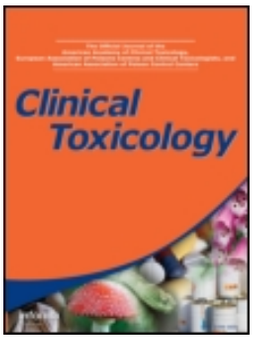

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ABSTRACTS

Abstracts of the 2011 International Congress of the European Association of Poisons Centres and Clinical Toxicologists, 24–27 May 2011, Dubrovnik, Croatia

1. GHB and its Analogues

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Discussion: Gamma-hydroxybutyrate (GHB) and its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (BD) are three compounds that emerged as recreational drugs among young people during the 1990s, mostly in some parts of Europe, the USA and Australia. GHB, BD and GBL are normally consumed as liquids but GHB also exists in crystalline form. Chemically GHB is a short-chained fatty acid, GBL is the corresponding lactone and BD is a diol. The precursor chemicals GBL and BD are rapidly converted to GHB in the body when ingested. They act completely as GHB within the organism. Furthermore, GHB can be easily manufactured from GBL and BD. The precursors are widely used in the chemical industry as solvents and are commercially available. The sodium salt of GHB, sodium oxybate is manufactured and licensed as a pharmaceutical drug for the treatment of narcolepsy. GHB, GBL and BD are used as recreational drugs due to their ability to induce euphoria, relaxation and anxiolysis. These drugs have several names among the users such as "Liquid ecstasy, G, GHB, Gamma-O, Blue Verve or Gobbe (swe)". The mechanism of action of GHB is similar to that of alcohol, barbiturates, and benzodiazepines. GHB is classified as a narcotic in most countries (Schedule II of the Convention on Psychotropic Substances) while GBL only in a few countries. Use of GHB and GBL is generally low but there is evidence of some sub-populations, settings and geographical areas, where it is commonly used, such as gay nightclubs in the UK and the USA. In other areas, such as in the Nordic countries it is more often used in private settings for purposes of recreation, bodybuilding and as a sleeping aid. Abuse of GHB is often mixed with other illicit drugs such as amphetamine, cannabis or cocaine, many times due to its strong ability to induce sleep. GHB has a steep dose-response curve where even a small increase in dose may cause nausea, vomiting, muscular jerks, hallucinations, amnesia and impaired consciousness. Both GHB and GBL are difficult to dose correctly with unpredictable effects, so, when consumed, an overdose is easily achieved. Patients who overdose GHB may present with hyperactivity, ataxia, confusion and aggression but also when larger amounts are taken deep coma, hypothermia, bradycardia and respiratory depression may be present. Severe overdose may finally lead to death, mainly due to hypoventilation, hypercapnia and hypoxemia. The depressant effect of GHB on the central nervous system is potentiated by alcohol, opiates and other sedative or anesthetic drugs. Most overdoses are accidental and account for a substantial proportion of acute emergencies admitted to hospitals related to illicit drugs. Pharmacologically, GHB acts mainly on dopamine release in a dose-dependent way. GHB acts at specific GHB receptors and at GABAB receptors. Small doses of GHB seem to increase the release of dopamine, while larger doses inhibit the release. GHB also inhibits norepinephrine release, increases the serotonin turnover and possibly increases endogenous opioid concentrations. The amount of GHB taken for recreational use is highly individual and development of tolerance is rapid. GHB is normally consumed as a liquid from a PET bottle where a cap normally contains around 2–3 g or 1 centiliter. Normal dosage is 0.5 to 1 g to achieve relaxation, 2–3 g for euphoria and 4–6 g for sleep. GHB dependence develops rapidly with regular consumption. Physical dependence may be seen already after 3 to 6 months of regular use. Finally, the users may be highly addicted with need for intake of GHB every 3 hours. In cessation of drug abuse GHB abstinence may present which is a severe clinical condition. GHB abstinence needs treatment in hospital for at least 3 weeks. First line treatment of abstinence is benzodiazepines in very high doses. *Conclusion:* Additional measures within the European Community and other countries seem to be necessary to control availability of the GHB precursors GBL and BD, to prevent further abuse of GHB.

2. Recent Advances in the Management of Opioid Toxicity

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Introduction: Opioid analgesic use is a significant cause of recreational, iatrogenic and deliberate self-poisoning in the community. Acute opioid analgesia toxicity commonly results in the toxidrome of reduced conscious state, bradypnoea and miosis and may result in death due to primary respiratory arrest. The application of basic or advanced life support measures to improve ventilation and oxygenation may be life-saving if administered in a timely fashion and should precede any antagonist therapy administration. *Discussion:* Opioid antagonists, such as naloxone, are well-known to effectively reverse the effects of opioid toxicity by competitive antagonism of opioid receptors in a dose-dependent manner. Naloxone is a relatively short-acting pure opioid antagonist (half-life less than 1 hour), widely used in the pre-hospital setting to reverse the effects of recreational opioid intoxication, in particular that related to heroin use. Longer acting antagonists such as naltrexone and nalmephene are also available but are not routinely used or recommended in the acute poisoning setting. Many patients presenting with suspected heroin intoxication are managed in the pre-hospital setting by paramedics administering naloxone by various routes with patients often refusing hospital transport. Recent recreational use and therapeutic abuse of prescription opioid analgesics seems to be increasing with a concomitant increase in the risk of adverse events related to the availability of these agents. As a result, it is important to be aware that when assessing patients with opioid toxicity, the toxic agent should be identified, the route of administration ascertained and the formulation of the drug confirmed. In view of the short duration of action of naloxone, reversal of acute opioid toxicity from a long-acting or sustained-release opioid analgesic without a prolonged period of observation may result in recurrence of toxicity that may require further antagonist administration by continuous infusion and/or ongoing respiratory support. Naloxone has a high first-pass metabolism with minimal oral bioavailability. As a result, it is administered by the intravenous (IV), intramuscular (IMI) or subcutaneous routes (SC). The response to naloxone is dose-dependent. Peak blood concentrations occur more quickly with IV administration but clinical response to IV and IMI have been reported as comparable when a larger IMI dose is used. In an attempt to reduce the risk of needle stick injuries to health care workers, particularly in the pre-hospital setting, a number of authors have reported success with intranasal (IN) naloxone administration in reversing opioid toxicity. Naloxone is best administered IN using a mucosal atomiser device (MAD) which achieves maximal exposure of the nasal mucosa to the drug. Intranasal drug administration is limited by the concentration and volume that can be delivered. Less than 1 mL is recommended as the maximum volume to each nares to prevent excess liquid escaping the nasal passage. The standard naloxone concentration for IV administration is 400 micrograms per mL. Using this concentration, 2.5 mL would need to be given to each nares to deliver 2 mg of naloxone. Studies reporting positive effects for IN naloxone have used higher concentrations of the drug (2 mg/mL) allowing for smaller volume administration to the nasal mucosa. Pharmacokinetic comparison of 2 mg doses of naloxone, using the 400 micrograms/mL concentration, by IV, IMI, IN routes to volunteers revealed bioavailability of 36% and 4% for the IMI and IN routes respectively. As a result, although positive clinical effects have been reported with the standard naloxone concentration by the IN route, higher concentration solutions are preferred to ensure more reliable absorption of naloxone. While IN administration of naloxone shows promise, further study is required to ascertain effectiveness, dosing and safety. Complications of opioid antagonist therapy include the induction of acute opioid withdrawal states, which may be induced by overzealous therapeutic administration of naloxone and with the use of other antagonists, such as oral naltrexone in attempts to undertake rapid opiate detoxification. Opioid-induced non-cardiogenic pulmonary oedema has also been described after naloxone administration, particularly in patients with significant hypoxemia and respiratory depression. Opioid antagonists' administration has been reported in isolated cases and case series of treatment of altered mental state in other acute poisoning scenarios (e.g. clonidine, valproic acid). To date, there is no good evidence to suggest that the use of opioid antagonists in non-opioid-induced sedative drug poisoning results in reliable improvements in mental state. Supportive care remains the mainstay of treatment for these situations. Finally, the orally active opioid antagonists, such as naltrexone, are reported to be effective in assisting the maintenance of abstinence in the chronic management of drug and alcohol dependence. *References:* 1. Wanger K, Brough L, Macmillan I, et al. Intravenous vs subcutaneous naloxone for out-of-hospital management of presumed opioid overdose. Acad Emerg Med 1998; 5:293–9. 2. Barton ED, Colwell CB, Wolfe T, et al. Efficacy of intranasal naloxone as a needleless alternative for treatment of opioid overdose in the prehospital setting. 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3. Hallucinogens - Disturbances of Perception, Mood and Thought

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Background: Hallucinogenic drugs (psychedelics), e.g. psilocybin-containing mushrooms and peyote cactus, have been used for several thousand years in religious, ritual and spiritual contexts to produce sensory distortions. The modern era started in 1943 with Albert Hofmann, who was unintentionally exposed to lysergic acid diethylamide (LSD) and experienced hallucinations. LSD was later marketed as the drug Delysid, used to treat several psychiatric disorders, including alcoholism. The development of new hallucinogenic drugs was frequently used to develop model psychoses. A large number of scientific papers on LSD were published from 1960 and onwards. From 1960–68 reports of LSD use were favourable, but reversed from that point to the present.[1] The term hallucination is derived from the Latin word *alucinari*, meaning 'to wander in mind or talk idly'. *Objective:* To provide a brief overview of the hallucinogens. *Results:* Hallucinogens are distinguished from other substances that produce hallucinations by inducing distortions of perception, mood and thought as a primary effect in the presence of an otherwise clear sensorium. Hallucinations are subjectively experienced sensations in the absence of an appropriate stimulus, but which are regarded by the individual as real. Illusions on the other hand are distorted perceptions of objects based in reality, so called misinterpretation of a real external, sensory experience. Hallucinogens have been divided into different classes; frequently occurring ones are, for example, phenethylamines (amphetamines), lysergamides (ergolines), tryptamines (indolalkylamines), arylcykloalkylamines (arylhexamines), piperazines, cannabinoids, harmine alkaloids, belladonna alkaloids and tropane alkaloids. In all these classification attempts, an additional miscellaneous group has always been needed, consisting of, for example, *Salvia divinorum*, nutmeg, kratom, and kava kava. Despite the differences in chemical structure these substances produce similar cognitive effects supporting the fact that most of these drugs are acting on several serotonergic receptors, mainly as partial agonists on central 5-HT2A-receptors found in vast amounts in the cerebral cortex.[2,3] The serotonergic effect is supported by the fact that high doses of lysergamides and phenethylamines work as partial agonists of 5HT2A-receptors. Despite the focus on serotonergic receptors, others are also important for drug-induced hallucinations, e.g. dopamine receptors, glutamatergic transmission, NMDA-receptors and maybe even kappa-receptors. The LSD molecule has the structures of both serotonin and dopamine, which may contribute to its strong hallucinogenic effect. A relatively new theory is the 'thalamic filtering' which includes interference of multiple neurotransmitters, e.g. dopamine, acetylcholine, GABA and glutamate. The thalamus receives signals from cortical regions and brain stem regions filtering relevant sensory input to the cortex. If there is a defect in the filtering process this could lead to an increased input of information in the end creating psychotic symptoms.[4] Today, the increase in recreational drug availability on the Internet has made it very easy and attractive for adolescents and young adults to use hallucinogenic drugs. Current popular recreational psychedelics are mainly cathinone derivatives and synthetic cannabinoids. Hallucinogens may produce clinical effects mediated by the locus coeruleus and include e.g. mydriasis, hyperactivity, ataxia, tachycardia, hypertension, seizures and hyperthermia. These symptoms occur shortly after ingestion and often precede the psychedelic effects. Physiologic effects are described as everything from mild symptoms to life-threatening. Lysergamides give rise to less prominent sympathomimetic symptoms than phenethylamines. LSD, the most famous of all hallucinogenic substances is a lysergamide derivative, and other lysergamides, e.g. lysergic acid hydroxyethylamide, occurs naturally in *Ipomoea spp*, *Argyreia nervosa* and *Rivea corymbosa*. A group with many derivatives is the tryptamines consisting of both synthetic (e.g. dimethyltryptamine (DMT)) and naturally occurring compounds (e.g. psilocybin, 5-methoxy-dimethyltryptamine (5-MeO-DMT)). The most widely known naturally occurring phenethylamine is mescaline, and main synthetic derivatives include the well-known MDMA (ecstasy), amphetamine and metamphetamine. Miscellaneous hallucinogens include *Salvia divinorum* (Salvinorin A and C), Kratom (mitragynin) and nutmeg (myristicin, elemicin). Arylcycloalkylamines are represented by ketamine, phencyclidine (PCP) and dextromethorphan (DXM). The psychological effects are mainly serotonergic and dopaminergic, and are dose dependent. The response is related to the person's mindset, emotions or expectations and can be influenced by the environment. It is common that symptoms include intensified sounds or visual disturbances. Hallucinations occur frequently and are normally visual, auditory, tactile and olfactory. One particular set of symptoms is the 'out-of body' experience that seems to especially occur with ketamine, phencyclidine and dextromethorphan. Adverse reactions are a common cause of seeking medical attention; these include psychiatric effects like psychosis and depressive reactions. Most hallucinogenic poisonings produce only mild or moderate symptoms, and treatment with benzodiazepines is normally sufficient when agitation, tachycardia, hypertension, seizures and hyperthermia occur. It is vital to protect the patients from external stimuli, e.g. noise and bright light. Antipsychotics have not fully been investigated as treatment of hallucinogen-induced agitation, especially haloperidol and risperidone may increase the possibility of inducing a hallucinogen perception disorder (HPPD). Long-term LSD use can lead to HPPD which is dominated by recurrent flashbacks leading to difficulties in social behaviour or work capacity. *Conclusion:* Internet access has increased the popularity of hallucinogens again and a large number of different hallucinogenic substances are widely available on the World Wide Web. Luckily, most of the poisonings with hallucinogens are only mild or moderate. *References:* 1. Abraham HD, Aldridge AM, Gogia P. The psychopharmacology of hallucinogens. Neuropsychopharmacology 1996; 14:285–98. 2. Aghajanian GK, Marek GJ. Serotonin and hallucinogens. Neuropsychopharmacology 1999; 21:16S-23S. 3. Marek GJ, Aghajanian GK. Indoleamine and the phenethylamine hallucinogens: mechanisms of psychotomimetic action. Drug Alcohol Depend 1998; 51:189–98. 4. Gaudreau JD, Gagnon P. Psychotogenic drugs and delirium pathogenesis: the central role of the thalamus. Medical Hypotheses 2005; 64:471–75.

4. Novel and Emerging Drugs: A Chemical Overview for the Toxicologist

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Objective: To give a simple overview of the chemistry of novel psychoactive substances that are currently being marketed on the Internet. The United Kingdom has witnessed a massive increase in Internet sales of so-called 'legal highs'. These are either single chemicals which are related to existing drugs of abuse or herbal materials which contain psychoactive natural products or have been adulterated with psychoactive compounds. These materials are outside of the UK 1971 Misuse of Drugs Act and the synthetic drugs are probably produced as close structural drug-analogues specifically to fall outside of this legislation but to retain the psychoactive qualities of the parent compound. In April 2010 the UK Government took the decision to control certain legal highs related to the natural product cathinone and these included mephedrone,[1] methylone and methedrone. This was quickly followed by the control of the related naphthalene analogue naphyrone. All of these compounds are analogues of cathinone, a plant-derived natural product from the popular stimulant *Catha edulis* (*Celastraceae*), which is used socially by various communities in the United Kingdom, East Africa and the Arabian Peninsula. *Results:* A wide range of new psychoactive drugs are appearing on the internet and are being sold in UK 'Head Shops' and these include chemicals which show high structural similarity to many controlled drugs of abuse categories. These include the phenethylamines (MDAI, 5-IAI, MDAT, MMDAT, benzofury, bromo-dragonFLY, D2PM), cocaine derivatives (dimethocaine, fluorotropacocaine), benzodiazepines (phenazepam), tryptamine analogues (5-MeO-AMT) and very worryingly, ketamine (methoxetamine) and phencyclidine-related compounds (e.g. 3 and 4-MeO-PCP). This lecture will describe the relationship between naturally-derived chemicals (natural products) and commonly used drugs of abuse and show that many of the legal highs which are appearing have close chemical structure to classical psychoactive drugs e.g. mescaline. Herbal materials such as Kratom (*Mitragyna speciosa*)[2] and Hawaiian Baby Woodrose (*Argyreia nervosa*)[3] are becoming increasingly popular. *Conclusion:* Further research on the true chemical identity of these materials and evaluation of their toxicology is urgently needed to understand the risks associated with the consumption of these materials. *References:* 1. Gibbons S, Zloh M. An analysis of the legal high mephedrone. Bioorg Med Chem Lett 2010; 20:4135–9. 2. McWhirter L, Morris S. A case report of inpatient detoxification after kratom (Mitragyna speciosa) dependence. Eur Addict Res 2010; 16:229–31. 3. Klinke HB, Müller IB, Steffenrud S, et al. Two cases of lysergamide intoxication by ingestion of seeds from Hawaiian Baby Woodrose. Forensic Sci Int 2010; 197:e1-e5.

5. Novel and Emerging Recreational Drugs: A Clinical Toxicology Perspective

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Background: The use of recreational drugs remains common, particularly amongst those who frequent the night-time economy (e.g. pubs/bars, nightclubs, discotheques). In addition to the use of classical recreational drugs, such as MDMA ('ecstasy'), cocaine, ketamine and amphetamines, over the last five to ten years there has been increasing use of 'novel psychoactive substances' (sometimes known as 'legal highs'). *Discussion:* The market for novel drugs is rapidly changing and the majority of novel drugs that have become available over the last few years fall into the following classes or groups of drugs: piperazines, cathinones, pyrovalerones and pipradrols. Some of these novel substances remain widely used over time, for example the cathinones, with the use of others declining due to a perception amongst users of a lack of the desired effects or unwanted effects associated with their use. The overall population prevalence of use of novel recreational drugs is not known, as large national/international population-based studies and reports, such as the British Crime Survey and the UN World Drug Report, do not enquire about these substances as they focus on established recreational drugs. There are a number of small sub-population surveys that have been undertaken, largely in the UK. These suggest that overall use of novel substances is high, particularly amongst clubbers, with use within the last month of drugs such as mephedrone (4-methylmethcathinone) being similar to that of established drugs such as MDMA and cocaine. Although some individuals may

choose to purchase and use these novel substances, others will be exposed to them when they are mis-sold a novel substance instead of the classical drugs that they had intended to purchase from a dealer. The challenge for the clinical toxicologist and others with a specialist interest in novel recreational drugs in addition to the identification of the compounds, is trying to determine the true pattern of acute toxicity associated with an individual novel substance. Firstly, as noted above, the individual presenting with acute recreational drug toxicity may not be aware that they have taken a novel drug. Secondly, the healthcare professional treating an individual with acute recreational drug toxicity who reports the use of a novel substance, may either not record this information appropriately or may mis-interpret what the individual has told them. This was commonly seen when individuals self-reported the use of mephedrone, which clinicians recorded as methadone (although similar sounding in name, the actions and toxicity of these drugs are very different). Thirdly, national data collection systems tend to be based around the World Health Organisation (WHO) International Classification of Diseases (ICD-10) system. This system does not have the flexibility to adapt in the short-term to include novel substances as they appear, and therefore will not capture acute toxicity associated with the use of novel substances. Finally, routine toxicological screening of biological samples (blood and/or urine) is generally not undertaken in the majority of patients presenting with acute recreational drug toxicity. Not only are detailed analytical results often not available in a time-frame to influence the management of that individual patient, but the robustness of the results is dependent on the quality and breadth of the existing analytical libraries. Therefore, initially the information available to clinical toxicologists, other clinicians and legislative authorities on the patterns of acute toxicity associated with the use of legal highs is often limited. Users will often report the desired and unwanted effects, sometimes in great detail with associated physiological parameters, they have experienced following the use of a novel substance. These are unsubstantiated in that no analytical information is available and the underlying rate of use of the substance is not known to determine the prevalence of unwanted effects. More detailed reports of the pattern(s) of toxicity associated with an individual novel recreational drug typically come from specialist hospitals/units seeing larger numbers of patients with recreational drug toxicity. Reports where confirmatory toxicological screening to confirm lone use of the suspected novel drug has not been undertaken have limited value in determining the pattern of acute harm associated with the novel substance. There is the potential that the individual may not have taken the drug that they self-reported, or they may have taken a combination of drugs, all of which will have contributed to the pattern of toxicity. Despite these issues, there have been numerous reports in the medical literature and to national and international drug monitoring centres (e.g. the European Monitoring Centre for Drugs and Drugs Addiction) on the patterns of acute harm associated with the use of novel drugs. Review of these cases appears to show that for the majority of the groups of novel recreational drugs (for example the cathinones, piperazines, pipradols and benzodifurans) the patterns of acute harm seen in individuals with confirmed use is similar to that seen with the use of classical sympathomimetic recreational drugs. Clinical features seen in individuals include agitation, psychosis, delirium, tachycardia, hypertension, chest pain and seizures. *Conclusion:* In conclusion, it is likely that the pattern(s) of acute toxicity/harm associated with the use of novel recreational drugs is broadly similar to that seen with classical stimulant recreational drugs and that utilisation of healthcare resources will be similar. It is important that clinical toxicologists, along with others groups with an interest in this area, continue to collate data on the patterns of acute harm associated with the use of novel recreational drugs, and that this data should be confirmed with systematic screening of individuals presenting with acute recreational drug toxicity to be able to determine the true pattern of toxicity associated with these drugs and ensure that both clinicians and legislative authorities are appropriately informed about the risks associated with their use.

6. New Drugs of Abuse: Acute Intoxication by Smoking Herbal Products Containing Synthetic Cannabinoids

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Objective: "Herbal" mixtures are advertised via the internet as legal alternatives to cannabis in several European countries. Since 2008 various synthetic additives have been identified in these mixtures, among them CP-47,497-C8, JWH-018, JWH-073, JWH-081, JWH-250 and JWH-122.[1] There is little or no information about acute toxicity of these compounds. We report on 13 ED patients with analytically confirmed consumption of synthetic cannabinoids. *Case series:* Thirteen patients (age 14–28 years, median 17.5; sex: 12 m, 1 f) had smoked products like 'Spice', 'Smoke', 'Jamaican Gold', 'Monkees go bananas' or 'Ninja'. Severity of poisoning was moderate (10) or minor (3). Consumption was analytically confirmed in serum samples (1–10 hours post ingestion) by using a liquid-liquid extraction followed by LC-MS/MS analysis as described by Dresen et al.[1] Finally, JWH-018 (7), JWH-081 (4), JWH-122 (4) and JWH-250 (4) were found. In case of monointoxication with JWH-018 tachycardia, dyspnoea, thoracic pain, changes of perception, hallucinations, agitation, somnolence, shivering, vomiting, and/or hypokalaemia were reported. Furthermore, consumption of JWH-081, JWH-250 and/or JWH-122 was associated with shaking, acute psychosis, generalized seizures, myoclonus, muscle jerking, muscular pain and moderate hypokalaemia of 2.9 mmol/L. *Conclusion:* Symptoms were similar in most cases to severe cannabis intoxication, but the occurrence of seizures and pronounced hypokalaemia is alarming. Since the synthetic cannabinoids found here act as cannabinomimetics and show much higher affinity to the CB1 receptor than Δ9-THC, they should be significantly more potent. Interaction effects cannot be excluded, since in a third of the presented cases at least 2 synthetic cannabinoids were detected. Development of dependence and tolerance was described after continued abuse of a product containing CP-47,497-C8 and JWH-018.[2] Therefore especially cannabinoid naive users may be vulnerable to toxic effects. *References:* 1. Dresen S, Kneisel S, Weinmann W, et al. Development and validation of a liquid chromatography-tandem mass spectrometry method for the quantitation of synthetic cannabinoids of the aminoalkylindole type and methanandamide in serum and its application to forensic samples. J Mass Spectrom 2011; 46:163–71. 2. Zimmermann US, Winkelmann PR, Pilhatsch M, et al. Withdrawal phenomena and dependence syndrome after the consumption of "spice gold". Dtsch Arztebl Int 2009; 106:464–7.

7. Clinical Identification and Analytical Confirmation of New Synthetic Cannabinoids Poisonings in Italy: Role of the Pavia Poison Centre in the National Early Warning System for Drugs of Abuse

Lonati D[1], Giampreti A[1], Petrolini V[1], Vecchio S[1], Papa P[2], Valli A[2], Bigi S[1], Buscaglia E[1], Mazzoleni M[1], Manzo L[1], Serpelloni G[3], Rimondo C[4], Locatelli C[1].
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Objective: At the end of 2008 the Department for Antidrug Policies - Presidency of the Council of Ministers (DPA) activated in Italy the National Early Warning System for Drugs (NEWS), within which the Pavia Poison Centre (PPC) has been identified as Coordinating Centre for the clinico-toxicological aspects. We report the cases in which the use of synthetic cannabinoids was related to specific analytical data, thus contributing to the endorsement of regulatory actions. *Case series:* Since 2008 the PPC has identified 10 cases (age ranging from 14 to 55 years) of laboratory-confirmed synthetic cannabinoid poisoning. In one case a herbal mixture named "Spice" was involved; the patient presented with agitation and confusion. In 6 other cases a herbal blend named "N-joy" was reported; JWH-018 was identified in the consumed products (in one case also confirmed in patient's blood). Clinical manifestations were tachycardia (6/6), agitation (6/6), confusion (5/6), hallucinations (4/6), dyspnea (1/6). In the remaining three cases a herbal pot-pourri named "Forest Green" was involved; JWH-250 and JWH-122 were identified by the laboratory in the product and JWH-250 was also detected in blood and urine samples of all the patients. These patients presented coma (2/3), seizures (1/3), psychomotor agitation (2/3), tachycardia (2/3), mydriasis (2/3), xerostomia (2/3), vertical nystagmus (1/3), and vomiting (1/3). All the patients received supportive/symptomatic treatment and benzodiazepines for neuroexcitatory effects. All patients were discharged asymptomatic within 24 hours from exposure; no sequelae were observed so far. *Conclusion:* The early PPC identification of "sentinel" cases contributed to identifying the health and social risks related to the use of cannabis substitutes masquerading as "herbal-blend". The laboratory confirmation on the residual product and patients (performed in a few hours) permitted the relationship between substances and clinical effects to be ascertained. This is crucial for permitting regulatory actions for prevention and control. In fact, these cases allowed the DPA and Ministry of Health to activate procedures to include these substances in the Italian list of drugs of abuse and illicit psychotropic substances. *Acknowledgement:* Study carried out with the support of Italian Department for Antidrug Policies - Presidency of the Council of Ministers (www.politicheantidroga.it)

8. Novel and Emerging Recreational Drugs: Routes of Supply and the Role of the Internet

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Background: The availability and patterns of use of recreational drugs changes over time, driven not only by changes in legislation to control these drugs, but also by changes in their availability and sources of supply. *Discussion:* In the latter part of the 20th century, the commonest drugs used recreationally included cocaine, ketamine and amphetamines including MDMA ('ecstasy'). Typically these drugs were sourced from street level drug dealers and they became controlled under relevant international and national legislation. In addition to these 'classical' drugs there has been an increase in the use and availability of novel and emerging recreational drugs (sometimes referred to as 'legal highs') over the last 5 to 10 years in Europe and many other areas of the world. This, together with the increase in the use of the Internet has changed not only the patterns of substances being used recreationally, but also the methods by which they are sourced and supplied. There have been a few studies that have assessed the sources of novel and emerging recreational drugs. These have shown that, although street level drug dealers are a source for some users, the Internet and high street 'head shops' are increasingly important, particularly when the drugs first become available. These studies have also suggested that the sourcing of drugs is age dependent. For example, use of the Internet to source drugs is uncommon in those aged under 16-18 years, probably as they do not have banking/credit cards to be able to order over the Internet. There are many hundreds of websites that sell novel and emerging recreational drugs to users. A number of

studies, including snapshot surveys carried out by the European Monitoring Centre for Drugs and Drug Addiction and through the Psychonaut project, have looked at these websites. The drugs are often sold under names such as "bath salts", "plant food" and/or labelled as "not for human consumption" or "research chemical". This marketing is to circumvent national and/or international drugs legislation. In addition, the websites and the packaging of these drugs often contain little information on the actual drugs being sold, the 'recommended' dose(s) or the risks of adverse effects associated with their use. In the early to mid 2000s it appeared that most of the websites were based outside of Europe, but increasingly these sites are now based in Europe. Most of the websites will ship orders across international borders, sometimes to countries in which the substance they are selling has been classified. These websites do not advise purchasers that they may therefore be putting themselves at risk of prosecution for possession of a classified drug. The majority of the sites are English-language based, but there has been a significant increase in the last two to three years of non-English language based sites. It appears that most of these novel drugs are manufactured in China and other areas of South East Asia. They are shipped into Europe and North America in bulk quantities and then may be packaged into smaller dose quantities before delivery to the user. There is also evidence of tabletting and encapsulation of these drugs within Europe prior to their supply to users. A number of studies have assessed the content of the novel and emerging recreational drugs supplied from both head shops and the Internet. These have shown that it can be difficult to purchase the same product month on month; therefore users have to frequently change the products that they are using putting them at risk of exposure to different drugs/compounds. Of more concern, the content of the products often changes over time; in one study up to 25% of products contained a different drug when supplied on a second occasion. Therefore if a user purchases what they think is the same product there is the potential that they will be using a different recreational drug with the inherent risk of associated toxicity. *Conclusion:* Finally, analysis of compounds purchased from both head shops and the Internet has shown that they often supply drugs that are classified. Therefore users purchasing drugs which they think are legal compounds may be purchasing illegal drugs and therefore putting themselves at risk not just of toxicity associated with their use but also of arrest and a potential criminal conviction if they are found in possession of the drugs.

9. The European Early Warning System: Responding to Novel and Emerging Recreational Drugs

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Objective: The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) provides the European Union and its Member States with 'objective, reliable and comparable information at European level concerning drugs and drug addiction and their consequences'. The epidemiological, statistical and technical information processed or produced by the Centre helps provide its audience with an overall picture of the drugs phenomenon in Europe. The Centre collects data on the overall drug situation, responses made by European Union Member States, and developments in policies and laws. An important aspect of the EMCDDA activities is the mechanism for the rapid exchange of information on new psychoactive substances that may pose public health and social threats (the Early Warning System/EWS[1]). *Objective:* The EWS is a multidisciplinary network which collects, appraises and rapidly disseminates information on new drugs. The identification and monitoring of emerging trends demands a different approach from the commonly used indicators for estimating levels of drug use, drug availability and associated problems. Therefore, the EWS builds on a variety of information sources such as health and care providers, law enforcement organisations, sources closer to drug users, media, the Internet, etc. This mechanism also provides for an assessment of the risks associated with these new substances. *Results:* A record number of new drugs (24) were officially reported in 2009 to the EMCDDA and Europol via the EU early-warning system. All of the new compounds were synthetic, including new 'designer medicines' - substances based on slight modifications of the chemical structures of medicines with known psychoactive properties.[2] In 2010, the number of new substances reported increased to more than 30. It can be anticipated that the concept of 'designer drugs', from those based on fentanyl in the 1980s, to ring-substituted phenethylamines in the late 1980s and tryptamines in 1990s, to piperazines and cathinone derivatives in the 2000s, will continue to change at an unprecedented speed. With rapid technological developments, for example cheap organic synthesis coupled with the increased use of the Internet for marketing and selling new drugs, it may be expected that synthetic analogues of other major drug groups will appear. New synthetic opioids and cocaine derivatives have already been identified via the EWS, albeit as isolated cases. The appearance of a large number of new unregulated synthetic psychoactive compounds or products containing them, marketed on the Internet as 'legal highs' or 'not for human consumption' and specifically designed to mimic the effects of known (established) drugs in order to circumvent existing drug controls, presents a growing challenge to current approaches to monitoring, responding to and controlling the use of new psychoactive substances. Under the so-called 'Spice' phenomenon - smokable herbal products laced with synthetic cannabinoids - more than 20 new synthetic cannabinoids have been reported via the EWS since 2008.[3,4] Over 25 synthetic cathinones are currently being monitored through the EWS. Towards the end of 2009, increased evidence of the use and availability of one of these drugs, mephedrone, prompted the EMCDDA to scientifically assess the health and social risks of the drug in 2010.[5,6] In the wake of this risk assessment, the EU launched a procedure to control the substance at European level. The spate of new drugs is largely due to the increased complexity and volatility of the European drugs market. In addition, the speedy appearance of new attractive alternatives to controlled drugs underlines the ability of this market to respond rapidly to changes in the legal status of psychoactive substances. To 'design' a drug to replace a controlled substance is not a new concept. In the past, though, designer drugs were illicitly produced and marketed directly on the illicit market. An important difference today is that we are seeing a new interaction between the illicit and non-illicit markets, whereby chemicals are legally sourced but then sold as replacements for illicit psychoactive substances. *Conclusion:* It is likely that synthetic psychoactive substances will continue to be predominantly identified in the framework of the EWS. There is a need to remain vigilant and respond rapidly to new chemical groups identified. The use of quantitative routine epidemiological indicators, qualitative research and a wide range of multidisciplinary and supplementary information sources and leading-edge indicators should be combined in order to obtain a holistic picture of new trends at European level. Leading-edge indicators such as hospital emergencies and monitoring the online availability of (new) psychoactive substances can be considered particularly sensitive to change. However, this sensitivity, by definition, is associated with volatility. As such, leading-edge indicators may be unreliable in the medium term if viewed in isolation and not triangulated with other data sources.[2,7–9] *References:* 1. EMCDDA, 2007. Early-warning system on new psychoactive substances - operating guidelines. Publications Office of the European Union, Luxembourg. 2. EMCDDA 2010. Annual report 2010, the state of the drugs problem in Europe. Publications Office of the European Union, Luxembourg. 3. Sedefov R, Gallegos A, King LA, et al. Understanding the 'Spice' phenomenon. Thematic papers, European Monitoring Centre for Drugs and Drug Addiction, 2009. 4. Griffiths P, Sedefov R, Gallegos A, et al. How globalisation and market innovation challenge how we think about and respond to drug use: 'spice' a case study. Addiction 2010; 105:951–3. 5. EMCDDA, 2010. Risk assessment of new psychoactive substances: operating guidelines. Publications Office of the European Union, Luxembourg. 6. EMCDDA, 2010. 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10. A Swedish Early-Warning System on Novel and Emerging Recreational Drugs: The STRIDA-Project

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Objective: In recent years, the number of inquiries to the Swedish poisons centre related to novel and emerging recreational drugs has increased considerably. In order to investigate the risks associated with the use of these drugs, and to identify new drug trends, the STRIDA-project was initiated. *Methods:* Urine and serum samples from drug exposed patients in Sweden were analysed free of charge for the hospitals, and the corresponding medical records were collected. All samples were screened and analysed for pharmaceuticals, alcohol, "classic" narcotics and 27 different novel drugs. *Results:* During the project's first eight months in 2010 the Swedish poisons centre received 255 inquiries from hospitals concerning intoxications with drugs of abuse. In 72 (28%) of these cases urine and serum samples were analysed. The male/female ratio was 80/20, and the ages varied between 14–47 years. Adolescents constituted 45% of the patients. Fifty-eight samples (81%) contained one or several drugs of abuse. The drugs identified included various "classic" narcotics, as well as 14 different novel recreational drugs. The most frequently occurring novel substance groups were synthetic cannabinoids (16 cases) and cathinone derivatives (5 cases). Other substances found were 4-HO-methylethyltryptamine, mitragynin, dextromethorphan and phenazepam. Routes of administration were predominantly oral or inhalation. Three substances found are currently not classified as narcotics in Sweden, namely JWH-015, 4-OH-methylethyltryptamine and mitragynin. *Conclusion:* The STRIDA-project acts as an early-warning system which aims to improve information and treatment guidelines regarding exposure to novel recreational drugs. The benefits are several, analytical results and clinical symptoms combined facilitate estimation of toxicity and risk assessment of new recreational drugs. Moreover, new drug trends will be easier to detect and concerned authorities can rapidly be alerted when novel recreational drugs emerge.

11. Novel and Emerging Recreational Drugs: A Hong Kong Perspective

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Objective: To report the trend for drug abuse, the increasing importance of ketamine as an abuse drug, the toxic effects of ketamine and the problem of

drugged driving. *Methods:* Information on drug abuse in Hong Kong was obtained from published studies and reports of various Government Departments. *Results:* In Hong Kong, there was a rising trend for young drug abusers aged under 21, with an increase of 55.4% from 2003 to 2008. The proportion of those aged under 21 increased steadily from 14.0% in 2003 to 24.2% in 2008. The place of abusing drugs included the Mainland (mainly Shenzhen). Among the young drug abusers, ketamine was most commonly involved (85.4%), followed by ecstasy (15.6%), metamphetamine (14.9%), cocaine (9.3%) and cannabis (9.0%). The most common symptoms of ketamine abuse were impaired consciousness, abdominal pain, lower urinary tract symptoms and dizziness. Ketamine abusers often presented with upper gastrointestinal symptoms, the commonest of which was epigastric pain. Heliobactor pyloric negative gastritis was the most common histopathological finding. Abstinence from ketamine abuse could lead to relief of symptoms. A syndrome of cystitis and contracted bladder could be associated with ketamine abuse. Secondary renal damage could occur in severe cases which might be irreversible, rendering patients dependent on dialysis. The duration and frequency of abuse apparently correlated with the severity of the symptoms and degree of damage to the urinary tract. The prevalence of drugged drivers among non-fatal driver casualties was on the increase and ketamine was the most commonly detected drug of abuse. *Conclusion:* Drug abuse in young adults has become a very serious problem. Ketamine was most commonly involved among young drug abusers and drugged drivers. Ketamine abuse may result in gastrointestinal and lower urinary tract complications.

12. Clinical Features Associated with Recreational Use of 'Ivory Wave' Preparations Containing Desoxypipradrol

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Objective: In August 2010 the UK National Poisons Information Service received many enquiries relating to a recreational 'legal high' called 'Ivory Wave'. Although previously reported to contain methylenedioxypyrovalerone (MDPV) and lignocaine[1], the constituents of these recent Ivory Wave batches was unknown. Here we describe clinical features and analytical information obtained from recent users. *Case series:* Between 2nd and 23rd August 2010, 26 patients (19 male, 7 female, aged 16 to 40 years) presented to the Emergency Departments of the Royal Infirmary of Edinburgh (n = 19) and Frimley Park Hospital (n = 7). The interval since exposure, when reported (n = 20), ranged from 3 hours to 1 week. Undesirable psychiatric effects were observed in 25 (96%) patients, including hallucinations (58%), insomnia (46%), agitation (38%), paranoia (23%), anxiety (15%), restlessness and aggression (each 4%). Tachycardia (73%), palpitations (8%), chest pain (4%), raised creatine kinase (62%) and movement abnormalities (e.g. dystonia, hemiballismus and akathisia, 27%) were also reported. Marked *livido reticularis* was seen in one patient; this had not resolved completely after two days. Analysis of a sample of the 'Ivory Wave' product associated with the Edinburgh cases confirmed the presence of desoxypipradrol (2-diphenylmethylpiperidine, 2-DPMP) but not MDPV or other active compounds. Biological samples from these Edinburgh cases all contain desoxypipradrol. *Conclusion:* Ivory Wave exposure was associated with marked psychiatric and neurological effects, together with cardiovascular features and evidence of muscle toxicity. Analysis is not available for all cases, but when performed confirms the presence of 2-DPMP. The reported psychiatric features resemble those described in Ireland after exposure to 'whack', also found to contain 2-DPMP with flourotropacocaine.[2] In response to this apparent increasing recreational use, an import ban for 2-DPMP was introduced in the UK on 4th November 2010.[3] *References:* 1. Kavanagh PV, McNamara S, Angelov D, et al. The Characterization of 'Legal Highs' Available from Head Shops in Dublin. http://www.addictionireland.ie/_fileupload/publications/Legal_Highs_Poster.pdf (accessed 16 October 2010). 2. Herbert JX, Daly F, Tracey JA. "Whacked!" BMJ letters Published 15th July 2010 http://www.bmj.com/content/341/bmj.c3564.full/reply#bmj_el_238830 (accessed 16 November 2010). 3. Home Office. Imports of Desoxypipradrol (2-DPMP, 2-Benzhydrylpiperidine, 2-Diphenylmethylpiperidine). http://www.homeoffice.gov.uk/publications/drugs/drug-licences/desoxypipradrol/ (accessed 15 November 2010).

13. Poisonings due to Substance Abuse Reported to the Poisons Information Centre Erfurt

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Objective: The aim of the study was to evaluate characteristics of all poisonings due to substance (ethanol excluded) abuse (PSA) reported to the Poisons Information Centre (PIC) Erfurt over a ten year period. *Methods:* A retrospective analysis of PSA-related inquiries to the PIC Erfurt was undertaken for the years 2000 to 2009. *Results:* PSA (in total 3064) and all exposures (in total 147,973) increased from 293 and 10,677 in 2000 to 370 and 18,436 in 2009, respectively, while the relative frequency of PSA to all exposures fell from 2.7% to 2.0% over the same period. Persons involved were mainly adolescents and middle aged adults. Males were involved three times more frequently in PSA than females. Cannabinoids (12%) and amphetamine derivatives (19%) were among the substances most frequently taken throughout the whole study period. Poisonings by *Brugmansia* and *Datura* species were quite frequently registered in 2000 (19%) and 2001 (20%), while poisonings by gamma-hydroxybutyric acid (GHB) increased from 2.2% in 2007 to 5.0% in 2009. The ratio of mono- to poly-intoxications remained stable at 1.23 ± 0.31 during the whole study period. Compared to all exposures, PSA induced more moderate (6.2% versus 17.1%) and severe symptoms (3.2% versus 5.5%) and resulted more frequently in death (0.2% versus 0.4%). In total, 13 deaths (10 in mono-intoxications, 5 with amphetamine derivatives, 3 with inhalation of butane/propane) due to PSA were observed (all between 2000 and 2006). From 169 severe PSA, 39 were seen with GHB, 30 with amphetamine derivatives, and 20 with heroin. *Conclusion:* The observed rise of PSA was probably caused by the simultaneous increase in all exposures registered by the PIC Erfurt from 2000 to 2009. While the abuse of some substances like amphetamine derivatives and cannabinoids was high throughout the whole study period, the abuse of other substances like *Brugmansia* species or GBH changed with time. Although no deaths due to PSA were observed in the last three years, the contribution of substance abuse to severe poisonings remained high in comparison to all exposures.

14. Suicide Attempts with Methadone in France: A 2 Year National Survey Since the Availability of Capsules in 2008

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Background: Before 2008, methadone used in France for opiate substitution was only available as syrup. In 2007 the French Health Authorities permitted the availability of solid forms (up to 40 mg/capsule). A national survey was performed in order to evaluate the modification of poisonings (suicide attempts) induced by such a new pharmaceutical form. *Methods:* A prospective study was set up (April 15, 2008 [availability of capsules in France] - April 15, 2010) with the analysis of suicide attempts managed by the French Poison centres. *Results:* One hundred and thirty-five cases of suicide attempts with the 2 different forms of methadone were reviewed (syrup 90 patients, capsules 45 patients). Comparison shows that patients were similar for both forms (no significant difference concerning age [median 31 years], sex ratio [M/F 3.1] and previous history). The quantities of methadone ingested were higher with the syrup (average 155 mg versus 80 mg with the capsules, $p = 0.04$). However, using the Poisoning Severity Score, there was exactly the same severity profile with both forms (deaths 7% in the two series). Poisoning features were equivalent: no difference in the percentage of association with other products, nature of the associated products (benzodiazepines $\pm$ ethanol in 50–60% of suicide attempts); clinical features (coma 24% and apnoea about 30%); and the evolution and the duration of the hospitalization. The single laboratory which produces methadone in France gave the history of the number of treated patients each month: irregular variations with 30,000 to 45,000 patients using syrup during the period of study, but progressive increase of capsule treated patients with about 700 patients in April 2008 increasing to 12,000 patients in April 2010. Taking account of this evolution the risk of poisoning with methadone in a suicide attempt is 2.6 fold higher when the patient is treated with the capsule form ($p < 0.001$). *Conclusion:* Despite a higher risk of voluntary intoxication with the capsules, there are no other differences between the two forms in this type of poisoning. As a result of this the French Health Authorities have decided to stop the prospective study concerning suicide attempts with methadone.

