning, which were diagnosed three weeks after the beginning of the complaints. This is the second known case of group criminal thallium poisoning in the country over the last 10 years. A 61-year-old woman and her 38-year-old daughter presented with a history of diffuse myalgia, muscle weakness, ataxia, paresthesiae, stomatitis, eczematous lesions around the mouth, abdominal pain, constipation, headache, insomnia, depression, fluctuating pulse and blood pressure, hypohidrosis, hair loss progressing to diffuse scalp alopecia (over a period of two weeks after the beginning of symptoms). Thallium poisoning was diagnosed on the basis of symptoms described and confirmed by the subsequent analysis of thallium in plasma, urine and hair. On admission the blood thallium concentrations were 240 ng/mL (mother) and 120 ng/mL (daughter). One week later thallium concentration was less than 100 ng/mL (lower toxic range). Thallium was also found in hair segments in both patients. Axonal neuropathy with motor and sensory impairment was found on electromyography. Electroencephalography showed data for nonspecific slow-wave activity. No ocular abnormalities were found. Treatment included forced diuresis with potassium loading under close monitoring for exacerbation of symptoms and urinary output of thallium; symptomatic treatment of gastrointestinal and neuropsychological symptoms. Due to the lack of antidote availability, Prussian blue treatment was started on day 15 after hospitalization.

Conclusion: Thallium poisoning is known for its diverse manifestations, often causing delays in diagnosis. The combination of abdominal pain and painful neuropathy in lower extremities, followed by diffuse alopecia is an important early diagnostic clue for thallium toxicity and should be followed by diagnostic toxicological analysis in difficult and unclear cases. Potassium chloride is a choice for rapid displacement of thallium from the body, but the initial dose must be carefully adjusted according to the initial thallium level, due to the possibility of high-peak displacement resulting in aggravation of clinical symptoms.

239. When work comes home: Delayed elevation of plasma mercury concentration after an occupational mercury exposure

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Background: Mercury exposure can occur from dietary, environmental, and occupational sources. If the mercury contamination source is not appropriately identified and abated, chronic exposure can result in neurologic sequelae. We report a case of occupational exposure resulting in home contamination and a ninety-five-fold increase in plasma mercury concentrations over six months following an initial mercury contamination.

Case report: A 53 year-old man was referred to the toxicology clinic with symptoms of irritability, emotional lability, and social isolation for three months, associated with intermittent gum bleeding, metallic taste, and nocturnal polyuria. Seven months prior to referral, the patient's face was exposed to metallic mercury while repairing a clogged sink in a secondary school science laboratory. The local health department confirmed the exposure two weeks later and worksite decontamination occurred. Two months after the exposure, the plasma mercury concentration was 10 micrograms/L, which increased to 215 micrograms/L during the following 4 months. Subsequent plasma mercury and 24-hour urine mercury concentrations were 948 micrograms/L and 2737 micrograms/L, respectively, 11 days later. On presentation, his vital signs and physical examination, including a complete neurological assessment, were normal. Radiographs of the chest, abdomen, and upper extremities were normal, and proteinuria was absent. Random plasma and urine mercury concentrations were 508 micrograms/L and 1939.4 micrograms/L, respectively. The patient's asymptomatic wife was also evaluated. Her plasma and random urine mercury concentrations were 412 micrograms/L and 689 micrograms/L, respectively. The patient received succimer for 19 days; the wife was not chelated. The local department of health investigation of the patient's home found extensive mercury contamination; the peak air mercury concentration was 800 micrograms/m³ (Environmental Protection Agency reference range: 0.03 micrograms/m³). The highest mercury concentration was detected in the patient's slippers. The patient and his wife were relocated during abatement measures. At a three week follow up evaluation, their plasma mercury concentrations had declined to 101 micrograms/L and 142 micrograms/L, respectively.

Conclusion: Occupational exposures can affect both workers and their absent family members. Early recognition and appropriate decontamination is required. Environmental remediation in both the workplace and the home prevented further mercury poisoning for the patient and his wife.

240. Time to reevaluate guidelines for aluminium content in dialysate solutions?

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Objective: Dialysis-dependent patients are particularly susceptible to the toxic effects of aluminum (Al) because of their impaired ability to eliminate it. Al contamination of dialysis fluid remains a particular threat in this population.¹ Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines propose target [Al] in dialysate < 10 ug/L but accumulation at these levels appear to be nevertheless possible. The mechanism for Al diffusion is not known. Our objective is to verify, in Al-poisoned patients in our center as well as cases described in the literature, the postulate that direction of Al mass transfer is dependent on the difference between ultrafiltrable [Al]_s and [Al]_d.

Methods: Assuming an ultrafiltrable fraction of Al = 18–23% of [Al]_s, the following literature search was chosen: (“dialysis” OR “plasmapheresis”) AND (“transfer” or “clearance”) AND (“aluminum”). Only papers which included [Al]_s, [Al]_d (if > 0), and direction of Al transfer (positive = from dialysate to plasma, negative = from plasma to dialysate) were selected. We also included 4 patients from our own cohort. Cases were considered contrary to our hypothesis if either of the following was present: Negative Al transfer when [Al]_d > [Al]_s * 23%, positive Al transfer when [Al]_d < [Al]_s * 18%.

Results: The search yielded 98 articles, of which 12 were selected for review. Individual patients from our own cohort as well as those from the literature review were mapped. Only one out of 87 patients had actual Al transfer contrary to the hypothesis.²

Conclusion: Comparing ultrafiltrable Al to dialysate Al permits to accurately predict the direction of Al transfer. Al would therefore accumulate in end-stage renal disease (ESRD) patients, even at low [Al]_d. Taking the K/DOQI higher limit of accepted [Al]_d (10 ug/L), [Al]_s could realistically reach 50 ug/L. [Al]_d should therefore be < 20% of the maximally acceptable [Al]_s. If we assume this to be 20 ug/L (K/DOQI), [Al]_d should be maintained < 4 ug/L instead of 10 ug/L.

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241. Excessive iron intake over two days resulting in liver transplantation. A case report

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Objective: Severe iron intoxication is a rare event in Germany. If it occurs it is usually due to self-harm. We present a severe intoxication as a result of a dosing error.

Case report: The 19-year-old woman presented to the emergency department with abdominal and thoracic pain and dyspnoea after taking 50 tablets (5000 mg) within 2.2 days which were prescribed because of a mild iron deficiency anaemia. She took the last dose the day before. The patient walked into the emergency room. The lab work showed a marked rise in transaminase levels (> 7000 U/L) lactic acidosis, and compromised coagulation (Quick's test $< 10\%$). At presentation the serum iron concentration was $372 \mu\text{g/dL}$. Fluid replacement and deferoxamine infusion were started immediately. Shortly after admission the patient's general condition deteriorated with rising transaminases and decreasing levels of all liver synthesized pro-coagulant factors, tachycardia, and hypotension. She developed pulmonary congestion and the metabolic acidosis deteriorated. The patient, now treated with catecholamines developed anuric renal failure and was transferred to a transplantation unit. After further deterioration of liver function the patient received an orthotopic liver transplantation on day 6 after admission. During surgery the patient needed cardiac resuscitation. The following days she developed further complications: heparin-induced thrombocytopenia with pulmonary embolism and multiple venous thromboses, intra-abdominal hematoma with stenosis of the portal vein and hepatic artery requiring surgical draining, and leakage of the bile duct with stent implantation. Infection of the hematoma resulted in stenosis of right and left liver artery and consecutive percutaneous dilation and stent implantation.

Conclusion: The dose ingested (71.5 mg/kg) is expected to cause severe intoxication. In this patient the symptoms of iron intoxication developed gradually due to the protracted intake. Due to presentation one day after cessation of exposure most procedures of poison elimination were not indicated. Chelation was started late because of late presentation and it could not stop multiorgan failure.

242. Puberty blues - copper salt exposures in Australian schools

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Objective: Copper sulphate, also known as blue vitriol, is used chiefly for agricultural purposes. In New South Wales (NSW) high schools, copper sulphate crystals are often grown in chemistry classes as a school experiment. We are reporting a case of intentional copper sulphate ingestion and data from the NSW Poisons Information Centre (PIC) on exposures to copper salts obtained at school.

Case report: A 14 year old male presented 1 hour after ingestion of copper sulphate crystals. The crystals were obtained from school and he stated he ingested 10 g in a self-harm attempt. He immediately induced vomiting. On examination he was haemodynamically stable and had throat erythema and epigastric tenderness. He was treated with intravenous fluids and pantoprazole. He developed a mild elevation of his bilirubin to $84 \mu\text{mol/L}$ on day 2. Copper levels taken 9 hours post ingestion were not elevated. A gastroscopy performed 16 hours post-ingestion showed grade 2 ulcerations at

the antrum and pylorus of the stomach. He made a full recovery and was discharged home after 4 days. A retrospective review was completed of all calls made to the NSW PIC about copper salt exposures attributed to schools from 1st Jan 2004 to the 3rd September 2012. NSW PIC receives approximately 110,000 calls per year. Ninety-nine cases were identified, of which 86 were copper sulphate, the majority involved ingestion ($n = 56$) but were accidental ($n = 84$). The most common symptoms recorded were local irritation or pain ($n = 14$), nausea ($n = 13$) and vomiting ($n = 10$). Thirty-four presented to or were referred for medical assessment, and there were no major complications in our cohort.

Conclusion: In our cases there were no serious clinical complications, but copper sulphate ingestion can result in acute haemolysis, renal failure, acute hepatitis, gastrointestinal bleeding and pancreatitis. A case series of copper sulphate poisoning from South-West India of 35 patients, reported a mortality rate of 22.9%.¹ The ease of availability of a potentially toxic substance in Australian schools should be reviewed.

Reference

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243. Metal-on-metal hip arthroplasty and the risk of cobalt intoxication: A follow-up procedure

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Background: After a Medical Device Alert in 2010, cobalt and chromium levels in patients with Metal-on-Metal (MoM) hip arthroplasty are routinely measured. Chromium is predominantly released as Cr^{3+} and toxicologically of less concern. On average, MoM hip prostheses cause a 5- to 10-fold increase in blood cobalt concentrations. Blood concentrations of these metal ions correlate with implant wear and corrosion, and orthopedic associations have developed guidelines for how to perform follow-up on the MoM prosthesis and when to perform a hip revision. Also Poisons Information Centers are increasingly consulted about potential health risks of elevated cobalt blood levels. Toxic blood cobalt concentrations may be accompanied by hypothyroidism, polyneuropathy, impairment of optic (II) and auditory (VIII) nerves, and cardiomyopathy. In order to prevent systemic cobalt poisoning a follow-up procedure is developed.

Discussion: Based upon blood cobalt concentrations, the Dutch Orthopedic Association set up management recommendations: < 2.4 micrograms/L: considered normal; 2.4 – 5.1 micrograms/L: mildly elevated, regular check-up of patient; 5.1 – 10.2 micrograms/L: elevated, indication for magnetic resonance imaging (MRI), computed tomography (CT) or ultrasound of hip; > 10.2 micrograms/L: in combination with local complaints and radiological imaging findings hip replacement may be necessary. Signs of systemic toxicity have been described at cobalt concentrations as low as 9 – 12.7 micrograms/L. In order to fit in with the concentration ranges of the Dutch Orthopedic Association we suggest a cobalt blood concentration of 10.2 micrograms/L (170 nmol/L)

as a starting level for toxicological follow-up in patients who do not have hip replacement. At this time ($T=0$) thyroid function, visual- and hearing tests should be performed. Repeat measurements should be carried out at 6 and 12 months in the first year, and subsequently once a year. In case of abnormalities, most likely related to the MoM prosthesis, hip replacement or chelation therapy must be considered, and an individual follow-up schedule must be established.

Conclusion: At present, it is unknown at which cobalt concentration the various toxic effects occur, and it needs to be determined which pathophysiological effect can be used as sentinel for toxicity. This follow-up procedure serves as a start and can be modified as soon as more information becomes available.

244. Chelation therapy with intravenous high dose N-acetyl-cysteine for cobalt release from metal on metal hip replacement: A first case report

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Objective: To report a case of significant cobalt (Co) and chromium (Cr) release from metal on metal (MoM) total hip replacement where intravenous high dose N-acetyl-cysteine (NAC) has been given to treat high Co-Cr blood levels.

Case report: A 75-year-old-male patient underwent bilateral total hip prosthesis with a ceramic-on-ceramic (CoC) implant in 1999. In 2006 the left ceramic head broke after an accidental fall and MoM Co-Cr alloy hip arthroplasty revision was performed. In May 2011 the patient complained of local hip pain, asthenia and 2 cyst-like nodules on the medium third of the left thigh. In July 2011 abrasion of the left metal head with local metallosis was diagnosed and a CoC revision was performed. Echocardiogram revealed a dilated left ventricle with diffuse hypokinesia (ejection fraction (EF) 32%; n.v. > 55%) associated with pericardial exudate and increased pulmonary pressure (43 mmHg; n.v. 15–28 mmHg). Thyroid tests and electromyography results were normal. Co-Cr serum levels before MoM explantation were 352.6 (n.v. < 0.9) and 67.85 (n.v. < 0.5) micrograms/L respectively; they reduced to 49.3 and 51.7 micrograms/L respectively six months later. In October 2012 high Co-Cr blood levels (46.5 and 77.1, respectively) persisted and chelation with intravenous high dose N-acetyl-cysteine (NAC) (150 mg/kg bolus followed by 300 mg/kg/day for 5 days) was performed: this treatment dropped the serum concentrations to about 51% and 40% of the pre-chelation levels, respectively. Currently the patient presents a stable condition associated with episodic dyspnoea and a clinical picture of moderate heart failure.

Conclusion: Cobaltism can result in deafness, blindness, peripheral neuropathy, cardiomyopathy and hypothyroidism. The general medical community is unaware that patients with MoM bearings are at risk of cobaltism and scientific literature lacks shared data concerning the treatment of cobalt poisoning from MoM hip release. Chelation therapy for Co release from MoM implant has

been described only with EDTA and DMPS.^{1,2} In our case blood Co-Cr levels remained elevated after 15 months from the MoM explantation, and NAC infusion was effective and safe in reducing Co-Cr serum levels. This first case of Co-chelation with NAC appears promising.

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245. Antidotes availability in the Italian health system: A national survey

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Objective: To survey and to improve the availability of antidotes in the Italian Health System (NHS), and also for chemical, radiological and nuclear (CRN) emergencies; to update the National Antidote Database (BaNdA at www.cavpavia.it); to compare the actual antidote availability in the NHS with the previous data collected in 2003¹.

Methods: In April 2012 a questionnaire was sent to the emergency services (emergency departments (EDs), intensive care units (ICUs), and poison centres) and to pharmacies of all Italian hospitals, requiring information on the availability of 94 antidotes/molecules useful in the treatment of poisonings.

Results: Preliminary data from 192 questionnaires (137 EDs and 55 ICUs) and relative to 23 antidotes (folic acid, physostigmine, activated charcoal, ethanol, fomepizole, amyl nitrite, sodium thiosulphate, hydroxocobalamin, cobalt edetate, pralidoxime, Viper-Fab, Fab-antidigoxin, glucagon, N-acetylcysteine (NAC), methylene blue, Prussian blue, PEG 400, BAL, DMSA, DMPS, Ca-DTPA/Zn-DTPA, vitamin C) have been analyzed until now. Three antidotes (DMSA, DMPS, Ca-DTPA/Zn-DTPA) and 4 antidotes (fomepizole, cobalt edetate, DMPS, Ca-DTPA/Zn-DTPA) were not available in EDs and in ICUs that participated in the survey, respectively. The comparison with data collected in the 2003 survey showed an increase in the availability of fomepizole (6.8% in 2012 vs 0% in 2003), sodium thiosulphate (24.5% vs 6.7%), hydroxocobalamin (33.1% vs 0.5%), glucagon (69.9% vs 0.5%) in the EDs and of hydroxocobalamin (12.7% vs 0%) and glucagon (27% vs 0%) in ICUs. Only for NAC, pralidoxime and Fab-antidigoxin a reduction in availability was registered: this is probably due to difficulties in purchase and to the availability of these antidotes in strategic stockpiles. No differences have been registered for the other analyzed antidotes. Considering the recommended dose to treat an adult for 24 hours, a dramatic decrease in the percentage of hospitals that stock a sufficient amount of antidotes was registered.

Conclusion: Preliminary data show an increase of availability of antidotes for methanol/ethylene glycol, cyanide and beta-blocker poisonings in Italian hospitals. The Poison Centers remain the only

services that ensure a prompt and complete availability of all the antidotes.

Acknowledgements: Study carried out with grants of the Department of Civil Protection–Presidency of the Council of Ministers and of the Ministry of Health, 2012.