15. Risk Assessment of Moderate to Severe Alcohol Withdrawal - Predictors for Seizures and Delirium Tremens in the Course of Withdrawal

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Objective: Withdrawal seizures (WS) and delirium tremens (DT) are well known complications of severe alcohol withdrawal (AW). A history of WS and/or DT in previous withdrawal episodes is a known predictor for a complicated course of AW. We investigated whether other predictors could also be established using a large cohort of inpatients treated for moderate to severe AW (n = 827). *Methods:* Cohort study population treated between 2000–2009. All patients received a score-guided and symptom-triggered therapy comprising clomethiazole, clonidine and haloperidol with the additional use of either carbamazepine (n = 374) or valproate (n = 453). Multivariable binary logistic regression models with stepwise variable selection procedures were conducted providing odds ratio (OR) estimates. The c-index was calculated with 95% confidence interval to depict the prognostic overall performance of a final prediction model. Nomograms were provided to enable an easy clinical application. *Results:* In the multivariable regression, significant predictors of WS during AW therapy independent of the administered treatment were a delayed climax of withdrawal severity since admission (OR for every increase of 10h: 1.23; 95% CI: 1.1–1.4; $p < 0.001$), prevalence of structural brain lesions in the patient's history (OR 6.5; 95% CI: 3.0–14.1; $p < 0.001$) and WS as the cause of admittance (OR 2.6; 95% CI: 1.4–4.8; $p = 0.002$). The c-index of this prediction model was 0.73 (95% CI: 0.66–0.88). Significant predictors at admission for occurrence of DT independent of the administered therapy were lower serum potassium (OR per an increase of 1 mmol/L: 0.33; 95% CI: 0.17–0.65; $p = 0.001$), a lower platelet count (OR per an increase of 100,000: 0.42; 95% CI: 0.26–0.69; $p = 0.001$) and

prevalence of structural brain lesions (OR 5.8; 95% CI: 2.6–12.9; $p < 0.001$). The c-index of this prediction model was 0.81 (95% CI: 0.74–0.87). *Conclusion:* In this large retrospective cohort, some easily determinable parameters at admission may be useful to predict a complicated course of alcohol withdrawal regarding occurrence of WS or DT. Using the provided nomograms, clinicians can estimate the percentage likelihood of patients developing either WS or DT during their course of withdrawal. Prevalence of structural brain lesions in the patient's history does strongly warrant a careful observation of patients.

16. Usefulness of Animal Data for Poison Centres

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Background: Most inquiries to Poisons Centres are related to acute poisoning and overdose. Routinely Poisons Centres use human data from published studies, case reports and series, and from own experience to assess the individual risk and prognosis in acute poisoning. Because human volunteer studies to determine acute toxicity of chemicals are ethically debatable (although carried out in certain settings)[1], animal toxicity data may be used in certain circumstances. Acute toxicity studies (i.e. determination of animal LD50) of chemicals are mainly conducted for classification and labelling, for the setting of exposure limits, and for emergency response planning. Additionally an often cited reason to perform such studies is the presumed need to support the clinical management of accidental and intentional human poisoning. While such studies are no longer required in preparing first clinical trials for human pharmaceuticals, it remains unclear if such studies are necessary in drug development and non-pharmaceutical chemicals to support the management of overdose.[2] First attempts have been made to clarify this question on the basis of expert opinion.[3] Most toxicologists and Poisons Centres question the usefulness of animal LD50 tests to support the management of human poisoning,[4,5] although some find them useful in certain situations: lack of human data, for the comparison of human and animal toxicity and to elucidate mechanisms of toxicity; if the toxic effect is mainly physicochemical in nature (e.g. corrosion); if the toxic effect is uniform in humans and animals; and if there is high fatality (e.g. cyanide, colchicine, paraquat). Animal toxicity data can be useful in veterinary toxicology if the animal data are concerning the species in question (e.g. dog LD50s in canine poisoning). There are various reasons why the value of LD50 tests in the context of human poisoning is very limited in most situations: 1) If human poisoning data are available, they are preferred as a source of information in a clinical setting. 2) Treatment decisions in human poisoning are taken on clinical grounds, depending on symptoms, irrespective of animal toxicity data. 3) LD50 testing does not provide information on target organ toxicity, mechanisms of toxicity, symptomatology, and reasons and manner of death. Animal experimentation can be useful if it generates data on clinical symptoms, time course of poisoning, toxicokinetic data, insight on mechanisms of toxicity, target organ toxicity including histopathology, and proofs of principle. Information on acute toxicity as currently provided by classification and labelling is of limited value in managing human poisoning because animal susceptibility may differ dramatically from human susceptibility, the hazard classification derived from lethal dose estimates are of little or no value for directing therapy, because the accompanying hazard and precautionary statements vary little between toxicity categories, and hazard classification is not always a good predictor of outcome in human poisoning (e.g. in organophosphorus poisoning[6]). *References:* 1. Lockwood AH. Human testing of pesticides: Ethical and scientific considerations. Am J Public Health 2004; 94:1908–16. 2. International Conference on Harmonisation (ICH). Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3. 2009. 3. Chapman K, Creton S, Kupferschmidt H, et al. The value of acute toxicity studies to support the clinical management of overdose and poisoning: A cross-discipline consensus. Regul Toxicol Pharmacol 2010; 58:354–9. 4. Zbinden G, Flury-Roversi M. Significance of the LD50-test for the toxicological evaluation of chemical substances. Arch Toxicol 1981; 47:77–99. 5. Robinson S, Chapman K. Are acute toxicity studies required to support overdose for new medicines? Regul Toxicol Pharmacol 2009; 55:110. 6. Eddleston M, Eyer P, Worek F, et al. Differences between organophosphorus insecticides in human self-poisoning; a prospective cohort study. Lancet 2005; 366:1452–9.

17. Respiratory Toxicity of Maintenance Therapy in Drug Addicts: Contribution of Animal Models

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Background: Treatment of heroin addiction underwent a profound revolution with the development of maintenance therapies including methadone and buprenorphine (BUP). Substitution programs allowed significant reduction in intravenous drug abuse-related fatalities, viral transmission, and criminality. However, opioid overdoses remain a major concern worldwide, causing numerous fatalities. Interestingly, despite ceiling effects in relation to BUP pharmacological properties, several fatalities and poisonings have been attributed to BUP misuse or concomitant benzodiazepine (BZD) ingestion.[1] *Objective:* Our objectives are to discuss the contribution of animal models to the understanding of opioid-related respiratory toxicity. *Methods:* Review of recently published articles regarding the study of opioid-related respiratory toxicity. *Results:* Opioids depress respiration in response to acute hypoxia or hypercapnia.[2] Opioid-induced respiratory depression is characterized by a dose-related, naloxone-reversible depression of the resting ventilation with a proportional reduction in tidal volume, decreased PaO_2, and arterial pH along with increased $PaCO_2$. Respiratory depression has been attributed to the interactions with mu-, while delta- and kappa-opioid receptor roles appear limited. Respiratory effects of four opioids administered to rats at 80% of their LD50 were compared. All opioids increased the inspiratory time (TI). Methadone and fentanyl induced hypoxemia, hypercapnia, and expiratory time (TE) increases, morphine caused both hypoxemia and hypercapnia, while BUP caused only hypoxemia. Methadone, a pure OR agonist, is responsible for a dose-related respiratory depression.[4] Respiratory effects as a function of plasma R-methadone concentrations showed decrease in PaO_2 at lower concentrations than those necessary for $PaCO_2$ increase. Similarly, increased TI was obtained at lower concentrations than those for TE. There was a real potential for increasing respiratory depression with methadone/diazepam co-administration.[5] The major mechanism of interaction is pharmacokinetic. Repeated administration decreases the toxicity potential of this association due to tolerance. In contrast, the exact mechanism of BUP toxicity remains misunderstood. Dose-effect relationships suggest a plateau of respiratory effects. A single intravenous high-dose of BUP up to 90 mg/kg did not result in significant respiratory depression in rats, whereas its association with midazolam induced sustained respiratory acidosis.[6,7] In a randomized study, flunitrazepam altered BUP lethality in rats.[8] Norbuprenorphine (NBUP), the BUP cytochrome P450 (CYP) 3A-derived metabolite, is a potent respiratory depressant. BUP can reverse, and is protective against, NBUP-related respiratory effects.[9] In dexamethasone-pretreated rats, there was no alteration in respiratory parameters, despite significant increase of plasma NBUP-to-BUP ratio, suggesting a limited role of drug-mediated CYP3A induction in the occurrence of BUP-attributed respiratory depression.[10] However, the relative ability of NBUP to cross the blood-brain-barrier remains the matter of research. Experimental studies confirm the deleterious BUP/BZD interaction, suggesting hypotheses regarding its mechanism. Flunitrazepam pre-administration did not alter the distribution kinetics of BUP neither in plasma nor in striatum,[11] while BUP significantly altered the kinetics of desmethylflunitrazepam, a flunitrazepam metabolite, suggesting the likelihood of interaction of BUP with the distribution of flunitrazepam.[12] The main hypothesis regarding the respiratory effects of BUP/BZD combination relies on a pharmacodynamic basis. We suggested that BUP may alter the response of the brainstem respiratory centers to BZD-induced increase in the upper-airway resistance. Reversal of BUP-related respiratory effects was studied in various models. Reversal with naloxone is possible but depends on the BUP dose and the correct naloxone dose window. In healthy volunteers, because respiratory depression from BUP may outlast the effects of naloxone boluses, a continuous infusion may be required.[13] In BUP poisonings, although mental status and respiratory depression are unresponsive to low-dose naloxone, we recently suggested that flumazenil may be effective in BUP overdoses involving BZD.[14] *Conclusion:* Experimental models are helpful to understand opioid-related mechanisms of toxicity. Improvement in safety of maintenance therapies requires a better integration of pre-clinical data into clinical observations of toxicity. *References:* 1. Kintz P. Deaths involving buprenorphine: a compendium of French cases. Forensic Sci Int 2001; 121:65–9. 2. Shook JE, Watkins WD, Camporesi EM. Differential roles of opioid receptors in respiration, respiratory disease, and opiate-induced respiratory depression. Am Rev Respir Dis 1990; 142:895–909. 3. Chevillard L, Mégarbane B, Risède P, et al. 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18. Respiratory Depression Related to Buprenorphine and Diazepam Combination in Rats: Study of the Pharmacodynamic Mechanism of Interaction

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Objective: Buprenorphine (BUP) is responsible for ceiling respiratory effects; however, deaths due to asphyxia were attributed to BUP/benzodiazepine (BZD) co-ingestion. When experimentally administered alone, both drugs did not induce deleterious respiratory effects. Our objective was to study the pharmacodynamic interaction between BUP and diazepam (DZP) on rat ventilation. *Methods:* In Sprague-Dawley rats, we studied the respiratory effects (using plethysmography and arterial gases) of DZP (20 mg/kg SC)/BUP (30 mg/kg IP) association [4 groups: solvent (SVT)/SVT, DZP/SVT, SVT/BUP, DZP/BUP; $n = 8$/group]. Reversion of DZP/BUP effects was analyzed following the pre-administration of specific opioid-receptor (naloxonazine (NLZ) [mu-antagonist]; naltrindole [delta-antagonist]; nor-binaltorphimine [kappa-antagonist]) and GABA antagonists (flumazenil (FLZ) [GABA-A-antagonist]; saclofene [GABA-B-antagonist]) [2 groups for each antagonist: SVT/DZP/BUP and antagonist/DZP/BUP; $n = 6$/group] at doses, time, and route of administration allowing complete receptor blockage. Comparisons were performed using ANOVA for repeated measurements followed by Bonferroni post-tests. *Results:* DZP/BUP combination resulted in a significant, rapid-onset, and short-duration respiratory depression: $PaCO_2$ increase ($p < 0.01$) and minute volume decrease (VE, $p < 0.001$). The effect was additive regarding $PaCO_2$ ($p = 0.05$) and synergic regarding VE ($p < 0.001$). Like DZP/SVT group ($p < 0.05$), DZP/BUP group ($p < 0.001$) resulted in a significant tidal volume (VT) decrease in comparison to the SVT/SVT and SVT/BUP groups ($p < 0.001$). VT decrease was compensated in the DZP/SVT group by an increase in the respiratory frequency (f), in comparison to the SVT/SVT group ($p < 0.05$), corresponding to a decreased expiratory time (TE) ($p < 0.01$), which was not observed in the DZP/BUP group. Like BUP alone, DZP/BUP combination resulted in a significant increase of the inspiratory time (TI, $p < 0.001$), compensated by a significant decrease in TE ($p < 0.05$); f was significantly decreased in the DZP/BUP group when compared to the DZP/SVT ($p < 0.001$) and SVT/BUP groups ($p < 0.05$). However, although not significant, TE decrease was less marked with the association. Only NLZ and FLZ significantly reversed $PaCO_2$ ($p < 0.05$) and VE ($p < 0.01$), while FLZ significantly increased f ($p < 0.05$) and NLZ increased VT ($p < 0.05$). *Conclusion:* DZP/BUP combination is responsible for an early-onset and short-duration respiratory depression, related to the combination of a significant VT decrease, a significant TI, and a mild TE increase. Mu opioid- and GABA-A-receptors are responsible of the pharmacodynamic interaction between both molecules.

19. Fomepizole: A Classic Translation of Mechanistic Animal Data to Marketed Antidote

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Objective: Translational toxicology involves the movement of potential antidotes from basic mechanistic research in animals to the human bedside as a marketed therapeutic. Because poisonings are infrequent, the clinical development of antidotes is fraught with complex multi-center trials and many tribulations involving technology transfer. Academic scientists often conduct basic mechanistic work with antidotes, but until recently have not been frequently involved in further drug development. The development of 4-methylpyrazole (4MP or fomepizole) as an antidote for toxic alcohol poisonings, particularly methanol and ethylene glycol (EG), acts as an interesting case study. *Methods:* Early mechanistic research established that both methanol and EG were not poisonous *per se*, but had to be metabolized to toxic metabolites. Initially both are metabolized by alcohol dehydrogenase (ADH), to formaldehyde and glycolaldehyde respectively, then by formaldehyde and aldehyde dehydrogenases to formic acid, the proximate toxicant for methanol, or to glycolic acid, which produces the severe metabolic acidosis of EG poisoning. Glycolate can be further metabolized to oxalic acid, which is poorly soluble in the presence of calcium and leads to the formation of calcium oxalate crystals, which is the primary mechanism for the renal toxicity of EG. Antidotal treatment of these poisonings up to the 1970s included empirical doses of ethanol to compete for ADH, reducing toxic metabolite formation. However, this therapy brought on its own problems including the erratic kinetics and adverse effects of ethanol *per se*. *Results:* The story of 4MP began with its synthesis in the late 1960s, followed by studies of its activities, in animals as well as interestingly in human subjects. The goal at the time was to inhibit ADH in order to diminish the adverse metabolic effects of ethanol, thus advancing the therapy of alcoholism. The key mechanistic study for its therapeutic efficacy, reported in 1975, showed that 4MP could reverse and totally prevent methanol toxicity in animals by completely inhibiting the accumulation of formate. Translational work in the early 1980s defined the effective doses and plasma levels in the animal model, where 4MP levels above 9 μM were sufficient to prevent accumulation of formate. Further studies in the 1980s showed that it was also efficacious in treating EG poisoning in animals, and in fact was superior to the use of ethanol. Although this basic research in animals strongly suggested that 4MP would be effective in treating methanol and EG poisoning in humans, translation of 4MP as a marketed drug in the US was slow for a number of reasons, including the difficulties inherent in conducting clinical toxicology research, a lack of interest to fund these types of studies by the National Institutes of Health and the lack of drug development by the pharmaceutical industry except for diseases that would make a lot of money. Although studies progressed slowly in the US through the 1980s, it was already being used with apparent success to treat several cases of EG poisoning in France. Thus, a major event in the development of 4MP in the US was passage of the Orphan Product Act (indirectly aiding its development in Europe also). This act led to the funding of Phase 1 studies that examined the safety and metabolism of 4MP and that eventually led to the liaisons with the drug company-sponsored clinical efficacy trials (the META study) in both methanol and EG poisoned-patients. Soon after completion of these clinical trials, fomepizole was approved by the FDA in the US, first for treatment of EG and a few years later for methanol, the latter at exactly 25 years after it was shown efficacious in animals. *Conclusion:* Development of antidotes for use in clinical toxicology, even as orphan products, is not easy. Among the problems that are encountered include the need for a suitable drug source (Good Manufacturing Practice-certified for human use), an inability to attract seed money, difficulty with recruiting centers for the necessary multi-center trials, technology transfer issues, and the need for lots of time and patience (30 years from discovery of 4MP activity until it reached the market as fomepizole). Advancement of fomepizole for the treatment of methanol and EG poisoning only became possible through the mechanistic research showing the specific role of metabolites in producing the toxicities. Beyond the strong mechanistic research, other aspects that helped fomepizole reach the market were its undeniable preclinical efficacy, an evident therapeutic need, investigator perseverance, and pure luck (such as the Orphan Product act, timing of scientific collaborations, and development of innovative drug companies).

20. Advances in Understanding Sodium Hydroxide Eye/Skin Penetration: *In Vitro* and *Ex Vivo* Studies

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Objective: Sodium hydroxide (NaOH) is a common corrosive substance, causing severe eye/skin burns. Knowledge is lacking about eye/skin penetration speed as shown by pH evolution and histological damage. *In vitro* and *ex vivo* experiments were designed to elucidate these effects. *Methods: In vitro*: NaOH penetration was simulated through a semi-permeable cellophane membrane. NaOH (100 μL) was placed on the membrane surface and pH evolution was measured in a sodium chloride-containing compartment simulating the skin (9 g/L saline solution). Different NaOH concentrations were tested. *Ex vivo*: 41 human skin explants were exposed to 50% NaOH (30 μL); controls had no exposure. Histological sampling was done at various times from 1 minute to 24 hours. Alterations were evaluated by optical microscopy in stratum corneum, basal epidermis, and papillary and reticular dermis. *Results: In vitro* experiments were in accordance with the European classification, depending on NaOH concentration: 0.1 mol/L did not induce significant pH changes and did not penetrate. Penetration of NaOH for concentrations > 1 mol/L was < 2 minutes. Penetration of 50% NaOH was complete in approximately 1 minute. *Ex vivo*: At 1 minute, stratum corneum alterations were seen; at 4 minutes, lesions reached the stratum corneum basal layer; at 30 minutes, the stratum corneum was totally altered. After 2 hours, no cells remained viable in the epidermis and papillary dermis. *Conclusion:* The *in vitro* model mimics the irritating/corrosive danger of a chemical agent in accordance with European regulations. NaOH burning in the *ex vivo* model corresponds with evolution of accidental splash clinical lesions. Direct effects of corrosion were rapid, lesions progressed quickly, and severe tissue destruction was observed. Similar *ex vivo* studies have been done with hydrofluoric acid (HF) and sulfuric acid (H_2SO_4). The *ex vivo* model will lend itself to graduated rating scale development and confirmed the need for urgent and effective decontamination to prevent or minimize the severity of concentrated NaOH chemical burns.

22. Assessment of QT Prolongation in High-Dose Droperidol Administration Using Continuous 12-Lead Holter Recording

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Objective: There are concerns about the safety of droperidol and international drug regulatory bodies have removed it or restricted its use because of concerns about Torsade de Pointes and QT prolongation. However, there is little evidence to support claims that it causes QT prolongation.[1] We aimed to accurately measure QT interval changes following the administration of droperidol using continuous 12-lead Holter recordings. *Methods:* We undertook a prospective study of the implementation of intramuscular droperidol for the sedation of emergency department patients with acute behavioural disturbance. In addition to obtaining standard 12-lead electrocardiograms (ECG) we used continuous 12-lead Holter recordings (Mortara Instrument, Inc.) to obtain serial QT measurements for 4 to 8 hours after droperidol administration. Patients with acute behavioural disturbance were given 10 mg droperidol intramuscularly and an additional dose of 10 mg after 15 min, if required. A continuous 12-lead Holter recorder was attached when the patient was settled. Recordings were reviewed using Mortara software (H-Scribe) to obtain high-resolution digital 12-lead ECGs which were then imported into another program E-scribe

(Mortara, Inc.) to measure the QT interval. The QT interval was measured by the investigators using an overlapping view of the 12-leads with on-screen callipers. For each ECG the QT interval was plotted against the heart rate (HR) on the QT nomogram to determine if it was abnormal.[2] *Results:* Two hundred and two patients were sedated with droperidol for acute behavioural disturbance. Holter recordings were obtained in 29 patients administered droperidol – 16 received 10 mg, ten 20 mg, two 30 mg and one 40 mg. There were 502 QT measurements and only three abnormal QT,HR pairs (0.6%) in 3 patients. All abnormal readings were just above the QT nomogram for HR >100. *Conclusion:* The use of 10 to 40 mg of droperidol did not result in QT prolongation supporting the safety of its use for sedation of agitated patients. *References:* 1. Kao LW, Kirk MA, Evers SJ, et al. Droperidol, QT prolongation, and sudden death: what is the evidence? Ann Emerg Med 2003; 41:546–58. 2. Chan A, Isbister GK, Kirkpatrick CM, et al. Drug-induced QT prolongation and torsades de pointes: evaluation of a QT nomogram. QJM 2007; 100:609–15.

23. Poisoning by Serotonin Reuptake Inhibitor Antidepressants: A Ten Year Study

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Objective: Selective serotonin reuptake inhibitor (SSRI) and serotonin–norepinephrine reuptake inhibitor (SNRI) antidepressants have largely replaced traditional tricyclic antidepressants (TCA). The severity of acute SSRI/SNRI poisoning is usually regarded as low. The aim of this study was to compare the severity of poisonings with different SSRI/SNRI antidepressants commercially available in France. *Methods:* All parasuicidal poisoning cases involving SSRI/SNRI as a unique agent reported to the French poison and toxicovigilance centres (2000–2009) were analyzed. Age, gender and symptoms were collected. The "cardiac signs" were defined as the presence of arrhythmia, tachycardia (>100 bpm), bradycardia (<60 bpm) or cardiac conduction disorders, and "severity" by the presence of bradypnea, apnea, acute respiratory distress syndrome (ARDS), arrhythmia, circulatory collapse, cardiac arrest, coma or status epilepticus. Clomipramine or amitriptyline poisoning cases with a unique agent were analyzed as controls. *Results:* Nine different SSRI/SNRI compounds have been marketed in France. During this 10-year period 35,125 exposures to SSRI/SNRI compounds were collected; in 9,645 cases SSRI/SNRI was the single agent, and in 5,265 cases it was parasuicide (respectively 5,619 exposures, 2,059 single agent and 1,051 parasuicidal cases for clomipramine/amitriptyline). Parasuicidal cases with a unique agent are summarized in Table 1. *Conclusion:* Globally, the severity of SSRI/SNRI poisoning cases was low ("severity" 1.2% and deaths 0.15% versus respectively 11.1% and 0.4% for TCA). A notification bias is likely, as severe and deadly cases related to the older and better known TCA were probably less often reported to poison centres. For most indicators of SSRI/SNRI poisoning severity, venlafaxine had the highest index. *Acknowledgement:* The authors appreciate the assistance of the Poison and Toxicovigilance Centres of Angers (Dr Harry), Bordeaux (Dr Chanseau), Lille (Dr Mathieu-Nolf), Lyon (Pr Descotes), Marseille (Dr Hayek), Nancy (Dr Manel), Paris (Dr Garnier), Rennes (Prof Verger), Strasbourg (Dr Flesch) and Toulouse (Dr Cabot).

24. Alcohol-Based Hand Rubs Exposure: Retrospective Study from the French Poison and Toxicovigilance Centres

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Objective: To limit the transmission of influenza A(H1N1) virus, the use of alcohol-based hand rubs (ABHR) by the general public was reinforced in 2009. The French Health Products Safety Agency requested the French Committee of Toxicovigilance to assess the risk of adverse effects related to these measures. *Methods:* All poisoning cases involving ABHR reported to the French poison and toxicovigilance centres (PTV) from January 1, 2000 to December 31, 2009 were analyzed. Each PTV completed a standardized collection sheet. Detailed analyses of symptomatic cases focused on the year 2009. *Results:* Two thousand, two hundred and sixty-eight cases with exposure to an ABHR were recorded during the 2000–2009 period, showing a steady increase from 2000 to 2008 and a strong increase in 2009, especially from September. Among the 1,105 cases which occurred in 2009, 263 showed symptoms; 15 were excluded (ABHR poorly identified, absence of causality). The analysis therefore covered 248 cases corresponding to 41 different ABHR. The characteristics of poisoning cases according to the main circumstances were: home accident, 180 cases with: male 51%, median age 2.5 (5 months-84 years), ingestion (68.5%) or ocular exposure (41.5%), only symptoms of irritation except in 12 cases with drunkenness, agitation, drowsiness, confusion, without severe signs; professional exposure, 25 cases (in a health establishment in 8 cases) with: female 20 cases; median age 40 (19–50); ocular exposure 23 cases with in each case eye pain or conjunctivitis; other accidental exposure, 14 cases with: female 11 cases, median age 77 (12–86); ingestion 12 cases (storage outside of the original container, dementia, misuse or product used by mistake), absence of severe signs; suicide attempt, 11 cases (alcohol beverage associated in 3 cases) with: female 7 cases, median age 37 (15–80), coma 4 cases; chronic alcoholism, 5 cases (in hospital in 3 cases) with: male 4 cases, median age 36 (30–38), absence of severe signs of alcoholic intoxication. *Conclusion:* This retrospective study has shown an increase of ABHR exposure cases since 2000, parallel to the use of these products. Symptoms depended primarily on circumstances (route of exposure, estimated ingested dose). The risk of severe poisoning was low.

Table 1. Parasuicidal cases with a unique antidepressant agent

INN°		n	With symptoms (%)	Cardiac signs (%)	Seizures (%)	Severity (%)	Deaths (%)
citalopram		719	44.4	4.8	1.7	1.3	0.1
duloxetine		52	57.7	3.9	0	1.9	
escitalopram		314	44.3	6.1	0.6	1.0	
fluoxetine		859	40.3	2.0	0.2	0.8	
fluvoxamine		75	44.0	4.0	2.7	2.7	
milnacipran		120	50.8	6.7	0.8	0.8	
paroxetine		1,418	44.7	2.8	0.2	0.6	0.1
venlafaxine		964	49.5	11.2	3.2	2.7	0.6
sertraline		744	48.5	3.9	0.4	0.7	
Total	**(%)**		**45.6**	**4.9**	**1.1**	**1.2**	**0.15**
	n	**5,265**	**2,399**	**260**	**56**	**62**	**8**
TCA*		*1,051*	*65.6*	*17.6*	*4.1*	*11.1*	*0.4*

°International Non-proprietary Names; *clomipramine/amitriptyline.

25. Acute Hemolysis and Hemolytic Uremic Syndrome following N-Acetylcysteine Overdose

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Case report: A 21 year-old woman (70 kg) took an overdose of acetaminophen (APAP) and ethanol (EtOH) after allegedly texting a suicide note to a friend. Her [APAP] in the ED was >200 mg/L with a serum [EtOH] of 163 mg/dL. The ED physician ordered intravenous (IV) N-acetylcysteine (NAC). The pharmacist used the table in the Acetadote® package insert as a guide for mixing the three bags, but mistook the column indicating volume (mL) of NAC solution for the weight (grams) of NAC to be added to the base IV solution (D5W). This resulted in a 5-fold dose error of 52.5 grams of NAC in 500 mL of NS over 1 hour followed by the 17.5 grams of NAC in another 500 mL to run over 4 hours. The dose error was detected 20 minutes into the second infusion. Her [APAP] fell quickly over the course of the day. Her AST and ALT gradually rose to maxima of 494 IU/L at 38 hrs after presentation and 494 IU/L at 42 hours after presentation, respectively, but her hemoglobin and hematocrit quickly dropped from 14.8 g/dL and 44.0% on admission to 6.2 g/dL and 17.3% on day 7. She had hematuria on first urinalysis 19 hours after presentation (and 16 hours after NAC infusion stopped). Her creatinine doubled in the first 6 hours from 0.6 to 1.2 g/dL and rose steadily to 8.27 g/dL by day 3. She was transferred to a tertiary care hospital for further care, where she underwent hemodialysis every 2 days, transfusions of packed red blood cells, and plasmapheresis due to concerns about possible thrombotic thrombocytopenic purpura (TTP). Hematology tests later excluded TTP, and her final hematologic diagnosis was "atypical hemolytic-uremic syndrome". She had some dyspnea and required supplemental oxygen for several days. The mechanism of hemolysis after NAC overdose is unclear, but may be related to the extremely hyperosmolar NAC solution (calculated to be 1511.3 mOsm/L). *Conclusion:* A 5-fold overdose of NAC resulted in hemolysis and acute renal failure. The complicated dosing system for Acetadote® makes errors in preparation and administration more likely.

26. A Case Report of Trimethoprim/Sulfamethoxazole Induced Hypoglycemia

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Objective: Trimethoprim/sulfamethoxazole (TMP/SMX), a dihydrofolate reductase inhibitor antibiotic, is widely used for a variety of infections in the United States. Despite being an older medication, there are still misconceptions about its safety profile. A lesser known adverse effect (ADR) of this medication is hypoglycemia, usually occurring 1.5 h - 10 days after therapy initiation. We present a case of severe symptomatic

hypoglycemia after initiation of TMP/SMX. *Case report:* An 84-year-old female with history of anemia, hypothyroidism, hypertension and diabetes was admitted for hypoglycemia. In reviewing her medications she had had a recent dose increase in her glipizide with improved blood sugar control to 120–150 mg/dL (6.7-8.3 mmol/L). Two days after this dose increase the patient was started on TMP/SMX, one double-strength (DS) every 12 hours for lower extremity cellulitis. An additional two days later the patient was found minimally responsive with blood sugars of 21 mg/dL (1.2 mmol/L). After initial normalization of her glucose the patient had recurrent episodes of hypoglycemia despite repeat administration of dextrose as well as feeding. The patient's creatinine was 1.2 mg/dL (105.6 micromol/L) (creatinine clearance ~30 mL/minute (0.5 mL/s)) at presentation. TMP/SMX was discontinued 12 hours after admission and subsequent blood sugars normalized without further treatment. *Conclusion:* Risk factors for TMP/SMX induced hypoglycemia include renal dysfunction, advanced age, diabetes mellitus, co-administration of a sulfonylurea, malnutrition, hepatic dysfunction, sepsis and higher medication dosage. The mechanism is secondary to a SMX-induced sulfonylurea-like effect in the pancreas. SMX directly binds to K-ATP channel in pancreatic islet beta-cells thereby stimulating insulin release. SMX-induced hypoglycemia has been seen in non-diabetic and diabetic patients. Our patient had many risk factors for this drug toxicity: advanced age, malnutrition, decreased renal function and diabetes although the primary contributing factors were most likely the patient's renal insufficiency and lack of dose-adjustment of TMP/SMX. We used the Naranjo adverse drug reaction probability scale to calculate the probability of ADR. The Naranjo score was 4 indicating "possible" ADR. The risk of this toxicity can be minimized by: adjusting dose for renal dysfunction, cautious use in elderly, AIDS and diabetic patients and careful monitoring of glucose when co-administered with a sulfonylurea.

27. Pediatric Button Battery Exposures

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Objective: Button batteries are often easily accessible in many households where younger children may encounter them and ingest them intentionally in their normal course of environmental exploration. In addition to their potential to cause airway or gastrointestinal obstruction, button batteries may also carry the potential to cause serious direct tissue injury through electrical and caustic burns that may sometimes lead to tissue perforation and scarring. Because of the potential for serious injury, invasive removal procedures are sometimes performed, particularly for cases of retention or obstruction. We sought to examine the features of pediatric button battery ingestions in order to better characterize the potential clinical risks. *Methods:* We retrospectively analyzed data collected on a total of 1341 human exposures related to button battery ingestions in children under 6 years in age reported to six poison centers in the USA during the ten-year period from the year 2000 through 2010. *Results:* Of the reported exposures identified, 52% occurred in males and 80% in children of ages over 1 through 4 years old. Over 95% of our cases occurred at home. All but 14 were classified as intentional ingestions. One case was judged a suspected suicide attempt. There were no clinical effects reported in 50%, minor and moderate effects in 1.6% and 1.8% respectively, and unrelated effects in 0.4% of our cases. The remainder consisted of exposures not followed and judged as non-toxic in 4.8% or productive of minor clinical effects 30.7%, or were not able to be followed and judged as potentially toxic exposures. The most common signs, symptoms or findings reported were radiograph signs (1.5%), vomiting (1%), abdominal pain (1%), diarrhea (0.6%), choking or coughing (0.6%) and oropharyngeal irritation (0.4%). Although melena was reported in one case, no perforations were reported. Treatment modalities included dilution/irrigation/washing in 33%, food/snack in 17%, and other in 17%. *Conclusion:* Our data shows that serious airway and gastrointestinal signs and symptoms are relatively uncommon. However, because of the unpredictability of potentially severe clinical effects, evaluation and management decisions in button battery ingestions remains clinically challenging.

28. Toxicity Profile of Duloxetine: A Poisons Centre Cohort Study

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Objective: Limited toxicity data exists on the effects of the serotonin and noradrenaline reuptake inhibitor duloxetine (Cymbalta®). This study aims to describe the toxicity profile of duloxetine for both accidental paediatric ingestions and deliberate self-poisoning. *Methods:* Cases were prospectively recruited through the NSW Poisons Information Centre from September 2009 - November 2010. A two page clinical research form was faxed to hospitals at the time of the initial call. A copy of the patient's medical record for the admission was also requested retrospectively. Telephone follow-up was attempted for accidental ingestions within 72 hours of the initial call. *Results:* A total of 59 cases of duloxetine poisoning with outcome information was collected. Patients were classified as: i) Accidental paediatric exposures (n = 15; median age: 26 months; IQR: 24–39 months; range: 1–12 years), 7 were symptomatic (estimated dose: 60–120 mg): lethargy (n = 5), hyperactivity (n = 4), nausea (n = 3), vomiting (n = 2), rash (n = 1), sweating (n = 1), leg weakness (n = 1), fever (n = 1; temperature: 38°C). Eight remained asymptomatic (estimated dose: 5–240 mg). Six were observed in hospital, two were seen by a general practitioner. ii) Deliberate self-poisoning (n = 44): 26 cases involved duloxetine only and of these, 24 (92%) were symptomatic (Table 1). Median dose ingested: 1005 mg; IQR: 495–1410 mg; range: 240–2400 mg. Two patients remained asymptomatic (dose: 420–780 mg). *Conclusion:* In this series, duloxetine in doses up to 240 mg resulted in mild or no toxicity in accidental paediatric ingestions. One case of serious toxicity involving serotonin syndrome complicated by rhabdomyolysis occurred in an overdose patient taking 1440 mg. Other deliberate self-poisonings of up to 2400 mg resulted in none to moderate toxicity.

Table 1. Clinical findings in duloxetine single-drug overdoses

Clinical findings in duloxetine single-drug overdoses	Number of patients with finding	% (N=26)
Drowsiness (lowest GCS: 14)	13*	50*
Nausea	13	50
Vomiting	10	38
Tachycardia (maximum HR: 140bpm)	10	38
Sweating[#]	7	27
Agitation[#]	6	23
Tremor[#]	6	23
Hyperreflexia[#]	5	19
Mydriasis	5	19
Hypertension (maximum BP: 170/105)	3	12
Visual hallucinations	2	8
Dry mouth	2	8
Confusion	2	8
Myoclonus	2	8
Headache	2	8
Hypotension (minimum BP: 86/50)	1	4
QRS widening (maximum QRS: 118ms)	1	4
Clonus[#]	1	4
Pyrexia (maximum temperature: 38.5C)[#]	1	4
Epigastric pain	1	4
Rhabdomyolysis (CK: 2982, no elevation in creatinine, urine test- blood: small, ketones: >160 g/dL, protein: 30 mg/dL)	1	4
Ataxia	1	4
Constipation/decreased bowel sounds	1	4
Difficulty urinating	1	4
Dizziness (no associated hypotension)	1	4
Hot flushes	1	4
Pins and needles	1	4
Hypertonia[#]	1	4

*All seven patients who had co-ingested alcohol were drowsy.
[#]Clinical features contained in the Hunter Serotonin Toxicity Criteria. Four cases (ingesting 420–2400 mg) met these criteria but only one was severe and required treatment with diazepam.

29. Toxicity from the Use of Miracle Mineral Solution (Sodium Chlorite)

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Background: The complementary and alternative medicine Miracle Mineral Solution (MMS) is supplied as 28% sodium chlorite and is designed to be mixed with 10% citric acid and diluted immediately prior to use by the patient. Several other brands exist and may be marketed as water purification drops but are all very similar. They have various therapeutic claims, from general well-being to curing cancer and malaria. Products are sold through some complementary medicine practitioners and via the Internet. There is very limited human toxicity experience with this product but several regulatory bodies around the world have issued consumer warnings on these products (but not Australia). *Objective:* To report on the adverse effects associated with the 'therapeutic' use of sodium chlorite. *Methods:* A retrospective review of calls made to the New South Wales Poisons Information Centre during 1 January 2004–12 November 2010 involving adverse effects from the use of sodium chlorite-containing 'therapeutic' preparations. Search terms (and truncations) included: sodium chlorite, MMS, Miracle Mineral Solution, Water Purification Drops Oxygo. A follow-up phone call and medical record request (if hospitalised) was attempted for each case. *Results:* There have been ten cases of toxicity directly reported to the NSW Poisons Information Centre in the period October 2008 to October 2010. Symptoms reported are gastrointestinal in nature with severe persistent abdominal cramping, nausea, vomiting and diarrhoea the common complaints. This resulted in hospitalisation of five of these patients. No sequelae have been identified. The other Australian Poisons Information Centres reported a further nine cases in 2008–2009. All presented with similar symptoms, with two of these cases observed in hospital. Most cases involved use of the product incorrectly diluted. *Conclusion:* Sodium chlorite has the risk of significant morbidity, particularly when used outside the 'recommended dose'. This case series and unlawful therapeutic claims prompted the Australian Therapeutic Goods Administration to act in mid-2010 and a number of Australian websites have now ceased to operate and those remaining have had to remove all therapeutic claims. Further public protection is still required as it can still be legally marketed as a water purification drop (with no written therapeutic claims) and it lacks child-resistant packaging.

30. Prolonged Psychosis from Omega Conotoxin Toxicity

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Background: Omega conotoxin is a peptide from the venom of the marine snail *Conus geographus*. It has an estimated analgesic effect of 100 to 1000 times that of morphine. A synthetic version, thought to inhibit calcium channels and prevent release of substance P, has been used as an intrathecal analgesic drug, ziconotide. *Case report:* A 37 year old male with history of idiopathic peripheral neuropathy was treated with intrathecal ziconotide with the dose gradually increased because of worsening neuropathic pain. He presented to the hospital with profound confusion, visual hallucinations, and tremor of three days duration. Review of systems (ROS) was negative for fever, headache or overdose. Routine medications included bupivacaine, fentanyl patch, hydromorphone, metoprolol, venlafaxine and alprazolam. Initial exam revealed a blood pressure 154/97, Temp 36.6°C, respiratory rate 18/min and heart rate 72/minute. The patient was tremulous, actively hallucinating, and incoherent. He had significant hyperesthesia in the lower extremities, with reduced range of motion in the joints. Other system examinations were unremarkable. Laboratory data revealed normal chemistries and complete blood count and cerebrospinal fluid (CSF) (including viral serology). Panculture of blood, urine and CSF specimens were negative. RBC cholinesterase was 45.1 u/g Hb (nl) and urinary heavy metal screen was negative. ECG showed a QRS duration of 106 sec, and QTc of 459. CT and MRI of the brain where normal. CSF ziconotide level was requested but not available. Ziconotide dose was gradually decreased from 1.5 mcg/day to 0.0353 mcg/day, with complete resolution of the delirium over 6 days. Treatments with benzodiazepines and opiates had not been decreased or changed arguing against specific withdrawal syndromes. *Conclusion:* Our patient's presentation most likely resulted from ziconotide toxicity. Extensive work up for infection, withdrawal syndrome or functional psychiatrist disorder was negative. Although we were unable to locate a laboratory to perform CSF ziconotide levels, our patient's symptoms resolved with gradual reduction in the ziconotide dose. One case report[1] exists describing similar symptoms from intrathecal ziconotide. The mechanism of the delirium is unknown but felt to be from delayed CNS neuronal changes over time. *References:* 1. Levin T, Petrides G, Weiner J, et al. Intractable delirium associated with ziconotide successfully treated with electroconvulsive therapy. Psychosomatics 2002; 43:63–6.

31. Accidental Benzydamine Hydrochloride (Tantum Rosa®) Poisoning Due to Ingestion of Sachets: Pavia Poison Centre Case Series

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Objective: Benzydamine hydrochloride (BH) is a non-steroidal anti-inflammatory drug currently administered for relief of painful/inflammatory conditions. BH is usually available as a topical solution or sachets (mouthwash, dermal cream, vaginal irrigation), or as suppositories or pills. It is well absorbed from the gastrointestinal tract with an elimination half-life of 13 hours. Side-effects including neurological symptoms are reported during therapy, incorrect use[1,2] and abuse. We report a Pavia Poison Centre (PPC) case series of side-effects due to erroneous ingestion of BH. *Case series:* From December 2009 to October 2010, PPC registered 13 cases (approximately 1.2 cases/month) of BH wrong-use due to ingestion of Tantum Rosa® (BH 500 mg/sachet), normally intended for vaginal irrigation. In the previous months the incidence was calculated as approximately 0.5 cases/month. Such an increase seemed to follow the drug re-classification as over-the-counter and the consequent confounding advertising campaign. All patients declared that they had misunderstood the indication and thought the drug had to be consumed orally. All of them denied recreational purposes. Seven patients ingested one sachet diluted in a glass of water; six ingested a variable quantity after correct dilution (one sachet in 1000 millilitres of water). All patients were female (age 23–87). Four presented vomiting and mouth paraesthesiae; four referred neurological symptoms (vertigo, hallucinations in one case), and four patients were asymptomatic. Twelve cases were evaluated in Emergency Departments and three needed 12 hours' observation. All patients fully recovered within 18 hours from admission. PPC made a report to the Italian Agency for Drugs (AIFA), reporting the relevant increase of the erroneous utilization, in order to invite the pharmaceutical producers to clarify the correct modality of use. Advertising and label indication were thus modified and cases of accidental ingestion decreased significantly. *Conclusion:* This case study outlines the importance of correct marketing of drugs and points out the relevant role of poison centres for prompt and effective recognition of emerging health problems. *References:* 1. Anand JS, Glebocka ML, Korolkiewicz RP. Recreational abuse with benzydamine hydrochloride (tantum rosa). Clin Toxicol (Phila) 2007; 45:198–9. 2. Gomez-Lopez L, Hernández-Rodríguez J, Pou J, et al. Acute overdose due to benzydamine. Hum Exp Toxicol 1999; 18:471-3.

32. From an "Unimportant" Cutaneous Rash Without Itch to Toxic Epidermal Necrolysis

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Objective: Toxic Epidermal Necrolysis (TEN) is a severe adverse drug reaction related to an idiosyncratic mechanism, characterized by low incidence but high mortality.[1,2] We report a case of severe diphenylhydantoin-related TEN. *Case report:* A 74 year-old female was admitted to the Rehabilitation Unit (RRF) with a diagnosis of "Left hemiparesis after surgery of frontal and right parietal repetitive lesions". One month before, a well-tolerated therapy with diphenylhydantoin 100 mg/tid had been started at a Neurosurgery Institute. A week after RRF admission, an erythema without itch appeared in the jugular and parasternal region. It was absent in the areas covered by clothing. Loratadine 10 mg/day was started. The next day the erythema extended on the neck, so topical dexamethasone was added. During the following four days the patient presented erythema extending to the back with a tendency to confluence of the lesions. Therapy with diphenylhydantoin was discontinued and replaced with levetiracetam. Serum diphenylhydantoin was 11.4 mcg/mL (n.v. 10–20). A skin biopsy confirmed the suspected diagnosis of toxic epidermal necrolysis. Therapy with methylprednisolone 80 mg/day, antibiotics, fluids, electrolytes and albumin up to 3000 mL/day of intravenous solution was performed. The patient was then sent to a Dermatology Burns Unit where supportive therapy and treatment with immunoglobulin were administered, followed by gradual resolution of signs and symptoms within the following month. *Conclusion:* TEN is a reportedly rare disease (incidence 0.01%) but burdened by 61% mortality if skin loss is more than 30%. The disease onset is insidious and it can appear as an "unimportant" cutaneous rash, without itch. The blisters appear quite late, then the disease progresses rapidly. TEN may be related to several drugs including antiepileptics, allopurinol, cephalosporins, penicillins, oxicam. When TEN is suspected immediate drug discontinuance and prompt replacement with other drugs (that are not reported to be risky for TEN) must be evaluated. *References:* 1. Lissia M, Mulas P, Bulla A, et al. Toxic epidermal necrolysis (Lyell's disease). Burns 2010; 36:152–63. 2. Bastuji-Garin S, Fouchard N, Bertocchi M, et al. SCORTEN: a severity-of illness score for toxic epidermal necrolysis. J Invest Dermatol 2000; 115:149–53.

34. Neonatal Citalopram Toxicity Related to Serum Concentrations

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Objective: Late gestational exposure to serotonin reuptake inhibitors (SSRI) with long half-lives, like citalopram, can be associated with a neonatal toxicity syndrome with immediate onset at birth or soon after birth and sometimes may be confounded with neonatal withdrawal syndrome. We report a case of neonatal toxicity in a newborn after *in utero* exposure to citalopram. *Case report:* A 3860 g infant boy was delivered by normal spontaneous vaginal delivery at 40 weeks gestation. The mother had a positive history of major depression and she had been taking citalopram 20 mg/day until the day of delivery. At birth, the infant had Apgar scores of 8, 8, and 10 at 1, 5, and 10 minutes, respectively. Ten minutes after birth, the baby became hypertonic. Muscular rigidity attenuated with diazepam 0.8 mg/day. Electroencephalogram and routine laboratory tests were normal. Symptoms resolved over the following 14 days, when the infant was discharged. Citalopram and desmethylcitalopram levels at 31 hours of age were 73 ng/mL and 26 ng/mL respectively (normal adult levels <200 ng/mL). Citalopram and desmethylcitalopram levels decreased to 20 ng/mL and 8.5 ng/mL respectively at 98 hours of age, to 18 ng/mL and 6.5 ng/mL respectively at 146 and 218 hours of age and to <10 ng/mL at 338 hours of age. *Conclusion:* Both drug levels and time-course of symptoms suggest that neonatal citalopram toxicity is the most probable diagnosis. The extended duration of symptoms may be related to the prolonged half-life of citalopram: in adults, citalopram's half-life is about 33 to 37 hours, but in infants it may be much higher because of the poor glucuronidation capacity during the first months of life. Citalopram blood levels, when available, are very helpful for the definitive diagnosis, as they help distinguish between citalopram toxicity and withdrawal syndrome.