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246. Antidotes supply in emergency from Pavia Poison Control Centre

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Objective: Antidotes can play a critical role in the management of poisoned patients. In Italy, one of the planned Poison Centre functions is monitoring antidote demand and managing the antidote stockpile to ensure their prompt availability in the emergency setting. The antidote supply by the Pavia Poison Control Centre (PCC) to the emergency departments (EDs) of the National Health System is evaluated.

Methods: A retrospective analysis of antidote supply in emergency for human poisonings from 1st January 2007 to 15th November 2012 was conducted. Antidote mobilization for treatment of animals or preventive stocking (hospitals, industries, other settings) were excluded.

Results: 151 cases (20 different antidotes) of supply in emergency were registered. Thirty-nine mobilizations were related to fomepizole 1.5 g (min/max, 1–9 vials), 15 calcium gluconate gel (3–21 tubes), 15 N-acetylcysteine (6–50 vials), 12 Viper-Fab-antivenom (2–6 vials), 12 digoxin-immune-Fab (2–12 vials), 10 glucagon (30–100 vials), 7 pralidoxime (60–400 vials), 7 succimer (15–180 capsules), 5 physostigmine (1–20 vials), 4 Ca-EDTA (1–20 vials), 4 hydroxocobalamin (2–3 kit), 4 penicillamine (100–200 capsules), 4 activated charcoal (3–10 bottles), 4 ethanol (30–50 vials), 2 PEG400 (2 bottles), 2 sodium thiosulfate (50–100 vials), 2 levocarnitine (15–20 vials), 1 atropine (50 vials), 1 cyproheptadine (2 vials), 1 pyridoxine (18 vials). In 45% of cases, antidotes were provided for immediate administration (availability in 30 minutes). The antidote was supplied in other Italian regions in 47% of cases. Most antidotes were mobilized for ethylene glycol/methanol, hydrofluoric acid, mushrooms, digoxin, beta blockers and viper bite poisonings.

Conclusion: 45% of the emergency supply activity involved antidotes that should be available in EDs within 30 minutes, and 20% regarded antidotes not registered in Italy. Eighty per cent of the supplied antidotes were sent directly from the Pavia PCC stockpile, whereas in 20% of cases the PCC moved antidotes from other hospital stockpiles, identified through the “national antidotes database” (www.cavpavia.it). This data-base, available since 2005,

represents a unique operating system that permits the management and optimization of all the national hospital stockpiles of antidotes. The results point to the critical role of Pavia-PCC in early mobilization of antidotes for timely management of acutely poisoned patients in Italy.

247. Validation of criteria to guide pre-hospital antidote administration for drug overdoses

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Objective: Criteria have been derived to predict successful response to naloxone and dextrose in pre-hospital patients transported by Emergency Medical Services (EMS) with altered mental status.¹ We validated predictors of response to EMS interventions as well as efficacy of different hypoglycemia interventions.

Methods: Secondary data analysis of an ongoing prospective cohort study of suspected acute drug overdoses at one urban tertiary care emergency department (ED). Electronic prehospital care reports (ePCR) included naloxone criteria (respiratory rate (RR) < 12, miotic pupils, and on-scene drug paraphernalia), dextrose criteria (tachycardia, diaphoresis, history of diabetes), vitals, pupil examination, and mental status graded by AVPU (Alert, Verbal, Painful, Unresponsive) and Glasgow Coma Scale (GCS). EMS interventions (dextrose, naloxone, glucagon, endotracheal intubation) were compared for effective antidote response (EAR), defined as immediate improvement in RR, pulse oximetry, AVPU or GCS. Assuming 15% responders, we calculated the need to enroll 250 subjects for 10% CI widths (80% power, 5% alpha).

Results: EMS transported 249 overdoses over 17 months (48% males, mean age 41.5, advanced life support (ALS) 33.7%). 28 (11.2%) patients met naloxone criteria and 15 (6%) met dextrose criteria, of whom 55.6% and 93.3% received antidotes, respectively. Other drug overdose interventions (sodium bicarbonate, calcium, pralidoxime, or hydroxocobalamin) were not administered to anyone in the cohort. Naloxone criteria significantly predicted EAR (OR 7.0, $p < 0.05$) with 83% sensitivity (CI 55–95) and 58% specificity (CI 32–81). Miotic pupils (OR 20.0, $p < 0.01$) outperformed RR (OR 2.3, $p = \text{NS}$) as the best single criterion with 91% sensitivity (CI 62–98) and 89% negative predictive value (NPV) (CI 57–98). Serum glucose < 60 mg/dL predicted EAR for dextrose ($p < 0.05$), while vital signs and GCS did not. Efficacy of hypoglycemia interventions in descending order were: 1) both glucagon/dextrose (100%), 2) glucagon only (80%), 3) dextrose only (70%), 4) neither (0%). Glucagon was more likely than dextrose to elicit EAR (OR 1.71, $p < 0.05$).

Conclusion: We validated pre-hospital criteria to guide naloxone administration and hypoglycemia interventions. Prehospital interventions for overdose were highly underutilized. Future research should explore barriers to pre-hospital antidotal interventions.

Reference

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248. Management of antidotes in a North Italian Region

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Objective: The Emilia Romagna Region (RER) has approximately 4.4 million inhabitants and 18 healthcare companies. In 2011, with a special legislative act, the Regional Reference Center for the allocation of antidotes (CRR) was set up at the University Hospital of Ferrara. The CRR is responsible for the organization of a network (hub and spoke) in all regional health authorities for the management of antidotes, and also provides guidelines for the proper use of antidotes in the same region through a regional website. The aim of the Centre is to provide antidotes to all health centers in the region, constantly monitoring the supply and the use of antidotes themselves. The objective of this study is to describe how the allocation of antidotes to health care organizations in RER changed after the activation of the CRR.

Methods: The CRR has proposed and shared with the 18 regional health authorities a list of antidotes; this list has been prepared taking into account: the type of poisoning found in the region in the period 2005–2009, the maximum dosage, the antidote amount required for the complete treatment of an adult and the first dose required. After the release of this list to the regional health authorities, the change in quantitative / qualitative supply of stocks in the RER between the years 2011 and 2012 has been measured.

Results: In the first two years of the CRR for the allocation of antidotes in RER there was an increase in the quality and quantity available of 19/28 (68%) of the stocks of antidotes with Priority A and an increase of 11/13 antidotes with priority B and also of 3/5 (60%) other antidotes. During the present period decreased allocations of the following antidotes Priority A: physostigmine, atropine, thiosulphate, digoxin immune fab (–18%), charcoal (–12%), fomepizole (–9%), ipecac (–6%). Among those with priority B flumazenil decreased by 12%.

Conclusion: These data indicate that in the RER, the role of the CRR for the allocation of antidotes improved resource allocation and allowed further rationalization. The reduction of storage, for some antidotes, has been motivated by storage of a single starter dose in each healthcare company.

249. Antidote availability in acute hospitals in Ireland

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Objective: The National Poisons Information Service (NPIS)/College of Emergency Medicine (CEM) in the United Kingdom (UK) issued joint guidelines for antidote stocking in emergency departments and acute hospitals in 2008. We examined whether the acute hospitals in Ireland complied with these recommendations.

Methods: We distributed a one page questionnaire to the chief pharmacists of all 36 acute hospitals in Ireland surveying the

availability and location of 40 drugs from the NPIS/CEM guidelines in 2011. It enquired as to whether the antidote was available immediately in the emergency department or available within one hour (i.e. within the hospital).

Results: We received completed questionnaires from 32 of the 36 hospitals (88.8%). Only 5 hospitals (15.6%) complied with both the availability and location requirements of these guidelines. A further 8 hospitals (25.5%) had all the antidotes available but not in the required location. Thirteen antidotes (32.5%) were available in every hospital (acetylcysteine, activated charcoal, atropine, calcium gluconate, dantrolene, diazepam, flumazenil, glucagon, methylene blue, naloxone, procyclidine, protamine sulphate and sodium bicarbonate). Worryingly, 10 hospitals (31.3%) did not stock any antidote for cyanide toxicity and 2 hospitals (6.3%) did not have an antidote for toxic alcohol poisoning. Eleven hospitals (34.4%) stock fomepizole, which is recommended by the CEM/NPIS guidelines as the antidote of choice in toxic alcohol poisoning. Neither of the 2 designated paediatric hospitals in Ireland held fomepizole. Antidotes for heavy metal poisoning which are recommended to be held at a supra-regional level are held in a surprisingly large number of sites: dimercaprol 10/32 (31.3%), penicillamine 18/32 (60.0%), sodium calcium edetate 11/32 (36.7%), berlin blue (prussian blue) 10/32 (31.3%). DMSA and DMPS are not available in Ireland. Pralidoxime is stored at 10 hospitals in Ireland (31.3%). Ireland does not have any native venomous species and there are no anti-venoms stored in Irish hospitals. A protocol exists for rapid access to supplies of anti-venom from the UK.

Conclusion: Most antidotes recommended in the NPIS/CEM guidelines are available in Irish hospitals. More antidotes need to be stored in the emergency departments rather than the hospital pharmacy to comply with the NPIS/CEM guidelines.

250. Summary of telephone enquiries relating to antidote exposures, graded as moderate or severe, that were received by the UK National Poisons Information Service between 01/04/2008 and 31/03/2012

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Objective: To analyse retrospectively telephone enquiries relating to exposures to agents also used as antidotes, graded as moderate or severe, received by the UK National Poisons Information Service (NPIS) between 01/04/2008 and 31/03/2012.

Methods: Data concerning all telephone enquiries received by the four UK NPIS Units in Birmingham, Cardiff, Edinburgh and Newcastle are entered into the United Kingdom Poisons Information Database (UKPID). Poisoning severity is assessed for all enquiries using the Poisoning Severity Score detailed in Persson et al, 1998.¹ All UKPID data relating to enquiries in which poisoning severity was graded as moderate or severe between 01/04/2008 and 31/03/2012 were retrieved and analysed with particular respect to exposures to agents also used as antidotes; 31 common antidotes plus trade names were searched for.

Results: The total number of enquires received by NPIS during the four-year period was 209,302, of which 9062 (4.3%) enquiries

were graded as moderate or severe. One hundred and eighty-nine (0.1%) related to exposures to common antidotes; only 21 related to adverse reactions or toxicity from the use of the agent as an antidote; 14 to acetylcysteine, 4 to methylthionium chloride and 3 to naloxone. No fatalities were reported. The majority (168) of reported exposures occurred due to overdose or recreational abuse of agents that are also used as antidotes e.g. procyclidine, ethanol, or requests for antidote administration advice. Of note 14 moderate or severe reactions to acetylcysteine were reported, 12 out of the 14 were female patients and features reported included angioedema, glossitis, dyspnoea, hypotension, T-wave inversion and tachycardia. Four moderate reactions to methylthionium chloride were reported, all patients were female and all showed symptoms of serotonin syndrome. However, one patient received an overdose of methylthionium chloride (9.5 mg/kg) and in another the use of methylthionium chloride was contraindicated as the patient was taking citalopram therapeutically.

Conclusion: This retrospective analysis demonstrates that moderate or severe reactions to agents administered as antidotal therapies do not constitute a significant workload for the UK NPIS.

Reference

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251. Metformin induced lactic acidosis reported to the New South Wales Poisons Information Centre

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Objectives: To review the incidence and symptomatology of metformin associated lactic acidosis (MALA) reported to the New South Wales Poisons Information Centre (NSWPIC).

Methods: A retrospective review was made to determine the number of metformin poisonings referred to toxicologists at NSWPIC from 2004–2011, their symptomatology and outcome. All toxicologist reports in this period were searched for the word “metformin” and the reports were examined to determine if it is related to a metformin overdose. Information regarding age, sex, dose, coingestants, intent, symptoms, treatment and outcome were recorded.

Results: There were a total of 74 cases of metformin poisonings identified from 2004 to 2011. There were 39 females, 31 males and 4 unknown. The median age was 39 ± 2.4 (interquartile range - IQR: 23–51). There were 69 intentional poisonings, four were accidental ingestions and 5 chronic poisonings. In the acute group, the median age was 39.5 ± 2.4 (IQR: 23–49.5). The median dose was 12 ± 2.3 g (IQR: 5–25 g) for intentional overdoses and 1 g for accidental ingestion. The median lactate level for the acute group was 4 ± 0.5 mmol/L (IQR: 3–6; range: 0.9–12). Only eight patients had ingested metformin alone, the others had multiple co-ingestants. Two patients (3%) received haemodialysis. One patient who took 70 g metformin with a reported lactate 6.5, pH 7.26 and the second patient ingested 105 g with a reported lactate of 12. The first patient was not followed up, while the second

patient had a good outcome with supportive treatment and haemodialysis. All five patients who had chronic poisonings received haemodialysis. The median age was 60 ± 5 (IQR: 52–75). The median pH was 6.7 ± 0.04 (IQR: 6.5–6.7) and lactate level was 22 ± 1 mmol/L (IQR: 19–23; range: 18–24). Gastrointestinal symptoms were present in 3/5 patients and 3/5 patients had a brief cardiac arrest. Of particular importance is that the diagnosis was uncertain in all five patients initially, 4/5 patients survived, one was not followed up.

Conclusion: MALA is uncommon in acute metformin poisonings but more common in chronic ingestions. The diagnosis of chronic metformin poisoning leading to MALA is often difficult on presentation.

252. Metformin-induced refractory vasodilatory shock successfully treated with methylene blue

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Swedish Poisons Information Centre, Stockholm, Sweden

Objective: Metformin poisoning may be associated with lactic acidosis and profound vasodilatation.^{1,2}

Case report: A 66-year-old man with diabetes mellitus and ischemic heart disease presented awake to the emergency department with shortness of breath and back pain. His blood pressure was 160/100 mmHg and pulse 100 bpm. History revealed tiredness for a month and increasing nausea and breathlessness for the last day. Before calling the ambulance he had vomited and developed back pain. Blood gas analysis displayed pH 6.9, base excess –30 and lactate 18 mmol/L. He was brought to the x-ray department for abdominal computed tomography, but deteriorated with a fall in blood pressure, insufficient breathing and unconsciousness. He was intubated and transferred to the intensive care unit. Echocardiography displayed normal contractility and hemodynamic pressure measurements revealed very low systemic vascular resistance. He received lots of fluids, sodium bicarbonate and vasopressors. Adrenaline and noradrenaline were given in high doses and vasopressin was later added without any apparent effect. The patient was oliguric and s-creatinine increased to 832 micromol/L. Continuous venovenous hemodialysis was started. Despite these measures, the mean arterial pressure (MAP) was < 50 mmHg and the lactate remained high for 20 hours. At this point, the fact that the patient was on metformin (1000 mg three times daily) became evident and the poison centre was contacted. Chronic metformin poisoning was diagnosed. It was decided to administer methylene blue. A bolus of 100 mg was given intravenously followed by an infusion of 0.1 mg/kg/h for 24 hours. The effect was remarkable. Within 15 minutes of the bolus, MAP increased by 15 mmHg and the lactate started to decrease. The vasopressors could be phased out and four days later the patient was extubated. During the following day he was confused but thereafter recovered.

Discussion: Methylene blue, a guanylate cyclase inhibitor, has been proven effective as a vasopressor in many conditions associated with profound vasodilatation. There is one previously reported case of metformin poisoning in which methylene blue was successfully used.²

Conclusion: Methylene blue may be effective in metformin-induced refractory vasodilatory shock.

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253. Lactic acidosis and metformin: Intoxication or adverse effect?

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Objective: The causal association between metformin treatment and lactic acidosis remains controversial. The frequent presentation of acidosis as an epiphenomenon of another pathology leading to renal insufficiency, and the low number of cases in which metformin quantification has been performed, makes it difficult to be precise about the degree of responsibility of this medicine in this severe biochemical alteration. We present a series of 8 patients, in which the ingestion of metformin coexists with a severe metabolic acidosis, showing the relation between pH, lactate and plasma levels of metformin, and discussing the importance of making an early diagnosis and treatment.

Case series: We have studied the clinical and analytical characteristics of 8 patients attending the intensive care unit (ICU), in the last 12 months, with a clinical picture including metabolic acidosis, in which metformin implication was suspected. Only one (male, 22 year-old) was due to a suicidal ingestion and presented the lowest metformin plasma level (5 mg/L) and the best clinical outcome. The other 7 cases showed a completely different profile. They were 3 women and 4 men under standard metformin treatment for type II diabetes; mean age 70 years (range 61–81). The clinical picture developed after dehydration, due to vomiting or diarrhea, and some degree of functional renal failure, but no other causes of acidosis were found. All the patients had some degree of coma and six presented shock. Analytical data: mean pH 7 (range 6.80–7.27); mean lactate 16 mmol/L (range 4–45); metformin plasma concentration was available in 5 cases: 4.19, 5.03, 25.50, 44.80 and 45.10 mg/L. Haemodialysis was used in 6 patients. Two patients died.