35. Neonatal Paroxetine Toxicity

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Objective: Neonatal withdrawal syndrome following *in utero* exposure to paroxetine is a well known consequence but sometimes it may be confounded with serotonin toxicity, as both hyper- and hyposerotoninergic states can result in similar symptoms in newborns. We report a case of paroxetine toxicity in a newborn after *in utero* exposure to paroxetine and olanzapine. *Case report:* A 3060 gram male was born at 38 weeks of gestation to a 32-year-old mother treated with paroxetine 20 mg and olanzapine 5 mg once daily. Apgar scores were 4 at 1 minute and 8 at 5 minutes. At birth the infant was cyanotic, failed to show respiratory effort and was ventilated for 30 seconds. After 1 hour, he was bradycardic, hypotonic and with opisthotonus posturing; at 6 hours, convulsions ensued and lorazepam bolus was administered. The patient was discharged 5 days after delivery with

no symptoms and normal laboratory values. Cord blood levels of paroxetine and olanzapine at the time of delivery were 17.2 ng/mL and 4.6 ng/mL, respectively; neonatal serum concentrations at 24 h of age were 10.2 ng/mL and 4.5 ng/mL, respectively (adult therapeutic range, 10 to 100 ng/mL and 10 to 50 ng/mL, respectively). *Conclusion:* There is an ongoing debate about whether the adverse effects seen in some neonates are due to a paroxetine withdrawal syndrome, or are due to toxicity.[1] In our case, other causes explaining the observed clinical picture (e.g. peripartum asphyxia, CNS infections or metabolic disorders) were excluded. Neonatal serum concentrations of paroxetine in the typical adult therapeutic range and the onset of the symptoms immediately after birth render the hypothesis of serotoninergic syndrome more plausible; this is supported by both drug levels and time-course of symptoms. Normal or low plasma concentrations of paroxetine may be associated with serotoninergic perinatal complications in susceptible infants when exposed to paroxetine during late pregnancy. A definitive differential diagnosis between paroxetine toxicity and withdrawal syndrome is possible only if neonatal paroxetine blood levels are available. *References:* 1. Koren G, Matsui D, Einarson A, et al. Is maternal use of selective serotonin reuptake inhibitors in the third trimester of pregnancy harmful to neonates? CMAJ 2005; 172:1457–9.

36. Brimonidine Eye Drops in Young Infants

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Objective: Brimonidine is a relatively selective alpha-2 adrenergic agonist. The drug lowers intraocular pressure via a reduction in aqueous humor production, and via an increase of uveoscleral outflow. Brimonidine is structurally similar to clonidine. Small children are especially susceptible to adverse effects of the drug, but brimonidine is still used also for children <6 months old. There is controversy about the use of naloxone as an antidote for brimonidine. *Case series:* Case 1: A nine week old boy (5.6 kg) was given 1 drop of brimonidine 0.1 percent into the right eye in hospital because of a congenital glaucoma. Within 30 minutes he developed hypopnoea (8/min) with irregular breathing pattern, restlessness, decreased muscle tone, and a sunken fontanelle. On admission in the Children's hospital he was somnolent (GCS 7) and pale. Miosis was noted. The application of naloxone failed to improve the symptoms. A continuous infusion of naloxone was without positive effect. The patient recovered within 12 hours. Case 2: After topical treatment with 2 drops brimonidine 0.2% a two month old infant developed within 90 minutes irritability, moaning, somnolence and periodic breathing similar to Cheyne-Stokes respiration. The patient recovered within 12 hours. Naloxone was not applied. *Conclusion:* Topical brimonidine therapy for glaucoma was associated with severe systemic side effects in young infants after only one drop of a 0.1% brimonidine solution. Naloxone was only given in one patient but was without any effect. Especially in small infants therapy with brimonidine eye drops should be initiated only under medical care because of the potential for serious side effects such as those reported here.

37. Poisoning Caused by Fire Lighters: A Ten Year Analysis of French Poison Control Centres' Data

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Table 1. Summary of cases of poisoning caused by fire lighters

	Liquid (n = 1394)	Solid (n = 2743)
Cases between April and September (Summer months)	947 (67.9%)	1,210 (44.1%)
Child <4 years	1,125 (80.7%)	2,461 (89.7%)
Adult >19 years	140 (10.0%)	141 (5.1%)
Sex ratio male/female	1.7	1.3
Place of ingestion:		
home	95%	97%
family garden	8%	3%
Ingestion	1,338 (96.0%)	2,716 (99.0%)
Presence of symptoms	736 (52.8%)	328 (12.0%
Cough	490 (35.2%)	46 (1.7%)
Fever	66 (4.7%)	10 (0.4%)
Vomiting	203 (14.6%)	77 (2.8%)
Pneumonia	89 (6.4%)	0 (–)
Hospitalization	605 (43.4%)	266 (9.7%)

Objective: At the meeting of the Limitation Working Group in July 2006, Germany reported on accidents with lamp oils and grill lighters. French Poison Control Centre (PCC) data concerning all hydrocarbon and liquid fire lighter (LFL) ingestions were analyzed and the report was transmitted to the Ministry of Health in 2007. The aim of this study was to compare exposure to LFL with exposure to solid fire lighters (SFL). *Methods:* SFL and LFL recorded in the French national database of substances and products were selected and cases of poisoning were collected in the French national database of toxic exposures (FNDTE) and analysed. *Results:* Among the 1,240,792 cases recorded in the FNDTE between January 1999 and January 2009, 1394 cases were related to LFL (0.11%) and 2743 (0.22%) to SFL. Table 1 summarizes the main results. *Discussion:* Children were concerned in more than 80% of the exposures to fire lighters, which occurred almost exclusively at home. Between April and September exposures to LFL were more frequent (68% versus 44% for SFL), mainly in the family garden (8% versus 3% for SFL) where LFL are more often used to light barbecues. Considering the LFL exposures, symptoms were 4.4 more frequent and the number of the hospitalizations 4.5 times greater. Eighty-nine cases of aspiration pneumonia were observed with the LFL (6.4%) and none with the SFL. *Conclusion:* Although SFL exposures are twice as frequent as LFL exposures, no case of pneumonia was observed with the SFL. The French Commission for Consumer Safety recommended in July 2009 that SFL be used preferentially in fire-places, barbecues and stoves.

38. Too Much of a Good Thing: Dosing Errors with Infant Vitamin D3 Supplements

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Objective: Since May 2010 it has been the policy of the Irish Department of Health & Children that all infants, from birth to 12 months, be given a daily supplement of 5 micrograms (200 IU) of vitamin D3, to prevent deficiency. The impact of this policy on enquiries to the National Poisons Information Centre (NPIC) about accidental vitamin D overdose was reviewed. *Methods:* All enquiries to the NPIC about vitamin D overdose in infants aged from birth to 12 months, from January 2005 to October 2010 inclusive, were extracted from the NPIC enquiries database. Data was collected on the age of the patients, circumstances of poisoning, vitamin D dose administered, and the treatment advised. *Results:* There were no enquiries before 2009. Since then the NPIC has received enquiries about 12 cases of vitamin D3 overdose in infants; 8 incidents occurred in the five months after the policy was introduced, compared to four in the preceding 17 months. Patient ages ranged from 6 days to 36 weeks (median 6 weeks). Nine of these 12 cases were due to therapeutic error, where a parent had administered an excessive dose on a single occasion (5 cases), repeatedly over periods of 2–10 days (3 cases), or chronically (for 6 weeks in 1 case). Two infants were given an acute overdose because of problems with the dropper or bottle dropper-top, and one case involved accidental ingestion by a 9-month old child. Four infants had received the European tolerable upper intake of 1000 IU vitamin D3 per day and 6 had exceeded it. Four infants who had received excessive doses repeatedly were referred to hospital to check for hypercalcaemia. *Conclusion:* These cases demonstrate again that poisons centres can rapidly detect the unintended consequences of public health measures.[1] They suggest that parents have problems with the dosing instructions and method of administration for infant vitamin D3 supplements, leading to acute or chronic overdose. The dosing instructions should be revised to prevent further accidents occurring. *References:* 1. Herbert JX, Tracey JA. The toxicological impact of two public health protection measures in Ireland. J Toxicol Clin Toxicol 2003; 41:495.

39. Hyponatremia Associated with Levamisole-Adulterated Cocaine

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Objective: To describe hyponatremia in patients using levamisole-adulterated cocaine. Cocaine is often "cut" with other agents to expand the volume and quantity available. Levamisole-adulterated cocaine is increasingly prevalent, up to 70% containing levamisole.[1] Levamisole, previously used as an immunomodulator, has been shown to cause hyponatremia.[2,3] We present three cases of unexplained hyponatremia associated with levamisole-adulterated cocaine use. *Case series:* A 26 year old man presented with chest pain after insufflating cocaine and drinking beer; serum sodium: 120 mEq/L. A 39 year old man with history of daily cocaine use presented with chest pain, myalgias and shortness of breath; serum sodium: 113 mEq/L. A 57 year old man with untreated non-insulin dependent diabetes presented with malaise; serum sodium: 124 mEq/L. Laboratory values and pertinent physical findings are presented in Table 1. Workup for possible etiologies including medications and thyroid disease,

Table 1. Laboratory values and physical findings for patients presenting with hyponatremia

Age (years)	Serum Sodium (mEq/L)	Urine Osm (mOsm/L)	Urine Sodium (mEq/L)	Serum Osm mOsm/L)	Physical examination
26	120	45	<10	–	Tachycardia: 104 beats/min, Blood pressure: 183/97 mmHg, no dehydration
39	113	135	<10	234	Tachycardia: 113 beats/min, Blood pressure: 101/70 mmHg, agitation
57	124	262	<10	262	Tachycardia: 120 beats/min, Blood pressure 102/68 mmHg, mild dehydration

was negative. Urine drug screens excluded other toxins but confirmed benzylecgonine and levamisole by gas chromatography-mass spectrometry in all patients; normalization of sodium concentrations occurred promptly with rehydration. *Conclusion:* Unexplained hyponatremia may be the result of levamisole-adulterated cocaine in some patients. While the mechanism is not clear, sodium and water handling is transiently impaired. An epidemiologic study to evaluate the association between hyponatremia and exposure to levamisole-adulterated cocaine use is proceeding. *References:* 1. National Survey on Drug Use and Health. 2008. http://oas.samhsa.gov/nsduh/2k8nsduh/2k8Results.cfm 2. Berghmans T. Hyponatremia related to medical anticancer treatment. Support Care Cancer 1996; 4:341–50. 3. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. Am J Kidney Dis 2008; 52:144–53.

40. Delayed Acute Liver and Renal Failure After Deliberate Chloroform Inhalation

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Objective: Since the use of chloroform has been widely banned, acute overdoses are rare. We report on a case of acute deliberate chloroform inhalation in which severe liver and renal failure developed after a latency of 50 hours. *Case report:* A 42-year-old depressive female was admitted after she had deliberately inhaled 250 mL of pure chloroform that was soaked in a towel. She woke spontaneously after 7 hours with nausea and dizziness. At admission, the patient was awake (GCS 15), vital signs were stable and physical examination was unremarkable besides a skin degradation lesion on the left shoulder. Blood gas analysis, ECG and laboratory were normal at admission and the following day. Quantitative toxicological analysis revealed a chloroform concentration in plasma of 3.9 mg/L and 0.2 mg/L some 10.5 hours and 32 hours after exposure, respectively. There were no signs of rhabdomyolysis or cardiotoxicity. About 50 hours after exposure, the patient developed oliguric renal injury, hepatic failure (ALT 10943 U/L, AST 16936 U/L, bilirubin 5.5 mg/dL, LDH 10362 U/L) and severe coagulopathy (INR 3.5, fibrinogen 165 mg/dL). The patient was transferred to our ICU and received vitamin K, fresh frozen plasma and intravenous antidotal treatment with acetylcysteine, as phosgene - an intermediate highly reactive hepatotoxic metabolite of chloroform - depletes hepatocellular glutathione. Hepatotoxicity peaked about 60 hours after exposure and the patient developed anuric tubulo-toxic renal failure that required renal replacement therapy. Due to ensuing hepatic encephalopathy I° and severe coagulopathy, we were prepared for high-urgency liver transplantation. However, both the clinical and clinical-chemical condition of the patient improved within the next 24 hours during symptomatic and antidotal treatment, thus liver transplantation could be circumvented. Intermittent haemodialysis was required for another week and the patient finally made a full recovery with restored renal and hepatic function 21 days after her suicidal attempt. *Conclusion:* Life-threatening complications after chloroform inhalation can occur with remarkable clinical latency. Beside antidotal therapy with acetylcysteine, frequent re-evaluation of the clinical as well as the laboratory condition of the patient is thus required and patients should be transferred early to specialized toxicological units where urgent liver transplantation is feasible.

41. Acetaminophen (Paracetamol) Exposures: A Profile of Life-Threatening and Fatal Outcomes

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Objective: Exposures to acetaminophen (paracetamol) alone or in combination with other pharmaceuticals are the most common exposures managed by poison information centers in the United States. Most exposures have a favorable outcome but some are life-threatening or fatal. This project profiles the life-threatening and fatal acetaminophen exposures as reported to American poison information centers. *Methods:* The AAPCC NPDS was searched (2000–2007) for all human exposures to acetaminophen alone or in combination with other pharmaceuticals. Descriptive statistics were used to characterize the data. *Results:* A total of 616,395 exposures to acetaminophen were identified. Life-threatening outcomes accounted for 13,016 (2.1%) exposures and there were 1,217 (0.2%) fatalities. Acetaminophen in combination with another pharmaceutical was implicated in 85.1% of the fatalities compared to 92.5% of the life-threatening exposures. Intentional exposures for substance abuse purposes or self-harm were responsible for 87.2% of the fatal outcomes and 89.9% of life-threatening exposures. In fatal outcomes 36.4% had an acute-on-chronic or chronic (duration of exposure that exceeds 8 hours) component to the exposure; in life-threatening outcome patients 26.0% were acute-on-chronic or chronic exposures. Females accounted for 63.4% of the fatalities and 60.7% of life-threatening exposures. Less than 0.9% of fatal and life-threatening outcomes occurred in children less than 6 years of age; adults over 20 years of age accounted for 87.4% and 92.9%, of life-threatening and fatal outcomes, respectively. *Conclusion:* The majority of fatal and life-threatening exposures involved multiple pharmaceuticals, not just acetaminophen. Fatal and life-threatening exposures were more likely to occur in adults and fatalities were rare in children less than 12 years of age. A chronic exposure to acetaminophen was slightly more common among patients with fatal outcomes.

42. The Role of a Poisoning Centre in Pharmacovigilance

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Objective: To demonstrate the role and the means of action of a Poisoning Centre in pharmacovigilance. *Case report:* Dentocalmin, a product used as a local anesthetic, analgesic and antiseptic in dental practice contains lidocaine, menthol and phenol and does not produce side effects when used in this way. The first case with Dentocalmin poisoning was reported in 2005 in a 3 year old boy who died as a consequence of seizures and acute respiratory failure. Between 2005–2008 the number of cases increased; another 27 cases being registered. The clinical appearance was very severe with seizures, respiratory arrest and hypotension requiring, in many cases, mechanical ventilation. There were four deaths and two patients recovered with severe neurological sequelae. In 2008 the Poisoning Centre decided to seek some explanation concerning the occurrence and reason for it happening. The first question was: why the poisonings had occurred recently although the product had been used in dentistry for a long time without side effects. The two possible explanations were: 1. the product is widely used and available from pharmacies without prescription because is considered a very safe product; 2. the bottle is quite similar with that of vitamin D3. Following this analysis we decided to send written referrals to the producer, to the National Medicines Agency and to the Ministry of Health (document no. 214/10.01.2008). Consequently their investigations resulted in the following: the marketing authorization of Dentocalmin stated that this medicine must be used only in dentistry practice, and not be for sale in community pharmacies. In all the cases the product was issued without prescription from the community pharmacies and wrongly given to children by their parents or accidentally ingested by the children themselves. The result was that the National Medicines Agency ordered the withdrawal of the drug from community pharmacies and the use only in dental clinics (document no. 642/30.012008). Consequently, the number of Dentocalmin poisonings slowly fell until July 1st 2009. *Conclusion:* The efficient and useful intervention of the Poisoning Centre determined the quick reaction of the authorities and the disappearance of a very severe poisoning, which may be life threatening for children.

43. Adverse Drug Reactions - Is The Patient in the Loop?

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Objective: Adverse drug reactions are common, and may cause readmission.[1] Our aim is to develop a best practice model based on published standards[2], incorporating our existing method of communication about adverse drug reactions (ADR) experienced during hospitalisation. *Methods:* Each ADR report is reviewed fortnightly by a multi-disciplinary ADR committee, which sends a letter and card detailing ADR advice to patients. The patient is requested to show the letter to their doctor and pharmacist. Patients were contacted by telephone to assess the value of this process. The hospital's consumer group was consulted on the format of the letter. Patients' discharge letters were assessed for ADR information. *Results:* From February to July 2010, 104 suspected drug reactions were reviewed, involving 124 agents. Sixty-eight patients were included in the study. Seventeen patients (25%) were admitted because of the ADR. Of all ADRs reported 23% were severe or life-threatening. Of the 56 patients contacted, four first found out about the ADR after they received the letter. 80% found the card useful, with 50% carrying the card in their wallet. 52% patients had shown or were intending to show the letter to their doctors. Only 2 (4%) had shown it to their pharmacist. 63% would like the letter sent directly to their doctor. The majority (94%) would recommend this system to other hospitals. Of the 49 discharge summaries available, the ADR was documented in 80% and specific management advice in 18%. *Conclusion:* The majority of patients kept the card, although the letter was not universally shown to doctors or pharmacists. Improvements are being made to format, legibility and terminology incorporating feedback from patients and other consumers. Current methods are being improved to further facilitate communication of ADR information between health care professionals and their patients in acute and ambulatory settings. *References:* 1. Zhang M, Holman CD, Preen DB, et al. Repeat adverse drug reactions causing hospitalization in older Australians: a population-based longitudinal study 1980–2003. Br J Clin Pharmacol 2007; 63:163–70. 2. Second National Report on Patient Safety: Improving Medication Safety: Australian Council Safety Quality Health Care, 2002. http://www.health.gov.au/internet/safety/publishing.nsf/Content/F0FD7442D1F2F8DDCA2571C6000894FF/$File/med_saf_rept.pdf [accessed 19 Nov 2010]

44. Safety of Exposures to Levetiracetam Reported to the American Association of Poison Control Centers from 2000 to 2009

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Background: Only very limited data is available exploring the safety of levetiracetam in cases of accidental or intentional exposure. *Methods:* All levetiracetam exposures reported to 61 American

poison control centers during 2000 to 2009 were identified. Demographics, dose, co-ingestants, symptoms, and medical outcome were abstracted from each exposure case. Univariate analyses were used to identify risk factors for major toxicity or death. *Results:* A total of 506 cases of levetiracetam exposures were reported during the study period. Median age was 29.5 years (interquartile range: 8.0 years, 50.0 years) and 52.0% were female. 232 (45.8%) cases involved levetiracetam exposure only. In 478 of 506 cases (94.5%), medical outcome was known. Two (0.4%) deaths were reported in patients with multiple substance ingestion, 18 (3.6%) and 50 (9.9%) cases resulted in major or moderate toxicity, respectively. Minor, minimal or no effects were reported in 388 (76.7%) exposures. Multiple substance ingestion and suicidal intention were strongly associated with major toxicity or death. There were no cases of major toxicity in children aged 6 years or less. In only one of 18 (5.6%) cases with major toxicity reported was exposed to levetiracetam only. *Conclusion:* Exposure to levetiracetam was safe in the vast majority of cases.

45. Aphasia: An Unusual Effect from Bupivacaine Regional Anesthesia

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Objective: Focal neurological deficits have rarely been described as complications of intrathecal and retrobulbar local anesthetic administration. We describe a patient who developed expressive aphasia after regional bupivacaine infusion. *Case report:* A 48-year-old woman with chronic neck pain received 28 mg bupivacaine as a cervical median nerve branch block in preparation for radiofrequency neurotomy. Shortly after the infusion she complained of shortness of breath and the sensation of tongue swelling so the procedure was aborted and she was turned from prone to supine. She developed hypotension with systolic pressure below 80 mm Hg and a pulse oximetry value below 50% saturation. She was treated with 500 mL saline bolus, 100% oxygen via bag valve mask, and 50 mg diphenhydramine intravenously for a suspected allergic reaction. She was then transported to the emergency department and manifested aphasia en route. On arrival, her vital signs had improved: blood pressure 147/28 mm Hg; pulse 108/min; respiratory rate 16/min; oral temperature 36.4 degrees Celsius; oxygen saturation 99% on room air; and capillary glucose 93 mg/dL. She appeared generally anxious in minimal distress with resting tremor of all four extremities, but was alert and cooperative. Cranial nerves II through XII were intact. Oropharynx was clear with somewhat dry mucous membranes. Neck examination was normal. She demonstrated no difficulty with secretions or apparent dysphagia. Lungs were clear to auscultation bilaterally. Heart was minimally tachycardic without murmurs, gallops or rubs. Radial and dorsalis pedis pulses were 2+ bilaterally. Motor strength was 4/5 throughout. She had no sensory deficits grossly, normal reflexes, and normal cerebellar function. Electrocardiogram demonstrated sinus tachycardia with normal QRS interval. Serum electrolytes were within normal ranges and serum troponin was negative. She was administered an additional 500 mL intravenous saline bolus, 125 mg methylprednisolone and 1 mg lorazepam, and was observed via continuous cardiac monitor. Within 90 minutes of arrival all symptoms had resolved and vital signs normalized. Her remaining hospitalization was uneventful. Serum bupivacaine concentration later returned 0.18 mcg/mL (reference range: <1.1 mcg/mL). *Conclusion:* Peripheral administration of bupivacaine proximate to central nervous system structures can precipitate temporary focal neurological deficits.

46. Rhabdomyolysis and Hepatitis in a Patient with Prostate Cancer Being Treated with High Dose Ketoconazole and Concurrent Simvastatin Therapy

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Objective: HMG-CoA reductase inhibitors such as simvastatin are associated with rhabdomyolysis through a decrease in Coenzyme Q10 concentration. Ketoconazole is a potent inhibitor of CYP3A4 which is responsible for the metabolism of simvastatin. We report a case of rhabdomyolysis and hepatitis related to concurrent ketoconazole and simvastatin therapy. *Case report:* A 77 year-old man with a history of hormone refractory prostate cancer, hypertension, and dyslipidemia presented to the hospital with progressive weakness over 2 weeks. He had obtained a prescription refill that included ketoconazole 400 mg TID, hydrocortisone, and simvastatin three weeks prior. Approximately one week after the refill, he complained of generalized muscle weakness and dark colored urine. Physical examination revealed diffuse muscle weakness most pronounced proximally, a normal neurologic examination and no evidence of spinal cord compression. The aspartate aminotransferase and alanine aminotransferase were 1500 U/L and 750 U/L respectively (normal <48 and 40 U/L, respectively) and the creatine kinase was 65,000 U/L with normal renal function. The urine was red, cloudy, and stained positively for myoglobin. He was admitted and received supportive care with discontinuation of simvastatin. The patient's transaminase and creatine kinase improved over his hospital course with no change in his renal function. It was later discovered that a pharmacy error resulted in the substitution of hydrocortisone for ketoconazole, resulting in the patient using 2000 mg daily rather than the 1200 mg prescribed. *Conclusion:* Rhabdomyolysis is a rare but potentially severe toxicity of statin therapy and is well-reported with simvastatin and lovastatin. It appears likely that the rhabdomyolysis experienced by this patient was related to the drug interaction caused by the increased dose of ketoconazole, a potent CYP3A4 inhibitor, resulting in accumulation of simvastatin. Clinicians should carefully monitor for potential rhabdomyolysis in patients who are taking a statin medication as well as medications which may inhibit the metabolism of statin medications such as ketoconazole. Patients should be vigilant of the potential for all medication errors including pharmacy dispensing errors.

47. Use of Naloxone and Vasopressin to Treat Prolonged Hypotension Following Valsartan Overdose

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Objective: Angiotensin II receptor blockers (ARBs) such as valsartan are commonly used to treat hypertension. ARBs bind at the AT1 receptors to inhibit vasoconstriction, renal sodium reabsorption, and sympathetic activation which are mediated by angiotensin II. Isolated overdoses of ARBs rarely produce hypotension, which commonly occurs when other cardiovascular toxins are co-ingested. We report refractory hypotension following a valsartan overdose successfully treated with naloxone and vasopressin. *Case report:* A 19 year-old healthy woman presented to the emergency department 30 minutes after ingesting 25 tablets of valsartan (80 mg) that was her stepfather's medication. No other cardioactive medications such as beta-blockers were available in the household. Initial vital signs were: BP 110/70 mmHg; pulse 80/minute; respirations 16/minute; temperature 37°C; room air pulse oximetry 99%. Her mental status was normal, but with a depressed affect. Initial laboratory studies included a normal chemistry panel and complete blood count. Paracetamol and salicylates were negative and her ECG was normal. Three hours after her ingestion, her blood pressure fell to 70/40 mmHg and her pulse increased to 111/min. Her hypotension was refractory to 3 L of intravenous normal saline and high-dose dopamine. At this time poison control center consultation was obtained and recommendations included: vasopressin starting at 0.05 units/min and naloxone bolus of 2 mg followed by a 1 mg/hour drip. Within 30-minutes the patient's blood pressure increased to 110/70 mmHg with a decrease in pulse to 80/min. Treatment was continued for 6 hours and eventually titrated down. She was discharged in good condition the following day. *Conclusion:* Most cases of hypotension following an ARB overdose typically occur in the setting of a mixed overdose with other cardioactive medications. Experimental models demonstrate naloxone antagonizes endomorphine inhibition of angiotensin II induced contractile response and negates the hypotensive effects of ACE-I given to healthy men. Studies have also demonstrated ACE-I and ARB prevent hemodynamic response of vasopressin. Cases have reported the use of vasopressin and vasopressin analogues to reverse hypotension induced by ACE-I and ARBs. While most patients who present with an isolated overdose of an ARB rarely develop hypotension, the use of naloxone and vasopressin should be considered for patients who develop hypotension refractory to standard treatment.

48. Electroconvulsive Therapy for Severe Refractory Neuroleptic Malignant Syndrome

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Objective: To describe the management of severe refractory Neuroleptic Malignant Syndrome (NMS) likely due to rapid escalation of clozapine dosage. *Case report:* An 18 year-old man with bipolar disorder, presented following 2–3 days of temperatures of 38.9–39.4°C and confusion. One week prior, he started to taper his olanzapine dose. Concurrently, approximately 12 days prior, he started clozapine and increased the dose from 100 mg to 125 mg the day prior to admission. Other medications included: lithium, valproic acid, benztropine, pravastatin, metformin, and allopurinol. His initial vital signs were: BP 120/70 mmHg; HR 103/min; RR 18/min; T 38.9°C; SpO_2 100% RA. Over the course of the next 24 hours, the patient became progressively more hyperthermic (T 40.4°C), confused, and agitated. He had a whole body tremor without rigidity and/or hyperreflexia. The patient was intubated, sedated, paralyzed, and actively cooled with an external cooling device. Within 48 hours of hospitalization, the patient displayed autonomic instability, with fluctuating blood pressures. When intermittently weaned off sedation, lead pipe rigidity was present, and bromocriptine was administered unsuccessfully for a diagnosis of NMS. He had a normal CT and MRI of the brain, lumbar puncture with negative viral and bacterial cultures, and an unremarkable EEG. The CK remained normal throughout hospitalization. Persistent rigidity and hyperthermia prompted initiation of dantrolene with noticeable relaxation of muscular tone. After three weeks of maximal therapy in the ICU with minimal clinical improvement, electroconvulsive therapy (ECT) was started to treat NMS and continued for five sessions. The patient gradually improved over a six weeks ICU stay. He returned to his baseline, and was discharged to home following physical rehabilitation. *Conclusion:* Severe refractory NMS may occur in a young patient likely due to rapid escalation of clozapine dose while on olanzapine. Beyond rapid cooling, it is challenging to identify whether a single therapeutic intervention was more instrumental than others. Electroconvulsive therapy may be considered as therapeutic adjunct, following a complete medical evaluation and exhaustion of

therapeutic options, in a patient with recalcitrant NMS. *References:* Trollor JN, Sachdev PS. Electroconvulsive treatment of neuroleptic malignant syndrome: a review and report of cases. Aust N Z J Psychiatry 1999; 33:650–9.

49. Status Epilepticus After Chronic Topical Use of Camphor Cream

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Introduction: Camphor is a pleasant smelling cyclic ketone of the hydro aromatic terpene group. The mechanism by which camphor produces toxicity is unknown. Within a period of 5 to 15 minutes, patients commonly complain of mucous membrane irritation, nausea, vomiting, and abdominal pain. Generalized tonic-clonic convulsions are often the first sign of significant toxicity and can occur soon after ingestion. Central nervous system depression is commonly seen, such as headache, dizziness, confusion, agitation, anxiety, hallucinations, myoclonus, and hyperreflexia. *Objective:* The aim of the study is to describe a unique case of generalized tonic-clonic convulsions, after one week of dermal applications of camphor cream in an elderly patient. *Case report:* A 66-year old female was brought to the University Clinic for Toxicology in Skopje, with status epilepticus, after several generalized tonic-clonic seizures. On arrival, the patient was somnolent, with severe headache, hypotensive (14/9 kPa), with partial amnesia, relaxed muscles, a small amount of blood in the month and a specific odour. Five minutes later, during standard examination, the patient developed another generalized tonic-clonic seizure. 10 mL diazepam was given intravenously to stabilize the patient, and a few minutes later the patient woke up. Heteroanamnesis taken from her husband showed that she had had another similar convulsion ten days previously. EEG, CT and MRI taken previously, did not show any abnormalities. The specific smell, repeated seizures and especially the dermal application of camphor cream, suggested poisoning with camphor. The toxicological examination showed a positive result. After excluding the camphor cream, the patient did not manifest further seizures. *Conclusion:* Chronic topical use of camphor cream can result in serious toxicity. *References:* 1. Manoguerra AS, Erdman AR, Wax PM, et al. Camphor poisoning: an evidence-based practice guideline for out-of-hospital management. Clin Toxicol (Phila) 2006; 44:357–70 2. Chevallier A. Encyclopedia of Herbal Medicine. 2nd ed. London, England. Dorling-Kindersley, 2000. 3. Ody P. The Complete Guide to Medicinal Herbs. 2nd ed. London, England. Dorling-Kindersley, 2000.

50. Long-Acting Olanzapine Injection Can Produce Rare Severe Neurological Events. A Case Report

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Objective: To describe a case of an adverse event after a long-acting olanzapine (LAO) injection. *Case report:* A 59 year old Caucasian manic depressive male presented with seizures, 150 minutes after a third olanzapine 300 mg intramuscular injection. His daily therapy was valproate 50 mg and cyamemazine 25 mg. Clinical examination showed post-critical confusion, miosis, clonus of the arms; intravenous clonazepam was given. BP was 110/70 mmHg, HR 95 bpm, SpO_2 100%. ECG showed no QT abnormality. Temp was 37.1°C. Dextrose was 6.2 mmol/L and lactate 2.6 mmol/L. In the following hours, he presented delirium, no verbal contact; awoke at H16; discharged at H30 with oral clobazepam 10 mg daily dose. Olanzapine level (HPLC) on H16 was 376 microgram/L with valproate level 58 milligram/L. Alcohol and other known drug inducers were absent. Other biological specimens and CT scan were normal. Further blood samples for olanzapine showed 35 micrograms/L on Day 15 and 7 micrograms/L on Day 43. *Discussion:* LAO is a pamoate salt of olanzapine, administered by intramuscular injection with an intended slow release of olanzapine during several weeks. Olanzapine plasma level was 7.1 microgram/L at H4.4 with 5 mg by oral route and 5 fold more with 5 mg by intramuscular route.[1] After LAO injection (150–300 mg) olanzapine levels went from 4.2 to 73.2 microgram/L, some cases up to 600 microgram/L, returning to therapeutic range within 24–72 hours; half-life was 30 days.[2] Olanzapine overdose usually produces miosis, hypotension with tachycardia, extrapyramidal syndrome and dyskinesia. No hypotension or respiratory depression have been reported with LAO. LAO can produce a Post Injection Delirium-Sedation Syndrome (PDSS) either immediately or in the following 3–5 hours. From 45,000 injections in 2054 patients in the years 2000 to 2008, very few (0.07%) cases of PDSS have been reported in the company studies.[2] A European post-marketing study has been going on since 2008, co-managed by France and Denmark. *Conclusion:* LAO requires attentive nursing in the immediate hours after injection. *References:* 1. Markowitz JS, DeVane CL, Malcolm RJ, et al. Pharmacokinetics of olanzapine after single-dose oral administration of standard tablet versus normal and sublingual administration of an orally disintegrating tablet in normal volunteers. J Clin Pharmacol 2006; 46:164–71. 2. Detke HC, McDonnell DP, Brunner E, et al. Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, I: analysis of cases. BMC Psychiatry 2010; 10:43.

51. Foveal Damage in 10 out of 30 Cases of Visual Disturbance in Poppers Users

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Objective: To update the regulation of poppers in France according to their toxicity profile, the French Health Products Safety Agency requested the French Committee of Toxicovigilance for the analysis of cases reported to the French poison centres. The discovery of cases with visual disturbances (VD) during this 1st study justified a complementary inquiry targeted on this new risk. We report the results of this 2nd study. *Methods:* A retrospective study collected all cases of poppers inhalational exposure reported to the French Poison and Toxicovigilance centres between 1999 and May 2010. Cases resulting from direct ocular contact with poppers were excluded. *Results:* 829 cases of inhalational exposure to poppers were identified and 30 with VD appearing a few minutes to a few days after inhalation. The two main complaints were visual acuity decrease (more than 2/3 of the cases) and phosphenes (light or flashing spots, dazzling flashes, in 50% of the cases). Fundoscopy showed a yellow dot or stain in the fovea in 10 of the 11 investigated cases. High resolution optical coherence tomography showed damage of cones in the external segment of the fovea (9 cases). The involved poppers were butyl nitrite in 2 cases, isopropyl nitrite in 6, and n-propyl nitrite in 4; the nature of the remaining 18 poppers was unknown. Inhalation of poppers was associated with alcohol intake in 8 cases, with cocaine in 2, and a combination of the 2 in a further case. *Conclusion:* Three previous cases of VD after poppers inhalation have been reported: visual acuity deterioration was associated with yellow dots in the fovea in 2 cases and with damage to the fovea external segment in one. Poppers users and ophthalmologists (as well as all other physicians) should be informed of this retinal toxicity, and the latter, of the investigations to be conducted. Due to the heterogeneity and limited number of known cases, a prospective study should be performed to better characterize this adverse effect and identify its risk factors.

52. An Unusual Cause of Interstitial Lung Disease in a Teenager

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Objective: To present a case of interstitial lung disease in a previously healthy teenager, caused by an unusual environmental exposure. *Case report:* A 15 year-old Caucasian female presented with 17 days of fever and cough, and one year of fatigue and weight loss. Past medical history was significant for asthma, anemia non-responsive to iron supplements, and facial acne. Physical examination was only remarkable for facial acne, with heavy make-up. Chest radiograph demonstrated severe, diffuse, coarse interstitial lung pattern bilaterally. High-resolution computed tomography of the chest demonstrated: bilateral patchy interstitial infiltrates, areas of ground glass opacity, honeycombing pattern, and subcarinal lymphadenopathy. Flexible bronchoscopy demonstrated blood-tinged secretions in the distal trachea. Laboratory evaluation demonstrated normocytic non-hemolytic (Coombs negative) anemia (Hgb: 9.4 mg/dL), and elevated acute phase reactants (ESR: 90 mm/1hr, CRP: 138 mg/dL). Viral and fungal serologies were negative. Bacterial, mycobacterial, and fungal cultures from blood and broncho-alveolar lavage fluid were negative. Flow cytometry with leukemia/lymphoma panel was negative for malignancy. Sweat chloride was normal, and the genetic testing for cystic fibrosis and alpha-1-antitrypsin deficiency were negative. Lupus panel, ANCA antibodies, and complement levels were normal. Tuberculin skin test was negative.[1] Inquiry about environmental exposures revealed the use of more than twelve 30-gram containers of facial make-up within the past 2 years, to cover her facial acne. The active ingredients were: titanium dioxide and zinc oxide; the inactive ingredients included: silica, calcium silicate, soil minerals, mica, and iron oxides. Lung biopsy demonstrated sub-pleural foci of alveolar lipoproteinosis, with granular eosinophilic debris, prominent cholesterol clefts, and mild chronic interstitial inflammation, consistent with the clinical diagnosis of acute silico-proteinosis. This raised suspicion for acute silicosis[1], and the patient was started on systemic corticosteroids; she became afebrile, her symptoms resolved, and her hemoglobin normalized (12 g/dL) within four weeks of the initial presentation. *Conclusion:* To our knowledge, this is the first case of acute silicosis reported in a pediatric patient, and it should raise awareness about the risks associated with excessive use of powder make-up containing silica. *References:* 1. Greenberg MI, Waksman J, Curtis J. Silicosis: A Review. Dis Mon 2007; 53:394–416.

53. Carbon Monoxide Poisoning Caused by Waterpipe Smoking

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Objective: Waterpipe smoking is an old tradition in the Middle East that has been considered quite harmless. The use of waterpipes is spreading among young Europeans, but with a different pattern of smoking habits. We describe two cases of carbon monoxide (CO) poisoning caused by waterpipe smoking. Only two similar cases have previously been reported.[1,2] *Case series:* 1. A 15-year old girl was smoking a waterpipe on three consecutive days. After the first session she had no symptoms. Day two she became dizzy and got a headache after smoking. The third day she was smoking very intensively during 15 minutes when she became nauseous and stopped. One hour later she was dizzy, had a headache, and suddenly became unconscious. She had a short seizure, vomited, and then

woke up. The patient presented at the emergency room 1.5 hours after smoking. She was then confused, answered questions with delay, and complained of headache. An arterial carboxyhaemoglobin (a-COHb) sample, taken 2 hours 40 minutes after smoking, showed 21%. She was treated with 100% normobaric oxygen and the a-COHb had dropped to 1% at 8 hours post smoking. At follow-up she displayed no sequelae. 2. A 28-year old man was in a habit of smoking a waterpipe on his balcony. This time he was smoking inside in a friend's apartment. After the session he felt dizzy and cold, and soon thereafter he became unconscious. During acute transportation to hospital he awoke. At the emergency room he complained of headache and was unable to lift his arms and legs from the stretcher. The immediately measured a-COHb level was 32%. The patient was treated with hyperbaric oxygen and was discharged two days later in good condition. *Conclusion:* Waterpipe smoking involves a risk of severe carbon monoxide poisoning. Several explanatory factors contribute: a higher CO content per smoke volume compared to cigarettes due to incomplete combustion, a much larger volume of each waterpipe inhalation because of a low and comfortable smoke temperature, and probably, a more intense way of smoking among young Europeans. *References:* 1. Lim BL, Lim GH, Seow E. Case of carbon monoxide poisoning after smoking shisha. Int J Emerg Med 2009; 2:121–2. 2. Cavus UY, Rehber ZH, Ozeke O, Ilkay E. Carbon monoxide poisoning associated with narghile use. Emerg Med J 2010; 27:406.

54. Cerebral Venous Thrombosis Following Exogenous Thyroxine Exposure

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Objective: Cerebral venous thrombosis (CVT) is a rare complication of primary hyperthyroidism. We report the first case, to our knowledge, of CVT following exogenous thyroxine poisoning. *Case report:* A 27 year-old man presented to the Emergency Department (ED) immediately following a generalized tonic-clonic convulsion. He later reported that for approximately four weeks he was taking veterinary thyroxine 0.8 mg tabs purchased on the Internet up to three times daily for weight loss. He discontinued their use five days prior to presentation because of headache. Vital signs were: BP 154/77; pulse 169/min; respirations 35/min; temperature 37.6°C; O_2Sat 100% on a non-rebreather mask. On physical examination he was agitated but had no neurological deficits. Convulsions recurred in the ED and he became hypertensive to 204/105 mmHg. After multiple doses of intravenous benzodiazepines, three doses of intravenous labetalol (10 mg each), and a phenytoin load, he was intubated for airway protection. Head CT showed a left temporal intraparenchymal hemorrhage with subdural and subarachnoid extension and hyperdensity in the transverse and sigmoid sinuses concerning for CVT. Admission laboratories were significant for a free T4 of 3.67 ng/dL (normal, 0.800–2.00) and thyroid stimulating hormone (TSH) of $<$0.00400 mIU/L (normal, 0.400–4.60). After extubation on hospital day (HD) #2, agitation and headache gradually resolved. CT venogram and MRI demonstrated left temporal hemorrhage and filling defects of the left transverse and sigmoid sinuses, confirming CVT. Intravenous heparin was started and bridged to warfarin on HD #4. He was discharged with a normal neurological examination on HD #8. Hematologic evaluation revealed Factor VIII level of 165% (normal, 50–150%), heterozygosity for Factor V Leiden and MTHFR C677T, and borderline positive activated protein C resistance and anti-annexin A5. *Conclusion:* CVT is a described complication of primary hyperthyroidism, often in combination with other thrombophilic conditions including elevated Factor VIII. Our patient had elevated Factor VIII levels, although it is unknown if this was present previously or due to the hyperthyroidism. We suspect that hyperthyroidism precipitated CVT in our patient with underlying hypercoagulable risks. We conclude that excessive exogenous thyroxine exposure may be a risk factor for CVT.

55. "Octane Booster" Ingestion Causing Refractory Methemoglobinemia

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Objective: Methemoglobinemia generally resolves rapidly with methylene blue therapy. We report refractory methemoglobinemia following ingestion of an automotive fuel additive. *Case report:* A 26 year-old man presented to a rural hospital with cyanosis and altered mental status after ingesting 250 mL of Klotz Octane Booster. Vital signs were: pulse, 140/min; respirations, 45/min; BP, 130/50 mmHg; and room air O_2Sat, 82–85%. An ABG on supplemental O_2 revealed: pH 7.46, PCO_2 23 mmHg, PO_2 181 mmHg. The patient was intubated for airway protection. Co-oximetry was not available but the patient was empirically treated for methemoglobinemia with methylene blue (0.7 mg/kg) intravenously. No improvement in his cyanosis was noted. Fourteen hours later, on arrival to the tertiary care center, he was still cyanotic and received methylene blue 2 mg/kg intravenously with only mild improvement in his cyanosis. Two hours later, cyanosis recurred and co-oximetry revealed a methemoglobin level of 13%. He remained cyanotic with continually elevated methemoglobin levels that slowly trended down reaching 10% on day four, 5% on day five, and 2% on day six. His ICU course was complicated by hemolysis, pneumonia, and renal failure. His glucose-6-phosphate dehydrogenase (G6PD) deficiency screening and family history were negative for G6PD deficiency. Following three weeks of supportive measures, the patient was discharged home. The material safety data sheet for this Octane Booster listed only "petroleum distillage NOS" under hazardous components, failing to identify an agent with oxidizing potential. Review of the literature regarding refractory methemoglobinemia highlights dapsone and aniline as common causes. In one proposed mechanism, aniline's metabolite, phenylhydroxylamine (PHA), rapidly metabolizes to nitrosobenzene, oxidizing a molecule of hemoglobin to methemoglobin. Nitrosobenzene is then reduced back to PHA with the electron donor NADPH. This cycle continues, generating more methemoglobin and using more NADPH. Methylene blue only functions to reduce methemoglobin after being reduced by NADPH-methemoglobin-reductase to leukomethylene blue. This reaction also requires NADPH and is thereby competitively inhibited by aniline metabolism. The company was contacted and the chemical mixer reported that aniline was used as a stabilizer in this product. *Conclusion:* Aniline-induced methemoglobinemia may be prolonged and may not completely resolve with one dose of methylene blue.

56. Eight Orellanin Mushroom Intoxications with Acute Kidney Injury after the Ingestion of *Cortinarius orellanus*

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Objective: Mushroom intoxications can be categorised into 13 specific syndromes.[1] The gastrointestinal syndrome, the amatoxin syndrome and the phalloides syndrome are well-known to clinical toxicologists and poisons centres.[2] Severe orellanin intoxication is very infrequent and there exist only a few case series describing this rare entity.[1] Hence a case series of severe orellanin intoxications is presented. *Methods:* In this retrospective analysis the clinical course and long-term outcome of eight patients with orellanus syndrome is described. *Results:* All patients (four women and four men, 44–74 years of age) were members of a German tourist group who vacationed in Norway. Hunting mushrooms, they all mistook *Cortinarius orellanus* for the edible chanterelle. Two days later they all developed gastrointestinal symptoms, headache and myalgia. They went to see a physician 7 ($\pm$1) days later. All developed acute renal insufficiency (serum creatinine 1.7–18.4 mg/dL). Five patients were oliguric and required renal dialysis. In addition, 6 patients were treated with steroids and N-acetylcysteine. The duration of their hospital stay was from 7 to 33 days. At present, 2 years after the intoxications, 3 patients are still treated by chronic hemodialysis. In the other 5 patients renal function has not fully recovered resulting in advanced chronic kidney disease. Treatment with steroids and N-acetylcysteine did not affect outcome. *Conclusion:* Orellanin is a nephrotoxic substance that can cause severe renal tubular damage. Due to the infrequency of this syndrome and the long latency between the ingestion of the mushrooms and the emergence of symptoms the syndrome is difficult to diagnose. Therapy is symptomatic and depends on the severity of the acute kidney injury. Steroids and N-acetylcysteine seem not to be effective and advanced chronic kidney disease is a frequent long term outcome. There is no specific antidote. *References:* 1. Flammer R, Horak E. Giftpilze - Pilzgifte. Pilzvergiftungen. 1st ed. Basle, Switzerland: Schwabe Verlag, 2003. 2. Annual Reports of GIZ-Nord Poisons Centre, 1996–2007.

57. Survival Despite Lethal Level of Methemoglobin

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Background: Many substances are known to cause methemoglobinemia including foods containing nitrates. The concentration of methemoglobin usually correlates with severity of symptoms. Patients are rarely symptomatic with methemoglobin fractions below 15%, and the generally accepted lethal level of methemoglobin is 70%-80%. *Case report:* A 38 year old male and a 42 year old male, both previously healthy, presented to the emergency department 2 hours after ingesting cooked pork which they said tasted horrible. The 38 year old was lethargic, cyanotic, hypotensive and tachycardic. His methemoglobin level was 81%, anion gap was 20 and lactic acid level was 9. He was started on dobutamine, given methylene blue and fresh frozen plasma and admitted to the ICU. The patient initially appeared to improve, but he then had seizure activity and became unresponsive and hypotensive again. He was intubated and placed on a ventilator. Repeat methemoglobin level had risen to 86%. He was given a second dose of methylene blue. Nine hours after ingestion, his vitals had improved and his methemoglobin level dropped to 29%. The next day, he was extubated and had a methemoglobin level of 0.8%. He was discharged from the hospital after 4 days. On arrival to the ED, the 42 year old male vomited and appeared to be bluish-gray as well. He was evaluated and found to have a methemoglobin level of 19%. Following a dose of methylene blue, he was admitted to the hospital overnight. His methemoglobin level decreased to 0.6% before being discharged. Later, a home visit revealed the men had purchased a meat seasoning and had used 1 teaspoon per pound of pork. The label was written in Chinese lettering, and it was determined to be potassium nitrate (saltpeter). *Conclusion:* Consumption of potassium nitrate "meat seasoning" provides enough oxidant stress to cause potentially lethal levels of methemoglobin. Lethal levels of methemoglobin may be successfully treated with rapid supportive care and methylene blue therapy. Poison control centers should be aware

that food additives or seasonings may contain potassium nitrate or other nitrates.

58. Fatal Suicidal Poisoning by Injection of *Vipera lebetina* Snake Venom

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Background: Snake bites are quite common in Azerbaijan. The most frequent are *Vipera lebetina* bites. More than 100 cases are registered annually. However no medical reports about intravenous injection of *Vipera lebetina* snake venom exist in the literature. We present a case of fatal suicidal envenomation by *Vipera lebetina* snake venom. *Case report:* A 54 year old man with a past medical history of attempted suicidal poisoning with barbiturates occurring 2 months previously was admitted to the emergency department of the toxicological center 3 hours after deliberate intravenous injection of *Vipera lebetina* snake venom. On arrival the patient was comatose. His vital signs were BP 70/30 mmHg, HR 128 beats/min, RR 28/min, Temp 35.7°C, O_2 saturation 93% on room air. Initial laboratory tests showed leukocytosis - 20,700/mkL and mild anemia (hemoglobin level of 8.0 g/dL). Treatment was started with intravenous fluid infusion, corticosteroids and vasopressors. The patient received 3 doses of viperinae polyvalent antivenom. One hour later the patient presented severe gastrointestinal bleeding (recurrent coffee-ground vomiting and melena). Bleeding from the injection sites and development of vast hematomas were also observed. Blood tests showed thrombocytopenia (33,000 platelets/mkL), low level of fibrinogen - 93 mg/dL, prothrombin time prolonged to 17 seconds, an activated partial thromboplastin time prolonged to 66 seconds, fibrin split products were 45 mkg/mL. Due to gastrointestinal bleeding and coagulopathy the patient received a transfusion of 2 units of red blood cells and 2 units of fresh frozen plasma. Despite aggressive supportive treatment the patient died 3.5 hours after admission due to cardiac failure and symptoms of disseminated intravascular coagulopathy (DIC). *Conclusion:* Intravenous injection of *Vipera lebetina* snake venom can lead to DIC syndrome and may be fatal.

59. Overdose of Methimazole

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Objective: The acute toxicity of organic thiourea antithyroid drugs is considered to be low. In contrast to reports about adverse effects due to therapeutic use,[1] human poisoning cases were not known up to now. Firstly, the aim of the study was to evaluate cases of acute overdose. Secondly, we present the lethal course of a chronic overdose. *Case series:* 69 cases of accidental and intentional overdose (27 single, 42 multiple drug ingestions) with methimazole were reported to the PIC Erfurt from January 1994 to October 2010. Children and adults were involved in 24 and 45 cases, respectively. Female gender of patients predominated (40 f, 20 m, 9 not registered). Children and adults ingested 2.5 to 5000 mg (0.2 to 85 mg/kg) and 2.5 to 12,500 mg (0.04 to 179 mg/kg), respectively. All patients with acute overdose were asymptomatic or had nonspecific symptoms. Only one case with gastrointestinal complaints was reported after ingestion of 60 mg/d over 5 days. *Case report:* An 84-year-old woman with diabetes mellitus was treated with methimazole 5 mg/d over a long period. Despite chronic renal failure, the daily dose was not changed. She complained of gastrointestinal discomfort for weeks before and was admitted in a generally grave condition. Clinical features and laboratory findings showed severe hypothyroidism. In addition, marked chronic heart failure was diagnosed. High doses of thyroid hormones were administered in addition to symptomatic measures. The patient developed a myxedema coma as a consequence of decompensated hypothyroidism. She died two days after admission. *Conclusion:* No specific poisoning symptoms are expected after a single overdose of methimazole. It is unknown whether hormonal status will be changed when a very high dose is ingested. In such cases, we recommend control of thyroid-stimulating hormone and thyroid hormones a few days after ingestion. In chronic overdose, hormone synthesis may be depressed dramatically resulting in a life-threatening hypothyroidism. *References:* 1. Bartalena L, Bogazzi F, Martino E. Adverse effects of thyroid hormone preparations and antithyroid drugs. Drug Saf 1996; 15:53–63.

60. Difficulties in Therapy of Poisonings by Carbamates

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Objective: To investigate the efficacy of various oximes and anticonvulsants for carbamate poisoning. *Methods:* Carbamates belong to a group of compounds having a broad spectrum of toxicity - from relatively nontoxic to highly toxic compounds comparable with nerve agents. The current treatment of poisoning by organophosphates consists of the combination of cholinolytics like atropine and some oximes. The efficiency of oximes is not, however, satisfactory in the case of carbamate poisoning because oximes are not able to reactivate carbamylated acetylcholinesterase (AChE). It is considered that for treatment of carbamate poisoning administration of different cholinolytics only is effective. In this paper a number of oximes (toxogonine, pralidoxime, dipiroxime, HI-6, HS-3, HS-6, HGG-12), muscarinic (atropine, scopolamine, amysile) and nicotinic (arpenale, pentaphene) cholinolytics have been tested to protect mice against poisoning by carbamates. The effectiveness of a few anticonvulsants (diazepam, phenazepam, clonazepam) was investigated also. The following carbamates were used: insecticides (carbaryl, aldicarb), drugs (physostigmine, aminostigmine, neostigmine, pyridostigmine) and a few pyridile and quinoline carbamates with almost irreversible action on AChE. Oximes alone or with a mixture of cholinolytics and anticonvulsants were administered 15 minutes prior or 1 minute after the intoxication. In the experiments *in vitro* the possibility of oximes reactivating the carbamylated purified human erythrocyte AChE was studied. *Results:* By use of different groups of oximes quite different effects were observed. All tested oximes reduced the toxicity of aminostigmine, aldicarb and neostigmine whereas no effect could be determined on the toxicity of physostigmine and pyridostigmine. The toxicity of carbaryl and irreversible carbamates was significantly increased by toxogonine, dipiroxime and pralidoxime. Oxime therapy reduced the protective effect of cholinolytics against poisoning with these types of carbamates. The high efficiency of the mixture of atropine, arpenal and phenazepam for treatment and prophylaxis of carbamate poisoning was shown. As demonstrated by experiments *in vitro* oximes did not reactivate carbamylated AChE. The oxime HI-6 and TMB-4 increased the toxicity of irreversible inhibitors. For the first time the high prophylactic effect of reversible inhibitors galantamine and tacrine as drugs for prophylaxis of poisonings by irreversible carbamates has been shown. *Conclusions:* Thus, these data indicate that the efficiency of oximes against carbamate poisoning is, at best, very limited and unsatisfactory. Therefore, there has been an active search for a broad spectrum antidote against poisoning by carbamates. The potential threat of terrorist usage of carbamates is connected with the high toxicity of compounds and the absence of universal antidotes.

61. Coma Blisters in Confirmed Phenobarbital Poisoning Associated With Other Central Nervous System Depressants: An Immune-Mediated Response?

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Objective: To report a case of coma blisters, with histopathological and immunofluorescence findings, after confirmed intentional phenobarbital poisoning. *Case report:* A 45-year-old woman was found unresponsive at home by family members. Tablets of her current medications (clonazepam, promethazine, oxcarbazepine, quetiapine and phenobarbital) were found beside her. The patient was admitted to the local Emergency Department with a Glasgow coma scale of 5, bilateral miosis, HR = 98 bpm, and BP = 90/50 mmHg; initial procedures included endotracheal intubation, gastric lavage and a single dose of activated charcoal. She was subsequently referred to the university hospital, where the presence of bullous lesions over the right knee and left thumb was noticed. Laboratory results at admission revealed a plasma phenobarbital level of 63 μg/dL (RV 10–25) and a serum total CK level of 3,581 U/L (RV < 145). The patient was then treated with fluid replacement, multiple doses of activated charcoal and urinary alkalinization. A biopsy from the left thumb blister taken on day 4 revealed focal necrosis of the epidermis, a subepidermal blister partially filled with fibrin and necrosis of sweat gland epithelial cells. Direct immunofluorescence was strongly positive for IgG in superficial blood vessel walls but was negative for IgM, IgA, C3 and C1q. The patient remained on mechanical ventilation for 12 days and was discharged on day 21, with no sequelae. At discharge, she "confirmed" the ingestion of an overdose of all her current medications. *Conclusion:* Blister formation and eccrine sweat gland necrosis is a rare cutaneous manifestation associated with states of impaired consciousness, more frequently reported after overdoses of CNS depressants, particularly phenobarbital. Bullous lesions have been noted in 6.5% of a series of patients who suffering barbiturate poisoning, within as early as 4 h post-ingestion. The pathogenesis of coma blisters remains unclear, and their distribution cannot be explained simply by pressure effects in comatose patients. Hypoxia, hypotension, direct local toxic effects and autonomic instabilities in sweat gland function could contribute to blister formation and sweat gland necrosis. The positive results obtained here and in other studies by direct immunofluorescence indicate that an immune-mediated pathogenic mechanism cannot be excluded.

62. Fake Marijuana Causing Real Problems in Texas

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Objective: The use of synthetic cannabinoids in herbal-based products is gaining popularity as a method through which users can enjoy drug effects while avoiding drug test detection and legal complications of marijuana use. These products contain any of several synthetic compounds, such as JWH-018 and JWH-073, analogues of Δ9-tetrahydrocannabinol, the main psychoactive component in marijuana. Regulation and legal classification of these products are currently under review by U.S. government organizations, including the DEA, FDA, CDC, and local and state governments. There has been a significant increase in the reported use of marijuana homologs or synthetic marijuana in the State of Texas, increasing from 4 to 57 per month (1325% increase) over a ten-month period in 2010. *Methods:* We retrospectively analyzed 328 human exposures related to marijuana homologs reported to Texas poison centers during the ten month period of January-October 2010. *Results:* Of the identified cases, 75% (N = 246) of reported exposures occurred in males, 89% (N = 292) were considered to be classified as due to abuse or misuse, 74% (N = 242) were exposed at their own residence, of which 80% were exposed through

inhalation. Of all marijuana homolog exposures, 75% (N = 246) of exposures were managed at healthcare facilities. When examining the geographic distribution of calls, out of all 254 counties in the State of Texas, 73 counties had at least one reported exposure. Two of the most populous counties in Texas, Bexar (11%) and Harris County (11%) accounted for a large proportion of reported exposures. The most common signs and symptoms reported, in descending order, were tachycardia (38%), drowsiness (18%), agitation (18%), vomiting (17%), hallucinations (13%), and hypertension (11%). *Conclusion:* Greatly increased reported marijuana homolog exposures may be attributed to a number of causes, including an increase in accessibility, relatively exaggerated or adverse drug effects and recent extensive media attention. There should be careful monitoring of marijuana homolog exposures and the clinical effects and outcomes from reported cases. The increase in reported cases and potential health risks from undeclared ingredients in these products makes clinical recommendations challenging.

63. Preliminary Data on Exposure to Mephedrone in Pregnancy

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Objective: Mephedrone (4-methylmethcathinone, 4-MMC) is a synthetic cathinone structurally related to the naturally occurring alkaloids methcathinone and cathinone found in the khat plant (*Catha edulis*), which is commonly chewed for its stimulant properties. There are no published epidemiological studies or case reports describing fetal outcomes following the use of mephedrone in pregnancy. In view of reports of mephedrone-induced peripheral vasoconstriction,[1] there is a possibility of reduced placental perfusion and intrauterine growth restriction (IUGR), which has been observed in the offspring of regular khat users.[2,3] This research was performed to provide preliminary data on fetal outcomes after mephedrone exposure during pregnancy. *Methods:* Using standardised procedures, the UK Teratology Information Service (UKTIS) has provided fetal risk assessment for nine women exposed to mephedrone during pregnancy. Of these, outcome data has been obtained for four infants, the remaining pregnancies are ongoing. Two further pregnancy outcomes were reported to UKTIS retrospectively. *Results:* Of the six pregnancies with known outcomes, all exposures occurred in the first trimester of pregnancy. The prospective outcomes included two live-born infants (one premature, born at 24/40) with no congenital malformations and two elective terminations for social reasons. The two live-born infants that were reported retrospectively did not have congenital malformations but one displayed features suggestive of neonatal withdrawal, including jitteriness, hypertonia and high pitched screaming. *Conclusion:* This is the first data that we are aware of documenting pregnancy outcomes following fetal exposure to mephedrone, although data are inadequate to allow reliable conclusions to be drawn. Further data are required for this ongoing series. *References:* 1. James D, Adams R, Spears R, et al. Clinical characteristics of mephedrone toxicity reported to the UK National Poisons Information Service. Emerg Med J 2010; Aug 25 [Epub ahead of print]. 2. Eriksson M, Ghani NA, Kristiansson B. Khat-chewing during pregnancy-effect upon the offspring and some characteristics of the chewers. East Afr Med J 1991; 68:106–11. 3. Abdul Ghani N, Eriksson M, Kristiansson B, et al. The influence of khat-chewing on birth weight in full-term infants. Soc Sci Med 1987; 24:625–7.

64. Bath Salts and Plant Feeder Pills: Synthetic Cathinone Abuse in Ireland

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Objective: To investigate the prevalence of synthetic cathinone abuse in Ireland. *Background:* BZP (benzylpiperazine) was declared a controlled drug under the Misuse of Drugs act 1977 on 31st March 2009. As a result of this legislation the head shops started to sell products containing synthetic cathinones as an alternative. These products were sold as 'bath salts' and 'plant feeder pills' and marked 'not for human consumption' but were used as drugs of abuse. *Methods:* We examined all enquiries to the National Poisons Information Centre (NPIC) regarding so called 'bath salts' and 'plant feeder pills' from head shops for an 18 month period from 1st April 2009. The Garda Forensic Science Laboratory (Irish Police) analysed test purchases of various head shop products and provided a spreadsheet detailing the active ingredient of each product. We used this spreadsheet to identify the active ingredients in the products taken. *Results:* We identified 116 enquiries regarding 117 patients that had consumed different branded products sold as 'bath salt' or 'plant feeder pills'. The active ingredients involved in the enquiries to the NPIC were mephedrone 31.6%, methylone 14.5%, methylenedioxypyrovalerone (MDPV) 6.8%, butylone 6%, flephedrone 0.9% and naphyrone 0.9%. The ingredient was not identified in 39.3% of enquiries. The majority of enquiries originated from hospital emergency departments (EDs) (86.2%). Eighty patients were male (68.4%), 35 were female (29.9%) and 2 patients were of unknown sex. The age range of patients was 14–42 years (average 24.2, median 22.5). The symptoms displayed were tachycardia (40.2%), agitation (25.6%), mydriasis (21.4%), chest pain (18.6%), hypertension (14.5%) and palpitations (13.7%). The Poisoning Severity Score of all exposures was: none = 2, minor = 20, moderate 90, severe = 5 and fatal = 0. The Irish media (newspaper, radio, television) developed a considerable interest in head shops and 'legal highs' in the middle of our 18-month study. The majority of enquiries (82.8%) occurred in the final eight months of the study, after the media interest began. *Conclusion:* Synthetic cathinones exposure was associated with sympathomimetic features. Most patients had moderate symptoms. The number of patients presenting to EDs with cathinone intoxication increased dramatically during sustained media interest.

65. The Impact of the Classification of the Synthetic Cannabinoid Receptor Agonists on the Content of UK Spice Products

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Objective: Spice (also known as K2) has been available in Europe in head shops and over the Internet since 2006/7. A number of the synthetic cannabinoid receptor agonists (sCRA) were classified as Class B agents in December 2009 under the UK Misuse of Drugs Act, 1971 using specific and generic controls. The aim of this study was to assess the impact of this legislation on the sCRA present in Spice and to determine whether new sCRA outside of the legislation are now available. *Methods:* Spice products were purchased from Internet legal high websites selling to UK consumers. Products were purchased from the same website prior to and after the legislation and, where possible, the same products were purchased (if the product was not available, the replacement product or a product with a similar name was purchased). Products were analysed using liquid chromatography high-resolution tandem mass spectrometry (LCMSMS). Identification of the sCRA detected was undertaken by comparison to existing analytical databases or comparing the fragmentation pattern of novel substances using '*in silico*' methods. *Results:* 16 products were purchased prior to and 20 after the December 2009 UK control of sCRA. All of the pre-legislation products and 17 (85.0%) of the post-legislation products contained at least one sCRA; 3 (15.0%) of the post legislation products did not contain a sCRA. There were 9 different sCRA in the pre-legislation products; 8 of these and an additional 8 were detected in the post-legislation purchases. Fourteen (87.5%) of the sCRA in the post-legislation products were classified substances, 2 sCRA not covered under UK generic legislation were found in post-legislation products. *Conclusion:* Despite the UK Spice legislation, classified sCRA continue to be supplied over the Internet to UK users. Furthermore, new sCRA not covered by the legislation are also appearing in Spice products. Ongoing surveillance work is required to track the sCRA in Spice products and determine the potential for toxicity associated with these products. Consideration needs to be given to reviewing the UK legislation so that suppliers cannot circumvent it by supplying legal alternatives to the classified synthetic cannabinoid receptor agonists.

66. Abuse of Over-The-Counter Codeine-Ibuprofen Analgesics

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Background: Over-the-counter codeine-ibuprofen preparations have been available in pharmacies for many years. Nurofen Plus® is the market leader and contains ibuprofen 200 mg and codeine phosphate 12.8 mg per tablet. Anecdotal reports of abuse due to the codeine content and complications due to the ibuprofen content prompted the Australian Therapeutic Goods Administration to reschedule combination codeine products. In May 2010 they became behind-the-counter pharmacist only supply with restrictions on pack size. There has only been one published Australian case series on the misuse of codeine-ibuprofen products.[1] This series from the state of Victoria reported on 27 cases where predominant symptoms were gastrointestinal haemorrhage/erosions (n = 10), opioid dependence (n = 10), and hypokalaemia (n = 3). *Objective:* This review of poisons centre calls will characterise the extent and nature of abuse of over-the-counter codeine-ibuprofen analgesics. *Methods:* A retrospective review of calls made to the NSW Poisons Information Centre (the most populated state in Australia) during 1 January 2004–12 November 2010 involving the abuse of combination codeine-ibuprofen products. No outcome data was obtained. *Results:* 57 cases of abuse were found - an increase from 3 cases in 2004 to 14 in 2009. Of note, no cases have been reported after the date of rescheduling (1 May 2010). The brand was Nurofen Plus® in 39 cases and Panafen Plus® in 14, with four undocumented. The amount abused varied from 7 to 150 tablets (median: 24, interquartile range: 20–48; mode: 48 tablets daily), with the duration from weeks to years. Sixteen patients had complications of abuse reported, these included: opioid withdrawal effects (n = 7), renal failure (n = 3), renal tubular acidosis (n = 3), gastrointestinal bleed (n = 1), anaemia (n = 1), severe abdominal pain (n = 1), dehydration (n = 1), seizures (n = 1). *Conclusion:* Abuse of ibuprofen-codeine products can carry significant morbidity. Changes in codeine scheduling have decreased the reporting of abuse and thus it is expected that fewer cases of toxicity will result. Monitoring the impact of scheduling changes can further assist the authorities in making decisions in response to toxicovigilance activities. *References:* 1. Frei M, Nielsen S, Dobbin M, et al. Serious morbidity associated with misuse of over-the-counter codeine–ibuprofen analgesics: a series of 27 cases. Med J Aust 2010; 193:294–6.

67. Seizures Following Ingestion of the Synthetic Cannabinoid JWH-018

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Objective: To report a case of seizures following synthetic cannabinoid ingestion. *Background:* Synthetic cannabinoids (SC) are used as "legal highs" because they are not classified by the US designer drug laws. Reports of serious toxicity following confirmed use of synthetic cannabinoids are rare. We report severe toxicity including seizures following intentional ingestion of the synthetic cannabinoid JWH-018 which was confirmed by laboratory analysis. *Case report:* A healthy 48 year old man had a generalized seizure within thirty minutes of intentionally ingesting a slurry of ethanol and a powder he purchased from the internet in an attempt to get high. Seizures recurred in the ambulance and the Emergency Department (ED) and both episodes abated with lorazepam. Initial vital signs were: pulse 106/min; BP 140/88 mmHg; respirations 22/min; temperature 37.7°C. Shortly after arrival at the ED he was intubated for airway control. Noncontrast CT of the brain and EEG were negative. Initial laboratory values: sodium 134 mEq/L, potassium 4.6 mEq/L, chloride 98 mEq/L, bicarbonate 24 mEq/L, BUN 8.2 mmol/L, creatinine 88.4 micromol/L, glucose 8.04 mmol/L, ethanol 0.825 mmol/L, CPK 2649 U/L. Paracetamol and salicylates were not detected. Urine drug screening by EMIT, and confirmed by GCMS, was negative for common drugs of abuse, including tetrahydrocannabinol (THC). The patient developed a supraventricular tachycardia that was refractory to medical management and required electrical cardioversion on hospital day two, but ultimately he made a full recovery and was discharged 10 days later in good health. A sample of his original white powder was confirmed by GCMS to be JWH-018 and metabolites of this SC were detected in the patient's urine at a concentration greater than 100 ng/mL. *Discussion:* Synthetic cannabinoids are legal in many parts of the world and easily obtained over the Internet. Data on human toxicity are limited and real-time confirmatory testing is unavailable to most clinicians. Potential for toxicity exists for users mistakenly associating the dosing and side effect profile of SC to those of THC consumed by conventional methods. *Conclusion:* Ingestion of JWH-018 can produce seizures. Clinicians, lawmakers, and the public need to be educated about the unique toxicity of this drug.

68. Naphyrone Toxicity

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Objective: To assess the severity and diversity of symptoms associated with exposure to naphyrone, a recreational cathinone. *Methods:* Records of enquiries to the UK National Poisons Information Service (NPIS) for the period April 2009 to October 2010 relating to naphyrone exposure were retrospectively reviewed and analysed. *Results:* In the 56 telephone enquiries received throughout the study period, the most frequently reported symptoms were tachycardia (in 21% of cases), and agitation (19%). Anxiety, somnolence and chest pain were each associated with 11% of enquiries. Other features observed included hallucinations, nausea and vomiting, palpitations, paranoia, visual disturbances and a raised temperature. In four cases raised serum creatine kinase was observed, the highest recorded being 3070 U/L. The severity score for the majority of exposures (55%) was considered to be minor with 28% reported as moderate. One patient was reported as severe, suffering a cardiac arrest en route to hospital, he subsequently died of respiratory failure following complications from inhaling gastric contents and underlying emphysema. Cause of death was not recorded as exposure to naphyrone. The youngest patient reported was 14 years old; 38% of patients were less than 20 years, 43% between the ages of 21 and 40 years, 11% were over 40 years and 8% were of adult age unknown. The most commonly reported route of exposure was ingestion (73%) - other routes included inhalation (12%), injection (3%) and unknown (12%); a few cases reported multiple routes of exposure. Most cases (81%) involved exposure to naphyrone alone, in ten cases there was a single co-ingestant and one patient was also exposed to mephedrone, cocaine and alcohol. *Conclusion:* The NPIS regularly receives enquiries regarding new or emerging drugs of abuse. While the symptoms seen with this particular drug appear to be minor in most cases, some patients experience moderate or potentially life threatening toxicity. The number of naphyrone enquiries increased rapidly following the classification of mephedrone as a Class B drug in April 2010. In July 2010 naphyrone was also classified as a Class B drug - increased vigilance is required as other substances of unknown toxicity seek to fill this new gap in the market.

69. Effects of Legal Control on Enquiries to the UK National Poisons Information Service Relating to Recreational Cathinone Use

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Objective: Since 2009 the UK National Poisons Information Service (NPIS) has received increasing numbers of enquiries relating to recreational cathinone use, especially involving mephedrone.[1] The UK government controlled mephedrone and most other cathinones as class B drugs under misuse of drugs legislation in April 2010, with naphyrone controlled in July 2010. This research was performed to assess the impact on these legislative changes on the frequency of toxicity as reflected by Internet and telephone enquiries to NPIS. *Methods:* National study of telephone enquiries and TOXBASE® accesses between March 2009 and October 2010 relating to recreational cathinone use. Data for cocaine and methylenedioxymethamfetamine (MDMA) was also obtained for comparison. *Results:* There were few telephone enquiries relating to cathinones between March and June 2009. Subsequently cathinone enquiry numbers, expressed as cathinone totals, with those specifically relating to mephedrone in brackets, increased month on month from 5 [5] in June 2009 to 128 [119] in March 2010. Enquiry numbers then fell to 72 [59], 46 [26], 39 [19], 26 [11], 31 [18], 14 [11] and 17 [14] for the months April to October 2010. Similar patterns were seen for TOXBASE® accesses to cathinone entries, which peaked at 2648 [1679] in March 2010, falling to 698 [347] in October 2010. There was a small increase in monthly enquiry numbers relating to naphyrone after April 2010, peaking at 17 (telephones) and 346 (TOXBASE®) in May 2010. Monthly telephone and TOXBASE® enquiry numbers for cocaine and MDMA did not change significantly over the period of study, averaging 15 (telephone) and 476 (TOXBASE®) for cocaine and 11 (telephone) and 636 (TOXBASE®) for ecstasy. *Conclusion:* Legal control of recreational cathinones has resulted in reductions in telephone and TOXBASE® enquiries to NPIS. This is likely to reflect a reduction in episodes of toxicity and attendances to hospital. Enquiry data collected by poisons units are valuable for following trends in toxicity of recreational drugs and the impact of control measures. *Acknowledgement:* Submitted on behalf of the UK National Poisons Information Service. *References:* 1. James D, Adams R, Spears R, et al. Clinical characteristics of mephedrone toxicity reported to the UK National Poisons Information Service. Emerg Med J 2010 Aug 25. [Epub ahead of print]

70. Buprenorphine Abuse in the United States: Comparison to Methadone Using Five Surveillance Programs Simultaneously

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Objective: Buprenorphine and methadone are used widely in the United States for treatment of opioid abuse. Abuse of methadone is well known, however, the abuse of buprenorphine is disputed. This analysis compares abuse of methadone and buprenorphine using concurrent data systems. *Methods:* The Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System is a non-governmental postmarketing surveillance system focusing on prescription drug abuse. The system has five components: Drug Diversion (DD) investigators, Poison Centers (PC), Methadone Treatment Program (OTP), Survey of Key Informant Patients (SKIP), and College Student (CS) Survey. Rates of events associated with buprenorphine and methadone were determined quarterly through June 2010. All rates are expressed as events per 100,000 population. *Results:* In DD, methadone case volume increased from 0.04 in 2002 to 0.16 (average annual increase, or slope, of 0.025, $p < 0.001$) and from 0.00 to 0.13 (slope 0.019, $p < 0.001$) for buprenorphine. In the PC program, methadone calls have increased from 0.14 in 2003 to 0.33 (slope 0.023, $p < 0.001$) and from 0.00 to 0.15 (slope 0.023, $p < 0.001$) for buprenorphine. In OTP, methadone rates increased from 0.44 in 2005 to 1.27 (slope 0.086, $p = 0.005$) and from 0.02 to 0.38 (slope 0.034, $p < 0.001$) for buprenorphine. In SKIP, methadone rates increased from 0.39 in 2008 to 0.78 (slope 0.160, $p = 0.001$) and from 0.06 to 0.26 (slope 0.051, $p = 0.096$) for buprenorphine. In CS, methadone cases increased from 0.01 in 2008 to 0.03 (slope 0.018, $p = 0.157$) and buprenorphine increased from 0.00 to 0.02 (slope 0.023, $p = 0.329$). The geographical distribution of cases was similar to other abused prescription analgesics. Poison center data indicate that outcomes associated with buprenorphine cases are less severe than for methadone, both in adults and in young children. *Conclusion:* Data from five different programs indicate that abuse of methadone and buprenorphine continues to increase. It is particularly concerning that rates appear to be increasing among new initiates. Poison center data suggest that buprenorphine may have an improved safety profile compared to methadone.

71. Exposure to MDAI: A Case Report

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Objective: 5,6-methylenedioxy-2-aminoindane (MDAI), an indan analogue of methylenedioxyamphetamine (MDA), a drug of abuse widely available to buy over the Internet. There is limited information available on the toxicity of MDAI, which is thought to be similar to that of MDMA but with less marked serotoninergic effects.[1] We describe a patient who developed multiorgan failure after apparent exposure to MDAI. *Case report:* A 21 year old male reported that he had ingested 5 grams of MDAI. Shortly afterwards he became confused, with evidence of psychosis and self injured. On presentation to the Emergency Department he was hyperpyrexial (>40°C) and tachycardic (150 bpm). He was intubated and sedated and transferred to the intensive care unit. Subsequently he developed rapidly progressing multiorgan failure including liver (ALT 9541, ALP 42, bilirubin 128 and INR 4.33) and renal failure (creatinine 503), rhabdomyolysis (CK 40,000) and disseminated intravascular coagulation (DIC). Veno-venous haemofiltration (CVVH) was instituted

to manage anuria and he was treated with blood and blood products for DIC. He was transferred to the liver intensive treatment unit and treated on a fulminant care pathway including fluid resuscitation, vasopressin, high frequency oscillatory ventilation, high volume CVVH, noradrenaline (for hypotension), N-acetylcysteine and vitamin K. After 6 days liver function results were AST 457, ALP 160, bilirubin 269 and INR 2.43 continuing and the patient was showing signs of waking. The patient made gradual improvement and was subsequently transferred to a psychiatric hospital where he remained at least 3 months after exposure. *Conclusion:* To the best of our knowledge, this is the only report of multiorgan failure secondary MDAI exposure. This has not been confirmed analytically and this is a limitation in view of the reported discrepancy between reported contents and laboratory analysis for legal highs purchased in the United Kingdom.[2] *References:* 1. Nichols DE, Brewster WK, Johnson MP, et al. Nonneurotoxic tetralin and indan analogues of 3,4-(methylenedioxy)amphetamine (MDA). J Med Chem 1990; 33:703–10. 2. Brandt SD, Sumnall HR, Measham F, et al. The confusing case of NRG-1. BMJ 2010; 341:c3564.

72. Clinical Characteristics of 6-(2-Aminopropyl)benzofuran ('Benzo Fury') Toxicity Reported to the UK National Poisons Information Service

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Objective: 6-(2-aminopropyl)benzofuran (6-APB, 'benzo fury') is a substituted methylenedioxyamfetamine drug used recreationally because of its stimulant and enactogenic properties. This research was conducted to document the clinical features of toxicity related to the recreational use of 6-APB in the United Kingdom as reported in recent enquiries to the National Poisons Information Service (NPIS). *Methods:* Data from records of telephone enquiries to the NPIS, recorded on the United Kingdom Poisons Information Database (UKPID), were assessed up until 15th September 2010. The first case on our data set was 19th August 2010. *Results:* There were 32 telephone enquiries relating to 6-APB. Of these, 28 (87%) telephone enquiries concerned Benzo Fury alone, one each in combination with alcohol, mephedrone, sildenafil and dimethocaine. Common clinical features reported included tachycardia (n = 13, 41%), agitation or aggression (n = 12, 37.5%), hypertension (n = 7, 22%), insomnia (n = 8, 25%), anxiety (n = 6, 19%) and palpitations (n = 5, 16%). Fever or sweating were reported in 5 (16%), paraesthesiae in 4 (12%) and hallucinations in 4 cases. Chest pain was reported in 2 cases and ST elevation in one case. Syncope was described in one patient. Clinical features were reported to persist, for more than 24 hours post exposure in 18 cases (56%) and more than 48 hours in 17 (53%). NPIS use the Poisons Severity Score (PSS) system for qualitatively defining the severity of poisoning. In this case series 2 cases had a moderate PSS (37.5%) and 20 had minor PSS (62.5%). *Conclusion:* Clinical features of 6-APB toxicity appear similar to those of amfetamines and cathinones and can be prolonged. Analytical confirmation is not available in these cases which is a limitation considering the common discrepancies between product descriptions and laboratory analysis for other legal highs.[1] *References:* 1. Brandt SD, Sumnall HR, Measham F, et al. Second generation mephedrone. The confusing case of NRG-1. BMJ 2010; 341:c3564.

73. Clinical Profile of Patients who Visited the Emergency Department due to Substance Abuse Related Injuries

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Objective: The incidence of substance abuse, particularly drug abuse, increased rapidly in Taiwan in recent years. The aims of the current study were to evaluate the clinical profile of substance abuse related injuries in adult trauma patients in a medical center. *Methods:* A 3-year retrospective study was conducted. All adult trauma patients who met the DSM-IV-R diagnostic criteria of substance abuse/dependence were identified by 2 researchers through chart review. Information on demographic data, injury severity, clinical treatment, and outcome after the injuries were then abstracted from the medical records and were tabulated for final analysis. To evaluate the predictors of injury severity, we further classified the study population into two groups according to their injury severity score (ISS $>=16$ vs. <16). Logistic regression analyses were then employed to identify the risk factors of severe injury. *Results:* A total of 538 patients were eligible for final analysis, resulting in a prevalence of substance abuse of 1.1% during the study period. The study population consisted of 441 (82.0%) alcohol abusers and 97 (18.0%) drug abusers. In comparison with alcohol abusers, drug abusers were younger and more likely to have certain psychiatric diseases. Furthermore, many drug abusers were injured due to attempted suicide and/or deliberate injury, which led to higher ISS, more hospitalizations and higher case-fatality rates. In multivariate analysis, use of central nervous system depressants (OR 5.7; 95% CI 1.4–23.5) or mixed drugs (OR 13.0; 95% CI 2.8–60.0), aged 51–60 years (OR 3.9; 95% CI 1.1–14.2), residents of Taipei county (OR 5.3; 95% CI 1.8–15.5) or living outside Taipei metropolis (OR 9.5; 95% CI 2.9–31.6), visiting the emergency department by ambulance (OR 5.3; 95% CI 1.2–23.7) or transfer from other hospitals (OR 34.7; 95% CI 7.5–160.6) were associated with more severe injury as compared with their counterparts. *Conclusion:* Substance abuse related injuries were not uncommon in Taiwan. Drug abusers suffered more severe injuries than alcohol abusers and had higher rates of hospitalization and death, which might be attributable to their underlying psychiatric diseases and related deliberate injury and/or attempted suicide.

74. Clenbuterol: Retrospective Study of Cases from the French Poison and Toxicovigilance Centres Between 2000 and 2008

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Objective: Clenbuterol is a β2-mimetic substance, used in France only for veterinary medicine (bronchodilation and tocolysis) and in some European countries for humans (bronchodilation). Its lipolytic and protein anabolic properties are a source of misuse in cattle breeding and among humans (doping, body-building). The discovery of a new use for weight loss purposes has prompted the Health Protection Branch of the Ministry for Health to ask the National coordination committee for toxicovigilance to estimate the extent of that misuse. *Methods:* All cases involving clenbuterol, reported between 2000 and 2008, to the French poison and toxicovigilance centres, Addictovigilance centres, National Toxicologic Veterinary Centre and all Regional pharmacovigilance centres were analysed. *Results:* 56 cases were collected, 42 (74%) of them with symptoms. Most clinical signs were due to β2's mimetic properties (tachycardia, shaking, anxiety, sweating, minor digestive disturbances, hypokalaemia and hyperglycaemia); 6 severe cases were reported. These exposures were rare between 2000 and 2007 (4 to 7 per year) but increased in 2008 (16 cases). Half of these cases are misuse, occurring among rather young people (median age was 30) and with a sex distribution linked with the type of misuse (6 women among the 8 cases for "weight loss", 16 men among the 19 cases for "doping/body-building"). The analysis of other exposures revealed the presence of the product at home (4 home accidents, 2 therapeutic errors, 2 food confusions while preparing a feeding-bottle) or were evocative of a masked misuse (7 imprecise voluntary circumstances). In 29 cases, the product was a veterinary drug. In 9 cases it was a transborder drug. The other 18 uses were not specified. The origin was sometimes specified: the Internet (14 cases), other countries (8), chemist's (probably 5), supplied by the sports centre (2). *Conclusion:* A modification of the circumstances of exposure as time goes by is to be noted. The previous poisonings due to the consumption of contaminated meats were replaced by exposure in a context of doping (increasing) and a search for weight loss (appeared in 2006). In such contexts of misuse, the users are unlikely to be aware of the risks. Therefore, the general public should be informed of those risks.

75. The Italian National Early Warning System for Drugs of Abuse: Toxicovigilance on New Psychoactive Substances

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Objective: Clinical effects of new (non-conventional) drugs of abuse (e.g. synthetic cannabinoids, cathinones, smart-drugs) are not well defined and generally poorly known by emergency physicians. Moreover, the number and severity of patients admitted to emergency departments (EDs) for new drugs of abuse is unknown in Italy. In this field, the National Early Warning System (NEWS) was created to identify new sentinel cases, to collect and evaluate the few available clinical features, to diffuse clinical signals to the health system, and to promote preventative and regulatory actions. The activities of the NEWS in 2009–2010 are analyzed. *Methods:* Activities of the NEWS concerning (i) improvement of the number of Collaborative Centres included in the system (ii) response capability of the Coordinating Centres, (iii) rapidity of the signal release (system's reaction-time), and (iv) percentage of the delivered signals distinguishing among three established levels (information, attention, alert) were evaluated. *Results:* The number of Collaborative Centres increased from 25 at the beginning of 2009 to 50 in October 2010. The Coordinating Centres were able to release the critical response in 100% of cases, with a mean reaction-time that improved from 34 to 22 hours during the last year. There were 42 delivered clinical/toxicological signals in 2009–2010, comprising 33 (78.6%) "information", 4 (9.5%) "attention" and 5 (11.9%) "alert". The signals were delivered by the NEWS and addressed to all the national EDs and Collaborative Centres. *Conclusions:* In accordance with the EU Council Decision 2005/387/JHA, the Department for Antidrug Policies - Presidency of the Council of Ministers has activated in Italy the NEWS for drugs, whose interface with European and international institutions is the Reitox Italian National Focal Point (within the Department). The first evaluation of the performance of the system shows an increase in the number of the Collaborative Centres, of the response capability and the reaction-time of the system, and of the knowledge of substances available for abuse (and

their continuous variation) in the operative services of national health system (e.g. EDs and Poison Control Centres). *Acknowledgement:* Study carried out with the support of Italian Department for Antidrug Policies - Presidency of the Council of Ministers.

76. Medical and Social Dimensions of Acute Alcohol Poisoning in Children: Psychosocial Aspects and Prevention of Alcohol Abuse (Final Results)

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Objective: The aim of the study is to analyze the medical and social dimensions of acute alcohol poisoning in children. *Methods:* Patients up to 18 years of age with acute alcohol poisoning hospitalized for the period 2006–2008 were studied. Data were retrieved from hospital records. The initial blood ethanol level was measured by thin-layer chromatography. Psychiatric interview and inquiry method (questionnaire consisting of 39 questions specially created for the purpose of the survey) were used. *Results:* We studied 137 children with alcohol poisoning. Average age was 14.91 ± 1.45 years. Seventy-seven (56.2%) were boys and 60 (43.8%) girls. A tendency towards an increase in poisonings at weekends and in late afternoon and evening was observed. On admission different levels of depressed consciousness were seen: 61.3% - somnolent, 28.5% - soporous and 5.1% - comatose. Blood ethanol level was over 2.00 mg/mL in 40.2% of cases. In 21 cases (15.3%) the alcohol poisoning occurred at time of first alcohol consumption. Repeated hospitalizations for alcohol poisoning for the studied period were not registered. The combination alcohol-illicit drugs was observed in 13 children. Children most often used one type of alcoholic beverage. The most frequent alcoholic beverage was vodka (63.1%). Sixty-four per cent of the children come from complete families. Both parents had secondary education in 79.7% of cases and were employed in 53.3%. Sixty per cent of the patients were the first born child in the family. First alcohol consumption was at the age of 12 years and 10 months (boys), and 13 years (girls). The most frequent reason for alcohol consumption was meeting and communication. *Conclusion:* Our study represents the first systematic research on alcohol intoxications among children in Bulgaria. For the majority of adolescents alcohol intake corresponds to an attempt to build self-esteem, for integration in society or in a group of friends. Based on the results we developed a programme for the prevention of alcohol consumption and poisonings among children. Effective preventative strategy is based on both a psychological and a social approach.

77. Serum Catalase Activity Remains Unaffected by Chronic Abuse of Heroin

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Objective: To determine serum catalase activity in chronic heroin users and to examine whether serum catalase values correlate with the duration of abuse or with the presence of anti-HCV antibodies, since infection with hepatitis C virus (HCV) is associated with a decreased capacity of the antioxidant defence mechanism. *Methods:* Thirty-four chronic heroin users and thirty controls, age and sex matched, participated in this study. Heroin users were recruited upon admission to the Addiction Department "Ianos" of the Psychiatric Hospital in Thessaloniki, Greece, which is a residential facility running a 21 day detoxification program. All participants provided written informed consent. The study protocol was designed in accordance with the Declaration of Helsinki. Serum catalase activity was determined by a spectrophotometric method. *Results:* There was no significant difference in serum catalase activity between chronic heroin users (mean $\pm$ SD, 90.76 ± 63.56 U/mL) and healthy controls (mean $\pm$ SD, 104.98 ± 38.80 U/mL) ($t = -0.75$, $DF = 62$, $p = 0.456$). Serum catalase values did not correlate with the duration of heroin abuse ($r = -0.96$, $DF = 32$, $p = 0.593$) and did not differ significantly between seropositive (mean $\pm$ SD, 84.57 ± 67.68 U/mL) and seronegative (mean $\pm$ SD, 95.10 ± 61.92 U/mL) heroin users ($U = 129.0$, $N1 = 14$, $N2 = 20$, $p = 0.700$). *Conclusion:* We have previously shown[1] that prooxidant-antioxidant balance is disrupted in favor of prooxidants in the serum of the same heroin addicted individuals. The findings currently reported indicate that catalase does not participate in the generation of this imbalance and that other members of the antioxidant defence system could be lacking or inhibited. According to the available literature, heroin addicts are usually under-nourished with vitamin intakes lower than recommended.[2] Therefore, a possible vitamin deficiency could account for the previously shown oxidative imbalance in the serum of these individuals. *References:* 1. Kovatsi L, Njau S, Nikolaou K, et al. Evaluation of prooxidant-antioxidant balance in chronic heroin users in a single assay: an identification criterion for antioxidant supplementation. Am J Drug Alcohol Abuse 2010; 36:228–32. 2. Santolaria-Fernández FJ, Gómez-Sirvent JL, González-Reimers CE, et al. Nutritional assessment of drug addicts. Drug Alcohol Depend 1995; 38:11–8.