Conclusion: It is important to bear in mind that metformin associated with lactic acidosis is not a rare event in aged diabetic patients. Due to the high number of prescriptions of metformin, it is imperative to include this possibility in the differential diagnosis of lactic acidosis in this kind of patient, where prognosis can depend on early treatment based on haemodialysis, not only to clear metformin itself, but also lactate.

254. Severe metformin-induced lactic acidosis: Case series of 10 patients

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Table 1. Summary of results.

	Median	Range	Units
Age	66	(51–82)	years
pH	6.9	(6.7–7.0)	
pCO ₂	2.7	(1.8–8.4)	kPa
Base deficit	29	(20–31)	
S-lactate	19	(6–22)	mmol/L
S-potassium	5.4	(4.7–8.6)	mmol/L
S-creatinine	677	(154–1176)	umol/L
S-metformin	330	(157–760)	umol/L

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Objective: Metformin is widely used to treat diabetes. A recent Cochrane review has indicated that there is no overrepresentation of lactic acidosis among metformin users. This conclusion has, however, been questioned by several clinical toxicologists and Poisons Information Centres. Data on 10 patients admitted for metformin-induced lactic acidosis is presented.

Methods: Ten patients with metformin-induced lactic acidosis admitted to our department or other departments where we have been consulted over a three-year period were included prospectively.

Case series: Ten patients with subacute metformin-induced lactic acidosis were admitted (Table 1). All episodes were preceded by pre-renal failure with dehydration causing metformin accumulation. Median age was 66 years and 5 were males. The median stay was 8 days (range 1–39) and 3 patients died. On admission, the median pH was 6.9, the median S-lactate level was 19 mmol/L, the median base deficit was 29 and the median pCO₂ was 2.7 kPa. The median S-creatinine on admission was 677 umol/L, the median potassium was 5.4 mmol/L and the median S-metformin level was 330 umol/L. All but one patient were treated with dialysis; two with intermittent hemodialysis, seven with continuous veno-venous hemodialysis and one with both.

Conclusion: Information regarding metformin use may not be present on admission as many patients are somnolent or in coma. Metformin-induced lactic acidosis must therefore be considered in patients admitted with metabolic acidosis of unknown origin and elevated S-lactate concentrations.

255. A case of cardiac arrest related to therapeutic use of metformin: Clinical and toxicological aspects

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Objective: Metformin is a biguanide oral hypoglycaemic agent used for diabetes mellitus. A concurrent disease may induce acute renal failure leading to metformin accumulation. Metformin can

cause severe complications such as severe lactic acidosis by suppressing pyruvate carboxylase.

Case report: A 66 year old woman presented at hospital anuric, suffering abdominal pain, vomiting and diarrhoea for three days. She had a history of Brugada syndrome, hypertension and diabetes treated with metformin. Arterial blood gas (ABG) showed severe metabolic acidosis (pH 6.88, HCO_3^- 2.7 mmol/L). Lactate was 11 mmol/L. Glycaemia and abdominal ultrasound were normal. Two hours after admission to the nephrology department, cardiac arrest occurred. She was successful resuscitated, intubated and transferred to the intensive care unit (ICU). At admission to ICU, ABG was: pH 6.74, HCO_3^- 4.5 mmol/L, lactate 20 mmol/L. Blood urea and serum creatinine were 303 (n.v. 11–49 mg/dL) and 11.9 (n.v. 0.7–1.3 mg/dL) respectively. Sodium bicarbonate 300 mEq was administered. Serum metformin was 40 micrograms/mL (upper limit < 2). Continuous veno-venous haemodiafiltration (CVVHD) was started despite a systolic pressure (50 mmHg with high dosage norepinephrine). Metformin concentration in serum and in ultrafiltrate was measured by high-performance liquid chromatography. The amount of metformin removed by the first CVVHD was 845 mg. Serum metformin, at the end of CVVHD (6 hours) was 26 micrograms/mL; ABG improved: pH 7.29, HCO_3^- 12 mmol/L. On day 2 a second CVVHD was performed (again 6 hours): the amount of metformin removed was 223 mg. CVVHD improved acid-base status: pH 7.32, HCO_3^- 21 mmol/L, lactate 3.2 mmol/L. On day 3 the patient became polyuric, with ABG normalized; metformin serum concentration was 2 micrograms/mL and lactate normal. Patient no longer needed CVVHD. The following days haemodynamic and renal function improved to normal and the patient became collaborative. She was transferred to a medical ward after 13 days and recovered without sequelae.

Conclusion: Metformin-related acidosis is a potentially lethal condition, especially occurring in the setting of acute renal failure. Early diagnosis, aggressive airway management, cardiovascular support, bicarbonate and early CVVHD can result in successful outcome.

256. Severe metformin poisoning survived by continuous venovenous hemofiltration and extracorporeal membrane oxygenation

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Objective: To report a case of metformin poisoning and discuss treatment options.

Case report: Metformin is a biguanide antihyperglycemic drug, widely used in type 2 diabetic patients. Compared with other antihyperglycemic drugs, such as sulfonylureas, thiazolidinediones and insulin, there are fewer side effects of hypoglycemia. However, the severe toxicity of metformin had been reported to be associated with lactic acidosis. We present a case of a 61-year-old man with a history of type 2 diabetes who ingested over 20 grams of metformin in a suicide attempt. He was sent to the emergency department about 4 hours later with consciousness disturbance, acute renal insufficiency and severe lactic acidosis. Profound

hypotension was also noted and blood pressure (BP) dropped to around 60/40 mmHg within 2 hours of arrival. Compensated metabolic acidosis was noted and the blood gas analysis showed: pH 7.219, PCO_2 38.2 mmHg, HCO_3^- 15.3 mmol/L, base excess –12.5 mmol/L. Other lab data were as follows: lactate 254.95 mg/dL, glucose 498 mg/dL, ethanol < 10 mg/dL, serum creatinine 1.7 mg/dL, anion gap 15, and osmolar gap 10. The lactate acidosis seemed incompatible with the severity of the patient's condition. However, shock was not improved even under aggressive hydration plus inotropic agents, and his BP remained around 60/40 mmHg. Due to his grave cardiovascular condition, extracorporeal membrane oxygenation (ECMO) was performed and the patient was transferred to our hospital. ECMO with continuous venovenous hemofiltration (CVVH) was used for seven days. The vital signs were stabilized from the 3rd day after initiating ECMO and CVVH. Consciousness recovered to full Glasgow Coma Score on the 5th day. Finally, the patient was extubated and discharged 2 months later. The blood metformin levels were measured, and the initial level was 222 µg/mL at the 32nd hour after exposure. The clearance of metformin (CL) [$\text{CL} = k_e \text{Vd} = C_0 \text{Vd}/\text{AUC} = \text{A}/\text{AUC}$] was calculated to be 52.44 mL/min, which was under first order elimination with its half-life being around 13 hours.

Conclusion: In this case, initial metabolic acidosis did not correlate well with the clinical severity. The refractory shock may have been due to the cardiovascular effect of metformin. However, aggressive ECMO plus CVVH could be a good choice of treatment for severe metformin poisoning.

257. Methotrexate toxicity treated with continuous venovenous hemofiltration and leucovorin

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Objective: High-dose methotrexate (MTX) therapy may produce acute kidney injury (AKI), further impairing MTX elimination. Glucarpidase significantly reduces MTX concentrations. However, when MTX concentrations remain elevated despite glucarpidase in patients with AKI continuous venovenous hemofiltration (CVVH) may enhance MTX elimination without the hemodialysis-associated rebound that results from the large volume of distribution (Vd) of MTX.^{1,2}

Case report: A 79 year-old man with diffuse large B-cell lymphoma and central nervous system involvement received 12 mg of intrathecal MTX and 6,195 mg (3.08 g/m²) of intravenous MTX on hospital day (HD) #1 and HD#4, respectively. Approximately 34 hours after intravenous MTX, his serum concentration was 59.05 micromol/L, and his creatinine doubled to 178.6 micromol/L. Urinary alkalization and leucovorin reduced the MTX concentration to 11.06 micromol/L. Pancytopenia on HD#7 was treated with red blood cell and platelet infusions. Intravenous glucarpidase 4,000 units was given within 96 hours of MTX, and leucovorin dosing was increased. On HD#8, serum MTX decreased to 0.81 micromol/L; creatinine was 312.1 micromol/L. Although MTX and creatinine then trended down, fluid overload ensued, and intravenous hydration was reduced. On HD#14 MTX increased from

0.51 micromol/L to 0.63 micromol/L and continued rising. CVVH was initiated on HD#17 for AKI and to improve MTX clearance. Inflow and outflow MTX concentrations were 0.74 micromol/L and 0.58 micromol/L, respectively on HD#18, and 0.15 micromol/L and 0.15 micromol/L on HD#20. MTX concentrations declined to 0.09 micromol/L on HD#23 and 0.06 micromol/L on HD#24. CVVH was stopped upon discovery of an expanding subdural hematoma and lymphoma in acute leukemic phase. He was made do-not-resuscitate (DNR) and expired on HD#25.

Conclusion: While an uncommon adjuvant treatment for MTX toxicity, CVVH can help eliminate MTX from the serum and provide renal replacement. In this case, CVVH at initiation resulted in clearance of 64.9 mL/min and an extraction ratio of 0.21. MTX clearance and extraction were negligible at 0.15 micromol/L. One possible explanation is that low MTX concentrations may provide an insufficient gradient for removal.

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258. Increased serum osmolality and metabolic acidosis following massive γ -hydroxybutyrate consumption

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Objective: γ -hydroxybutyrate (GHB) and its precursors, 1,4-butanediol or γ -butyrolactone (GBL), are common causes of central nervous system and respiratory depression resulting in emergency department (ED) presentation. Although there are typically no consequential lab abnormalities, severe metabolic acidosis can occur.

Case report: Following a party, a 46-year-old man who recreationally used GHB drank a blue liquid left on a table. Immediately following ingestion he reported that it tasted like GHB, and shortly thereafter became unresponsive. The emergency medical services (EMS) noted a Glasgow Coma Scale score of 4/15 and a pulse of 40/min. Vital signs in the ED were: blood pressure 77/44 mmHg, heart rate 63/min. He was intubated for airway protection shortly after arrival and laboratory values included: arterial blood pH, 7.17 and PCO₂, 50 mmHg; anion gap, 9 mmol/L; measured serum osmolality, 330 mOsm/kg, osmol gap, 34 mOsm/kg. Four hours after presentation his arterial blood pH was 7.16 and PCO₂ 30 mmHg. His serum showed bicarbonate, 11 mmol/L, anion gap, 30 mmol/L, osmol gap, 3 mOsm/kg and lactate, 1 mg/dL. Serum ethanol, ethylene glycol, and methanol concentrations were negative. Urine sampled 7 hours after presentation showed GHB 7400 micrograms/mL. The patient underwent hemodialysis (HD) for metabolic acidosis. Post HD labs showed arterial blood pH, 7.41 and anion gap, 16 mmol/L. His urine GHB concentration 44 hours post presentation was 18 micrograms/mL. The patient was extubated on hospital day (HD) #5 and discharged on HD#9.

Conclusion: Prior work suggests GBL can increase serum osmolality.¹ GBL is metabolized by lactonase to GHB, an unmeasured anion that increases the anion gap.² While a high urine GHB concentration was noted in this case, the initially elevated osmol gap followed by the wide anion gap acidosis may suggest that the ingested agent was an osmotically active precursor, namely GBL.

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259. Ketamine and midazolam for procedural sedation prevents respiratory depression in life-threatening aspirin toxicity

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Objective: The ability of aspirin to cross the blood brain barrier (BBB) is partially dependent on serum pH. Since aspirin is a weak acid, an acidic environment favors its non-ionized form that more readily crosses the BBB and exerts its toxic neurologic effects. In severely poisoned patients, agitation is a challenge as procedural sedation is frequently necessary to safely secure venous access for hemodialysis. Unfortunately, sedative use often causes respiratory acidosis from hypoventilation. We present a case of severe aspirin toxicity in which ketamine and midazolam were used for sedation to safely place a dialysis catheter for definitive treatment.

Case report: A 16 year-old girl was transferred to our institution after an intentional aspirin ingestion. At the first hospital, her initial serum concentration was 104 mg/dL; her pH was 7.5 and PCO₂ was 23 mmHg. A sodium bicarbonate infusion was started, but activated charcoal was not given due to altered mental status. She was transferred 9 hours after the ingestion for hemodialysis. Her vital signs were: BP, 145/59 mmHg; pulse, 153/min; respirations, 24/min, temperature, 36.2°C; and oxygen saturation, 100%. Physical examination revealed an agitated girl. She was tachycardic, tachypneic, and hyperpneic. Her lungs were clear, and her examination was otherwise normal. Procedural sedation for dialysis catheter placement utilized intravenous ketamine (50 mg) with intravenous midazolam (2 mg). Prior to sedation, the patient received an intravenous bolus of sodium bicarbonate (1 mEq/kg). A venous blood gas drawn during insertion of the catheter showed: pH, 7.61; PCO₂, 24 mmHg; and PO₂, 90 mmHg. Her sodium bicarbonate infusion was titrated to a serum pH of 7.5; she received a dexmedetomidine infusion until completion of dialysis. Her mental status and vital signs normalized, and her post-dialysis salicylate concentrations were followed until undetectable.

Discussion: Because most sedative agents cause hypoventilation, a combination of intravenous ketamine and midazolam was chosen due to its anticipated ability to better preserve respiratory drive. With a pre-sedation intravenous bolus of sodium bicarbonate,

this sedative combination allowed the patient to maintain her ventilatory drive.

Conclusion: Ketamine and midazolam may be a safe option for sedation in patients with salicylate toxicity as demonstrated in this patient's preserved alkalemia during procedural sedation.

260. Methylene blue used in the treatment of refractory vasoplegic shock resulting from severe quetiapine poisoning

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Objective: Methylene blue (MetBlue) inhibits nitric oxide synthase and guanylate cyclase as well as scavenging endothelial nitric oxide, decreasing vasodilation and increasing responsiveness to vasopressors. It is reported to improve haemodynamics in vasoplegic shock from various causes including septicaemia¹ and post-cardiac surgery². Reports of use in overdose are limited.³ We describe the use of MetBlue to treat a case of refractory vasoplegic shock following quetiapine poisoning.

Case report: A 41 year-old male presented following reported ingestion of 18 g extended-release quetiapine, 10 g controlled-release carbamazepine, 240 mg fluoxetine, 35 g enteric-coated sodium valproate, 375 mg oxazepam. He was comatose, intubated on presentation. Progressive hypotension developed. Electrocardiogram (ECG) revealed sinus rhythm, rate 82 bpm, QRS 120 msec, QT-interval 536 msec. Echocardiogram revealed a hyperdynamic left ventricle, suggesting vasoplegic shock. The patient remained hypotensive despite intravenous fluid-boluses, escalating infusion of metaraminol, noradrenaline and vasopressin. Hypotension was made worse after a single-dose of intravenous adrenaline (100 micrograms) with systolic blood pressure falling to 50 mmHg. Arterial blood gas revealed worsening metabolic acidemia and rising lactate (peak 13 mmol/L). At this point, MetBlue was administered as loading-dose of 1.5 mg/kg and continuous infusion (1.5 mg/kg/h for 12 hours, then 0.75 mg/kg/h for 12 hours). Rapid improvement in haemodynamic parameters and weaning of vasopressors resulted in the hour following the loading-dose. Serum quetiapine concentration was 18,600 ng/mL (30–160 ng/mL), collected at time of peak toxicity. Serum valproate concentration peaked at the same time and was 1221 micromol/L (300–700 micromol/L). Serum carbamazepine concentration was in the therapeutic range.

Conclusion: Severe quetiapine poisoning produces hypotension primarily from alpha-adrenoreceptor antagonism. Worsening hypotension has been reported previously following adrenaline administration. MetBlue may have utility in the treatment of vasoplegic shock resulting from quetiapine poisoning refractory to standard vasopressor therapy.

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261. Naloxone is overused in elderly patients in the prehospital setting

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Objective: Naloxone is often used prehospitally in elderly patients to assist in the diagnosis of those with altered mental status. Many clinicians would argue that the only appropriate prehospital use of naloxone is to improve ventilatory status. We sought to determine what percent of naloxone administrations in elderly patients are for hypoventilation and altered mental status and how often it has a positive outcome.