78. Drugs of Abuse: New Drugs or Old Ones? Epidemiological Survey of Acute Intoxications in Florence in the Last Five Years

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Objective: The aim of our study was to review the distribution and clinical significance of drugs of abuse acute poisonings among the patients admitted to the Toxicology Unit of Careggi Florence Hospital, from January 2006 to August 2010. *Case series:* The total number of acute xenobiotic intoxications was 5,876. Amongst them, 3,514 (59.8%) were acute poisonings involving drugs of abuse, including alcohol, opiates, cocaine, benzodiazepines and psychostimulant/hallucinogenic substances with an incidence rate of 324 cases/year per 100,000 persons. The frequency distribution of drugs of abuse acute intoxications was as follows: 3,206 (91%) for alcohol; 137 (3.9%) for opiate overdoses, 78 (2.2%) for cocaine intoxications, 42 (1.2%) for recreational benzodiazepine overdoses, 28 (0.8%) for psychostimulants/hallucinogens and 22 (0.6%) for cannabinoid (THC) abuse. Although the average hospitalization period was rather short (>60% released within 48 hours) and no deaths were observed, drugs of abuse acute poisonings presented difficult clinical management, showing patients with an altered mental state (29.8%), multiple medical emergencies (9.1%) and an altered GCS (8.7% with a GCS < 15 in the last year). Although acute alcohol poisoning was more frequent then psychostimulant/hallucinogen and THC intoxications, the medical complications in this group of patients were highly represented (13 out of 50 patients, 26%). The incidence of medical complications in acute cocaine, opiate and alcohol intoxications was 38.5%, 19.7% and 7.9%, respectively. *Conclusion:* New synthetic recreational drugs have been described in recent years. However, alcohol, opiates and cocaine are still the most important drugs of abuse causing acute poisonings and requiring medical intervention. Once hospitalized, psychostimulant/hallucinogen and THC poisonings show a high incidence of medical complications.

79. Levamisole-induced Occlusive Necrotizing Vasculitis in a Pregnant Woman after Use of Cocaine Contaminated with Levamisole

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Objective: It is estimated that over 2 million people in the United States use cocaine each month. Complications from cocaine use may also include toxicity from adulterants. Current estimates suggest that over 80% of cocaine originating in South America contains levamisole, an antihelminthic that is associated with agranulocytosis, occlusive necrotizing vasculitis, or leukoencephalopathy. We report occlusive necrotizing vasculitis in a pregnant cocaine-using woman. *Case report:* A 19 year-old woman, 18 week gravid presented to the Emergency Department with atraumatic painful purple discoloration of both ears and her neck of two days duration. Initial vital signs were: BP, 131/70 mmHg; pulse, 90 beats/minute; respirations, 20 breaths/minute; SPO_2, 99%; glucose, 7.2 mmol/L. She admitted to daily cocaine use. Laboratory studies revealed a WBC of 5,500 cells/mm^3. Her complete blood count, chemistry panel, coagulation panel, and liver enzymes were within normal limits. Urine was positive for benzoylecgonine. A positive p-ANCA and lupus anticoagulant were present, but a negative hepatitis panel. Patient was diagnosed with levamisole-induced occlusive necrotizing vasculitis by dermatology. Patient did well with supportive care and received drug counselling, and was discharged two days after her admission. *Conclusion:* In early 2003, the United States Drug Enforcement Administration discovered that cocaine contained levamisole. Since then, adulteration of cocaine with levamisole has become a major public health problem. Although it remains unclear why levamisole is added to cocaine, it is assumed to alter the pharmacokinetics, pharmacodynamics, or addiction rate. The pathogenesis of the cutaneous side-effect remains unclear but may involve formation of p-ANCA and lupus anticoagulant. Levamisole-induced occlusive necrotizing vasculitis should be suspected in patients who present with a necrotizing rash and history of substance. Other causes of vasculitis should be excluded. Typically lesions spontaneously resolve with cocaine abstinence and supportive care. If suspected, levamisole concentrations must be obtained rapidly as levamisole is readily cleared, usually within four hours.

80. Clinical Presentation of Atropine Co-Poisoning in Patients Hospitalized due to Toxic Effects of Novel Recreational Drugs

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Objectives: To analyse a case series of atropine co-poisoning in patients hospitalized for novel central nervous system stimulant drug toxicity. *Methods:* Retrospective review of records of all patients hospitalized with diagnosis of novel CNS stimulant drug toxicity between April and October 2010 and tested for atropine. The main diagnosis was established from the patient's self reporting or clinical presentation of sympathomimetic syndrome and after exclusion of illicit sympathomimetic drug use and the presence of substances with the same anticholinergic action as atropine. Atropine was evaluated qualitatively, using thin layer chromatography. *Results:* We found 88 patients fulfilling the criteria. Eighty-two of them were negative for atropine and 6 were positive. Subgroups did not differ significantly one from another with respect to age and sex. There was one death in the atropine subgroup on the 4th day after admission. The

following clinical symptoms and parameters on admission were eligible for comparison: anxiety, agitation, aggressive behavior, vertigo, drowsiness, hallucinations, cardiac symptoms (chest pain or dyspnoea or palpitations) pupil diameter (mydriasis, normal, miosis) pulse rate, blood pressure. Frequency of analyzed symptoms and parameters did not differ significantly, however there was marked tendency for more frequent mydriasis in the atropine positive subgroup (66.67% vs 31.71% with $p = 0.081$). *Conclusion:* The main substances and additives found in novel recreational pills share mainly sympathomimetic properties.[1,2] Atropine is a well known anticholinergic hallucinogen but acts anticholinergically without activation of dopaminergic circle and therefore its detection was unexpected in the studied population. Due to partially shared features of anticholinergic and sympathomimetic syndrome and presumed multiplicity of substances involved in this kind of poisoning, clinical diagnosis may pose a challenge. We think that co-poisonings, particularly with atropine, may increase the risk of death, however, data are insufficient to support this due to the low mortality in the whole group. Mydriasis should be the most important sign suggesting need for laboratory testing for atropine. *References:* 1. Davies S, Wood DM, Smith G, et al. Purchasing 'legal highs' on the internet – is there a consistency in what you get? Q J Med; 103:489–493. 2. Ramsey J, Dargan PJ, Smyllie M et al. Buying 'legal' recreational drugs does not mean that you are not breaking the law. QJM 2010; 103:777–83.

81. Acute Marijuana Intoxication Emergency Department Presentations

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Objective: Marijuana is one of the most frequently abused drugs. Intoxications rarely present to emergency departments (EDs). The purpose of this study is to characterize acute marijuana intoxications presenting to New Jersey and New York emergency departments. *Methods:* Design: A multi-center retrospective emergency department (ED) cohort. Study setting: 20 New Jersey and New York EDs. Subjects: Consecutive patients with the ED diagnosis of poisoning hallucinogenic agent, (ICD10 code = T40.7) and cannabis abuse (ICD10 code = F12) were identified from October 1, 2008 to September 30, 2009. Only completed charts with the primary diagnosis of cannabis abuse and (+) THC on urine drug screening were included. Additionally, multi drug ingestion or multiple drugs found on urine drug screening were excluded. *Results:* Out of 1,590,248 consecutive patients, 78 patients met inclusion/exclusion criteria (0.0053% of all ED patients). The patient demographics were as follows: mean age = 20.7 years (range: 14–42 yrs), gender = 60% males. 9% of patients admitted their ED presentation was their first usage of marijuana. The route of exposure was inhalational for 98% with the remainder via ingestion. The most common presentation was feeling strange or not feeling well (38%). 20% had altered mental status while 18% were reported as acting strange. Additional findings included palpitations (14%), dizziness (12%), nausea or vomiting (10%), weakness (10%), lightheadedness (9%), parasthesias (8%), chest pain (6%) and hallucinations (5%). No patients were hospitalized and no deaths were recorded. *Conclusion:* Marijuana ingestion presents uncommonly to EDs. Toxicity appears to be mild and self-limiting.

82. Acute Toxicity of Gamma-Butyrolactone: Retrospective Study of the Cases of Addiction Notified to French Poison Control Centres and Toxicovigilance Between 2005 and 2009

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Objective: Because of the registration of gamma-hydroxybutyric acid (GHB) on the French list of narcotic compounds and the constant research for new drugs, gamma-butyrolactone (GBL), a chemical precursor of GHB used as an industrial solvent, represents a growing alternative in the addiction to GHB. *Methods:* A request to the national information system of the French poison control centres (CAPTV) was carried out between 2005 and 2009, in order to list products containing GBL and to study human exposure cases to these products, symptomatic or not. *Results:* GBL was found as a component in 47 products (medicines, cosmetics, biocides, plant protection products - PPPs, cleaners). Concentrations of GBL were mostly below 14% and 40% respectively for cosmetics and PPPs, and could reach 99% for some cleaners. Forty-five voluntary exposures were identified among which 30 cases of addiction (or recreational use) and 3 additional cases (circumstances were not defined but were suggestive of a misuse). Thirty-two cases of addiction were symptomatic (involving 5 women and 27 men). The symptoms were, to varying degrees, minor digestive and psychiatric disorders to neuro-respiratory disorders with alterations of the vital functions. Eight serious cases in men presented deep coma with respiratory distress syndrome; one of whom died. Two weaning syndromes were reported. One patient was seriously burned by an explosion after mixing GBL with sodium hydroxide (probably to synthesize GHB). Wheel cleaners sold on the Internet are involved in 7 cases. The purpose of their misuse is clearly described in newsgroups, as well as the risks of overdose or ingestion with alcoholic drinks. *Conclusion:* Notified GBL addiction cases increased 3 to 4-times between 2008 and 2009. In order to reduce the associated risks, several measures can be proposed including a higher degree of information intended for addictive users and the reduction of GBL concentrations in products. A sale ban should not be recommended as a recent measure against poppers showed that such a ban had triggered a transfer towards other narcotic compounds of the same class. A constant surveillance of new notified cases of GBL exposures will be implemented.

83. Cooling Alone Appears to be Ineffective in Preventing Rhabdomyolysis in MDMA-Induced Hyperpyrexia

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Background: MDMA can cause severe hyperpyrexia and associated multi-organ failure in a small but significant proportion of users. First line management of this hyperpyrexia is cooling and early use of benzodiazepines. Subsequent management remains controversial, particularly around the use of dantrolene and/or serotoninergic agents such as cyproheptadine and more aggressive cooling techniques. *Case report:* A 40 year old man presented to the Emergency Department (ED) following ingestion of Ecstasy (MDMA) at a nightclub. On arrival in the ED, his initial observations were: Glasgow Coma Score (GCS) of 3/15, heart rate 180 bpm, blood pressure 88/44 mmHg and temperature 42°C. Clinical examination demonstrated evidence of lower limb hypertonia and inducible clonus in keeping with acute serotonin toxicity. A 12 lead ECG showed ventricular tachycardia, and initial treatment of this included DC cardioversion and loading with intravenous amiodarone. In view of his reduced level of consciousness he was intubated to protect his airway. On the advice of the regional toxicology centre he was commenced on fluid resuscitation with cold IV fluids and an intravenous infusion of midazolam. A serum sample collected following admission analysed using gas-chromatography mass-spectrometry (GC-MS) confirmed lone MDMA use (concentration 2.12 mg/L). Despite this initial management, his temperature remained elevated at 38.6°C. It was therefore decided to attempt to control his core temperature using the external "Coolguard" endovascular cooling system (AlsiusCorp, Irvine, CA). The external control unit temperature was set to 36.5°C; he was maintained at this set temperature for 80 hours. Despite achievement of this temperature within 1 hour, over the subsequent 72 hours, he developed features of rhabdomyolysis (peak creatinine kinase 31913 IU/L) with associated acute renal failure (peak serum creatinine 264 micromol/L), liver impairment (peak ALT 3102 IU/L) and disseminated intravascular coagulation (DIC) (peak INR 2.3, lowest platelet count 24). *Conclusion:* It appears external cooling alone is not effective in preventing the complications related to MDMA-induced hyperpyrexia. Cooling alone may mask the ongoing direct muscular toxicity of MDMA, leading to ongoing rhabdomyolysis and associated multi-organ failure. Therefore, it is essential that clinical toxicologists ensure that optimal additional management is administered, including the use of specific serotoninergic agents such as cyproheptadine, not just cooling alone.

84. Impact of Classification of Piperazines and Cathinones in the UK

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Objective: Novel psychoactive substances are controlled when evidence of use and harm associated with their use is available; however there is limited information on the impact of these controls. Nightclub "amnesty bins" have been used to monitor local recreational drug trends. We analysed substances collected in amnesty bins to determine the impact of UK legislation to control piperazines (23-12-2009) and cathinones (16-04-2010). *Methods:* Powder, capsule, tablet and crystalline substances were obtained from amnesty bins in local nightclubs during three time-periods: Last quarter 2009 (period 1) - piperazines/cathinones both legal; First quarter 2010 (period 2) - piperazines illegal, cathinones legal; Second quarter 2010 (period 3) - piperazines/cathinones both illegal. These substances were analysed by gas chromatography with mass spectrometry (GC-MS). *Results:* 512 substances in total were analysed: 147 from Period 1; 105 from Period 2; and 285 from Period 3. The proportion of substances that were legal (contained no controlled compound) dropped from 57.8% in Period 1 to 35.2% in Period 2 and to 13.3% in Period 3. The proportion of samples analysed that were piperazines did not change following the UK legislation to control piperazines in December 2009 (35.4% Period 1 compared to 30.5% Period 2; $p = 0.42$). However, there was a significant increase in the proportion of substances that were cathinones after their control in April 2010 (24.8% Period 2 compared to 44.2% Period 3; $p = 0.0005$). Conversely there was an associated decrease in the proportion of substances that were piperazines over this time period (30.5% compared to 13.0%; $p < 0.0001$). *Conclusion:* This study suggests that legislation has a limited impact on the pattern of drugs available to recreational drug users and may be

associated with an increase in the availability of illegal/controlled substances; this was particularly apparent for mephedrone and the other cathinones. Legislative authorities, along with the help of clinical toxicologists, need to consider how to appropriately reduce the use of novel psychoactive substances and monitor substances being used to determine the true impact of any legislation changes.

85. Mixed Cathinone (Methylenedioxypyrovalerone, Butylone and Mephedrone) Toxicity in an Individual with Use of a Single White Powder Sold as Mephedrone

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Background: The use of novel psychoactive substances (commonly known as "legal highs") is increasing. A number of studies have shown that the content of legal highs purchased over the Internet is unreliable. We report here a case of an individual who believed that they had used mephedrone, but toxicological analysis showed that he had purchased and used a combination of mephedrone and other novel cathinones. *Case report:* A 28 year old male presented following use of a "white powder" that he believed to be mephedrone. He had purchased this prior to the classification of the cathinones in the UK in April 2010. He ingested 300 mg on the afternoon prior to presentation followed by a further 100 mg; on both occasions he mixed the powder with water prior to ingestion. Approximately 1 hour after the second ingestion he developed palpitations, anxiety, shortness of breath and felt light-headed. He denied used of any drugs other than the mephedrone. He presented approximately 6.5 hours after the symptoms had started, as they were persistent and associated with "chest tightness". On examination he had clinical features of sympathomimetic toxicity and a heart rate of 140 bpm, blood pressure of 210/103 mmHg and dilated 7 mm pupils; his temperature was 36.4°C. Neurological examination was normal, with no evidence of clonus or hypertonia. ECG on admission showed sinus tachycardia and normal QRS/QTc durations. A 12 hour Troponin T was negative. He was given 10 mg diazepam and his symptoms settled over the next few hours and he was discharged 24 hours later. Blood was collected at the time of presentation, and subsequently analysed by GC-MS. Mephedrone (concentration <0.005 mg/L), butylone (0.1 mg/L) and methylenedioxypyrovalerone (MDPV) (0.003 mg/L) were detected; no other recreational drugs were detected. *Conclusion:* We report a case of mixed novel psychoactive substance toxicity following the self-reported use of lone mephedrone. In addition, this is the first confirmed case of toxicity associated with MDPV. Clinical toxicologists and legislative authorities need to be aware that similar to classical drugs, there is the potential that novel substances are combinations, which may increase the risk of toxicity.

86. Stress Cardiomyopathy During Ethanol Withdrawal

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Objective: Stress cardiomyopathy is an acute, transient left ventricular dysfunction, associated with emotional stress.[1] Myocardial perfusion and contractility disturbances in ethanol withdrawal have been described.[2] This case is an example of stress cardiomyopathy in ethanol withdrawal with characteristic echocardiographic pattern and ECG changes. *Case report:* A 53 year old female, chronic alcohol drinker was admitted to the Internal Ward due to symptoms of acute pancreatitis. Fifteen months earlier she had undergone angioplasty of the circumflex artery with stent placement. On admission BP was 160/110 mmHg, HR 90/min. The ECG showed small ST decrease in II and V4-V6 leads. Troponin I was 0.04 ng/mL, serum ethanol 0.2 mmol/L. Abdominal ultrasonography revealed only a small amount of fluid around the pancreas head. Chest pain, shortness of breath, pallor, jugular vein congestion, bilateral crackles in the lung and tachycardia of 120/min appeared on the first day of hospitalization. ECG showed ST elevation in V2-V3, with T-wave inversion in V2-V6 leads; troponin increased to 0.49 ng/mL. Coronarography excluded significant changes in the arteries. In echocardiography apical akinesis and impaired left ventricular relaxation with ejection fraction (LVEF) of 30%, BNP 1025 pg/mL. By hospital day 3 disorientation and behavior disorders corresponding to alcohol withdrawal appeared. In subsequent days left ventricle systolic function improved. Only small apical hypokinesis was seen in echocardiography 14 days after the initial examination. LVEF increased to 53%, BNP fell to 247 pg/mL. Deep negative T-wave in leads I, II, aVL and V2-V6 in ECG persisted to the end of the 19th day of hospitalization. *Conclusion:* Acute heart failure may develop in alcohol withdrawal. Transient left ventricle contractility disorders are probably due to sympathicotony, in the same way as in cardiomyopathy associated with severe emotional stress. *References:* 1. Wittstein IS, Thiemann DR, Lima JAC, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med 2005; 352:539–48. 2. Pach D, Sowa-Staszczak A, Gawlikowski T, et al. Quantitative analysis of heart scintigraphy with regional myocardial wall motion and systolic thickening of left ventricle assessment for detecting myocardial damage in ethanol withdrawal patients. Przegl Lek 2010; 67:571–5.

87. Abuse of Benzodiazepines Among Heroin Addicts in Skopje Region

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Background: Benzodiazepines are the most widely used and abused psychotropic agents in the world. In our country, in the group of benzodiazepines, diazepam is the most used and abused of all benzodiazepines. Among heroin addicts diazepam is very often use to increase "flash". Diazepam use by heroin users increases their risk of overdose and serious coma. Recently we have noted abuse of diazepam by heroin addicts on the buprenorphine substitution programme. Consumption of benzodiazepines began after subjects had become addicted to heroin and indicates a clear trend to multiple drug abuse. *Objective:* The goals and primary objectives of this study were to examine the extent of benzodiazepine use in heroin addicts and investigate which is used most frequently. *Methods:* The study was carried out on a predominantly male group of 92 patients, active intravenous heroin users, aged 21 ± 4 years, of body mass 66.66 ± 8.0 kg. Participants were admitted for inpatient detoxification programme. They had been consuming heroin from 3 months to 8 years. This sample of heroin users was interviewed regarding their benzodiazepine use. Opiates and benzodiazepines were detected using FPIA technique. Anti HCV seropositivity was detected using Cobas Core Anti-HCV EIA. *Results:* The majority (92%) had used diazepam, 66% in the 6 months prior to interview. Diazepam was ranked first by 92% of patients, followed by flunitrazepam 6% and alprazolam 2%. The prevalence of diazepam use among heroin addicts is very high. Diazepam intravenously injected together with heroin was common in more than half of the addicts. *Conclusion:* Diazepam was taken orally, but also intravenously mixed with heroin. The mean daily dose was 30 mg/day, often associated with other drugs. Although diazepam appears to have potential for abuse, the available data does not rule out its therapeutic interest. *References:* 1. Laqueille X, Launay C, Dervaux A, et al. [Abuse of alcohol and benzodiazepine during substitution therapy in heroin addicts: a review of the literature] [Article in French]. Encephale 2009; 35:220–5. 2. Fatseas M, Lavie E, Denis C, et al. [Benzodiazepine withdrawal in subjects on opiate substitution treatment] [Article in French]. Presse Med 2006; 35:599–606.

88. Severe Medical Complications Connected with the Use of Psychoactive Drugs

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Objective: To establish what are the most common complications observed in a group of patients with acute heroin poisoning and when combined with other psychoactive substances (PAS). *Methods:* The study included 100 patients selected by lottery method from all hospitalized persons with acute heroin and combined with other PAS poisonings, hospitalized in the Toxicology Clinic, MHATEM "Pirogov". This was a retrospective study for a five year period. The patients were between the ages of 17 and 32 years; the ratio of male:female was 4:1. *Results:* As a complication of the nervous system, peripheral toxic neuropathy, stroke, and brain edema was observed in 21% of the patients. Complications of the respiratory system were expressed in the activation of old inflammatory changes in individual cases, pneumonia, pulmonary edema, ARDS (respiratory distress syndrome in adults) in 39% of the patients. Forty-four per cent of patients showed altered liver metabolism - values exceeding the reference values of bilirubin, transaminases (AST and ALT), presence of hepatitis B or C. In the study eight cases (8%) were registered with non-traumatic rhabdomyolysis with subsequent myoglobinuria and acute renal failure (ARF) - one of the most frequent renal impairments in acute heroin intoxication. Exotoxic shock was observed in 8% of the patients, anemia in 7% of the patients, and in five of them (5%) signs of sepsis. The results of the study show that in 29 patients there were multiorgan disabilities. The performed immunoassays established suppressed humoral and cellular immunity in patients with multiorgan disorders. These results showed the relationship between changes in immune reactivity and increased frequency and severity of various infections and complications. Death was recorded in three persons (3%). *Conclusion:* The results of the study showed that acute heroin intoxication and heroin mixed with other psychoactive drugs lead to severe complications of the various organs and systems, chronic damage, longer hospital stays and costly tests and treatment.

89. Pattern of Acute Ethanol Poisoning in Mashhad, Iran

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Introduction: Ethanol poisoning is undoubtedly a recognized common intoxication in most countries of the world. However, ethanol consumption in Islamic countries like the Islamic Republic of Iran is strictly prohibited. In spite of the regulation, patients with acute ethanol poisoning have been admitted to the Emergency Toxicology Clinic of this center. *Methods:* In this prospective study, 128 patients with acute ethanol poisoning out of 13,400 patients were admitted to the Emergency Toxicology Clinic between January 2008 and December 2009. Vital signs, oxygen saturation via pulse oximetry and blood glucose by glucometer were measured. Dextrose 50% was given as well as supportive care. Data were analyzed by SPSS (Version 13.0). *Results:* The mean interval between blood sugar measurement and last food consumption was 9.2 hours. Patients were predominantly male (92.1%) and single

(67.9%). Mean ± SD age was 23 ± 8.8 years and around half of the patients were in the 14–20 year age group. Patients consumed between 50 and 2000 mL (average 387) alcohol. Among these, 66% consumed alcohol during the night between 18 and 22 hours and 77% used homemade alcohol for recreational purposes. The most common findings included nausea and vomiting (92%) impairment of consciousness (69%), pupils were normal size in (67.7%), conjunctival hyperemia (63%), agitation (44%), ataxia (43.7%), epigastric pain (26%) and haematosis (12.7%). Pulse rate was 83 ± 11/min (60–120), respiratory rate 17 ± 41/min (10–30), systolic blood pressure 105 ± 14 (90–140) mm/Hg, oxygen saturation was 95 ± 14% (93–98) and blood sugar 98 ± 22.19 (57–167) mg/dL. *Conclusion:* The majority of cases were mild to moderate and supportive care was sufficient. Although spirit consumption is not legal and thus not common in I.R. Iran, acute ethanol poisoning is rather common (1%) in this holy city.

90. Ethnobotanical Substances - The New Recreational Drugs Used by Teenagers in Romania

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Objective: To evaluate the incidence, clinical manifestations and consequences of using ethnobotanical substances as new recreational drugs by teenagers. *Methods:* We have performed a retrospective study of ethnobotanical substances poisoning admitted in our department between January 1st 2009 and November 1st 2010. The following criteria were taken into consideration: type of substance, age, gender, symptoms, place of producing, hospitalization duration. *Results:* 32 patients with acute poisoning with ethnobotanical substances were admitted during the mentioned period. Bags bought from the new open stores were the products involved. The market name was identified in 20 cases as follows: Ninja 5 cases, Spice 2 cases, Smoke plus (2 cases), Magic (2 cases), Joy, White, Chocolate, Diesel, Ganja, Power Magic, Gold, Wild Plus (1 case each), Magic+Insomnia (1 case). In 12 cases the name could not be identified. The median age of the patients was 15.6 years. There were 22 boys (68.7%) and 10 girls (31.3%) reported in our statistics. In all the cases the poisoning was produced by inhalation (smoking). Regarding the place of consumption we noted in the majority of situations: clubs or during private parties (23 cases). The main symptoms were: dizziness in all cases, nausea and vomiting (28 cases), somnolence (7 cases), syncope (4 cases), confusion (4 cases), gait and balance disorders (4 cases), headache, dysarthria, agitation, coma, behavioral problems (3 cases each), tremor, hallucinations (2 cases each), tachycardia, chest tightness (1 patient each). The duration of hospitalization was one day in all cases with full recovery. In 21 cases the toxicological examination was negative and in one case revealed synthetic cannabinoids. *Conclusion:* The ethnobotanical substances represent a new option in recreational drug consumption among adolescents. Even although in all the cases the registered symptoms were mild they represent a real threat for children's health and behavior. *References:* 1. Dargan PI, Wood DM. Novel and emerging recreational drugs. Toxicol Lett 2010; 196:S16. 2. EMCDDA. 2010 Annual report on the state of the drugs problem in Europe. November 2010, Lisbon, Portugal. http://www.emcdda.europa.eu/publications/annual-report/2010.

91. The Psycho-Social Profile of The Teenage Ethnobotanical User

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Objectives: The assessment of the psycho-social profile of the ethnobotanical substances user. *Methods:* We studied all the patients with ethnobotanical substance poisoning examined in the psychology department between 1st November 2009 and 1st November 2010, using clinical interviews with the patient and his family. *Results:* Psychological examination was performed in 29 patients with ethnobotanical overdose admitted during the mentioned period. There were 21 boys (72.41%) and 8 girls (27.59%). The ethnobotanicals used were the following: Spice (18 patients), Gange (5 cases), Magic Power (2 patients), Diesel (1 case), Havana (1 patient), Puff (1 case), Boom (1 patient). All the patients presented with some of the common psychological characteristics of drug of abuse consumers, as follows: Personality factors: immature personality, hedonic orientation, attraction to new and forbidden experiences, rebel personality; Family factors: the absence of communication between parents and children, in conflict or broken families, educational style; Environmental factors: social network with high accessibility to drugs, affiliation to drug users, group values and norms which encourage drug abuse. The specific psychological characteristics for these types of users are the following: The reason for using ethno botanical substances was curiosity and group pressure (in all the patients); Most of the teenagers were at the beginning of drug use (23 cases); None of them had ever used high risk substances; The main reasons for choosing ethnobotanics was the "legal" status of these substances (low prices and the accessibility status) in all the studied teenagers. *Conclusions:* The psychosocial profile of the ethnobotanical users was very similar to that of other drug users. The specific characteristics of ethno botanical users are: the perception that these substances are not dangerous and do not produce addiction. *References:* Stancu I. Individual approach to drug addicts. In: Mitrofan I, ed. Psychotherapy - Theoretical, Methodological and Applied Landmarks. Ed. SPER, Bucharest 2008.

92. Anabolics Abuse and Cardiomyopathy in a Bodybuilder: A Case Report

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Background: Anabolic-androgenic steroids (AAS) are synthetic derivatives of testosterone that athletes use to enhance muscle mass and improve their performance. Adverse cardiovascular events attributed to anabolic steroid use, such as arrhythmias, myocardial infarction, cardiomyopathy, and sudden death, are rarely reported.[1] *Case report:* A 39-year-old male bodybuilder was admitted to the ICU with a 3-year history of AAS abuse over the previous 3 years. The most frequently used compounds were: methandrostenolone, stanozolol and oxymetholone (oral); and nandrolone decanoate, testosterone enanthate and trenbolone enanthate (intramuscular). He had no family history or personal history of cardiovascular diseases, alcohol abuse or acetaminophen intake. The patient was in good physical condition until approximately three weeks prior to admission, when he experienced increasing fatigue, decreased exercise tolerance and general malaise. Although he stopped exercising and self-administering the drugs, these symptoms continued to progress and he subsequently developed anorexia, shortness of breath during exertion and fatigue. His free testosterone and delta 4-androstenedione concentrations were elevated. Acetaminophen level was undetectable and anabolic steroid-induced toxic hepatitis was suspected. Chest X-ray revealed cardiomegaly without pulmonary congestion. Echocardiogram showed a dilated cardiomyopathy with an estimated ejection fraction of 35%. A diagnosis of severe toxic cardiomyopathy associated with anabolic steroids was made after ruling out other causes of non-ischemic dilated cardiomyopathy. Treatment included general rest, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, beta-blockers, spironolactone, and antiarrhythmic drugs. After 18 days hospitalization, the patient was discharged with oral therapy. *Conclusion:* Several years into chronic misuse of AAS, this power bodybuilder showed impaired myocardial function, strongly associated with mean dosage and duration of AAS use. The interval since the last AAS abuse was too short to be able to evaluate the improvement of left heart cavity function. *References:* D'Andrea A, Caso P, Salerno G, et al. Left ventricular early myocardial dysfunction after chronic misuse of anabolic androgenic steroids: a Doppler myocardial and strain imaging analysis. Br J Sports Med 2007; 41:149–55.

93. Does The Aspiration of Lamp Oil Increase the Alveolar Diffusion Barrier for Oxygen? Proving Clinical Findings in an *In-Vitro* Alveolar Space Chamber Experiment

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Background: Based on a Federal Institute for Risk Assessment (BfR) detailed analysis (57,093 reports between 1990–2008) of aspiration cases with liquid preparations, the aspiration risk is clearly associated with the ingestion of distinct aliphatic hydrocarbons with a chain length from C8 to C16. These are the main compounds of paraffin-containing lamp oils, grill-lighters and kerosene. Based on their typical low viscosity, low surface tension and low vapour pressure these substances can enter the deep spaces of the lung. More than 320 serious cases and five deaths of children have been documented in the BfR since 1990 with the typical signs of lack of oxygenation, giving strong clinical indications for an oxygen intra-alveolar diffusion barrier effect. To prove this hypothesis, the intra-alveolar surface and the oxygen transfer was simulated in an *in vitro* Alveolar Space Chamber (ASC) experiment. *Methods:* A gas-tight Plexiglass-measuring chamber (diameter 115 mm, height 115 mm, wall thickness 15 mm) was half-filled with fluorocarbon (FC-43) to generate a liquid-gas surface to simulate the alveolar surface. The oxygen-transport through the surface was measured in the bottom liquid part of the chamber by a Unisense oxygen micro sensor, connected to a high-sensitivity Pico-ammeter. *Results:* The results of the experiments revealed that the alveolar surfactant can be considered as a strong accelerator to the oxygen transfer into the liquid space of the capillary lung system. In contrast to these findings, generated microfilms of lamp oils reduce the transfer of oxygen through the surface to a high extent (minimum 9–15 fold). Transferring these findings to the clinical course of the documented serious lamp oil aspiration, the ASC-experiment could give clear indications of the pathophysiological mechanism. The characteristic physico-chemical properties of ingested lamp oils gives these liquids the capacity to spread deep into the lung, and finally into the alveolar spaces with the effect of building up a persistent diffusion barrier for oxygen. This could explain the severe asphyxia and death documented in BfR cases. *Conclusion:* The ASC-experiment gives a plausible understanding of the clinical findings in cases of serious lamp oil aspirations. The experiment is currently being extended to find new additional therapeutic tasks in cases of severe aspiration.

94. Water Horsetail as a Possible Cause of Haff Disease

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Objective: Outbreaks of an illness characterized by sudden, severe muscular rigidity and rhabdomyolysis after eating fish has been known as Haff disease since 1924.[1] However, the etiology of this illness is still vague and not well defined. *Methods:* Both experi-

mental and observational studies were performed during an outbreak in the Russian region Tyumen in the year 2000. Haff disease was identified in 28 people, who inhabited the same rural area. All of them had eaten crucian carp within 24 hours of the symptoms appearing. It was discovered in 43 cases in cats as well. An experimental study aimed at simulating the fish toxicity by feeding crucian carp (*Carassius*) with water horsetail (*Equisetum fluviatile*), which is supposed to be the cause of toxicity. *Results:* Twenty patients were treated in the Tyumen Poison Centre during May - July 2000. The most common symptoms were myalgia in all cases and weakness in 11 cases. Muscular stiffness was found in 7 cases and dark urine in 5 cases. Gastrointestinal symptoms developed in 4 cases, leucocytes which exceeded 8,000 were measured in 9 cases. Renal damage developed in 5 cases, four of them requiring hemodialysis (3–7 procedures). All patients survived, four of them were examined for 10 years and did not show renal function abnormalities. In an experimental study white mice, which were fed with modulated toxic crucian carp, developed the same clinical and pathological signs of toxicity as mice which were fed with fish from an endemic lake. *Conclusions:* Toxic alkaloids which were in water horsetail could be the cause of Haff disease. Renal damage occurred more often than was described in the previous publication.[2] *References:* 1. Buchholz U, Mouzin E, Dickey R, et al. Haff Disease: From the Baltic Sea to the U.S. Shore. Emerg Infect Dis 2000; 6:192–5. 2. Langley RL, Bobbitt WH 3rd. Haff disease after eating salmon. South Med J 2007; 100:1147–50.

95. Buprenorphine and Norbuprenorphine-Related Respiratory Effects in Mice: Role of P-Glycoprotein Transporter

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Objective: Several cases of death by asphyxia were attributed to buprenorphine (BUP). Norbuprenorphine (N-BUP), the active BUP metabolite was shown to be a major respiratory depressant in rats, while BUP was responsible for ceiling respiratory effects. Recently *in vitro* studies suggested that N-BUP, in contrast to BUP, is a good substrate of P-glycoprotein (P-gp), a major transporter of the blood-brain-barrier. The objective of this work was to study P-gp role in the modulation of BUP and N-BUP respiratory effects in mice. *Methods:* Using plethysmography, we studied BUP (10 mg/kg, IP) and N-BUP (1 mg/kg, IP) respiratory effects in wild-type and P-gp knock-out (KO) female FVB mice. Pre-administration effects of a powerful inhibitor of P-gp and P450 cytochromes (PSC833, 20 mg/kg SC) were studied. Comparisons were performed using ANOVA for repeated measurements followed by Bonferroni post-tests. *Results:* BUP was responsible for a dose-dependent respiratory depression, with a significant reduction in the minute volume (VE, $p < 0.0001$) and respiratory frequency (f, $p < 0.001$), without any alteration of the tidal volume (VT). A significant increase in the inspiratory time (TI) was observed with all doses >10 mg/kg, while a significant increase in the expiratory time (TE) appeared only at 30 mg/kg. N-BUP was responsible for a significant dose-dependent respiratory depression; however, a significant TE increase was observed with lower doses >1 mg/kg ($p < 0.01$). Pre-treatment with PSC833 significantly enhanced BUP- as well as N-BUP-related respiratory depression in comparison to controls, with mainly a significant increase of BUP-related effects on TI ($p < 0.001$) and N-BUP-related effects on TI and TE ($p < 0.0001$). In P-gp KO mice, we observed a significant enhancement of the respiratory depression induced by both molecules, with increased BUP-related effects on TE ($p < 0.0001$) and increased N-BUP-related effects on TI ($p < 0.0001$). *Conclusion:* In contrast to rats, both BUP and N-BUP are responsible for significant respiratory depression in mice. TE increase following the administration of low N-BUP doses assesses a more important N-BUP respiratory toxicity in comparison to BUP. Our study suggests a key-role for P-gp in the occurrence of BUP and N-BUP-mediated respiratory effects; however, additional studies are required to identify the exact mechanism of interaction with P-gp.

97. Experimental Justification for Using Ozonized Oil Solution in the Treatment of Chemical Burns of the Digestive Tract Caused by Acetic Acid

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Objective: Acetic acid poisoning takes third place in hospital mortality from acute poisonings in Russia. This experimental investigation tries to evaluate usage of ozonized oil solutions in the treatment of digestive tract burns. *Methods:* The experimental investigations were conducted in 90 male Wistar rats with initial weight 180–200 g. We defined two groups of 45 experimental rats. Mucosal injury was provoked by 0.5 mL of 20% acetic acid through the oral tube under etherization on an empty stomach. The ozonized oil has an antihypoxic action. It acts in two ways: through improvement of oxygen transport and by positive influence on the oxygen uptake process. The activation of oxygen transport to the body tissues with the ozone therapy is connected with the increasing partial pressure (pO_2) in arterial and venous blood, increasing erythrocyte deformation, and their abilities to penetrate into smaller capillaries, and finally with decreasing connection of hemoglobin with oxygen. The last circumstance is related to the activation of glycolysis in erythrocytes and 2,3-diphosphoglycerate connection, that improves the delivery of oxygen by hemoglobin to the body tissues. All animals got ordinary enteral feeding. The animals from control and experimental groups were taken out from the experiment on the 5th, 13th, 19th days after etching with the acetic acid. In addition the animals of the second group were given the ozonized vegetable oil. Morphologic, histochemical, flow DNA cytometry were performed. *Results:* Necrotizing ulcerative process was emerging in the upper GI tract on the fifth day after the introduction of the acetic acid. With the treatment using ozonized oil solution the alteration was limited to the surface coating of the epithelium after 5 days. The mucosal burns of the oesophagus, stomach and duodenum were smoothed over on the 13th day. In the group of experimental animals receiving the ozonized oil, DNA flow cytometry examination of the cell repair of the mucous coat of the stomach showed a significant increase in the size of the proliferative pool from $11.9 \pm 1{,}32$ to 14.2 ± 1.1, on average more than 20% ($p < 0.05$). This increase of the proliferative activity was linked to the increasing number of cells synthesizing DNA whose number, in the group of animals who were receiving treatment, was 34% higher ($p < 0.01$) in comparison to the control group. *Conclusion:* The use of ozonized oil during the treatment of chemical burns caused by acetic acid poisoning, favors the accelerated healing of the mucosal membrane of the digestive tract.

98. The Role of Macrophages in the Pathogenesis of Toxic Hepatitis in Rats Resulting from Tetrachloromethane Poisoning

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Objective: The use of tetrachloromethane (CCl_4) to produce toxic experimental hepatitis, has been a classic model for research into the mechanisms of chemical toxicants' influence on the liver tissue for more than 30 years. The aim of the research consists of the study of the possibility of correcting pathological changes to the liver with toxic hepatitis when modelling the activity of macrophages. *Methods:* The experiment was performed in 50 white male rats, according to the recommendations of international ethics committees for humane treatment of laboratory animals. CCl_4 was injected intraperitoneally in doses of 50 mg/kg. The histological and immunohistochemical changes were evaluated. The animals were divided into three groups: 1) intact; 2) control (toxic hepatitis); 3) experimental (toxic hepatitis while treating with a drug "3-aminophthalhydrazide"). *Results:* On the 3rd day after the introduction of tetrachloromethane into the experimental rats' livers signs of acute toxic hepatitis were noted that showed itself in the form of nidal necrosis of hepatocytes with perifocal lymph- leucocytal infiltration. As compared with intact healthy animals the quantity of cells, expressing CD 45+, perivascularly increased 20 times, (from 17.83 ± 2.31 to 367.62 ± 16.40 per unit of the section area), and in the liver parenchyma - 15 times (from 13.89 ± 1.39 to 187.98 ± 8.58 per unit of the section area), while on the 7th day of research the quantity of leukocytes in the organ reduced, but still was on average 4.5 times more than the reference level. During the immunophenotyping we found that the quantity of T-lymphocytes was increased 17 times in the early part of the experiment and was reduced to the ordinary value in the later part of the experiment. After activation of macrophages by the drug "3-aminophthalhydrazide", signs of a toxic hepatitis in rats' liver were less evident, inflammation signs are reduced, polymorphonuclear leucocytes in the infiltrate were solitary, and on the 7th day the nidal necroses without the perifocal cellular reaction remained only on the periphery lobule, granulosity of hepatocytes remained, while hepatocytes with hydropic degeneration were not detected. The quantity of cells, expressing CD 45+, both in liver parenchyma and perivascular were decreased to the value 123.77 ± 6.12 and 153.41 ± 8.53 per unit of the section area accordingly. *Conclusion:* The modulation of the macrophages' activity led to the removal of the inflammatory response, to the regeneration of the liver tissue after the toxic lesion, and therefore to the reduction of CCl_4 toxic action.

99. Treatment of Experimental Metoprolol Poisoning Using Levosimendan With and Without a Loading Dose

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Background: Levosimendan is an inodilator used to improve cardiac output (CO) and reduce afterload in heart failure. The mechanism of action is twofold: 1) myocardial calcium sensitizer producing increased inotropy and 2) vascular K^+-channel-blocker producing peripheral vasodilatation. Previously, we have reported that levosimendan with a loading dose and infusion improved cardiac output (CO) but not blood pressure (BP) in a rodent model of verapamil poisoning. Metoprolol does not cause peripheral vasodilation. Consequently, the vasodilatory effects of levosimendan may not influence BP to a similar degree as seen with verapamil. *Objective:* To assess the effect of levosimendan on CO, BP and HR in a rodent model of metoprolol poisoning. *Methods:* Male Wistar rats (350–450 g) were anesthetized and ventilated. Jugular venous, femoral arterial catheter and a carotid temperature probe, to measure CO by thermodilution, were inserted. Pre-metoprolol CO, mean arterial pressure (MAP) and heart rate (HR) were recorded. Metoprolol was infused continually through the experiment. When BP dropped to 50% of baseline (time-0) rats received one of 4 treatments: 1) normal saline bolus + infusion (Control), 2) levosimendan 36 microgram/kg loading-dose then 0.6 micrograms/kg/min (LevoL), 3) levosi-

mendan 0.6 microgram/kg/min (LevoI), 4) Adrenaline 0.5 microgram/kg/min (Adren). All groups received comparable fluid volumes. Haemodynamic parameters were recorded every 10 minutes for 70 minutes. CO MAP, HR of each group as well as area-under-the-curve (AUC) for each parameter was compared to Control using one-way ANOVA and unpaired t-test. *Results:* All groups (n = 10) had comparable baseline and time-0 BP and CO. LevoL and LevoI rats had significantly greater CO compared to Control by AUC analysis but animals remained markedly hypotensive. Adrenaline did not produce a significant increase in CO by AUC analysis compared to Control but did significantly improve MAP compared to the other 3 groups. *Conclusion:* Levosimendan produced moderate improvements in CO compared to Control without significant improvement in BP. There was no difference between CO or MAP with or without a levosimendan loading dose. Adrenaline improved MAP without improvement in CO suggesting this was an effect of peripheral vasoconstriction. The observed response to levosimendan was similar to that in verapamil poisoned rats.

100. Occult Lead Poisoning in Australia from Ayurvedic Medicines Produced, Prescribed and Purchased in India

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Introduction: We report three cases of lead poisoning from Ayurvedic medications purchased in India and brought back to Australia by patients. *Case series:* Case 1. A 28 year-old Indian resident of Australia presented with one-month history of epigastric pain and constipation. Laboratory investigations showed normochromic, normocytic anaemia with basophilic stippling. Whole-blood lead was 4.12 micromol/L (R.R. < 0.48). Occupational, social and environmental history did not reveal a source of lead exposure. Further questioning revealed he had been taking three Ayurvedic medicines for back pain prescribed during a recent trip to India - Vatyog, Sahacharadi, Gandharvahastadi (all blister packed and produced by a regional pharmaceutical company); two of each daily during the previous three months. Vatyog and Sahacharadi were analysed for heavy metals. Vatyog contained 448 micrograms of lead in the tablet tested. Case 2: A 40 year-old Indian chef presented with abdominal pain and GI bleeding three months after arrival in Australia. Investigations revealed basophilic stippling and whole-blood lead 5.79 micromol/L. Occupational, social and environmental history revealed no source of lead poisoning. The patient had diabetes for which he was prescribed an Ayurvedic medication called 'Safe Diabetes' in India. Case 3: 46 year-old Indian lady presented with abdominal pain, weight loss and vomiting. Initial investigations revealed anaemia with basophilic stippling. Whole-blood lead was 5.05 micromol/L. She was taking Ayurvedic medicine imported from India for her. *Discussion:* Heavy metals are sometimes used as active ingredients in Ayurvedic medicines. Their presence may be incidental from poor quality control of manufacturing, storage or transporting of ingredients. In these cases there was no acknowledgement of lead on the packaging. While traditional medicines authorised for supply in Australia are regulated by the Therapeutic Goods Administration to meet set standards of manufacturing and quality there is no quality assessment or regulation of medicines brought in from overseas for personal use. *Conclusion:* Lead poisoning due to patient-imported Ayurvedic medicines is a potential public health problem. Sophisticated packaging is no guarantee of safety of preparations. Doctors in developed countries should be alert to the possibility of lead contamination in Ayurvedic medicines in patients travelling from India with evidence of lead poisoning.