Methods: Setting: A large, suburban, two-tiered emergency medical services (EMS) system with approximately 25,000 Advanced Life Support (ALS) requests per year. Design: Retrospective cohort study. Population: Consecutive patients age 60 and over treated prehospitally with naloxone over a 60-month period. Vital signs on initial ALS evaluation and on arrival in at the emergency department (ED) were recorded. *A priori*, hypoventilation was defined as an initial respiratory rate (RR) < 10 or a pulse oximetry < 92%. A positive response to naloxone was defined as an increase of 4 or more breaths per minute or final pulse oximetry over 95% in a patient that was not intubated. Altered mental status (AMS) was defined as having a Glasgow Coma Score (GCS) of less than 14. Percentages and 95% confidence intervals (CI) were calculated.

Results: Of 105,183 ALS requests, 230 (0.2%) were for patients 60 years or older that were given naloxone. 92% (CI: 88, 95) had a dispatch category other than Ingestion or Overdose. 84% (CI: 78, 89) had an initial GCS less than 14. Only 22% (CI: 16, 27) of patients were hypoventilating at the time of naloxone administration. All of these hypoventilating patients also had an AMS. Of the hypoventilating patients with AMS, 16% (CI: 6, 26) had a positive response. Of all the patients age 60 or over that were given naloxone, only 4% (CI: 1,6) had a positive response.

Conclusion: More than 75% of elderly patients treated with naloxone are not hypoventilating, suggesting that it is being administered for other reasons - probably altered mental status. When used in elderly patients with AMS and hypoventilation, one-sixth improve. Overall, only 4% of patients age 60 or over given naloxone seem to improve, suggesting it is being overused.

262. Renal replacement in dabigatran intoxication

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Table 1. Laboratory parameters in a case of dabigatran intoxication.

Day	0 (OR)	1 (ICU)	2 (ICU)	3 (ICU)	Reference
APPT	–	>5.00	>5.00	>5.00	0.83–1.23
INR	>7.5	4.0	2.9	1.7	<1.2
Platelets	532	197	127	63	145–390*10E9/L
Creatinine	149	126	119	68	60–105 micromol/L
GFR	39	48	51	>90	>60 mL/min
Thrombelastograph (TEG®), R-time	94	80	50	21	3–8 min
RBC	14	22	11	5	unit
FFP	10	28	15	7	unit
Platelet concentrate	2	8	3	2	unit
Continuous renal replacement therapy	–	+	+	+	

Objective: Bleeding related to dabigatran carries a high risk of morbidity and mortality, and currently there is no specific antidote. Dabigatran is predominantly renally eliminated, and in case of renal failure, renal replacement therapy (RRT) has been suggested. We present a case of dabigatran intoxication symptomatically treated with RRT.

Case report: 79 year-old man, atrial fibrillation treated with dabigatran (150 mg x2/day) and mild chronic obstructive pulmonary disease (COPD), but otherwise in good health and self-reliant; hospitalized due to low-level fall and respiratory failure. After one week renal failure and gastrointestinal bleeding developed, and total colectomy due to colonic ischemia was performed. Massive bleeding developed during surgery, clotting showed severe coagulopathy related to dabigatran intoxication and massive transfusion was required. On arrival in the intensive care unit (ICU), bleeding was surgically controlled, but dabigatran induced coagulopathy was still present augmented by the renal failure (Table 1). RRT due to anuria and attempting to increase dabigatran elimination was initiated without further anticoagulation (continuous veno-venous haemodialysis (CVVHD), NxStage1, CAR500, blood flow 100–300 mL/min, fluid exchange 2000–4800 mL/hr). Later on ICU day 1 re-do surgery was performed due to increasing abdominal pressure, and massive and coagulopathic bleeding was observed but no obvious surgical bleeding. Massive transfusions were given and supportive prohaemostatic treatment with recombinant factor VIIa was considered but not administered due to the thromboembolic condition. On ICU day 3 re-do surgery revealed increasing intestinal ischaemia and coagulopathic bleeding incompatible with survival.

Conclusion: Despite three days of CRRT and several exchanged blood volumes, the effect of dabigatran intoxication (severely prolonged APPT and thrombelastograph R-time) was unexpectedly still present.

263. Lactate as a guide in nitrite treatment of hydrogen sulfide poisoning

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Objective: Hydrogen sulfide poisoning can occur in occupational exposure. It is treated with supportive care and antidotal therapy

with sodium nitrite. We report a case of hydrogen sulfide poisoning resulting in change in consciousness and lactic acidosis. Nitrite therapy was guided by lactate level.

Case report: A 32-year-old male presented with rapid loss of consciousness - “knock down” - while entering asphalt tanks. On presentation to our emergency department (ED), his vital signs were heart rate of 114 beat per minutes, respiratory rate of 29 per minutes, blood pressure (BP) of 189/102 millimeters of mercury (mmHg), and Glasgow Coma Scale of E1V4M5. He appeared with some blackish material coated on his clothes, bilateral eye conjunctivitis and a rotten egg odor. The blood gas analysis revealed: pH 6.935, pCO₂ 75.8 mmHg, O₂ 86.8 mmHg, and HCO₃ 15.7 mmol/L. We intubated him, performed external and internal decontamination, and started antidotal therapy with a slow infusion of sodium nitrite (300 milligram). The lactate level before nitrite therapy was 96.4 mg/dL. Thirty minutes after nitrite therapy, we rechecked lactate and it had decreased to 49.9 mg/dL. Another half dose of sodium nitrite (150 mg) was then given. His BP dropped during the second nitrite infusion and we gave him fluid challenge and norepinephrine infusion. About 30 minutes after nitrite infusion, we rechecked lactate level and the result was 29.6 mg/dL. The patient was then moved to the intensive care unit (ICU) for care. He regained consciousness without obvious neurological deficit in ICU. However, extracorporeal membrane oxygenation (ECMO) was initiated for acute pulmonary edema and following acute respiratory distress syndrome (ARDS).

Conclusion: Hydrogen sulfide poisoning can induce lactate acidosis due to cellular hypoxia. Antidotal therapy with sodium nitrite may be guided by the lactate level. In addition, in patients with toxin related ARDS, ECMO could be life-saving.

264. Naloxone used to prevent intubation in a patient with severe hepatic encephalopathy

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Background: Elevation of plasma opioid peptides occurs in animal models of hepatic encephalopathy (HE). We present a case of a patient with severe HE due to alcoholic cirrhosis whose respiratory depression and depressed mental status improved following naloxone.

Case report: A 58-year-old man with a history of alcoholic cirrhosis and benzodiazepine use discontinued lactulose and rifaximin three days prior to presentation. The night prior to presentation, he developed total body tremors and jerking for which he self-administered alprazolam 10 mg. The following morning he was lethargic and presented with a respiratory rate of 6–8 breaths/min, a blood pressure of 113/57 mmHg, pulse of 68 beats/min, an oxygen saturation of 100% on 4 L. Physical examination revealed 3 mm reactive pupils, minimal response to sternal rub, normal breath and bowel sounds, and no evidence of track marks. His family reported no access to opioids. Flumazenil was avoided due to his history of

benzodiazepine use. Following the administration of naloxone 0.04 mg followed by 0.08 mg intravenously (IV) the patient awoke and began answering questions. His respiratory rate increased to 12–15 breaths/min. A naloxone IV infusion was initiated at 0.06 mg/hr and the patient was given 2 doses of lactulose. Laboratory values were significant for ammonia of 73 $\mu\text{mol/L}$, glucose of 217 mg/dL, an anion gap of 10, and urine toxicology screen that was positive only for benzodiazepines and a blood alcohol level was negative. Ten hours later, his mental status and respiratory rate remained normal and the naloxone infusion was discontinued. He denied taking any opioid containing medication.

Discussion: Organic toxins found in patients with HE may stimulate opiate receptors. This case suggests that opioid effects were reversed with naloxone with improvement of HE, preventing intubation and an intensive care admission.

Conclusion: IV naloxone may be useful for the reversal of respiratory depression associated with HE.

265. On the phone medical dispatching of acutely self-poisoned patients: A three-year retrospective study

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Objective: Telephone control of medical dispatching for poisoned patients is a complex task because of the dynamic course of acute poisoning and the difficulties in anticipating deterioration of patient condition. Our aim was to review the different pre-hospital pathways in poisoned patients' care and to assess dispatch accuracy.

Methods: We conducted a three-year retrospective study in a University hospital. Emergency phone calls relating to patients over 18 y/o with acute drug self-poisoning were included. Calls were answered by senior emergency physicians who could either dispatch paramedics from the emergency medical services (EMS) or a mobile intensive care unit (MICU) to the scene. According to on-scene patient evaluation, patients were taken either to the emergency department (ED) or directly to an intensive care unit (ICU). Therefore, we defined two efficient medical dispatches: a paramedic pathway, with patients being taken to the ED without any intensive treatment; a MICU pathway, with patient transferred directly to the ICU or being treated with an antidote in the pre-hospital setting. Others pathways were considered as inappropriate. Epidemiological, toxicological and clinical data were recorded. A logistic regression analysis was used to detect risk factors for inappropriate pathways.

Results: 2218 patients were included. Median age was 41 y/o [30; 49] and 63% were women. Benzodiazepines and other sedative drugs (77%) were the most frequently ingested drugs followed by neuroleptics (18%) and acetaminophen (12%). MICU was dispatched following 309 (14%) calls and 329 (15%) patients were admitted to ICU, either directly (9%) or after ED admission (6%). Two thousand and nineteen (91%) patients were included in the appropriate pathway. Dispatchers underestimated clinical severity in 124 (6%) calls and overrated it in 75 (3%). Male gender [OR: 2.6; CI: 1.3–4.7], significant comorbidities [OR: 8.1; CI: 3.0–21.8]

and neuroleptics intake [OR: 2.0; CI: 1.1–3.8] were associated with underestimation.

Conclusion: On the phone dispatch of patients acutely self-poisoned with drugs is accurate when provided by an emergency physician. However, 6% of emergency calls lead to risk underestimation and delayed ICU admission. When making a decision, medical dispatchers should pay attention especially to gender, past medical history and drug class intake to evaluate the patient's condition properly.

266. Whole bowel irrigation indications in poison control centre overdose patients

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Background: Whole Bowel Irrigation (WBI) for toxicologic patients has a number of specific indications. Few studies have assessed the poison control centre (PCC) usage of this gastric decontamination method. The objective of this study is to assess the types of indications that WBI is used in a busy PCC.

Methods: This was a prospective, Institutional Review Board (IRB) approved study over a 3 month duration at a busy PCC with an annual call volume of 80,000. The inclusion criteria were poison center patients, patients with a toxicologic emergency, and patients that met an American Academy of Toxicology (AACT) WBI position paper indication for the use of WBI. Upon study enrollment, WBI procedures were explained by phone to a health practitioner. In addition, the PCC attempted to fax WBI directions in each case. Data collected included patient demographics, overdose information and WBI information.

Results: 22 patients were enrolled. 73% were male with a mean age of 28.8 years. Indications for WBI included were: ingestion of a substance poorly adsorbed by charcoal-41% (lithium accounting for 77%); ingestion of enteric-coated or sustained-release drug-32%; ingestion of a foreign body-27%; and ingestion of a massive overdose-0%. 95% of cases involved intentional ingestions.

Conclusion: WBI is an uncommonly used and labor intensive procedure recommended in specific toxicologic patients. The most common indication was for substances that were poorly adsorbed to charcoal.

267. Implementation and evaluation of high-fidelity simulation cases for the acutely poisoned patient: An inter-professional approach

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Objective: Teamwork and inter-professional collaboration are now common activities within health care, and are expected to be included within the education of all health care professionals.¹

Because many poisonings are rare clinical occurrences, there is limited opportunity for health-care trainees to practice a collaborative approach to the management of these patients. This study aims to examine the medical knowledge and attitudes of health-care trainees before and after a high-fidelity simulation exercise.

Methods: Faculty from the School of Medicine, the School of Pharmacy and the San Francisco Division of the California Poison Control Services (CPCS-SF) collaborated with the Kanbar Simulation Center to develop two simulated patient exercises: 1. Severe agitation and hyperthermia due to methamphetamine overdose and 2. A calcium channel blocker overdose. The exercises were integrated into the existing curriculum of the CPCS-SF medical toxicology elective. In each simulation, an inter-professional team consisting of medical students or residents and pharmacy students worked together to render appropriate therapies and resolve the case. Trainees were given a survey to complete before and after the simulation to assess knowledge acquisition and attitudes towards inter-professional care.

Results: From October 2011 to November 2012, 47 pre-simulation surveys and 43 post-simulation surveys were completed. Pre-simulation, 13 (27.7%) felt comfortable with managing severe agitation vs 20 (46.5%) post-simulation. There was an increase in those who believed clinical pharmacists should assist in differential diagnosis and management pre-simulation (25, 53.2%) and post-simulation (35, 81.4%). There was also an increase in understanding the term "closed-loop communication" before and after the simulation (74.5% vs 97.7%). Post-simulation, 40 (93%) rated the experience as "valuable" or "highly valuable".

Conclusion: High-fidelity simulation cases are a potentially useful adjunct to medical toxicology and inter-professional education. Participants reported increased confidence in the management of severe agitation. They also appeared to gain a better understanding of the role of the clinical pharmacists in the management of acutely poisoned patient as well as the idea of "closed-loop communication".

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268. Rabies: Are we aligned with the international and national guidelines?

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Objective: Rabies exposures in humans are associated with bites or scratches by rabid animals. Post-exposure prophylaxis (PEP) must be applied (according to the international guidelines) with prompt administration of vaccine alone or combined with human rabies immunoglobulin (HRIG). Incorrect PEP is related to a fatality rate of nearly 100%. Rabies is not endemic in Italy, and only a few cases are detected annually in wild animals in

the north-east regions. Nevertheless, in the last 5 years, 22 cases of potentially rabid patients were presented to the Pavia Poison Control Centre (Pavia-PCC) for clinical management and vaccine and/or HRIG supplying. Five cases, involving travellers from other countries where rabies is endemic, required the rapid co-administration of vaccine and HRIG; in these cases the HRIG was unavailable in the relevant emergency departments (EDs), and it was difficult to find it all over the country. To improve the availability and supply of vaccine and HRIG in Italy, a national survey has been conducted.

Methods: In September 2012, the Pavia-PCC sent by email/fax to the Italian emergency departments (EDs) a questionnaire to evaluate (i) the existence of standardized procedures for the management of patients bitten by potentially rabid animals, (ii) the availability of HRIG and/or (iii) vaccine.

Results: Preliminary data from 116 EDs were analysed. In 68.2% neither procedure, nor vaccine nor immunoglobulins were present. In 29% a protocol for the management of potentially rabid patients was present; vaccine and HRIG, vaccine alone, and HRIG alone were present in 16.4, 12.0 and 3.4%, respectively. Vaccine and HRIG are mainly located (74%) in EDs of the north-east of Italy, where a periodic reappearance of rabies involving wild animals is registered.

Conclusion: Despite Italy being declared free from rabies since 1973, cases of imported rabies due to international travellers have shown an increase in recent years. Our preliminary data show a lack of uniform preparedness of EDs and a lack of active/passive immunisation in some potentially infected cases. A critical revision of the procedures for the fast treatment of potentially affected patients and a new specific storage system for HRIG and/or vaccines has now been adopted in Italy.

269. Medical practitioners and their poison

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Objective: Poisoning has always been regarded as a hidden art, practiced by the few murderers who would have their crime covered up by the ruse of natural death. The purpose of this review was to identify the doctors who have been convicted of murder by poisoning and to identify their poison of choice. This may help to identify trends for future prevention of clinicide.¹

Methods: A literature search was performed of Medline using the Pubmed interface. Results were reviewed by abstracts and if appropriate the original articles were electronically retrieved and studied. Citation searching was performed on all articles retrieved. The grey literature was also reviewed with regards to doctors who have murdered using poison.

Results: Thirty-seven doctors have been identified who have killed and who were convicted or strongly suspected of having murdered by the use of poison. Forty-three per cent of the doctors were punished by execution and 27% were imprisoned. The United States of America was the greatest source of medical murderers (13 doctors). Most of the murders were financially motivated (46%) and they were all committed by male doctors. Of the 37 doctors, they accrued a body-count of over 1500. Arsenic, opiates and cyanide were the drugs most commonly employed, with morphine being the most common. The body-count of the medical murderer is

much higher than the average non-medical serial killer. This is due to the easy access to drugs, the trust in the medical profession and the hidden aspect of the crime.

Conclusion: Looking at the trend of medical serial killers over the last century, there will soon be another case of medical serial murder. The only way to prevent this is by learning from the crimes that have already been committed.² This review has identified trends and characteristics of the medical murderer and may be employed

in the future to help us prevent doctors from becoming serial killers.

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