101. Mineral Miracle Solution: Acute Poisoning After Oral Use of a Sodium Chlorite-Containing Pseudo-Medicine Sold on the Internet

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Objective: Mineral Miracle Solution (MMS) is a product sold on the Internet, which is advocated to cure many pathological conditions including AIDS, malaria, cancers etc. According to the information available on visited websites, MMS is sold as 120-mL flasks containing a 28% sodium chlorite solution. It is recommended that one to 15 drops of the solution be allowed to react with an acid (i.e. 10% citric acid sold as an "activator" kit) to generate chlorine dioxide. The final product is then ingested after dilution in water or fruit juice. Few cases of human poisoning have so far been reported. However, if instructions for preparation are ill-understood, severe poisoning may ensue as the present case report shows. *Case report:* A 27-year-old woman born in Cameroon, without any remarkable medical history, ingested several mLs of MMS to treat constipation. Shortly thereafter, she developed nausea, vomiting, abdominal pain, shivering, and then marked anemia and dark urine. Three days later, she asked for medical advice due to persisting symptoms. Sinus tachycardia and conjunctival icterus were noted. Biological abnormalities included severe hemolytic anemia with a sharp drop in hemoglobin level (4.7 g/dL). Methemoglobinemia was not measured. She was given globular concentrates on 4 occasions. No other cause of the intravascular hemolytic anemia could be found, except for G6PD deficiency that had so far remained asymptomatic despite prior consumption of fava. The patient recovered uneventfully without recurrence of hemolysis or renal failure. *Conclusion:* Only one case of human poisoning with methemoglobinemia (59%) and hemolysis (Hb: 7.1 g/dL) has been published following the deliberate ingestion of 10 g of sodium chlorite.[1] Methemoglobinemia has been described in cats with doses of 20 mg/kg and above. The present case report confirms the hematological toxicity of sodium chlorite. Reinforcement of the surveillance of risks associated with the use of pseudo-medicines sold on the Internet is therefore recommended. *References:* 1. Lin JL, Lim PS. Acute sodium chlorite poisoning associated with renal failure. Ren Fail 1993; 15:645–8.

103. Racial-Ethnic Association with QT Prolongation following Acute Drug Overdose

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Objective: QT prolongation has been identified as a strong predictor of adverse cardiovascular events in suspected poisoning.[1] While gender differences are a well-known genetic influence on susceptibility for QT prolongation, racial disparities in drug-induced QT prolongation are unclear. Therefore, we aimed to evaluate the association between race, ethnicity, and drug-induced QT prolongation for patients with acute overdose. *Methods:* In a cross sectional observational study at two urban teaching hospitals, we evaluated consecutive adult Emergency Department patients presenting with acute drug overdose over a two year period. Standard demographic, racial-ethnic, and clinical variables were collected. Racial-ethnic classification was self-reported and based on two subdivisions: (a) race was classified as White, Black, Asian, or other; (b) ethnicity was dichotomized as either Hispanic or non-Hispanic origin. Based on the initial ECG computer generated QTc (Bazett), the cutoff of QT prolongation was defined as 460 (men) or 470 (women). Factors associated with QT prolongation were assessed with chi-squared, t-test, and logistic regression analysis. Assuming 20% risk factor prevalence and 10% QT prolongation, we calculated the need to enroll 466 patients for 80% power to detect 2-fold risk difference. *Results:* In 766 patients screened, we excluded 216 (age < 18, lack of ECG, alternate diagnosis); thus 550 patients were analyzed (53% female, mean age 41) with QT prolongation occurring in 11.4%. The most common drugs ingested in the prolonged QT group were opioids, anti-depressants, anti-psychotics, and benzodiazepines. Racial composition of all subjects was 38% Whites, 21% Blacks, 10% Asians, 30% other, while ethnic composition was 48% Hispanic origin. Non-Hispanic ethnicity was significantly associated with prolonged QT using univariate analysis (OR 1.87, $p < 0.05$) as well as multivariate analysis (OR 2.1, $p < 0.05$) adjusted for age, heart rate, race, ethnicity and serum potassium concentration. *Conclusion:* In this large urban study of acute drug overdose, non-Hispanic ethnicity was independently associated with QT prolongation. Implications for genetic susceptibility to drug-induced QT prolongation require future study. *References:* 1. Manini AF, Nelson LS, Skolnick AH, et al. Electrocardiographic predictors of adverse cardiovascular events in suspected poisoning. J Med Toxicol 2010; 6:106–15.

104. Identification of the Botanical Origin of Commercial Pine Nuts Responsible for Dysgeusia by Gas-Liquid Chromatography Analysis of Fatty Acid Profile

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Objective: Pine nuts are traditionally consumed in Europe, but local production is not enough to meet the current demand. Therefore, pine nuts are primarily imported from Asian countries such as China, Korea or Pakistan. Over the last 10 years complaints were increasingly reported from consumers experiencing taste disturbances following consumption of pine nuts.[1] Problems were reported with imported products, but the exact geographical origin or botanical identities of the products were not reported. *Methods:* Authors previously proposed a method based on the analysis of pine nuts' fatty acid profile by GLC to unravel the botanical origin of pine nuts. This method has been used to confirm that some of the pine nuts found in commercial products originate from species such as *Pinus armandii* that is not reported as traditionally consumed.[2] *Results:* Sixteen suspected pine nuts samples were analyzed. The fatty acid composition of the samples was determined and diagnostic index values were used to identify the botanical origin. *Pinus armandii* nuts were identified in all the samples, pure (n = 12) or in mixture with *P. koraiensis* nuts (n = 4). *Conclusion:* All the samples contained nuts from *P. armandii* in mixture or not with *P. koraiensis* nuts, confirming that consumption of *P. armandii* nuts may lead to dysgeusia. The nature of the compound(s) responsible for the dysgeusia remains unknown. *P. armandii* is not reported as edible by the Food and Agriculture Organization.[3] Based on the present study and previous work, we advise companies to trade pine nuts from traditionally recognized species. Additionally we think that the food regulatory authorities should introduce a positive list of edible pine nuts in the legislation. *References:* 1. Munk MD. "Pine mouth" syndrome: cacogeusia following ingestion of pine nuts (genus: pinus). An emerging problem? J Med Toxicol 2010; 6:158–9. 2. Destaillats F, Cruz-Hernandez C, Giuffrida F, et al. Identification of the botanical origin of pine nuts found in food products by gas-liquid chromatography analysis of fatty acid profile. J Agric Food Chem 2010; 58:2082–7. 3. Seeds, fruits and cones. In Non-wood forest products from conifers, Food and Agriculture Organization, Rome. [Online] 1995. http://www.fao.org/docrep/X0453E/X0453e12.htm. Accessed on 7 November 2010.

105. Novel Synthetic Cannabinoids, CRA13, JWH-015, JWH-081 and JWH-210 - Detected in a Case Series

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Objective: Inquiries to the Swedish PC concerning "Spice", and similar products, have increased rapidly during 2010. These are plant materials abused by smoking and known to be deliberately spiked with synthetic cannabinoids (e.g. CP 47 497, HU-210, JWH-018, JWH-073) which are generally more potent than Δ-9-tetrahydrocannabinol, the main ingredient of cannabis. This study aimed to evaluate poisons centre cases and compare these with analytical data. *Methods:* Telephone inquiries from 2007 until the end of October 2010 concerning Spice-products, including product name, co-ingestants, inquirer, geographic location, age, sex and clinical features were collected. All cases with sufficient information were scrutinised and graded according to the poisoning severity score (PSS), and, when obtainable, compared to analytical data. Confiscated materials of Spice-products were analysed by the Laboratory of Forensic Science and the Customs Laboratory and serum samples from poisoning cases were analysed by Karolinska University Laboratory. *Results:* A total of 214 cases were found; 42% were under 20 years old and 96% were 25 years old or younger, with males being over-represented (78%). One hundred and forty-five cases were graded: 74% were mild (PSS 1); and 26% were moderate (PSS 2) poisonings. No severe or lethal (PSS 3 and 4) cases were registered. Most common clinical symptoms were tachycardia (51%), drowsiness (36%), mydriasis (28%), muscular symptoms (26%), hypertension (13%) and vomiting (12%). In 56 of these cases, 26 unique Spice-products were identified. Three new synthetic cannabinoids CRA13, JWH-081, JWH-210 were detected, and JWH-081 and JWH-250 occurred most frequently. In 22 cases, serum samples were available. Fourteen of these were positive for one or two cannabinoids; JWH-018 (2 cases), JWH-081 (11 cases), JWH-250 (2 cases) and another new cannabinoid JWH-015 (3 cases). Most of these patients experienced typical symptoms but a few also presented atypical symptoms, e.g. unconsciousness and loss of eyesight and speech. *Conclusion:* In the literature a few cases regarding Spice have been published. In our study four new synthetic cannabinoids were detected, CRA-13, JWH-015, JWH-081 and JWH-210. Recently three of these became controlled substances in Sweden. Clinical features in this case series were mild or moderate.

106. Effects of BQ-788, an Endothelin B Receptor Antagonist, on Amitriptyline-Induced Cardiovascular Toxicity in Rats

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Objective: Sodium channel blockade in the heart and the decrease in peripheral vascular resistance are the main mechanisms of amitriptyline-induced hypotension.[1] Although endothelin raises blood pressure via endothelin A (ETA) receptors by causing vasoconstriction, it can cause vasodilation by stimulating nitric oxide and prostacycline release via ETB receptors. We investigated the effects of BQ-788, an ETB receptor antagonist, on amitriptyline-induced cardiovascular toxicity.[2] *Methods:* Rats were anaesthetized with urethane/chloralose. Mean arterial pressure (MAP), heart rate (HR), duration of QRS were recorded. Toxicity was induced by infusion of amitriptyline 0.94 mg/w/min until the 50% inhibition of MAP. After finishing the amitriptyline infusion, 5% dextrose ($n = 8$) and BQ-788 ($n = 6$) were given to control and experimental groups, respectively. *Results:* Amitriptyline infusion caused a significant decrease in MAP ($48.7 \pm 1.1\%$ and $50.3 \pm 1.8\%$), prolongation in QRS ($183.4 \pm 6.3\%$ and $166.7 \pm 8.6\%$) and decrease in HRs ($73.3 \pm 4.5\%$ and $69.5 \pm 8.8\%$ for control and BQ-788 groups, respectively). BQ-788 improved MAP at 5, 10 and 15 minutes ($61.2 \pm 5.4\%$, $22.6 \pm 4.1\%$ at 5 min; $70.5 \pm 9.1\%$, $23.6 \pm 5.3\%$ at 10 min; $69.6 \pm 10.2\%$, $19.3 \pm 8.5\%$ at 15 min; $p < 0.001$, $p < 0.01$ and $p < 0.05$, respectively). BQ-788 also shortened the prolonged QRS at 5 and 10 minutes ($150 \pm 11.4\%$, $254 \pm 25.2\%$ at 5 min; $144.4 \pm 7.0\%$, $225.0 \pm 25\%$ at 10 min; $p < 0.01$, respectively) and increased HRs at 5, 10 and 15 minutes ($72.3 \pm 9.9\%$, $31.4 \pm 6.7\%$ at 5 min, $74.6 \pm 7.5\%$, $35.8 \pm 12.8\%$ at 10 min and $83.9 \pm 3.8\%$, $40.4 \pm 9.6\%$, at 15 min, $p < 0.05$, respectively). Although all of the amitriptyline infused rats survived 30 minutes in BQ-788 group, all of the amitriptyline infused rats died within 20 minutes in the control group. *Conclusion:* BQ-788 bolus reversed the hypotension, QRS prolongation and corrected HRs in an amitriptyline toxicity model of rats. Further investigation is needed to clarify the role of ETB receptors in amitriptyline-induced hypotension and QRS prolongation. *References:* 1. Kalkan S, Hocaoglu N, Arici AA, et al. Effects of adenosine receptor antagonists on survival in amitriptyline-poisoned mice. Drug Chem Toxicol 2010; 33:233–7. 2. He G, Liu M, Yang Q, et al. Role of endothelin-1 receptor antagonists in vasoconstriction mediated by endothelin and other vasoconstrictors in human internal mammary artery. Ann Thorac Surg 2007; 84:1522–7.

107. Epidemiology of Acute Intoxication in Croatia

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Objective: Epidemiology of acute intoxications and the rate of complications in Croatia were studied. The data were compared with our older results and data from other countries. *Methods:* All patients with acute intoxications admitted to the ICU during last year were included. Glasgow coma score (GCS), APACHE II score were measured on admission (GCS0) and after 24 hours (GCS1). Toxi-lab and gas-chromatography were performed. Level of consciousness, blood pressure, pulse, oxygen saturation, gas exchange and other laboratory findings were measured on a daily basis. X-rays were performed on admission, later if patients developed febrile complications and on discharge from ICU. *Results:* 34 patients were admitted in ICU during one year (9.7% of all ICU admissions), 16 male + 18 female, mean age 48.1 ± 17.1 (range 20–79). The majority of the patients (23), were intoxicated with psychopharmaceuticals (71%), 7 patients were addicts intoxicated with methadone or in overdose (18%), 4 patients had mushroom intoxications (*Amanita phalloides*). GCS0 8.5 ± 3.3 GCS1 13.3 ± 3.2, APACHE II0 9.9 ± 4.6, APACHE II1 13.2 ± 3.2. All patients needed additional oxygen supply, 5 patients needed artificial ventilation, all patients needed volume substitution, 3 needed vasoactive support. Two patients died, one from mushroom intoxication in multiple organ failure (MOF) and one by MOF caused by drug overdose. *Conclusion:* The total incidence of acute intoxications admitted to ICU in our country is stable. Compared to the results from our earlier epidemiology data, the incidence of drug abuse and severe complications in our country is increasing. The majority of the patients according our results were intoxicated with psychopharmaceuticals, as published in other countries. Artificial ventilation and vasoactive therapy improve the ICU outcome of acute intoxicated patients, but severe multiple organ failure is an ominous sign for survival. *References:* 1. Gašparović V, Gjurašin M, Ivanović D, et al. Management of common poisoning in the Intensive Care Unit. In: Gallo A, ed. Critical Care Medicine. Trieste, Italy: Springer Verlag, 1995:845–57. 2. Smit SB, Maguire J, Mauck KF. Clinical cases in acute intoxications. Hosp Pract (Minneap) 37:84–92. 3. Frithsen IL, Simpson WM. Recognition and management of acute medication poisoning. Am Fam Physician 2010; 81:316–23. 4. Rentsch KM. Laboratory diagnostics in acute poisoning: critical overwiev. Clin Chem Lab Med 2010; 48:1381–7. 5. Exiara T, Mavrakanas TA, Papazoglou L, et al. A prospective study of acute poisonings in a sample of Greek patients. Cent Eur J Public Health 2009; 17:158–60.

108. The Public Health Role of Poisons Centres - Signals from Human Cases. Examples of Collaboration Between Poisons Centres and Public Health Authorities

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Background: With the Chemicals Act (ChemG), legislation in the Federal Republic of Germany has provided a basis "to protect humans and the environment from harmful effects of dangerous substances and preparations, particularly to make them recognizable, to avert and to prevent the development of such effects". Data on human toxicology that are obtained from the evaluation of cases of poisoning in humans are especially important for a realistic assessment of risks for human health. A physician who is consulted for treatment or evaluation of sequelae of diseases caused by chemical substances or products is obliged to submit essential data on poisonings to the "Centre for Documentation and Assessment of Poisonings" at the Federal Institute for Risk Assessment (BfR). Additionally, in different regulations, manufacturers or distributors of products are obliged to notify formulations of chemical products (1990), cosmetics (1997), biocidal preparations (2002) and detergents (2007) to the BfR for risk assessment and to provide the German Poison Centres (PCs) with formulations for emergency advice. The PCs assist the BfR by submission of data on health hazards resulting from their work. So in cooperation with BfR Committee: "Assessment of Poisonings" which has members of the German PCs, Industry, Universities, Consumer Councils and Ministries and based on two joint research projects with the German PCs, the BfR has implemented an effective toxicological network. *Results:* Since 1990 the BfR has received more than 78,000 reports. Additionally, the German PCs were provided with more than 280,000 product records. The "classic" distribution of cases in PCs is different to the BfR reports: The greatest part (90%) was due to accidents, 6% were hazards during normal use and only 2% of the cases were related to attempted suicides. More than 90% of the cases happened in adults, most of them at the work place. Only 7% happened in children. Collaboration between PCs and Public Health Authorities: 1) The national Committee: The national Committee for the Assessment of Poisonings was established in 1964 within the former German health authority (BGA), modelled on the American Food and Drug Administration (FDA) committee "National Clearing House for Poison Control Centers", together with the "Centre for Documentation and Assessment of Poisonings". Likewise, poison information centres were established in the Länder (German federal states) according to the American model. Renowned experts were appointed to the Committee who supported the German poison information centres' consultation and treatment of accidents. The Committee, on which more than 190 experts have collaborated up to now, provides input for legislative procedures. For instance with the backing of the Committee BfR proposed the EU-wide restriction of the sale of paraffin-containing, coloured and perfumed lamp oils which led to a marked drop in the number of intoxication accidents with these oils. Also the EU standard on "Child-resistant closures", the restrictions on methanol in consumer preparations and changes in formulations and warnings on mechanical dishwashing products are all down to the initiative of Committee members. 2) Product labelling initiative: A general German analysis of the product labels especially in the fast-growing and fluctuating international markets of household and cosmetic products has shown that there must be better orientation on the labels and packages to identify the real trade-name in emergencies. To improve the product identification on the basis of the true trade name, the BfR has initiated investigations to preserve an "Easy-to-Identify Area" on the labels of consumer products in close proximity to the

barcode via an EC-standardisation procedure. The CEN standardisation (EN 15178) came into force in October 2007 and led to a German process of better product identification starting with detergents. Signals from Human Cases: 1) As a consequence of documentation and evaluation of health hazards, a "Toxicovigilance" procedure for rapid dissemination of information to industry, ministries and industrial associations on health risks of products on the basis of immediate and summarised reports has been inaugurated. For severe cases of toxic effects in humans, producers - as well as responsible authorities and ministries - are directly informed and asked for risk reducing measures. From 1998–2010 we had 30 immediate reports. With the periodically summarised reports more than 250 manufacturers/distributors were informed every year. These reports led to additional warnings, classification, labelling, bans and promoted, for example, the development of substitutes for e.g. lamp oils, grill lighters, dishwasher detergents etc. 2) Studies: a. Since lamp oils involve the highest risk of severe health effects in infants and small children in household chemicals in Germany, the BfR initiated different measures for risk minimisation: child-resistant closures, warnings, a new R 65-Phrase and a new EC-standardisation of oil-lamps in accordance with the competent ministries, which at least led to sale restrictions from July 1st, 2000 onwards in all EU countries. This has consequently led to the introduction of lamp oil substitutes into the German and EU market. To investigate the consequences, a BfR monitoring study "Dangerous Lamp oils" was initiated together with 450 German Children's Hospitals. The results have shown that the exchange of paraffins by fatty acid esters obviously leads to a marked reduction of risk. b. To evaluate the circumstances of exposures during accidents, a study (BfR Exposure Study) was initiated to collect data describing the circumstances of exposures to a number of selected chemical substances (paints, solvents, glues and pesticides). Cases to be studied are selected from the reports sent to the BfR, and questionnaires are to be filled out by the exposed persons to collect data that can give a better description of the accident and to allow quantitative exposure evaluations. 3) Case reports: Cases of particular scientific interest (e.g. rare poisonings, high-/low-dose exposures, cases with unexpected clinical course, substances of special interest etc) were documented as case records and collected in a special BfR case database. The case reports were written in uniform documents, provided with keywords and additional information. The bilingual (German/English) case data base is implemented in the BfR intranet structure, but it will be opened for specialists in future. 4) Annual reports: Since 1995 the BfR has published regular annual reports with statistics, case reports and fields of special toxicological interest for physicians, industry, government, tertiary education and the public. Due to the increasing interest we have published annual reports also in English since 2004 from 2009 onwards based on the German harmonized categories. *Conclusions:* Signals from human cases, analysed on a national monitoring level, are of great importance for initiating preventative measures. The documentation of signals from human cases is mainly based on the excellent collaboration between PCs and Public Health Authorities. Having these signals as a monitoring instrument, Public Health Authorities might effectively support consumer safety and, in addition, case reports for the new REACH regulation can be analysed.

109. Notification and Reporting Health Threats Caused by Chemical Events Through RAS CHEM: Policy and Mechanism for Coordinating Public Health Measures at EU Level

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Introduction: The risk assessment and management of chemical health threats is intrinsically important to ensure the safety and security of EU citizens. Under the current Treaty the response to cross border health threats, including those of chemical origin, should be coordinated at EU level. The Health Security Committee (HSC) was set up in 2001 to ensure coordination and alignment of public health measures between national authorities, the Commission and the relevant EU agencies. The HSC has representatives from all EU countries and operates in 3 core areas: generic preparedness, influenza, and chemical, biological and radio-nuclear (CBRN) threats. One of the priorities of the HSC work plan is to set up a "mechanism for information exchange, consultation and coordination for the handling of health-related issues linked to attacks in which biological and chemical agents might be used or have been used". In addition to the currently existing mechanism of alert and response (e.g. the Early Warning and Response System for communicable diseases - EWRS, the Rapid Alert System for food and Feed - RASFF, and others) an EU Rapid Alerting System for Chemicals (RAS-CHEM) has been designed and developed to enhance the EU Member States capacity to identify and respond to chemical health threat events of cross border relevance. *Methods:* Feedback and discussion within the plenary meetings of the EU HSC and in the context of the CBRN Section of the HSC have been instrumental to steer the development of the RAS CHEM application, taking stock of the main lessons learned through the operations of the already existing alerting systems and, in particular, the one for the detection and coordination of public health measures in response to cross border events due to communicable diseases (i.e. EWRS). In addition a number of exercises have been planned to test the functioning of the system. RAS-CHEM has been developed as a voluntary based non-formal reporting system for chemical health threats. RAS-CHEM will identify sentinel exposure events allowing efficient communication of risk, assessment and management of these threats in a coordinated manner, from the local level up through national structures to the other EU Member States. In addition RAS-CHEM will operate in the context of the new International Health Regulation and in an international dimension using the mechanisms existing at EU level. *Results:* RAS-CHEM has been developed by the Commission under the auspices of the Alerting System for chemical Health Threats projects, phase I and II (ASHTI [2004212]; ASHTII [2007210]). RAS-CHEM provides a mechanism to facilitate the rapid communication of information concerning chemical health threats, ranging from reports on unusual cases to potential mass poisoning incidents. RAS-CHEM also provides toxicological profiles for toxic chemicals that can be used to identify potential agents of intoxication. RAS-CHEM has been extensively tested and the results from these evaluations have been fed into the iterative design of the system. The informatics application allows a real time exchange of information among two different sectors of users in the 27 EU Member States: the risk assessment sector and the risk management one, with precise rules and standard operational procedures. *Discussion:* The success of RAS-CHEM will depend on a number of crucial elements: 1: a clear definition of the scope, mandate and standard operation procedures for operating and accessing the system; 2: the successful implementation of the system in each Member State and the integration of the system into current health threat reporting structures from the local or regional level (poisons centres) through the National level (national public health officials or health ministers) to the International forum (Commission, EU Member States and WHO); 3: successful integration of RAS-CHEM into Member State reporting processes depending on the resources available, availability of training and robust protocols for the system, international policies, legislation and political will. *Conclusion:* Rapid and effective communication of risk, assessment and management of chemical health threats is essential to enable EU Member States to protect their citizens from these hazards; RAS-CHEM has the potential to provide this service throughout the EU.

110. Clinical Effect Profiles for Chemical Agents of Concern - Role of Syndromic Surveillance and Rare Symptoms

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Objective: The aim of the ASHTII project is to develop a Rapid Alert System for Chemical Health Threats (RAS-CHEM), to facilitate the rapid exchange of information on relevant events, which have the potential to become public health threats, and to improve national response strategies to real or potential chemical incidents, including deliberate and accidental releases, for the benefit of all EU Member States.[1] *Introduction:* As part of the ASHTII project, RAS-CHEM has been further developed and extended to allow different levels of access to the alerting system by the creation of the risk assessment (formerly termed EUPC Forum) and risk management tiers to RAS-CHEM. For RAS-CHEM to operate successfully in an interdisciplinary multi-language environment it is important to adopt standardised terminology to describe clinical effects associated with exposure to chemical agents and standardised classification and nomenclature for the agents. To effectively identify a comprehensive range of the clinical effects, features and symptoms of poisoning, a literature review on chemical agents identified as 'high-risk' and likely to cause severe health effects was undertaken. *Methods:* Following a review of resources the Meta-Directory ToxSeek was used as the initial starting point for all literature reviews. The literature review resulted in the production of acute-exposure Clinical Effect Profiles (CEPs) for a representative list of chemical agents. Meta-sources such as Poisindex, TOXBASE, INTOX and INCHEM were used in the first instance to compile CEPs information under the condition that they were able to provide detailed (quantified) information on human clinical effects, were current and regularly updated, peer reviewed, referenced, and easily accessible. In addition, the considerations included cost, language and prior familiarity and use in poisons centres. Where these criteria were not met, primary information resources such as case series and case reports were used. *Results:* CEPs were produced for 118 chemical agents included in RAS-CHEM to be accessed easily by both the poisons centres and public health authorities. The list included chemicals of concern in deliberate release scenarios, those posing a major threat from accidental release, and agents identified as interesting from a poisons centres perspective. The list was used as a reference point for the project; the agents therein described both typical poisonings, and those capable of testing the system. CEPs were designed to provide concise summaries of clinical effects reported in the literature. For each agent, information was collected and organised in a concise tabulated format according to body system and ordered chronologically. The poisoning severity score devel-

oped by IPCS/EAPCCT[2] was used, where appropriate. From the 118 chemical agents included in the literature review, over 1000 clinical effects were collated. This list was then cross-checked[3–5] for missing terms needed to describe additional important features or symptoms of poisoning that may have been missed during the initial literature review. An additional 200 terms not previously identified during the literature review were added to the list of clinical effects.[6] *Conclusion:* The ASHTII project team has further developed the concept of the RAS-CHEM to provide DG. SANCO with a central alerting tool enabling Member States to warn each other and to share information regarding chemical accidents or threats that may have cross border implications. It is important to the overall success of the ASHTII project that RAS-CHEM can capture the whole range of clinical effects associated with exposure, rather than being limited to non-specific broad clinical terms. CEPs are intended to be used as 'agent-related model cases' in the database. RAS-CHEM users with no knowledge of toxicology will be able to search for chemical agents and easily find selected or all potential symptoms caused by this agent. Another way of using the data from CEPs is to search for all agents that cause the symptoms selected by the user, including all real cases and all model cases stored in the database. The so called "syndromic surveillance" may be a key in the search for the cause of the increased frequency of unusual symptoms of unknown origin in the calls to the poison centres in one or several countries of Europe. *References:* 1. Wyke S, Orford R, Duarte-Davidson R, et al. Further Development of the Alerting System for Chemical Health Threats, Phase II (ASHTII). Clin Toxicol 2010; 48:271. 2. Persson HE, Sjöberg GK, Haines JA, et al. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol 1998; 36:205–13. 3. Diagnosis of Poisonings. In: Brent J, Wallace K, Burkhart K, eds. Critical Care Toxicology. 1st ed. Philadelphia, USA: Elsevier Mosby, 2005:13–28. 4. Initial diagnosis and treatment of the poisoned patient. In: Dart RC, ed. Medical Toxicology. 3rd ed. Philadelphia, USA: Lippincott Williams & Wilkins, 2004:21–31. 5. Leitsymptome der Vergiftungen. In: Moeshlin S, ed. Klinik und Therapie der Vergiftungen. 7th ed. Stuttgart, Germany: Georg Thieme Verlag, 1986:687–719. 6. Wyke S, Orford R, Duarte-Davidson R, et al. The Evaluation of Standard Medical Terminology Systems to Describe Symptoms of Poisoning, an Output of the ASHTII Project. Clin Toxicol 2010; 48:271. *Acknowledgements:* Project Alerting System for Chemical Health Threats Phase II (ASHTII; project number 2007210) which has received funding from the European Union.

111. Language Independent Description of Poisoning Symptoms in RAS-CHEM Using MedDRA Terminology

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Objective: The Rapid Alert System for Chemical Threats (RAS-CHEM) will provide a mechanism to facilitate the rapid communication of information concerning chemical health threats, ranging from reports of unusual cases to potential mass exposure incidents. Furthermore, RAS-CHEM will include toxicological profile data for toxic chemicals identified as potential agents and health threats.[1] Clinical effect profiles (CEP) were developed for over 100 'high-risk' chemical agent health threats. The CEP will be included in RAS-CHEM for access by public health authorities and poisons centres. CEP will be handled as 'agent-related model cases' in the database. RAS-CHEM users - with or without expertise in toxicology - will be able to search for chemical agent/s and display the entire set or a subset of potential symptoms associated with this exposure. Furthermore, RAS-CHEM users will be able to perform a symptom oriented ('backward') search: all agents that cause symptoms selected by the user will be listed or displayed - including all real cases and all model cases stored in the database. This may become an important feature in evaluating observations of symptom occurrence or increased frequency of unusual symptoms of unknown origin in patient groups (i.e. Syndromic Surveillance). Agent-related storage of medical symptoms in a highly structured relational database requires the use of a well defined medical terminology system to assure optimal search results. Several terminology concepts were carefully evaluated in the ASHT II project.[2] The Medical Dictionary for Regulatory Activities (MedDRA) was chosen as the most suitable independent terminology and was carefully evaluated and recommended as the most appropriate symptom description terminology to be incorporated into RAS-CHEM. MedDRA is a hierarchic multilingual terminology system of medical symptoms maintained by the MedDRA Maintenance and Service Organisation (MedDRA MSSO[3]). MedDRA terminology is widely used for a variety of medical purposes, especially for exchanging reports on adverse drug reactions between companies and authorities. The European Medicines Agency (EMA) uses MedDRA for symptom-related communication. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) strongly supports MedDRA use. *Methods:* All CEP data were combined in a single database table (column titles: agent name, symptom, related organ, time course). All terms chosen by ASHTII to describe poisoning symptoms were corrected for spelling errors and minimally different names were unified (e.g. edema/oedema). Subsequently all terms were matched with MedDRA low level terms (LLT) (version 12.1) by automatic and manual procedures. A change request to add missing poisoning symptoms was submitted to MedDRA MSSO. These changes were included in the revised version of MedDRA (version 13.0). Finally all symptoms identified in any CEP were matched to MedDRA version 13.0 terms. All CEP data including all MedDRA matched symptom terms were imported into a test database (DEV-EU PC Forum). Detailed evaluation was done with special attention to reporting in different languages. *Results:* In total 4036 symptom-by-agent relations were included in the data analysis. After editing the symptom list to erase double entries, correct typo errors and minimal spelling variations 1565 different medical symptoms were listed. 1492 symptoms (95%) could be matched with MedDRA terms either automatically (41%), semi-automatically ('algorithmic match' with expert checking (22%)), or manually (33%). Eighty-three symptoms (5%) could not be described or identified in MedDRA version 12.1 and were submitted for addition to MedDRA version 13.0. After acceptance, all 1565 symptom terms could be matched with 1139 MedDRA terms. After import into the test database, search and reporting functions tested satisfactory. *Conclusion:* 1139 terms were needed to describe all symptoms of more than 100 (mostly severe) intoxications. It was shown that MedDRA, a systematic nomenclature developed for reporting adverse drug effects, can be used to precisely describe poisoning symptoms. Cooperation with MedDRA MSSO gave substantial support for the project. The mapping of symptoms in the technical environment of a relational database enables multiple functions of data retrieval and reporting: Thus, the hierarchic ordering of symptoms in MedDRA enables searching not only for cases with identical symptoms but also for those with similar symptoms. Further evaluation may show whether MedDRA may be used for other tasks and projects where information of poisoning symptoms need to be compiled or exchanged in a harmonized and multilingual way, e.g. case documentation and case data exchange in poisons centres. *References:* 1. Wyke S, Orford R, Duarte-Davidson R, et al. Further Development of the Alerting System for Chemical Health Threats, Phase II (ASHTII). Clin Toxicol 2010; 48:271. 2. Wyke S, Orford R, Duarte-Davidson R, et al. The Evaluation of Standard Medical Terminology Systems to Describe Symptoms of Poisoning, an Output of the ASHTII Project. Clin Toxicol 2010; 48:271. 3. http://www.meddramsso.com (accessed: 2010-11-21).

112. Epidemiology of Cyanide/Nitrile Poisoning and Survey of Antidotal Treatment Used in Europe

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Objective: The aim of this study was 1) to assess the number of poisonings reported to Poison Centres/ICU/Industry (part A) and 2) to obtain more detailed information on exposure, substances involved, antidotal treatment used and outcome (part B). *Methods:* A structured questionnaire (part A; part B) was distributed and responses were received through the EAPCCT secretariat and personal contacts with the TF members with information from the Cyanide Forum and WHO-IPCS. *Results:* The return on questionnaire part A was limited to 20 respondents from 14 European countries. In this global overview a total of 482 cases are reported over a period from 1977–2009: 232 cyanide poisonings (48%) of which 5 fatal poisonings; 143 nitrile poisoning (29.6%); 103 cyanogenic compounds (21.4%); 4 smoke inhalations (0.83%). Furthermore 218 cases (45%) came with further details (questionnaire part B) and revealed: HCN poisoning in 42 cases treated with oxygen (n = 22); amyl nitrite (n = 4); sodium nitrite (SN) (n = 2); 4-DMAP (n = 4), sodium thiosulfate (STS) (n = 15), hydroxocobalamin (n = 4) and all patients recovered. Thirty-nine cases of cyanide salt poisonings treated with oxygen (n = 22); amyl nitrite (n = 1); SN (n = 3); 4-DMAP (n = 10), STS (n = 17), hydroxocobalamin (n = 15); dicobalt edetate (n = 1); 9 patients died and 30 recovered. A large series of 128 nitrile exposures was reported, mainly from industry, treatment consisted of oxygen (n = 19); 4-DMAP (n = 1); STS (n = 14); hydroxocobalamin (n = 5); all patients recovered. Moreover 2 mixed intoxications with HCN and nitrile were successfully treated with oxygen and STS. Natural cyanogenic compounds like plums and bitter almonds were involved in 3 case reports, treatment with SN and STS, started 11 hours after ingestion and reversed the symptoms rapidly. There were 4 cases of smoke inhalation treated with oxygen (n = 2); STS (n = 1); hydroxocobalamin (n = 1). *Conclusion:* From this survey it is obvious that a wide range of antidotes is available and used in cyanide/nitrile poisoning. Cyanide poisoning is a severe and rather uncommon and the problem remains in the selection of the appropriate antidote based on the efficacy and safety, depending on the condition of poisoning.

113. Prognostic Factors of Cyanide Poisoning. A Systemic Modelling Analysis from 283 Cases Using Adapted Poison Severity Score

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Objective: Prognostic factors of cyanide poisoning remain unknown. We attempted to assess determinants of the Poison Severity Score (PSS) in cyanide poisonings. *Methods:* Published and two unpublished cases with individual data induced by poisoning with cyanide and cyanogenic compounds, excluding smoke inhalation. Signs were recorded into the 4 classes of PSS by 2 different raters. PSS was adapted to cyanide poisoning with minor modifications by independent experts, except FJB. Analysis was made by an independent expert (PL) using Stepwise General Linear Model to predict PSS from the variables. All cases were analysed including those with missing data handled by maximum likelihood optimization. *Results:* In 283 cyanide poisonings, high concordance of PSS was found between the two raters (Kendall $\tau = 0.94$). Mild, moderate, severe, and lethal PSS were 33, 19, 29, and 19% respectively. Five determinants predicted severity ($R^2 = 0.377$, $p < 0.001$): 1) the dose with Incremental Effect IE = 1.07/Log(dose), 95%CI [0.85,1.29]; 2) the delay in presentation with 7-fold and 10-fold increase in PSS 3 and 4 when delay was more or less than 2 hours, respectively 3) age: greatest severity was observed in young and old patients; 4) women: more vulnerable than men. 5) gasesous HCN with greatest severity IE = +0.74 [0.53,94] compared with salts and cyanogenics. *Conclusion:* The most potent predictors of PSS were the dose and the delay in presentation. Age, gender, and cyanide type were secondary potent predictors. The delay in presentation, including recognition of cyanide poisoning and prompt treatment were factors that may be improved by preparedness.

114. Systematic Review of Efficacy and Adverse Effect of Methemoglobin Forming Antidotes in Cyanide Poisoning. Preliminary Results

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Objective: Acute cyanide poisoning is an extremely serious event due to the potentially fatal outcome. A study was undertaken by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) to rank the efficiency and adverse effects of methemoglobin forming antidotes using all available sources. *Methods:* Evaluation was performed of all case reports of cyanide intoxications which were treated by Met-Hb-forming agents ever published and of non-published cases from European PCCs. All cases (n = 336) were classified according to source of intoxication, severity determined by an adapted PSS (excluding PSS 0) and the outcome. Two hundred and sixty-four (78.5%) were treated with the US antidote kit (amyl nitrite, sodium nitrite, and sodium thiosulfate). Forty-one patients (12%) received amyl nitrite alone, 31 patients (9%) were given 4-DMAP and thiosulfate. One hundred and thirty-five persons (40%) were poisoned by HCN/cyanide salts, 155 (46%) by nitriles, 34 (10%) by cyanogenic glycosides and 11 (3%) by smoke inhalation. Two hundred and seventy-eight were grouped as mild or moderate (PSS 1–2), all survived. Severe or fatal intoxications were found in 58 patients (17.3%). Forty-eight were treated with nitrites, 10 with 4-DMAP. All patients who had suffered from cardio-respiratory arrest eventually died (PSS 4). In the nitrite group with PSS 3 at admission 26 of 40 (65%) survived. 4-DMAP was successful in 5 of 7 cases (71%). Mild to severe side effects were only seen if 4-DMAP was overdosed, namely hemolysis in 7 of 31 cases, two of whom had to have transfusions. For the nitrite group hypotension was seen in 8 of 264 cases (6 normal and 2 overdosed, 7 of whom could be compensated with catecholamines). Both antidotes were effective with tolerable adverse effects. *Limitation:* As the data were from the literature a safe stratification of the PSS was sometimes difficult. *Conclusion:* Methemoglobin forming antidotes are efficient in cyanide poisoning, but show partially severe side effects.

115. Potential for Effective Preclinical Use of Cyanide Antidotes after Fire Smoke Exposures

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Objective: Recently, hydroxocobalamin has become available for antidotal use in Germany and leading medical experts recommended its use for severe smoke intoxication immediately after.[1] To evaluate the potential improvement of medical management the incidence and mortality of smoke intoxications and the actual patient treatment were investigated for the year 2009. *Methods:* All media reports about presumptively severe fire smoke exposures in Germany listed in Google News Deutschland[2] in 2009 were analysed. In cases with Emergency Medical Service (EMS) treatment, additional information was requested from the local services by questionnaire within a 12 month period. For comparison, national statistics on mortality due to fire smoke exposures were evaluated.[3] *Results:* 141 cases of severe smoke inhalation treated by EMS were recorded. With 61 patients resuscitation was provided, failing in 39 cases. An additional 19 patients died after admission to hospital. Cyanide antidotes were available for 49 of 60 EMS providers: 41 carried dimethylaminophenol, 35 thiosulfate and 10 hydroxocobalamin. Administration was reported in one case only. Four hundred and thirty-two fire related fatalities were registered in Germany in 2009, in 238 of these cases smoke intoxication was stated as cause of death. Ten fatalities caused by hydrogen cyanide or cyanide salts were officially notified. *Conclusion:* Severe fire smoke intoxication is much more frequent than (pure) cyanide intoxication. At least 16% of smoke fatalities (39/238) died out-of-hospital despite intensive medical care. Cyanide antidotes are usually available for emergency physicians in the preclinical setting in Germany, the use in smoke inhalation exposures is rare. Recently started analytical studies, one of these in the authors' hospital, will provide further evidence on the role of cyanide and thus the potential role of cyanide antidote application in several fire smoke inhalations. *References:* 1. Zilker T, Sefrin G, Scherer B, et al. Intoxication through Smoke Inhalation (article in German, abstract in English). Der Notarzt 2010; 26: 95–102. 2. www.google.de, accessed 2009-01-01 to 2010-09-30. 3. Gesundheitsberichterstattung des Bundes, www.gbe.de, accessed: 2010-11-15.

116. A New Immunochromatographic Method for Rapid Sensitive On-Site Detection of Sulfur Mustard

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Objective: Sulfur mustard (SM) is a strong vesicant and a bifunctional alkylating agent targeting mainly nuclear DNA. Following a latency period of up to 24 hours, it induces blistering and inflammation. Early diagnosis and treatment improve the prognosis with regard to faster recovery and a lesser degree of permanent lesions. Our objective was to develop a sensitive immunochromatographic method for the rapid detection of SM, suitable for on-site application as a handheld test kit. *Methods:* 7-Hydroxyethylguanine (7-HETEG) is the predominant monofunctional adduct formed by SM. An antibody against this adduct, developed by TNO, The Hague, Netherlands[1] was applied to a test strip, developed by Securetec, Munich, Germany. A sampling pad was used to swipe surfaces or exposed to a test atmosphere. When SM was present, it was thus transferred to the test strip, allowed to react with a guanine-rich oligonucleotide and carried by a lateral flow of buffer solution towards the immobilized antibody. The antigen-antibody reaction was visualized by gold particles, conjugated to the antibody. *Results:* The method was tested under laboratory and field conditions. The detection limit for unbound sulfur mustard was established at 2 micromol/litre, 50 times below the vesicating dose in skin.[2] Under field conditions during a NATO exercise in Canada, a 200 micromolar solution of sulfur mustard, a 40,000-fold dilution of the agent, was successfully detected on pig skin. In another scenario, sulfur mustard vapours in a cave were successfully detected by a test strip that had been attached to the protective clothing of a soldier investigating the cave scenario. Test results were obtained within 10 to 20 minutes, depending on the concentration. *Conclusion:* The immunochromatographic detection of 7-HETEG is a sensitive, fast and reliable method to detect sulfur mustard under field conditions. *References:* 1. van der Schans GP, Scheffer AG, Mars-Groenendijk RH, et al. Immunochemical detection of adducts of sulfur mustard to DNA of calf thymus and human white blood cells. Chem Res Toxicol 1994; 7:408–13. 2. Smith, WJ. Vesicant agents and antivesicant medical countermeasures: clinical toxicology and psychological implications. Mil Psychol 2002; 14:145–57.

117. Analyzing the Diagnostic Value of Amatoxin-ELISA in Mushroom Poisoning

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Objective: Poisonings with amatoxin containing mushrooms are a common feature in autumn and provide a challenge for clinical toxicologists, poison centres and analytical facilities as well. Whereas symptoms are quite characteristic, the diagnostic value of amatoxin analytics remains under discussion. To evaluate this, clinical data of intoxicated patients were matched to analytical results. *Methods:* The Poison Information Centre Berlin processed 4122 calls concerning human mushroom exposures between January 2000 and October 2010. Comparing the last seven years, the number of contacts peaked in the year 2010 with a total of 493 calls which was due to a very rich occurrence of mushrooms. In 79 cases of these the diagnosis of amatoxin-poisoning was assumed or confirmed. In parallel, 52 urine samples were analyzed for amanitines using an ELISA method, (Fa. Buehlmann, Switzerland). *Results:* In ten patients amanitines were detected in a concentration higher than 10 ng/mL judged as positive. Nine of these intoxications occurred accidentally, in one case deliberate self-harm was assumed. The medial latency between the ingestion and start of symptoms was 14.5 hours. All patients were hospitalized 29.4h at median after the ingestion of mushroom. The medial concentration of amanitine in urine was 63.4 ng/mL (15.3–125.1 ng/mL). In four of ten cases amanitines were detected later than 48 hours after exposure (median 57.9 hours). All patients tested positive had the typical symptoms of amatoxin-intoxication - nausea, vomiting, abdominal pain, diarrhea, elevation of liver enzymes and coagulopathy. The medial maximal ALT-value was 3907 U/L, the medial maximal AST-value 3242 U/L and lowermost medial prothrombin time was 53%. Nine patients were treated with activated charcoal and laxative. All patients received silibinin intravenously. Three patients were additionally treated with penicillin. Six patients got N-acetylcysteine intravenously. All ten patients survived without liver transplant. *Conclusion:* The immunoassay is specific and sensitive enough to detect amatoxin intoxications. A positive correlation between amatoxin urine concentrations and maximum liver enzymes was observed. A further study has to be focused on the risk of false negative test results in early samples (< 8 hours). *References:* 1. Butera R, Locatelli C, Coccini T, et al. Diagnostic accuracy of urinary amanitin in suspected mushroom poisoning: a pilot study. J Toxicol Clin Toxicol 2004; 42:901–12.

Table 1. Plant cases with fatal outcome reported to the Swiss Toxicological Information Centre 1995–2009

Age	Plant	Symptoms	Therapy	Causality
44	*Taxus baccata*	Tachycardia, bradycardia, AV-Block Grade 3, asystolia	activated charcoal, atropine, magnesium, catecholamines, pacemaker, defibrillation	probable
3	*Colchicum autumnale*	Bradycardia, cerebral edema, vomiting, seizures, respiratory and hepatic failure	supportive therapy	analytically confirmed
57	*Colchicum autumnale*	Pulmonary edema, arrhythmia, coagulopathy, renal failure	Multiple dose activated charcoal, supportive therapy	analytically confirmed
62	*Colchicum autumnale*	Renal failure, myocardial necrosis, coagulopathy	Multiple dose activated charcoal, supportive therapy	analytically confirmed

118. Acute Severe and Fatal Plant Poisoning: Analysis of Clinical Features and Circumstances of Exposure

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Objective: Human contact with potentially toxic plants, which may occur in abuse or in an accidental or suicidal setting, is frequent and sometimes results in clinically significant toxicity. The aim of the present study was to identify which plants may lead to severe poisoning and to define the clinical relevance of plant toxicity for humans in Central Europe. *Methods:* By means of a retrospective case-study design, we analysed 42,193 cases of human plant exposure and 255 acute moderate, severe and lethal poisonings, which were reported to the Swiss Toxicological Information Centre between January 1995 and December 2009. We present here the severe and fatal cases. *Results:* We found 45 severe and 4 lethal poisonings. Fifteen plants were responsible for these cases, foremost among them the abuse of *Datura spp* by ingestion, although no fatalities resulted from its ingestion. Other frequently involved plants were *Atropa belladonna*, *Aconitum napellus* and *Euphorbia spp*. The 4 fatal cases: one suicide with *Taxus baccata*; and 3 accidental ingestions of *Colchicum autumnale* mistaken for *Allium ursinum* are reported in Table 1. In all but one of the severe cases, a complete recovery was documented (one case of permanent visual impairment after ocular contact with corrosive *Euphorbia* plant sap). *Conclusion:* Plant contact was rarely responsible for serious poisoning. Fatal intoxications were extremely rare and were caused by plants with cardiotoxic (*Taxus baccata*) or mitose inhibiting (*Colchicum autumnale*) properties. A complete recovery can usually be expected even in severe cases.

119. Epidemic of *Physalia physalis* Stings on the French Atlantic Coast During Summer 2010

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Introduction: Man-of-war (*Physalia physalis*) is a marine venomous animal which is the cause of severe envenomation in tropical seas. In Europe stings induced by this pelagic species are rare. During the summer of 2008, 40 cases were reported by the Bordeaux poison centre.[1] This first man-of-war epidemic case series was considered as an exceptional event but during the summer of 2010, such a phenomenon was observed again on the French Atlantic Coast. *Methods:* In order to evaluate the health impact of the second Aquitaine region man-of-war bloom, the Bordeaux Poison Centre performed a survey concerning the summer medical activity of 577 coastal practitioners and 57 first-aid stations on the beach. *Case series:* 124 observations were collected in 3 departments, "Landes" (79%), "Pyrénées Atlantiques" (16%), "Gironde" (2.5%) unknown location (2.5%). Patients were mainly men (OR = 1.6) with an average age of 19.4 years ± 14, with 58% of children less than 15 years. Surprisingly patients were mainly stung on the upper limb (66%) due to confusion with plastic toys. Man-of-war species was scientifically identified for 37% of the cases and highly suspected thanks to the patients' descriptions for 63%. Intense local extensive pain was the main symptom (100% of the patients describing burning, electric shock sensations, 36% of them with complete limb pain). Local skin burns were observed for all patients, and systemic symptoms were reported in 46% of them (26% myoclonus, 25% abdominal pain, 21% malaise, 14% nausea, 13% respiratory distress). All patients were managed by the first-aid beach system with referral to practitioners (11%) and to hospital (6%). All patients managed with symptomatic treatment in the hospital recovered in about 24 hours. *Conclusion:* The second epidemic case series of man-of-war stings observed in 3 years in the Aquitaine region is much more important than the first one (124 patients compared to 40). After the description of two collective episodes of man-of-war envenomations on the French Atlantic Coast, the local health structures must be prepared in order to be able to manage new blooms and more envenomed patients in future summers. *References:* 1. Labadie M, Lambrot AL, Mangwa F, et al. Collective Envenomation by Physalia physalis on the French Atlantic Coast. Clin Toxicol 2010; 48:309.

120. *Parabuthus granulatus* Identified as the Most Venomous Scorpion in South Africa: Motivation for the Development of a New Antivenom

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Objective: The efficacy of the currently available scorpion antivenom in South Africa is questionable. At best, a moderate therapeutic effect is seen 4–6 hours post administration. This antivenom is manufactured from the venom of *Parabuthus transvaalicus*. In view of the above, a study was undertaken to assess and identify the scorpion species responsible for cases of severe scorpionism in South Africa in order to facilitate the development of a more effective and rapid-acting antivenom. *Methods:* A retrospective study of all cases of scorpionism (scorpion sting associated with systemic toxicity) dealt with by the Tygerberg Poison Information Centre over a period of 10 years was undertaken. The geographical locations of all the cases as well as the identification of species involved were recorded. *Results:* Of the 148 cases studied, 95% occurred in the Western and Northern Cape provinces. In 38 of the 148 cases, the scorpion was available for identification. All of them were identified as *Parabuthus granulatus*. *Conclusion:* The medically important scorpions in southern Africa belong to the *Buthidae* family, of which the *Parabuthus* genus is the most important. *Parabuthus* scorpion sting may cause a life threatening toxic syndrome. Respiratory failure, which may develop within one to two hours post envenomation, is usually the primary cause of death. The finding that *P. granulatus* was the only scorpion species involved in scorpionism was unexpected. It is important to note that *P. transvaalicus* (the venom of which is used in the production of the current antivenom) does not occur in the Western and Northern Cape, areas known for a high incidence of scorpionism. The most probable reason, therefore, for the sub-optimal efficacy of the antivenom is that the venom of the wrong scorpion is used in its production. In light of this, a strong case exists for the development of a specific *P. granulatus* antivenom, or the inclusion of both *P. granulatus* and *P. transvaalicus* venom in the production of a polyvalent antivenom.

121. A Randomised Controlled Trial of Two Infusion Rates to Decrease Reactions to Antivenom

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Objective: Snake envenoming is a major clinical problem in Sri Lanka, with an estimated 40,000 bites annually. Antivenom is only available from India and there is a high rate of hypersensitivity reactions. This study aimed to investigate whether the rate of infusion of antivenom reduced the frequency of severe hypersensitivity reactions. *Methods:* This was a randomized comparison trial of two infusion rates of antivenom for the treatment of non-pregnant adult patients (>14y) with snake envenoming in Sri Lanka. Snake identification was by patient or hospital examination of dead snakes when available and confirmed by enzyme-immunoassay for Russell's viper envenoming. Patients were blindly allocated in a 1 to 1 randomisation schedule to receive antivenom either as a 20 minute infusion (rapid) or a two hour infusion (slow). The primary outcome was the proportion with severe systemic allergic reactions - grade 3 by Brown grading system[1] - within 4 hours of commencement of antivenom. Secondary outcomes included the proportion with mild and moderate allergic reaction (grade 1 and 2 Brown grading) and repeat antivenom doses. *Results:* Of 811 patients presenting with suspected snakebites, 225 patients received antivenom. Twenty-five patients were excluded or not recruited leaving 103 patients allocated to the rapid antivenom infusion and 97 to the slow antivenom infusion. The median duration of antivenom infusion in the rapid group was 20 minutes (Interquartile range [IQR]: 20–25 min) versus 120 minutes (IQR: 70–120 min) in the slow group. Severe systemic allergic reactions (anaphylaxis) occurred in 26 patients (25%) receiving the rapid infusion compared to 28 patients (29%) receiving the slow infusion which was not statistically significantly different (4%; 95% CI: -9% to 16%; p = 0.63). The frequency of mild/moderate reactions was also similar between groups. Similar numbers of patients in each arm received further doses of antivenom (71 of 103 versus 71 of 97). *Conclusion:* There was no difference in the frequency of anaphylaxis or any immediate type hypersensitivity reactions when antivenom was administered at a slower infusion rate, but a quarter of patients developed anaphylaxis. *References:* 1. Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 2004; 114:371–6.

122. Poisoning by Topical Medications

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Objective: To review the pharmacology and toxicology of transdermal drug delivery, including the functional barrier role of the skin, relevant physicochemical properties of chemicals, and clinical consequences of drug delivery misadventures. *Discussion:* Drug may be applied directly to the skin or may be applied in the form of a transdermal delivery system, or a patch. Medication delivery is driven by the concentration gradient between the skin and the patch. Many medications are available in transdermal formulations, including buprenorphine, clonidine, diclofenac, estrogens, fentanyl, nicotine, nitroglycerin, scopolamine, and testosterone. In order to access the circulation a chemical must pass through the stratum corneum, which is impervious to hydrophilic compounds, and subsequently dissolve in the aqueous subcutaneous tissue. A compound therefore must be sufficiently soluble in both lipid and water, or a carrier substance can be used to enhance permeation. Although there are clinical benefits of transdermal delivery (e.g. long term, continuous delivery; convenience) and the number of transdermal products is increasing, this route of absorption is subject to substantial inter and intra-individual variability that may prove consequential. Among the dermal variables that can predictably alter delivery are the thickness of the dermis, amount of subcutaneous adipose tissue, integrity of the epidermis, and hydration status. There are a number of patch technologies available, including matrix patches, reservoir type, membrane matrix hybrid type, drug-in-adhesive patches and micro reservoir patches. The reservoir patch holds liquid medication in bulk in contact with the skin across a semipermeable, rate controlling membrane. Medication in a matrix patch is dispersed within a polymer that is in contact with the skin. Regardless of the technology, patches typically contain a large amount of drug that can cause problems both to those intending to abuse (such as with fentanyl) and to children (such as with clonidine). Among the transdermal medications currently available, the fentanyl patch is associated with the greatest toxicologic importance. This patch formulation is indicated for the treatment of chronic pain in opioid tolerant individuals, and not indicated for the control of acute pain, intermittent pain, or postoperative pain, and should not be used for opioid-naïve patients. The drug initially absorbed forms a depot in the upper skin layers, and the drug slowly diffuses through the remainder of the skin and is uptaken systemically. Plasma fentanyl concentrations are barely detectable for about 2 hours after patch placement, and the time to reach maximum serum concentrations can range from 12 to 48 hours. When the fentanyl patch is removed, fentanyl continues to be absorbed into the systemic circulation from the cutaneous depot. Fentanyl concentrations decline gradually to about 50% in about 17 (range 13–22) hours. Fentanyl absorption may increase slightly with fever or substantially with the application of external heat (e.g. heating pad, hot tub). Concern over patch leak due to a manufacturing defect with subsequent poisoning led to a recall of certain lots of patches. Application of multiple patches provides additive increases in the systemic drug concentration. Fentanyl in the reservoir patch may be extracted with a hypodermic needle and self-administered. From 28–84% of the initial concentration remains in discarded patches, even after three days of use. The matrix patches may be applied to the buccal mucosa, bypassing the epidermal barrier. *Conclusion:* Although other patch formulations may lead to clinical toxicity, the abuse potential of fentanyl accounts for its greatest liability. *References:* 1. Grond S, Radbruch L, Lehmann KA. Clinical pharmacokinetics of transdermal opioids: focus on transdermal fentanyl. Clin Pharmacokinet 2000; 38:59–89. 2. Marquardt KA, Tharratt RS, Musallam NA. Fentanyl remaining in a transdermal system following three days of continuous use. Ann Pharmacother 1995; 29:969–71. 3. Anderson DT, Muto JJ. Duragesic® transdermal patch: postmortem tissue distribution of fentanyl in 25 cases. J Anal Toxicol 2000; 24:627–34. 4. Nelson L, Schwaner R. Transdermal fentanyl: pharmacology and toxicology. J Med Toxicol 2009; 5:230–41.

123. Notification and Reporting Health Threats Caused by Chemical Events Through RAS CHEM: The Informatics Tool, Networking for Risk Assessment and for Risk Management

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Introduction: Risk assessment and management of chemical health threats (as well as of other health threats of biological, radiological and nuclear origin) with cross border impact need to be coordinated to ensure the safety and security at EU level. Under the current Treaty the European Commission coordinates the response to cross border health threats, including those of chemical origin. A number of actions and initiatives are supported through funding targeted to strengthen preparedness and response to such health threats under the Health Program 2008–2013. The existing mechanisms of coordination through the EU Health Security Committee (HSC) allow additional support in order to ensure coordination and alignment of public health measures between national authorities, the European Commission and the relevant EU agencies. Among the priorities identified both in the HSC work plan and in the public health program initiatives are targeted to develop mechanisms for information exchange, consultation and coordination for the handling of health-related issues linked to attacks in which biological and chemical agents might be used or have been used. The current public health work programme seeks to address gaps in the effective assessment and management of chemical health risks at the local, national and EU level. Understanding and agreeing on how the deliverables from these actions and projects can be integrated into the public health measures of Member States is essential for the successful coordination of the response to cross border chemical health threats within the EU. *Methods:* To bridge gaps in the operational repertoire in order to respond at EU level in a coordinated and shared way to events caused by chemical incidents a number of innovative actions and projects have been funded under the Health Program 2008–2013: 1. The IT platform **RAS-CHEM** (Rapid Alerting System for Chemicals from the Alerting System for Chemical Health Threats Project [2007210]) aims to identify sentinel exposure events, detected at the poison centre level, allowing efficient risk communication, assessment and management of these threats in a coordinated manner to EU Member States. 2. **CARRANET** (Chemical and Radiological Risk Assessment Network service contract [2010 61 21] (implementing Framework contract 2009 61 05 Lot 2)]) aims to establish a network of experts and develop standard operating procedures and protocols for risk communication, assessment and management of chemical and radioactive threats and risks in EU Member States. 3. **CARIMEC** (Chemical and Radiological Inventory of Medical Countermeasures service contract [2010 61 22 implementing Framework contract 2009 61 05 Lot 2]) aims to create an inventory of public health measures and medical countermeasures to enable member states to respond to toxic industrial chemicals and radioactive threats and risks. 4. **CIE-Toolkit** (The Public Health Response to Chemical Incidents and Emergencies Toolkit [2007205]) aims to produce a standardised training manual and expert guidance for the risk management of chemical incidents. 5. **EU Chemical Exercises** (EU Chemical Exercises service contract [SI2.579369 implementing Framework contract SANCO/C3-2007-01]) are being run throughout 2011 to test current and emerging risk assessment, communication and response coordination strategies in 'real-life' scenarios. *Results:* The projects and service contracts described above will provide improved and robust mechanisms and tools to facilitate the rapid communication of information, risk assessment and risk management of chemical and radioactive threats and risks. Integration of these project deliverables (i.e. training manual, RAS-CHEM, inventory of public health measures and the network of risk assessors) will improve the safety and security of EU citizens from the risks associated with deliberate and accidental exposures to toxic chemicals. Such mechanisms will be integrated with the currently existing network for assessment and managements of the chemical risks at EU level. *Discussion:* The outcomes of the actions and projects presented will help in providing EU Member States and international partners with a set of tools and expertise to strengthen the existing expertise at National level in order to rapidly respond to chemical (and radio nuclear) incidents with cross border impact. Successful integration of these approaches into the EU networks for detection, assessment and response coordination to health threats due to chemical events is crucial to have a EU robust system in place and will depend on resources available, training, legislation and political will. *Conclusion:* Rapid and effective communication of risk, assessment and management of chemical and radioactive threats and risks is essential to enable EU Member States to protect their citizens from such hazards; the outcomes from these set of projects and service contracts funded under the Health Program 2008–2013 have the potential to contribute substantially to improve capacity and response at EU level.

124. European Poison Center Reporting Database - Building on the US Experience

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Objective: To summarize the National Poison Data System (NPDS) development experience and applicability to EU manufacturers and others. The American Association of Poison Control Centers (AAPCC) operates the NPDS. The original system became operational in 1983 with call data originally recorded on mark-sense paper case forms and then manually scanned for transmission to the central system. Over the past 27 years, the process evolved into today's near real-time National Poison Data System (NPDS) aggregating case data from the 60 US Poison Centers (PCs) serving the citizens of all 50 States, American Samoa, District of Columbia, Federated States of Micronesia, Guam, Puerto Rico, and the US Virgin Islands. Each PC submits data in a standardized format from information and exposure cases collected during the course of providing telephonic patient tailored exposure management. Most enter data contemporaneously during the call obviating the need for paper charts. Over 50 data fields are submitted to NPDS. These include a variety of demographic items such as case start date, State, Zip Code, age, and gender. Geographic identifiers allow for graphical representation of case data. NPDS is hosted in a protected facility and available via a secure website to PC staff at the 60 PCs. Each PC selects a regional organization administrator who assigns user roles for that PC. Thus the system is center centric. The PCs have access to their own data and US national aggregate data as well as several geocentric reports and the ability to create geocentric surveillance definitions. PCs may create subgroups for special studies - all under center control. The system is used daily by the PCs, researchers, state health departments and the Centers for Disease Control and Prevention (CDC). NPDS data is also accessed by many pharmaceutical and chemical manufacturers for product surveillance and regulatory compliance. *Methods:* PC case data submission files are stored in the NPDS relational data base. Each case is scanned by the system to determine if it meets a series of quality edits

and any of the more than 150 case based surveillance definitions (including syndromic surveillance) definitions that regional PCs and national users such as CDC have created to detect and track public health events. In addition, volume definitions on all case types and time series visualizations of product and other case parameter activity can be created. Surveillance detected anomalous case clusters have been used to identify product problems. Product stewardship tenets emphasize that both manufacturers and consumers understand health and environmental risk of product use. PCs and NPDS data tools play a vital role in this effort. PCs have the ability to share data with external organizations such as health departments and form groups with other PCs to pool data for studies and joint analysis. NPDS runs two web services to enable data access by external viewing systems such as RODS (Real-time Outbreak and Disease Surveillance). Data can also be accessed by enterprise reports and customized queries for both PC study and manufacturers. PCs attempt to specifically identify the products involved in each exposure. The PCs and NPDS rely on the products database (Micromedex® Healthcare Series [Internet database]. Greenwood Village, CO, US: Thomson Reuters [Healthcare] Inc.). The database includes US and international products. The products database contains over 360,000 pharmaceutical and chemical products and is continuously updated. Products are assigned to one of 958 generic codes in 67 major categories. Currently, NPDS uses a standard list of 131 clinical effects that have been developed over the past 27 years to characterize exposures. Case medical outcomes are categorized into one of 11 medical outcomes. *Results:* The cumulative AAPCC database now contains over 51 million human exposure case records. A total of 13,010,466 information calls have been logged by NPDS since the year 2000. The median time for data upload in 2009 was 19.9 minutes [9.7, 58.7] (median [25%, 75%]). Over 154 case based definitions, and 223 volume definitions run daily. Case data is shared with CDC National Center for Environmental Health - Health Studies Branch at the Centers for Disease Control and Prevention (CDC). NPDS has 518 active users who have executed thousands of enterprise reports and surveillance queries. Manufacturers request data about their products. Numerous product recalls from selenium to peanut butter have been tracked by NPDS. Several State Health departments access NPDS data via the web services in a federated approach. NPDS data can monitor single or multiple exposure outbreaks providing information to responsible authorities. This is a key feature of the NPDS that can assist manufacturers and government in tracking usage trends and events of public health significance. Rapid identification of unexpected exposure outcomes to products helps minimize risk and liability. Agencies can track the results of governmental rule changes and post marketing surveillance mandated efforts. Recent analyses have shown that DEA methadone rule changes impacted US methadone use. Although identification of the index case is the holy grail of computer surveillance systems, these systems are most valuable in showing evolving exposure patterns. With the advent of near - real time mapping (GIS), geographical visualizations can aid outbreak analysis. Lastly, outbreaks do not always stop at the shore. The ability to share event data between NPDS and other systems like RAS-CHEM is imperative. Maximizing the ability to share data especially during an outbreak is vital. Although data collection may be different, a common export such as use of MedDRA clinical effect terms is essential. *Conclusion:* NPDS contains 27 years of US poison information and exposure data. National aggregate data is freely accessed by the 60 US PCs and affiliated organizations. The Rapid Alert System for Chemical Threats (RAS-CHEM) shares features of NPDS and can provide similar EU reporting capability. Continued development of both systems in a federated manner is imperative. *References:* 1. Bronstein AC, Spyker DA, Cantilena LR Jr, et al. 2008 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 26th Annual Report. Clin Toxicol (Phila) 2009; 47:911–1084.

125. Effect of 21 Days of Antipsychotic Medication Administration on the Sensitivity of Mice to Acute Cocaine Toxicity

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Long-term administration of antipsychotic medications alters the distribution of several neurotransmitter receptors in animal models. Several of these neurotransmitter receptors are relevant to cocaine poisoning, but the effect of altering the distribution of these receptors on sensitivity of animals to cocaine poisoning is unknown. As many patients who abuse cocaine use antipsychotic medications, increased sensitivity to cocaine would have significant health implications. *Objective:* The hypothesis of this study was that administration of common antipsychotic medications for 21 days will decrease the LD50 of cocaine in a mouse model. *Methods:* This was a placebo-controlled, IACUC approved study using male CF-1 mice weighing between 25 and 40 g at baseline. Study drug doses were determined in preliminary experiments to produce therapeutic concentrations with oral dosing in drinking water. Study drugs were dissolved in 5% dextrose to deliver the following doses: haloperidol 3.3 mg/kg, olanzapine 10 mg/kg, ziprasidone 20 mg/kg. Placebo was 5% dextrose. After 21 days of treatment, drug was removed for a 12 hour washout period. Animals were then randomized to one of 5 ip cocaine doses (8 animals/dose) in 7 mg/kg increments between 91–119 mg/kg. Animals were continuously observed and the percent surviving at 30 minutes was determined for each dose. Dose-response curves were calculated using JMP; the primary outcome was LD50. *Results:* The LD50 for placebo, haloperidol, ziprasidone were similar (116, 122 and 108 mg/kg respectively). The LD50 for olanzapine was slightly lower than those observed for the other treatments and placebo (91 mg/kg). *Conclusion:* While there was a modest sensitization following treatment with olanzapine, our findings do not suggest that overall antipsychotic medications increase sensitivity to cocaine poisoning. As there is wide variability in the dose of cocaine that produces severe poisoning in humans, the small changes in sensitivity suggested by our work are not likely to translate into a substantially increased risk of cocaine poisoning for humans taking antipsychotic medications.

126. Clinical Effects and Treatment of Envenoming by *Hoplocephalus spp*. Snakes in Australia

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Objective: There is limited information on envenoming by snakes from the genus *Hoplocephalus* that occur in Eastern Australia. Reports suggest that bites by this genus test positive on snake venom detection kit (SVDK) to tiger snake and tiger snake antivenom is recommended for treatment. We investigated the clinical and laboratory features of definite *Hoplocephalus spp.* bites and antivenom treatment. *Methods:* Patients with definite *Hoplocephalus spp*. bites were included from the Australian Snakebite Project, a prospective multicentre study. Demographics, clinical information, laboratory tests and antivenom treatment were recorded prospectively. Expert snake identification was done if available. *Results:* There were 14 definite *Hoplocephalus spp*. bites including eight by Stephen's banded snakes (*H. stephensi*), three by broad-headed snakes (*H. bungaroides*) and three by pale-headed snakes (*H. bitorquatus*). Envenoming occurred in 12 patients. The two non-envenomed patients were bitten by identified *H. stephensi* snakes. The patient was a snake handler in eight cases and the snake was in captivity in another. The remaining five cases - four by *H. stephensi* and one by *H. bitorquatus* - occurred from non-captive snakes. Envenoming was similar for the three species and venom induced consumption coagulopathy (VICC) occurred in all cases. The median maximum international normalised ratio was >12 (Range: 1.1 to >13) and partial VICC with only incomplete fibrinogen consumption occurred in four patients. Non-specific systemic effects occurred in six patients and myotoxicity or neurotoxicity did not occur. Bite site SVDK was done in nine patients and positive for tiger snake in eight and black snake in one (*H. bitorquatus*). Urine SVDK was done in another two patients and was negative in one and positive for tiger in another. Ten patients received antivenom, median dose 3 vials (Range: 1–5 vials), which was tiger snake antivenom in all but one. Immediate type hypersensitivity reactions occurred in 6 cases including one case of anaphylaxis. *Conclusion:* Envenoming by *Hoplocephalus spp*. causes VICC and in half of cases non-specific systemic symptoms making it clinically similar to brown snake (*Pseudonaja spp*.) envenoming. However, the majority of cases tested positive to tiger snake on SVDK and were treated with tiger snake antivenom.

127. Taxines are not Effectively Removed by Hemodialysis

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Introduction: Yew plants are highly toxic, with reported fatalities in humans and animals. Taxine A and B, the toxic alkaloids of *Taxus baccata*, block sodium- and calcium-channels mainly in cardiomyocytes, inducing conduction abnormalities up to cardiac arrest. We present a severe *T. baccata* poisoning case, after an unsuspected intentional ingestion of the leaves, in a patient treated with hemodialysis. This allowed us to test the hypothesis - based on the physicochemical properties of taxines (molecular weight >500 Da, relatively water-insoluble) and the large volume of distribution (60 L/m^2) of the related chemotherapeutic drug paclitaxel - that taxines are not effectively removed by hemodialysis. *Case report:* A 17-year-old previously healthy man was found at home cyanotic, unresponsive, tachycardic and tachypneic. Only an empty blister pack of ibuprofen 400 mg was found. In the Emergency Department the ECG showed a polymorphic ventricular tachycardia with an irregularly variable QRS-axis (torsade-like). Magnesium (2 g) and amiodarone (300 mg) were administered i.v. and electrical cardioversion was performed. The dysrhythmias degenerated into pulseless electrical activity, followed by asystole. He was intubated and advanced cardiac life support was initiated (duration: 30 minutes). He regained a bradycardic broad-complex rhythm, but required repetitive intermittent cardiopulmonary resuscitation because of recurrent episodes of hemodynamically unstable sustained ventricular tachycardia. A temporary transvenous pacemaker was inserted and catecholamines were administered. Hemodialysis was initiated due to progressive metabolic acidosis unresponsive to sodium bicarbonate. The patient gradually improved over the following 24 hours with restoration of sinus rhythm. He recovered without sequelae. He admitted having ingested *T. baccata* with suicidal intention. The toxicological-screening was positive only for benzodiazepines. Quantification of serum and dialysate concentrations of taxine B was performed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Serum taxine B concentrations before, during and after (6 hours) dialysis were: 126 ng/mL ($=100\%$), 90.7 ng/mL (72%), and 83.2 ng/mL (66%), respectively. Dialysate taxine B

concentrations at beginning and end of hemodialysis were: both 3.8 ng/mL (3%). *Conclusion:* Taxine B is not effectively removed by hemodialysis. Supportive care with protection of the airways and hemodynamic stabilisation are the cornerstones of treatment for patients with severe *T. baccata* poisoning. Hemodialysis may be beneficial in patients with severe metabolic acidosis.

128. Snakebite Enquiries to the NPIS 2004–2010

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Objective: To describe trends regarding snakebite enquiries to the UK National Poisons Information Service (NPIS) from January 2004 to August 2010 and the indications concerning the use of Adder anti-venom with respect to the NPIS treatment guidelines. *Methods:* The UK NPIS Database was interrogated for enquiries from January 2004 to August 2010. Search terms used were "snake" and "snakebite". Information from the national dataset was available from Cardiff and Edinburgh units from 2004 onwards, Birmingham from June 2005 and Newcastle from September 2006. Data concerning snakebites in animals were removed. The data were analysed using descriptive statistics. *Results:* 510 cases were identified, of which 69% were male and 31% female. Average age of patients was 32 years ($\pm$2 years 95% confidence interval). The snake was identified as follows: European adder in 52% of cases, a non-native species in 26%, unknown in 18% and another UK snake in 4%. 82% of enquiries occurred between the months of April to September with frequency peaking during August (19%). 42% of cases reported envenomation. Clinical features were as follows: 94% oedema, 28% cardiovascular signs, 23% gastrointestinal features and 7% had anaphylaxis. Eighty-five patients were assessed as requiring anti-venom but only 84 received treatment with anti-venom. One patient refused treatment due to concerns of a possible allergy to the anti-venom. The most frequent indications for anti-venom were oedema involving two joints (64%), cardiovascular compromise (29%) and anaphylaxis (7%). No adverse reactions to the anti-venom were reported and resolution of clinical features was reported in all treated cases. Advice to use an antidote was followed in 98.8% of cases. *Conclusion:* Snakebites account for one to two NPIS enquiries per week. Adder bites account for over half of these cases. A quarter of enquiries were due to non-UK snakes kept in captivity within the UK. Envenomation was said to have occurred in just under half of all cases. Oedema was the most significant feature, although systemic features also occurred in over half of cases. The anti-venom appears to be safe and effective. Advice given by the NPIS appears to closely reflect national practice guidelines.

129. Disulfiram like Syndrome after Consumption of the Mushroom Freckled Dapperling (*Echinoderma aspera*) and Ethanol - a Case Series

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Objective: Disulfiram-like acetaldehyde syndrome is well known after consumption of the coprine containing mushroom *Coprinus atramentarius* in combination with ethanol. Here we report two events involving three patients who experienced similar symptoms after a meal of the mushroom *Echinoderma aspera* (formerly *Lepiota aspera*) with ethanol in Bavaria. *Case series:* Event 1: In August 2010 a 69 year old male (82 kg, history of MI, medication: aspirin, enalapril, bisoprolol) and his wife (62 years, 56 kg, no medical history) had eaten a meal of 7 self picked mushrooms (well sautéed for 20 minutes) they had taken for the edible *Macrolepiota procera*. Six hours later, 15 minutes after drinking 0.25–0.5 L beer both experienced facial flushing, palpitations, shortness of breath and dizziness. Symptoms had resolved completely when they arrived at the local hospital 45 minutes later. The Munich Poison Control Centre (PCC) was consulted and advised avoiding alcohol for the next few days under the assumption of a *Coprinus* syndrome and suggested the identification of the mushroom from the left-overs. Twenty-four hours later, the husband experienced facial flushing and palpitations again after another sip of beer against the PCC's advice. His wife abstained from alcohol. The mushroom was sent to our laboratory. The mycologist identified the mushroom by inspection and microscopy as *Echinoderma aspera*. Event 2: In October 2010 a 47 year old male with no medical history had eaten a meal of 7 self picked and well sautéed mushrooms he had taken for edible *Amanita rubescens*. Four hours later, 5 minutes after drinking 0.5 L beer he experienced a hot facial flush, tachycardia 110/min, and drowsiness. He went to the local hospital. The PCC gave the same advice as above. His physical examination revealed no pathology, laboratory tests including transaminases, prothrombin time, creatinine were all normal. The symptoms disappeared spontaneously after 90 minutes, however, a sip of beer the next day and the day after produced facial flushing again. The mushroom was identified by the mycologist as *Echinoderma aspera*. *Conclusion:* This is the first report of a *Coprinus* like syndrome after consumption of *Echinoderma aspera*. The nature of the toxin involved is not yet known.

130. Life Threatening Poisoning with *Taxus baccata* and Ecstasy

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Objective: The mortality rate of intoxication caused by *Taxus baccata* is very high and we have no antidote for this poisoning. *Case report:* A 27 year old man was admitted to a local hospital for sudden hypotension, bradycardia, vomiting and headache. Hemodynamic instability with symptomatic bradycardia (18/min) with extremely wide QRS, ventricular tachycardia and fibrillation were present early after admission. Acute renal failure, slight elevation of troponins and a mild hypocoagulation state were found. The patient denied any drug intake, however, urine toxicological analysis detected 1,200 mg/mL of ecstasy, a massive amount of 3,5-dimethoxyphenol and other derivates of phenol (GC/MS). The patient was transferred to the Department of Arrhythmias and Cardiac Pacing at the National Institute of Cardiovascular Diseases. Initially, the patient was hemodynamically unstable with significant bradycardia during non-captured temporary pacing and frequent monomorphic ventricular tachycardias and ventricular fibrillation, which required prolonged resuscitation with many DC shocks. A new temporary pacing lead was implanted but despite this, intermittently, the pacing was not captured. Treatment with activated charcoal was started, mechanical lung ventilation and inotropic support were provided. Sinus rhythm recovered after 3 hours with incomplete right bundle branch block, the patient was hemodynamically stable, extubated after 36 hours, conscious, without neurological disorders. After regaining consciousness the patient confessed to intake of *Taxus baccata* berries the day before. The National Toxicological Information Centre (NTIC) was consulted for a possible toxic origin of the event. On the basis of detailed analysis we found out that the patient was vomiting a green fluid on admission to the local hospital. In our opinion, it was tea made from yew needles. Eventually, the NTIC clarified that 3,5-dimethoxyphenol detected in urine was a marker of taxus ingestion (3,5-dimethoxyphenol is the aglycon of the *Taxus* ingredient taxicatine). In Slovakia there is no standard hospital laboratory test to identify taxine. *Conclusion:* In the absence of a history of toxic ingestion, the intensive treatment of severe cardiovascular symptoms can be life-saving even after a potentially lethal ingestion of *Taxus baccata* needles and ecstasy.

131. Plant Ingestions: A Profile of Fatalities

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Objective: The ingestion of plants is a common exposure that is managed by poison information centers. The majority of plant exposures occur in children less than 6 years of age and are associated with no toxicity or result in only minor effects. Fatalities due to the ingestion of plants are rare, but do occur. The objective of this project is to describe the demographic features of those who ingest plants and suffer a fatality as a consequence of the exposure and to identify the plants that are most commonly implicated in fatal outcomes. *Methods:* The annual reports of the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) were reviewed over the period of 1983–2008 to identify all fatal outcomes that were due to the ingestion of a plant. All plant ingestion exposures that were reported to American poison centers from 2000–2009 were provided to the investigators as an AAPCC data grant and analyzed using Microsoft Office Excel to identify all fatal outcomes and to profile patient demographics. Descriptive statistics were used to characterize the data. The project was approved by the institutional review board. *Results:* From 1983–2008, 2,330,162 plant exposures were reported to the AAPCC NPDS and 43 resulted in a fatality (0.002%). Over the period of 2000–2009, 668,111 plant ingestions occurred. Children less than 6 years of age accounted for 81.2% of all plant ingestions; whereas, the average age of those with a fatal outcome was 34.9 years. Only 3.9% of all plant ingestions were intentional compared to 51.2% of the fatal plant ingestions. *Datura* (e.g. jimsonweed) species, followed by *Cicuta* (e.g. water hemlock) and *Conium* (e.g. poison hemlock) species were responsible for 41.9% of the fatalities with no other species accounting for multiple fatalities. *Conclusion:* Fatal plant ingestions were most often intentional and many were a consequence of abuse or suicidal intent. No children less than 6 years of age died as the result of the ingestion of a plant.

132. Meadow Saffron Used as a Spice

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Introduction: Intoxications with colchicine usually occur by ingestion of meadow saffron leaves (*Colchicum autumnale*) which are mistakenly collected for alimentary purposes instead of the leaves of crow garlic (*Allium ursinum*). Colchicine, the main alkaloid of *Colchicum autumnale*, is present in all parts of the plant. We report a rarer source of mistake, i.e. between the flowers of *Colchicum autumnale* and *Crocus sativus*. The similarity in this case is limited to the appearance of the flowers, but *Colchicum autumnale*, which is also flowering in autumn, lacks the crimson stigma from which the saffron spice is derived from *Crocus sativus*. *Case report:* A 47-year-old woman collected the stamens of a flower resembling *Crocus sativus* for use as saffron. Her knowledge about *Crocus sativus* was limited to having seen this plant previously at a museum of saffron (Mund, Switzerland). She prepared a meal with rice using three pinches of "saffron" for ten tablespoons of rice. She and her 8-year-old child, both ate the usual amount of rice (6 and 2 tablespoons, respectively). The 2 brothers (4- and 9-years-old) only ate 3 teaspoons of rice each. A slightly bitter taste and the absence of a yellow

colouration were peculiar. Three to four hours after the meal, the mother developed nausea and contacted the Swiss Toxicological Information Centre, suspecting a plant misidentification. All family members were referred to the regional university hospital for administration of oral activated charcoal. No other symptoms were reported, notably no symptoms in the 8-year-old boy and his brothers. Colchicine serum concentration (blood sample obtained 15 hours after ingestion) measured by HPLC-mass spectrometry was 0.36 µg/L for the mother, and 0.13 µg/L for the 8-year-old child, respectively (therapeutic levels: 0.30–2.5 µg/L). *Conclusion:* This report demonstrates that a significant amount of colchicine may be absorbed even after ingestion of very small quantities of *Colchicum autumnale*, which in this case was confused with *Crocus sativus*. Serum colchicine concentrations in the sub-/therapeutic range can be quantified by HPLC-mass spectrometry, which allows a very sensitive and specific detection of this alkaloid in blood and urine.

133. More Auto-intoxications with Nutmeg: Is it a Serious Clinical Problem?

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Objective: Nutmeg is a kitchen spice that is easily obtainable worldwide. Rarely, nutmeg is used in high doses (grams) as a recreational hallucinogen. Since 2009 the number of nutmeg intoxications reported to the Dutch Poisons Information Center (DPIC) is increasing, which is a reason for further investigation. *Methods:* All cases of nutmeg intoxications reported to the DPIC from September 2009 to September 2010 (n = 23) were prospectively followed up for dose, clinical outcome and motivation to take nutmeg. Cases reported from 2005 until September 2009 (n = 14) were analyzed retrospectively. *Results:* In total 48 separate nutmeg overdoses were recorded, by 37 different patients (2 in 2005, 3 in 2006, 1 in 2007, 2 in 2008, 10 in 2009 and 19 in 2010). Three patients overdosed on nutmeg repeatedly. Patients were relatively young (57% under 30 years), the mean age was 30 years (range 1–71 years). In 33 cases gender was recorded, 88% were female. The mean estimated amount of nutmeg ingested was 24 grams (range 1–100 grams), generally ingested as powder (ground nutmeg) and in 3 cases as whole nuts. In 7 cases co-ingestion of medication and/or alcohol had taken place. As motivation for taking a large amount of nutmeg, 10 out of 23 prospectively followed up patients declared suicidal intent, 3 of these spontaneously mentioned finding information on using nutmeg as a suicidal aid on the Internet. Two patients wanted to hallucinate. Three times a large amount of nutmeg accidentally fell into food, which was consumed nonetheless. The one-year-old accidentally ingested a fingertip of ground nutmeg. Forty-one per cent of the calls were received from a general hospital, 21% from a psychiatric hospital and 21% from a general physician. Most patients were admitted for observation for several hours. In mono-intoxications only mild symptoms were observed. *Conclusion:* Observed clinical effects of ground nutmeg intoxication were mild even with estimated doses well above 10 grams, generally regarded as toxic. Suicidal intent was mentioned 5 times more often as motivation than wanting to hallucinate. The Internet possibly contributes to choosing readily available substances like nutmeg as uncommon suicidal aid.

134. Cases of Taste Disorder Following Ingestion of Pine Nuts Reported to the National Poisons Information Service

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Objective: To describe cases where symptoms of taste disorder have been reported to the National Poisons Information Service (NPIS) and recorded on the UK Poisons Information Database (UKPID), particularly following the ingestion of pine nuts. *Case series:* Seven cases of taste disorder have been reported to the NPIS following ingestion of pine nuts. All patients were adult, three male and four female. In five cases symptoms were limited to an unpleasant, metallic taste particularly when eating (dysgeusia). Two patients also described headache, one of whom complained of xerosis and thirst. The symptoms developed up to two days after the ingestion of pine nuts and persisted for up to 2 weeks. On interrogating UKPID for all cases with symptoms of taste disorder, 251 cases were reported since Jan 2008. The most common agents causing this phenomenon were metals or metallic compounds. Essential oils (particularly Olbas Oil), bleach, descaler, chlorine, antifreeze, carbon monoxide and fungi were each associated with several cases of taste disturbance. *Conclusion:* The first incidence of dysgeusia as a result of ingestion of pine nuts was published in 2001. The first case reported to the NPIS was in 2008 which suggests this is a relatively recent phenomenon in the UK. There are various theories as to the cause of dysgeusia due to pine nuts including possible oxidation of oils in the nuts due to spoiling, presence of contaminants or nuts sourced from different species of *Pinus* trees.[1,2] The dysgeusia is harmless and resolves uneventfully but can be distressing for the patient who may not associate the symptoms with recent pine nut ingestion. Other causes of dysgeusia include, tooth decay, heavy metal poisoning, gastritis, certain drugs (e.g. metronidazole), chemotherapy or jaundice. If dysgeusia can be attributed to ingestion of pine nuts in the first instance and resolves within two weeks then patients may be reassured and unnecessary medications or investigations avoided. *References:* 1. Mostin M. Taste disturbances after pine nut ingestion. Eur J Emerg Med 2001; 8:76. 2. Munk MD. "Pine mouth" syndrome: cacogeusia following ingestion of pine nuts (genus: pinus). An emerging problem? J Med Toxicol 2010; 6:158–9.

135. A US Perspective of *Latrodectus spp*. Envenomation: 2000–2008

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Objective: To describe black widow spider (BWS) exposures reported to US Poison Centers and identify factors associated with antivenom use. *Methods:* All exposures with the generic code for BWS envenomation and *Latrodectus mactans* antivenom reported to the American Association of Poison Control Centers (AAPCC) between January 1st, 2000 and December 31st, 2008 were reviewed. Cases with at least minor clinical effects, as defined by the AAPCC, due to BWS exposure were extracted. Descriptive statistics were generated and proportions were compared by chi-square and odds ratios. *Results:* Between 2000 and 2008, 23,409 BWS exposures were reported in 47 US states. Of these, 9,872 had at least minor clinical effects due to the exposure. The number of US exposures peaks in September and falls to a nadir in February. 58% (n = 5,751) were male and the mean age was 31 years of age (IQR 19–43 years old). The majority of symptomatic cases (58%, n = 5,741) were managed in a health care facility. While the majority of patients were classified with minor clinical effects (65.1%, n = 6,424), there were 3,309 cases (33.5%) with moderate effects and 139 cases with major effects (1.4%). Antivenom was administered in 374 cases (3.8%); 87 patients (1.4%) with minor effects, 258 (7.8%) with moderate effects and 29 (20.9%) patients with major effects. Antivenom use was more common in the moderate and major outcome groups (OR = 6.61, 95% CI 5.20–8.48). In patients with moderate or major outcomes, antivenom use was more common in the Southwest (OR 1.91, 95% CI 1.39–2.62) and West (OR 2.36, 95% CI 1.75–3.19). In the subset of patients with moderate and major outcomes, antivenom use was associated with symptom duration of less than 24 hours (OR 2.04, 95% CI 1.57–2.67). There was no evidence of symptom duration of less than 24 hours in patients who received benzodiazepines (OR 1.14, 95% CI 0.98–1.33) or calcium (OR 1.21, 95% CI 0.95–1.53). *Conclusion:* In the US, most symptomatic BWS exposures are minor and patients are more likely to be managed in a health care facility. Few patients get antivenom though antivenom is associated with shorter symptom duration.

136. Some Aspects of Intoxication with *Tricholoma equestre*

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Background: Rhabdomyolysis is a rare but potentially fatal condition. In 2001 Bédry and co-workers described rhabdomyolysis caused by overeating of *Tricholoma equestre*.[1] *Objective:* The aim of our study was to analyze some aspects of intoxication with these mushrooms. *Method:* Observational study. *Results:* We observed eight patients, including 3 females and 5 males, aged from 5 to 75 (average 44) years intoxicated with *T. equestre*. The amount of the mushroom dish varied from 1.7 to 4.7 (average 3.1) g/kg of body weight in adults; and 17.5 g/kg of body weight in children. The total dose of consumed mushrooms varied from 11.5 to 46.7 (average 25) g/kg of body weight in adults; and 70 g/kg of body weight in children. The time between the last meal and onset of clinical signs varied from 4 to 120 (average 69.5) hours. CK level varied from 11,993 to 53,515 (average 35,325) U/L in adults; and 309 U/L in child. In adults the AST and ALT varied from 432 to 2,002 (average 1,352) U/L, and from 209 to 670 (average 458) U/L respectively. The main clinical symptoms in adults included muscle pain, weakness and profound sweating. In children we observed muscle weakness up to respiratory failure. The time of recovery varied from 6 to 21 (average 13) days. A fatal outcome was observed in one case, a man aged 75 years who consumed 3500 g of *Tricholoma equestre* which was equal to 46.7 g/kg of his body weight. *Conclusion:* A total dose of consumed mushrooms more than 35–40 g/kg of body weight may be connected with serious events. In children the level of CK did not correlate well with the severity of clinical symptoms. The mortality rate was about 12.5%. *References:* 1. Bedry R, Baudrimont I, Deffieux G, et al. Wild-mushroom intoxication as a cause of rhabdomyolysis. N Engl J Med 2001; 345:798–802.

137. Recreational Use of *Salvia divinorum* in France: Experience of the National Toxicovigilance Net Between 2003 and 2010

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Background: Salvia divinorum is a Mexican plant producing a psychoactive molecule called Salvinorin A which induces hallucinations in humans. Since the beginning of the 21st century, its use as a recreational drug has increased due to worldwide distribution by Internet. The consequence of its abuse potential is the institution of legal restrictions for the plant and the Salvinorin A use in several countries. In order to evaluate the French situation concerning *S.divinorum*, a survey was performed by the National Committee for Toxicovigilance. *Methods:* A retrospective study was initiated in order to analyse cases of *S.divinorum* managed by the French Poison Centres since 2002 (8 years 8 month period). *Results:* 19 cases were studied

(16 men, 3 women). Patients were mainly teenagers or young adults (from 12 to 43 years old, median age of 17) who had a history of regular consumption of psychoactive drugs like cannabis or different hallucinogenic chemicals. The aim of *Salvia* use is generally to try new experiences with a natural substance (in Internet sites, the image is of a safe and ecological product due to its traditional shamanic use in Amerindian tribes). The dry leaves were eaten (5 cases), chewed (3 cases) or smoked (11 cases) and were often associated with other products like cannabis (5 cases), Hawaiian Baby Woodrose (1 case) or hallucinogenic mushrooms (1 case). The main symptom was hallucinations (visual, sometimes auditory) which can be at the origin of bad trips with near-death feelings, explaining why the second symptom was anxiety (7 patients). Behaviour disturbances were the main complication and all patients were medically managed (general practitioner 9 cases, emergency unit consultation 7 cases, hospitalization 3 cases). Hallucinations decreased quickly and disappeared in few hours. However, several symptoms like anxiety attacks, dizziness or cognitive troubles were reported by 5 patients between 2 to 5 days after a single Salvia use. *Conclusion:* In comparison with the importance of its Internet distribution, the abuse of *S. divinorum* seems to be limited in France. However, the results of this study were reported to the French Health Authorities who decided in August 2010 to impose legal restrictions in our country.

138. Mediterranean Spurge (Genus *Euphorbia*) Poisonings: A Case Series from the Marseille Poison Centre

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Introduction: In Mediterranean flora, all the indigenous species of the *Euphorbia* genus have an herbaceous general aspect with a short size (main species: *E. cyparissias*, *E. helioscopa*, *E. amygdaloides*, *E. characias*). The sap of the spurge is considered to be an irritating latex which can induce severe skin or eye burns. *Methods:* In order to evaluate the toxicity of local spurge species a retrospective study was performed. All poisonings due to this plant genus between January 2002 and December 2009 and managed by the Marseille Poison Centre were analysed. *Case series:* 89 observations were collected (53 men and 36 women, average age of 32.4 years $\pm$ 27, from 5 months to 99 years). Such intoxications occur along the entire French Mediterranean coast. During the studied period, the number of observations was stable, between 8 and 15 cases each year. Poisonings were described throughout the year, but cases were much more frequent in spring and the beginning of summer (spurge growing period in the Mediterranean biotopes). The different spurge species are ubiquitous, with human contacts in nature (35%) but also in private or public gardens. Children under 6 years old represented 27% of the series. Adult patients can be exposed during their work (8% were professional gardeners) or their leisure activities (gardening at home or trekking in the countryside). Poisonings were the consequence of contact of the toxic sap with skin (10% of cases), mouth (36%), eyes (40%) or several routes (14%), inducing intense local pain, swelling and irritation. Thirty-nine per cent of the patients remained at home, Thirty-five per cent consulted their family practitioner, 10% consulted a medical specialist (dermatologist or ophthalmologist) and 35% required an emergency unit management in the local hospital. All patients quickly recovered in a few hours proving that the sap toxicity is mild with our local *Euphorbia* species. *Conclusion:* Mediterranean spurges are able to induce human poisonings by several routes. The harmless aspect of these plants leads to accidental contact with the toxic sap. However, Mediterranean species seem to be less dangerous than tropical *Euphorbiacea*.

139. Two Severe Collective Ciguatera Poisonings Concerning European Tourists in Endemic Areas

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Introduction: Ciguatera poisoning is a rare event in Europe: a case series from the Marseille Poison Centre (MPC) published in 2003 described 18 poisoned patients managed between 1997 and 2002.[1] Between 2003 and 2009, 15 more ciguatera intoxications were observed by the MPC, concerning 62 patients (1 to 20 patients poisoned by one fish). In 2010, two collective ciguatera poisonings were reported to the MPC. *Case series:* Collective case 1: In March 2010, 4 adult French tourists (2 men, 2 women) in Mauritius ate a yellow-edged lyretail (*Variola louti*) bought in a local market and barbecued. In the initial phase, digestive troubles and cardiovascular symptoms were present (severe bradycardia, low blood pressure leading to medical management for the 4 patients, 2-days hospitalisation for one of them). Pruritus, thermoalgesia, and paresthesia were reported by the 4 patients during 30/45 days after the meal. Collective case 2: In May 2010, 2 adult French tourists and their 2 local friends (2 men, 2 women) in "Saint-Martin" Island (French West Indies) ate a silk snapper (*Lutjanus vivanus*) caught by one of them. The fish was cooked and shared. A 55 year old man who ate small quantities did not report acute symptoms but had asthenia and pruritus for 2 weeks. The man who ingested the largest quantities was managed in the local hospital as respiratory distress was observed less than 2 hours after the meal. Long term symptoms (asthenia, pruritus, paresthesiae, myalgias) were described for the 4 patients for 15 to 60 days. *Discussion:* European tourists are not aware of the dangers of ciguatera. In the concerned countries, tourism is an important resource. Giving advice to tourists may modify the image of the "beach paradise" and may reduce the number of visitors to the contaminated areas. This situation explains the total absence of local information about the potential risks of ciguatera. In consequence, prevention and education of tourists should take place in their country of origin. *References:* 1. de Haro L, Pommier P, Valli M. Emergence of imported ciguatera in Europe: report of 18 cases at the poison centre of Marseille. J Toxicol Clin Toxicol 2003; 41:927–30.

140. Oral Ricin Exposure - Less Poisonous than Expected

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Objective: The castor bean plant (*Ricinus communis*) is known to be highly toxic. The whole plant, especially the beans, contains the toxalbumin ricin that inhibits protein synthesis in the cells. However, its toxicity depends on the route of exposure and, if the beans are ingested, also on the degree of mastication. We present three cases of ricin poisoning where large numbers of chewed castor beans were ingested for suicidal purpose. *Case series:* Case 1. A 38-year old man thoroughly chewed and swallowed 27–30 castor beans together with antiemetics. After 5–6 hours he felt nauseous and developed intense vomiting and diarrhoea. Ten hours after ingestion he called for an ambulance. On admission to hospital he had normal vital parameters but was dehydrated. After intravenous rehydration he gradually recovered without any signs of organ damage. Discharge was possible after three days. Case 2. A 20-year old woman ingested 90 castor beans, several of them chewed. After one hour she felt nauseous and vomited several times. The vomit contained some beans. On admission to hospital she was fully awake with normal circulatory parameters and oxygen saturation but complained of abdominal pain, later followed by diarrhoea. Gastric lavage was performed 6–7 hours after the ingestion resulting in retrieval of three beans. Activated charcoal was given and intravenous fluids were infused. She developed mild anaemia (Hb 103 g/L), but had an otherwise uncomplicated recovery. Discharge after seven days. Case 3. An 18-year old man chewed and swallowed 24 castor beans. He developed increasing abdominal pain, diarrhoea and episodic hematemesis. On admission to hospital activated charcoal was given. He experienced transient chest pain and palpitations. Fever and facial rash ensued. Complete recovery. No organ damage. *Conclusion:* These three patients ingested large numbers of chewed castor beans. They all developed pronounced gastrointestinal symptoms but no signs of organ failure were seen. This indicates that the oral toxicity of castor beans is lower than reported in older literature. Poor intestinal absorption of ricin and possibly also decomposition of the toxin in the gut may explain this finding.

141. Coma After Intake of an Unknown Plant Root - Unintentional Anticholinergic Intoxication

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Objective: The clinical management following ingestion of an unknown toxic plant is challenging, particularly when the patient is unconscious on admission. This case describes the clinical management of an unconscious, unintentionally intoxicated patient followed by chemical analyses of the plant root ingested. *Case report:* An otherwise healthy 72 year old man without regular medication was found unconscious in a chair at his home. About 90 minutes earlier he had been weeding out plants in the garden, and tasted a root to demonstrate how people used plants as food in the past. On admission he was comatose with a GCS of 5, responding to pain and showing spontaneous movements of the extremities. His circulation and respiration were stable with a blood pressure of 140/80 mmHg and a heart rate of 109/minute. ECG and standard blood tests were normal. He had mydriasis and the pupils had no reaction to light. Neurological examination concluded with a clinical picture atypical for cerebral insult. His friend brought the plant root that was suspected to have been eaten. The poisons centre was contacted and identification of the root was initiated (picture electronically sent). Administration of physostigmine (2 mg i.v.) resulted in an immediate but transient increase in alertness. Two hours later the patient was again treated with physostigmine 2 mg i.v. (a total of 4 doses) because of hallucinations and restlessness. Observation continued 12 hours after administration of the last physostigmine dose and he was discharged well. Thin layer chromatography and gas chromatography-mass spectrometry analyses of the root confirmed the content of hyoscyamine and scopolamine. Exact identification of the remaining plant material was difficult, but the best suggestion after botanical examination and the chemical analyses was a species closely related to, but different from *Atropa belladonna*. *Conclusion:* Anticholinergic plant or mushroom poisoning should be considered in patients presenting with a low GCS of unknown origin. The clinical picture and the anamnesis pointed toward anticholinergic plant poisoning in our case. Other clinical causes were also ruled out. Exact identification of the remaining plant material was not possible, but analysis of the root confirmed the diagnosis.

142. Severe Parasol Mushroom Intoxication? An Attempt at Explanation

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Objective: To describe a case of severe mushroom intoxication and to point out difficulties in the evaluation of mushroom poisonings. *Case report:* In September 2010 a call was received from an emergency department of a smaller hospital in the countryside north of Berlin. A 10 year old boy had presented with vomiting for three days and diarrhoea for two days. The whole family had a meal of self-collected parasol mushrooms prepared as cutlets for two consecutive days. Only the boy developed vomiting two hours after the second meal. A day later the boy was brought to the family doctor with persistent vomiting. He prescribed an electrolyte solution and an antiemetic. The next day symptoms still occurred and in the evening the boy's little dog died 48 hours after eating the leftovers of the mushrooms. The next morning the boy was brought to the hospital still having diarrhoea and being in reduced general condition. Laboratory tests were performed revealing 100-fold elevated liver enzymes and a Quick $< 10\%$. The child was transferred immediately to the liver transplantation centre of the Charité Berlin and listed as high urgency for transplantation. Under intensive care therapy with transient liver replacement therapy the liver function started to recover within several days. Liver replacement therapy could be stopped seven days later and the boy was released from the hospital two weeks later. The mushrooms could not be identified initially by a specialist, because there were no leftovers. The parasol mushroom is difficult to mistake for any other. Among the related genus of *Lepiota* are mushrooms that may contain amatoxin but they are supposedly too small to be mistaken. *Conclusion:* This case shows the fundamental challenges in the evaluation of mushroom poisoning: 1.Even mushrooms that cannot be mistaken may be mistaken. 2. You may need knowledge of preparation to understand that even after a shared meal only a single person is poisoned. 3. Several consecutive mushroom meals may simulate short latency of onset of symptoms and masking severe amatoxin intoxication.

143. Animal Poisonings: 10 Years Experience from the Belgian Poison Centre

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Objective: To describe the profile of animal poisoning reported to the Poison Centre during a 10-year period (2000–2009). *Methods:* Our data-base was searched to retrieve figures for groups of intoxicants and types of animals involved. Certain obvious trends were further explored by looking at the individual case record charts. *Results:* We received 24,294 calls during this 10 year period concerning 26,820 animal exposures. The yearly number of exposures was quite stable (range 2,531–2,915). Dogs accounted for 69% of the victims, followed at a long distance by cats, birds (including chickens), horses and cows. Pesticides and biocides were responsible for 41% of the exposures, followed by domestic products (21%), drugs (18%) and plants (9%). The percentage of deceased animals at the time of call was 3.7% (985 animals), which involved 195 dogs, 176 cats, 165 birds, 96 cows, 88 sheep and 83 horses (among others). The main substances responsible for these deaths were pesticides and biocides (426 exposures), mainly anticoagulant rodenticides in dogs, and plants (203). We observed some obvious trends during this period. A rise in exposures to veterinary drugs was observed during the last two years (2008–2009) with respectively 114 and 121 cases recorded compared to an average of 62 in the 2000–2007 period. This was mainly due to a rise in exposures to spot-on products for cats. In 2000 there were 9 exposures to spot-on products. The figure for 2009 was 37 spot-on products. Another trend observed was a decline in mortality due to exposures to pesticides and biocides. This was in part due to a change in insecticide use. In 2000 there were 19 deaths attributable to insecticides with 11 aldicarb and 1 parathion exposures. In 2009 we observed only 2 deaths due to insecticides. None of them were attributable to aldicarb or parathion. A third trend observed was the rise in exposures to human drugs. In the first 5 years we observed a mean of 390 exposures (range 369–414). In the last 5 years on the contrary we found a mean of 558 exposures (range 490–628). *Conclusion:* The number of exposures, kinds of animal exposed and type of products used, remained quite stable during a 10-year period. A few trends can be observed, probably reflecting the altered use of some products.

144. Plant and Fungi Poisoning Incidents: Enquiries to UK National Poisons Information Service (Edinburgh)

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Objective: To examine the incidence of plant and fungi poisoning enquiries to the Edinburgh centre of the UK National Poisons Information Service (NPIS). *Methods:* Telephone enquiries involving plants and fungi reported to NPIS Edinburgh for 6.5 years from April 2004 to September 2010 inclusive were reviewed. *Results:* 385 enquiries (3.3% 385/11,532 of all enquiries) were received regarding plants or fungi over this period, of which 367 related to patients. Of the enquiries relating to cases, the majority were from medical professionals (89.4% 328/367), 6.8% (25/367) were from members of the public and 3.8% (14/367) from others (including schools, police, carers). 67.8% (249/367) of enquiries involved patients aged 9 years or less; 43.3% (159/367) involved patients aged 1–4 years. The majority had no (193/249) or minor (47/249) symptoms at the time of enquiry. Only 1.2% (3/249) had moderate symptoms, in 2 thought unrelated to the exposure. In 6 cases symptoms were unknown. At the time of enquiry 63.7% (234/367) were asymptomatic and 24.7% (91/367) had minor symptoms. Only 1.6% (6/367) involved patients with severe symptoms, one enquiry regarding *Cortinarius speciosissimus* related to 4 patients (renal failure), 4 (relating to 2 different patients) involved *Aconitum napellus* (cardiac features) and one involved an unknown mushroom (manic psychosis). In 90.1% (331/367) the exposure was accidental; in 3.8% (14/367) intentional and only 2 (one patient) involved severe features (*Aconitum napellus*). Ingestion accounted for 89.4% (328/367) of exposures, skin contact 8.7% (32/367), eye contact 2.2% (8/367), inhalation 0.5% (2/367) and other/unknown 0.5% (2/367). Of 270 plant ingestion enquiries, the plant part ingested was specified in 202 cases; 32.9% (89/270) involved berries, 20.3% (55/270) leaves, 11.1% (30/270) seeds, 10.4% (28/270) flowers, 2.2% (6/270) bulbs and 1.5% (4/270) stalks/stems. Some enquiries (10) involved more than one plant part. Most frequent plant species: Laburnum (4.8% 15/313), *Sorbus aucuparia* (Rowan) (4.5% 14/313), Lily (3.5 % 11/313) and Cotoneaster (3.2% 10/313). Of 367 enquiries relating to patients, 15.0% (55/367) involved fungi. In 74.5% (41/55) of these the mushroom was unidentified. *Conclusion:* Plant or mushroom enquiries to NPIS Edinburgh comprise a small percentage of the call load. A large proportion of these enquiries involve children of which only a few have more than minor symptoms at the time of the enquiry. Enquiries regarding severe plant or fungi poisonings are rare.

145. Collective Acute Intoxication after Ingestion of *Jatropha curas* Seeds by a Group of Children

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Objective: To report a series of cases of children intoxicated by *Jatropha curcas* seeds. *Case series:* Six children, between 10 and 14 years, ingested seeds from a plant identified afterwards by a botanist from our university as *Jatropha curcas*. Thirty minutes after the ingestion, the children started to present gastrointestinal symptoms which prompted the parents to take them to the pediatric ER, between 2 and 6 hours after the ingestion. Children ingested from 4 to 30 seeds each, as they are attractive and their taste is not bad, even a little sweet. All presented vomiting and abdominal cramps, some diarrhea, sleepiness, burning sensation in the oropharynx and bradycardia (in two children who ingested the greatest number of seeds, 20 and 30). Renal and liver function investigation showed normal values, similarly electrolyte measurements, during the 12 hours of observation. After 7 hours, four children did not present any symptoms and the others still had loose stools, recovering completely after 12 hours. All left hospital in good condition. *Discussion: Jathopha curcas* belongs to the *Euphorbiaceae* family and is known in many regions of Brazil as "pinhão roxo" or "Paraguaian pinhão" (physic nut). The plant has been researched and planted in many parts of the country as an economic source for biodiesel. It is also used in folk and popular medicine. Its toxicity is related to the presence of a lectin or toxalbumin, curcin, a protein that inhibits protein synthesis in the ribosome, like ricin and abrin. Curcin alters the normal development and renewal of gastrointestinal cells, inducing desquamation of the intestinal walls. Similar symptoms are described irrespective of the number of seeds ingested (2 to 50). The main manifestations post ingestion are: nausea, vomiting, abdominal cramps, diarrhea, a burning sensation of the oropharynx region, electrolyte and acid-base disturbances. Death frequently occurs in animals, but no fatal cases have ever been described in humans, so far. *Conclusion:* Despite the highly hazardous toxalbumin present in the seeds, even the ingestion of 30 seeds did not result in severe signs and symptoms. *References:* 1. Kulkarni ML, Sreekar H, Keshavamurthy KS, et al. Jatropha curcas - poisoning. Indian J Ped 2005; 72:75–6.

146. Human Intoxication by *Solanum Lycocarpum A. St-Hill* (Wolf's Fruit)

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Objective: To report a case of intoxication after ingestion of *Solanum lycocarpun A. St-Hill* fruit (Wolf's Fruit or "lobeira"). *Case report:* A 29 year-old man was seen at the ER complaining of diarrhea. He presented tachycardic (HR = 104 bpm). He reported having eaten a smelly fruit he had spotted in a nearby shrub in the garden close to his work place approximately 6 hours before. He reported that just after the ingestion he started feeling unwell, with nausea, vomiting, sialorrhoea, diaphoresis, abdominal cramps, followed by a bad feeling of "imminent death". He had no alterations in electrolyte balance and renal and liver function. The patient had brought with him a fruit from the same plant which was identified as *Solanum lycocarpun A. St-Hill* (Wolf's Fruit). He was rehydrated intravenously and kept under observation during 12 hours, leaving hospital asymptomatic and remained well thereafter. *Discussion: Solanacea* is one of the biggest and most complex plant families known, belonging to the Angiosperms, with 92 genus and around 2,300 species. *Solanum L.* is the biggest and most complex genus among *Solanacea*. The genus presents many toxic principles causing gastrointestinal and central nervous system ailments, including saponins and steroidal glycosides. Many species also contain flavonoids warranting their use in folklore medicine, due to their probable antioxidant properties. The species *Solanum lycocarpum A. St.-Hill* is typical of Brazilian "cerrado", a vast geographical semi-arid area situated in most of Brazil's Southeast and Central hinterland. It is an important part of the diet of the Brazilian wolf species *Chrysocyon brachyurus*, the biggest South American wild canidae. When mature the fruit is eaten by the wolves as well as used in the preparation of a popular medicine for diabetes, despite the absence of any pharmacological effect in experimental studies. The toxic saponins isolated from that plant are solasonin and solamargin. LD50 of solamargin for rats is 42 mg/kg, and lethality is related to its anticholinergic effect, as in many *Solanum* species.

Conclusion: Toxic effects from ingestion of "wolf's fruit" have not been described so far, and the present case shows the possibility of serious gastrointestinal symptoms.

147. Muscarine Syndrome: Report of 2 Cases of Severe Mushroom Poisoning Identified at Lyon Poison and Toxicovigilance Centre in 2010

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Objective: In 2010, 142 collective poisonings (i.e. 246 patients) related to a mushroom meal were identified by Lyon Poison and Toxicovigilance Centre (PTC). The recorded clinical features were typical of a gastrointestinal syndrome in 63 cases, muscarine syndrome in 23, amanita syndrome in 4 (7 patients), coprinus syndrome in 2, and pantherina syndrome in 2. Digestive disorders were attributed to morchella in 9 cases, associated with vertigo in one. Severe mushroom poisoning was evidenced in 7 patients (5 amanita and 2 muscarine syndromes). The objective is to focus on the unexpected severity of these 2 muscarine syndromes, which are usually considered benign. *Case series:* Case 1: A couple ate mushrooms and one hour later, developed nausea, vomiting, abdominal pain, sweating, pinpoint pupils, and flushing. The 59-year-old man with a history of lower limb arteriopathy obliterans (LLAO) leading to bi-femoral bypass surgery in 1989 presented with motor and sensory deficit in the lower limbs evidenced by the absence of distal pulses and signs of ischemia. He had bradycardia (30 bpm), bilateral tight miosis, hypothermia (34.5°C), dehydration, and functional renal failure. Administration of atropine (0.5 mg) accelerated his heart rate to 70 bpm. Echo-doppler ultrasonography showed bilateral lack of vascularization and vascular occlusive thrombosis in the right branch of the bypass, and left popliteal thrombosis. The obstruction was relieved surgically by vascular Fogarty catheter and thrombolysis with urokinase. The control angiography showed good revascularization. The outcome proved favourable despite reperfusion syndrome with elevated CPK serum levels (10,000 IU/L). Case 2: A couple ate mushrooms and 30 minutes later, developed abundant sweating, vomiting and profuse diarrhoea. The 76-year-old woman with a history of LLAO presented with bradycardia (28 bpm), cardiovascular collapse, bilateral tight miosis, hypothermia (33°C), dehydration and functional renal failure. Hemodynamic stability was obtained by the administration of atropine (0.5 mg). The outcome was favourable with improvement of renal function. *Conclusion:* Muscarine mushroom syndromes are usually of mild or moderate severity. As these two cases show, they may, however, be associated with severe manifestations, especially for patients with pre-existing cardio-circulatory disease.

148. Fifteen-Year Retrospective Analysis of Amatoxin Poisonings in Switzerland

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Objective: To analyse and describe all confirmed cases of amatoxin poisoning reported to the Swiss Toxicological Information Centre (STIC) between 1995 and 2009. *Methods:* Retrospective case study from the STIC database. *Results:* 32 cases of amatoxin poisoning confirmed by ELISA were included in this study (Table 1). Patient age ranged from 1.4 to 74 years with a median of 50 and an average of 44.2 years. There were 20 males and 12 females. The mushroom meals were either eaten alone (16 patients), by 5 couples and one family of six. In 30 of the 32 cases, the patients ate the amatoxin-containing mushrooms accidentally, in one case it was a suicide attempt (fatal outcome), and in another a suicidal intention was suspected (fatal outcome). None of the mushrooms were checked by a certified mushroom expert prior to consumption. *Conclusion:* Amatoxin poisoning was fatal in five of our 32 cases (15%). Decontamination methods included administration of oral activated charcoal (single or repeated) in most cases while gastric lavage, placement of a duodenal tube, and laxatives were used only in single cases. Antidotal therapy consisted of silibinin, combined with N-acetylcysteine (NAC) and/or penicillin although NAC in combination with silibinin is nowadays the standard treatment. Consistent with data from the literature, mild courses were characterized by gastrointestinal symptoms and moderate cases by gastrointestinal symptoms and/or liver function impairment. Severe and fatal cases were dominated by liver failure and consecutive coagulopathy and encephalopathy. Molecular Adsorbents Recirculation System (MARS) is not readily available and was not used in any of these cases.

Table 1. Summary of cases of amatoxin poisonings

Severity	Nr. of patients	Age (years) and sex	Latency	Treatment	Outcome
mild	8	1.7–74 7m, 1f	12–20 h (3 h in one case)	MDAC (n=4) S + NAC (n=7)	favorable (n=7) thrombotic-thrombocyto penic purpura (n=1)
moderate	8	23–69 3m, 5f	6–18 h	GL (n=1) MDAC (n=6) FD (n=1) laxatives (n=1) DT (n=1) S + NAC (n=5) S + P (n=2) S + NAC + P (n=1) none at all (n=2)	favorable (n=8)
severe	11	1.4–72 8m, 3f	6.5–12 h	MDAC (n=6) SDAC (n=1) FD (n=1) DT (n=2) S + NAC (n=10) S + P (n=1)	favorable (n=10) need of LMW heparin for 6 months after pulmonary embolism (n=1)
fatal	5	40–76 2m, 3f	8–12 h	MDAC (n=4) DT (n=1) S + NAC (n=2) S + P (n=1) S + NAC + P (n=2) liver TPL (n=1)	death within 3 to 9 days

149. Clinical and Epidemiological Profile of Envenomations in Azerbaijan

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Background: The epidemiology of envenomation in Azerbaijan is uninvestigated. We present a study of the envenomation profile in Azerbaijan for the past 10 years. *Methods:* We analyzed case records of 766 patients admitted to the Republican Center of Toxicology (RTC) MoH, Baku, Azerbaijan in 2000–2009. *Results:* 5.8 percent of RTC total hospitalizations were envenomations caused by snakes, "black widow" spiders, scorpions and hymenoptera. Most cases (546) comprised of snake bites, 101 cases - "black widow" spider stings, 89 cases - hymenoptera stings (bee, wasp etc) and 30 cases - scorpion stings. Ratio of male to female was 3:1. One hundred and seventeen patients (15.3%) were children (age <15 years). Five hundred and forty of 546 snake bite patients had severe symptoms of coagulopathy, local edema and hemorrhage typical for *Viperidae* venom envenomation. Ninety per cent of *Viperidae* snake bite patients were admitted to RTC with incorrect first aid actions such as tourniquet, cuts at the point of bite etc. Only 6 patients had neurotoxic manifestations typical for *Elapidae* snake venom envenomation. All these patients arrived from southern (Iranian border) regions of Azerbaijan. Ninety-five per cent of patients with snake bites received polyvalent antivenom at the time of presentation. Adverse reactions to antivenom were registered in 43 cases. Mortality due to snake venom envenomation was 2.7% (15 patients). Cases of "black widow" spider stings are new for Azerbaijan. Patients with the typical clinical syndrome of latrodectism (severe muscle pain and cramping, hypertension, arthralgia, lacrimation etc) started to register only in the last 15 years. No specific antivenom is available in Azerbaijan and only symptomatic treatment was provided for these patients. One case of "black widow" spider envenomation was fatal. Cases of scorpion and hymenoptera envenomations were mostly mild and no lethal cases were registered. *Conclusion:* Envenomations are a significant part of toxicological admissions in Azerbaijan. Most of the patients with snake and "black widow" venom envenomations showed marked clinical manifestations and may have severe prognosis. Scorpion and hymenoptera stings occurring in Azerbaijan do not cause life-threatening effects.

150. Analysis of Deaths by Scorpion Envenomation

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Objective: The aim of this study is to analyze risk factors due to scorpion envenomation in order to improve patient care and prevent both morbidity and mortality. *Methods:* Our work is a retrospective study of deaths by scorpion envenomation during the year 2005, based on a hospital in Beni Mellal province. *Results:* In our study we counted 18 deaths from 63 cases of envenomation; the rate of lethality at the hospital was 28.57%. 83.3% of these deaths concerned children aged ≤ 10 years. Scorpion envenomation occurs mainly during summer time, in particular during June and July (50%). Moreover, stings happen at night between 6PM and 6AM (72.2%). The sex ratio (M/F) is 1.25, not significant (chi-squared = 0.22). The average duration of hospitalization was 7.34 ± 1.23 hours. Several therapeutic measures were used of which the cardiac stimulant dobutamine represented by Dobutrex was recommended in 72.2% of cases. Statistical

analysis showed age less than 15 years and vital signs (neurological, respiratory and cardiovascular) are risk factors for envenomed patients. *Conclusion:* Scorpion envenomation remains a public health problem in Beni Mellal province.

151. Laburnum Intoxication with Unexpectedly Benign Outcome

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Objective: It is well known that *Laburnum anagyroides* is a toxic plant and that intoxications occur from time to time. In Norway this usually happens when children eat peas or pods by accident or at play. The amount producing symptoms is uncertain, but as few as 2–5 peas are reported to cause symptoms. We present a case of laburnum intoxication in a healthy adult man with an unexpectedly benign outcome. *Case report:* A 36 year old healthy man ate 20 pods (1–3 peas in each pod) of laburnum over an hour, just because he felt like it, describing the pods as edible, with a taste like cucumber and sweet peas. The man was not under influence of alcohol or drugs. Thirty minutes after ingestion he turned pale, started to sweat, got chills and felt intensely dizzy. He felt nauseous and threw up several times. About one and a half hour later the Norwegian poison information centre (NPIC) was contacted by his wife. The plant was not identified, but on description of the plant and information about symptoms we suspected a possible serious laburnum intoxication, and advised the patient to contact the emergency room. About two hours later the hospital contacted NPIC. The plant was identified as *Laburnum anagyroides*. The man was still nauseous, pale and dizzy, with episodes of vomiting. An ECG was performed which was found to be normal. Blood pressure and pulse were measured every other hour through the night and remained normal. There were no interventions. The patient was sent home the next day, feeling reasonably well, although he felt like he had a hangover. *Conclusion:* Considering that this was an ingestion of a large number of laburnum pods, we would have expected a more serious clinical development. The early onset and repeated episodes of emesis may efficiently have reduced the dose, resulting in only mild symptoms.

152. Epidemiology of Mushroom Poisoning in Southwest Germany

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Objective: Possible mushroom poisoning is considered a dangerous event, especially if gill fungi have been ingested. In case of late onset vomiting and diarrhoea amanitin poisoning must be excluded. Another harmful toxin is orellanine. Identification of the mushroom species by a competent mycologist is important, but often mushroom species are not available. To investigate the frequency of severe mushroom intoxications we analysed retrospectively the enquiries on mushroom ingestions. *Methods:* The database of the PC was searched for human mushroom ingestions from 2006 to 2010 (until Nov. 15th 2010). The data were analysed for involved mushroom species, severity of poisoning, age of the affected patients and circumstances of the intoxication. *Results:* Overall 1184 mushroom ingestions by humans were reported. Accidental exposures dominated (96%). Four hundred and sixty-nine patients were younger than 14 years. Severity of poisoning was: asymptomatic (523), minor (530), moderate (123), or severe (8). In only 74% of all symptomatic patients was the ingestion of mushrooms considered to be at least a possible cause of the symptoms. Severe mushroom poisoning concerned only adults. In 5 of these cases mushroom poisoning was suspected but was considered unlikely in retrospect. Amanitin containing mushrooms caused two severe poisonings, while orellanine containing fungi caused one severe poisoning. One patient died of liver and renal failure after a meal of unknown mushrooms. All moderately poisoned children (8) had consumed a meal of self picked mushrooms and presented with gastrointestinal symptoms. *Conclusion:* Possible mushroom poisoning is a frequent cause of enquiries to the PC of Baden-Wuerttemberg in southwest Germany. Accidental ingestion of parts of a mushroom by children did not result in more than minor symptoms. Severe mushroom poisonings are rare. Identification and documentation of the involved species should be improved.

153. Validity of Mushroom Identification by Photo in the Danish Poison Information Centre

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Objective: To evaluate the reliability of mushroom identification by digital photos sent from mobile phones (MMS) or by email compared to identification based on physical examination. *Methods:* As part of a 1-year prospective mushroom case-series study all inquirers were asked to send a digital photo of the mushroom by email or by mobile phone (MMS) to the Poisons Information Centre (PIC). Additionally the inquirer was asked to send the mushroom physically to the PIC for later definitive identification. Photos of mushrooms were identified by a panel of mushroom experts as part of the risk-assessment in relation to the intake. The collected mushrooms were later physically identified macro- and microscopically by one expert. The level of the identification of the mushroom (photo and macro) was classified as: a) cytotoxic/non-cytotoxic, b) genus-name, c) species-name. The results of photo identification at different levels were compared with macroscopic identification using the latter as reference. *Results:* A total of 160 contacts with the PIC related to acute mushroom intake occurred during one year: 112 identified by photo at inquiry; 64 mushrooms subsequently identified macroscopically by expert; 53 mushrooms identified both by photo and physically by expert (see Table 1). *Conclusion:* Identification of mushrooms by digital photos taken by mobile phone is a valid method for exclusion of the most toxic mushrooms. The method can be used in circumstances with intake of small amounts of a mushroom, when only the most toxic species will be a problem. When a precise identification is needed the identification must be macroscopic until the photo method is further refined.

Table 1. Matching identification by photo and macroscopic (expert)

	Mushrooms identified by both photo and expert (N)	Match between photo and physical identification (N)	Proportion with match (95% c.i.)
Species	15	13	0.87 (0.60–0.98)
Genus	51	40	0.78 (0.65–0.89)
±cytotoxic	53	53	1.0 (0.93–1.0)

154. Lethal Mushroom (*Inocybe*) Poisoning in a Puppy

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Objective: Reports of *Inocybe* poisonings in dogs are limited. We present a case of lethal intoxication in a Pomeranian puppy. *Case report:* The patient, a 3 month old Pomeranian weighing 1 kg (2 pounds), was observed by the owner eating one mushroom growing on a small lawn outside her office building. About 10 minutes later the dog started vomiting. The vomit contained mushroom and a lot of mucus. Shortly thereafter the dog had diarrhoea and probably also involuntary urination. The dog was brought to the veterinary clinic within half an hour. The dog had diarrhoea and continuous vomiting. Heart rhythm was irregular and mucus membranes were pale. Fluid therapy was initiated and activated charcoal was administered. The mushroom was identified by the poisons control centre as *Inocybe*, but the dog died before atropine was given. The dog died less than 2 hours after the ingestion. Although there are a limited number of published cases, anecdotal evidence suggests that it is not uncommon for dogs to eat these mushrooms and that they rapidly become quite ill. *Inocybe* are well known to produce muscarine intoxication in humans, but rarely severe. *Conclusion:* Even a small amount of *Inocybe* can be fatal to a small dog, and vets and poisons control centres must be aware of this, so that antidote treatment can be initiated without delay.

155. Paediatric Therapeutic Errors Reported to the UK National Poisons Information Service, Occurring in the Home

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Objective: A retrospective review of enquiries to the UK National Poisons Information Service (NPIS) relating to therapeutic errors in children under 19 years of age. *Methods:* Data between January and December 2008 were reviewed; exposures occurring in the home were examined to establish type of agent involved, reason for the error and route and type of exposure. *Results:* During the study period, 23,387 enquiries relating to this age group were received by the NPIS, 1998 enquiries (8.5%) were due to therapeutic error. Of these, 21% were in children under 1 year, 12% in 1 year olds, 9% in 2 year olds, 6% in 3 year olds and 5% in 4 year olds, the older year groups remained between 3 and 4%. A total of 1759 (88%) exposures took place in the home. Of these, 93% involved ingestion with the remaining 7% being due to inhalation, injection, skin or eye contact. Fifty-four percent of exposures in the home were considered acute, in 20% the patient had taken an excess of their own medication, 18% involved a staggered exposure and 6% a sub-acute exposure. The class of drug most commonly associated with therapeutic errors in this group was analgesics (35%); respiratory medication 16%, CNS depressants 13%, antibiotics 11%, cardiovascular drugs 7% and gastrointestinal medication 4% were also implicated. Of the 606 enquiries relating to analgesic exposure in the home, 321 (53%) were deemed to be due to parental error, 151 (25%) to patient error and 9 (1.5%) were due to error by a healthcare professional. An incorrect analgesic drug was administered in 80 enquiries and of the 400 cases where an incorrect dose was given, 151 patients received double their prescribed dose, 138 received less than double and 111 received more than double - commonly 10 times the recommended dose. 15% (88) of analgesic exposures were regarded as potentially serious ingestions resulting in hospitalisation and/or medical treatment. *Conclusion:* The majority of therapeutic errors in children occur in the home, often as a result of parents giving extra doses. Help, perhaps in the form of a simple dosing chart, may significantly reduce these exposures.

156. Antidepressant Patient Presentations to US Emergency Departments

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Objective: Antidepressants are a common cause of prescription medication poisoning in the US. Emer-

gency department care for these poisonings is poorly studied. The purpose of this study was to characterize antidepressant poisonings presenting to New Jersey and New York emergency departments. *Methods:* Design: A multi-center retrospective emergency department (ED) cohort. Study setting: 20 New Jersey and New York EDs. Subjects: All patients with the ED diagnosis of antidepressant poisoning, (ICD10 code = T43), were identified from October 1, 2008 to September 30, 2009. Only completed charts with documentation of an acute antidepressant ingestion were included. *Results:* Out of 1,590,248 consecutive patients, a total of 309 patients were diagnosed with antidepressant poisoning, (0.019% of all ED patients). The patient demographics were as follows: mean age = 27.2 years (range: 1–78 years), gender = 26% males. Nine poisonings involved children less than 4 years of age. The most commonly reported antidepressants were: escitalopram 24%, bupropion 12%, and trazodone 10%. Selective serotonin reuptake inhibitor and cyclic antidepressant poisonings accounted for 53% and 9% of cases, respectively. ED management for these patients included: measuring a serum acetaminophen level in 59% of cases, obtaining an electrocardiogram in 73% of cases, and performing gastrointestinal decontamination in 32% of cases. Overall, the poison center was notified in 50% cases. However, poison center notification was much higher among tricyclic antidepressant poisonings (78%) and pediatric patients < 4 yrs of age (89%). There were no recorded deaths in the ED. *Conclusion:* Most antidepressant poisonings presenting to US emergency departments are caused by selective serotonin reuptake inhibitors. ED mortality from antidepressant poisoning is likely to be extremely low.

157. Poisoning in Elderly People: Increasing Number of Cases Attended by the Spanish Poison Centre (Instituto Nacional de Toxicología y Ciencias Forenses)

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Objective: In recent years we have recorded a significant increase in the number of calls to the Spanish Poison Centre (SPC) related to poisoning of people above 70 years of age. Thus, we have studied this population group and fully characterized these cases to alert the authorities about the need to implement specifically focused preventative measures. *Methods:* We performed a retrospective analysis of selected calls received by the SPC between 2006–2009 which were related to poisoning in subjects above 70 years of age. Data included age, gender, etiology, exposure route and the type of toxic product. *Results:* The number of calls related to poisoned subjects older than 70 years (n = 6396) has increased from 0.8% in 2006 to 1.8% in 2009. Amongst these, 4.9% were due to suicide attempts, whereas the remaining cases were accounted for by accidental causes (37.1%), as well as errors in posology (34.9%) and administration routes (2.8%) of currently used therapeutic drugs. 47.2% of the patients were aged 70–79 years, 43.5% were 80–89 years, and the remaining cases were more than 90 years. When gender was considered, the majority were females (58.9%). The main exposure route was oral poisoning (88.7%). Regarding the type of toxic agent, therapeutic drugs were mainly involved (71.4%), followed by cleaning products (16.7%), agrochemicals (4.1%) and cosmetics (3%). More specifically, the type of therapeutic drug which generated the poisoning events were those more frequently provided to this population group: nervous system (26.3%); cardiovascular system (19.9%), alimentary tract and metabolism (8.7%); anti-infectives for systemic use (8.3%); respiratory system 7.9%; musculo-skeletal system (7.1%). *Conclusion:* There has been a significant increase in the number of calls received at the SPC involving elderly people, who have accidentally taken therapeutic drugs or cleaning products. Indeed, elderly people accumulate specific risk factors that increase the severity of poisoning, such as underlying pathological conditions and frequently, concomitant neurological problems such as confusion, dementia, slow reflexes and sensorial deficits (sight, smell, taste). The SPC has to alert the corresponding Health Authority about this circumstance, in order to focus and implement specific preventative measures directed towards the reduction of the incidence and morbidity of poisoning events in this population group.

158. Swedish Pharmacy Deregulation - Any Impact on Poisons Centre Consultations?

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Objective: To elucidate whether the deregulation of the Swedish pharmacy monopoly in 2009 has caused an increase of inquiries to the Swedish Poisons Centre (PC), in particular concerning over-the-counter (OTC) analgesics. The pharmacy monopoly was formally abolished in July 2009. Sale of certain drugs outside pharmacies has been allowed since 1st November 2009 (e.g. 500 mg paracetamol and 400 mg ibuprofen tablets). *Methods:* The number of inquiries to the Swedish PC concerning paracetamol and ibuprofen misuse/overdose during the year immediately prior to deregulation was compared to the corresponding figures during the year following deregulation. *Results:* The total number of inquiries about paracetamol and ibuprofen was 3764 (71% related to paracetamol) during the year prior to deregulation and 3841 (68% related to paracetamol) in the 12-month period following deregulation. There was a 12% rise in ibuprofen inquiries, which complies with the trend during recent years. There was no significant change in the pattern of consultations, e.g. the frequency of accidents in infants and deliberate overdoses in adults. With respect to adolescents (15–19 years old), the number of inquiries increased alarmingly from 2000 up to 2008, but has since decreased. This is also true when comparing the 12-month period preceding deregulation (588 inquiries concerning paracetamol and ibuprofen) to the 12 months after deregulation (527). *Conclusion:* The increased availability of OTC analgesics has not, so far, resulted in a significantly larger number of inquiries to the Swedish PC involving these drugs. This contrasts to the experience in Norway where a marked increase in inquiries concerning paracetamol was observed after pharmacy deregulation.[1] This issue needs to be followed closely during the years to come. It would be ideal if the PC statistics do reflect the actual frequency of poisonings, but these data must always be interpreted with caution. *References:* 1. Ziesler TA, Lorentzen HR, Knapstadet SE, al. Has increased availability of paracetamol had any effects on inquiries received by the National Poisons Information Centre in Norway? Clin Toxicol 2007; 45:368.

159. Continued Increase in Antidepressant Subgroup Drug (SSRI, SNRI, NARI, NaSSA) Poisonings in 15–34 Year Olds

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Objective: During the last four years, 2007–2010 (6 months), the Danish Medicines Agency has registered an increase in daily dose sales of antidepressant subgroup drugs - especially among the 15–34 year olds.[1] Our aim was to evaluate if we observed any similar change in the inquiries to the Danish Poison Information Centre (DPIC) regarding poisonings with antidepressant subgroup drugs in the mentioned time period. The age group in focus was 15–34 years. *Methods:* Details for every enquiry are recorded in the DPIC database. Data from 2007, 2008, 2009 and 2010 (6 months) were collected from these patient records. All ages were collected and divided into groups (< 15, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–54, > 54 years old), but only the focus group aged 15–34 years was included in further evaluation. Furthermore, we subdivided our data to observe any seasonal variation, male/female presentation, whether the patients had ingested only the antidepressant subgroup drugs or multiple drugs, the cause of poisoning and the enquirer. *Results:* A total of 2,143 cases were evaluated. Relative to the number of inquiries this corresponded to 3.3% in 2007, 3.5% in 2008, 4.5% in 2009, and 5.1% in 2010 (6 months). The annual variation was low, but shows a higher frequency during winter time. Age distribution showed that 15–34 year olds accounted for 43% in 2007, 42% in 2008, 45% in 2009, and 48% in 2010 (6 months). Females represented 79% in 2007, 76% in 2008 and 2009, and 81% in 2010 (6 months). The fractions of multiple drug ingestions were 63% in 2007, 50% in 2008, 57% in 2009 and 63% in 2010 (6 months). The cause of poisoning was approximately 92% suicidal/affect in all years. A minimum of 94% of the inquiries were from healthcare professionals. *Conclusion:* The relative number of registered poisonings at DPIC with antidepressants (SSRI, SNRI, NARI, NaSSA) increased from 2007–2010(6 months). The age distribution shows the highest frequency of inquiries was for those aged 15–34 years. The majority of the patients were female. In most cases the antidepressant drug was ingested concomitantly with other pharmaceuticals and the purpose was suicidal/affect. *References:* 1. http://www.medstat.dk/MedStatDataViewer.php

160. The Toxicology Investigators Consortium (ToxIC) Registry: A National Registry of Patients Seen by Medical Toxicologists at the Bedside

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Objective: In 2009, a survey of US based medical toxicologists established that 10,000–15,000 patients are directly evaluated each year by medical toxicologists; either at the bedside or in the clinic. The American College of Medical Toxicology subsequently established the Toxic Investigators Consortium (ToxIC) to develop a Registry of toxicology patients seen at the bedside and to provide a national network infrastructure for multicenter collaborative research. Beginning in February 2010 ToxIC began a Registry of patients seen at the bedside by medical toxicologists. We report on this Registry to date. *Methods:* An on-line, Health Information Portability and Accountability Act (HIPAA) compliant database was created that is accessible via the American College of Medical Toxicology (ACMT) website. After an initial pilot test, toxicology sites were recruited to participate in this program. Data elements that were collected included: location of encounter (inpatient, outpatient, ER), age, encounter type (ADR, pharm vs nonpharm agent exposure, environmental, occupational, envenomation), agent class, specific agent names, clinical signs and symptoms, and treatment. *Results:* 3230 cases were enrolled into the ToxIC database during the first 10 months of data collection. The data was collected by 26 sites who consulted and cared for toxicology patients at 44 medical centers. Over 80 medical toxicologists participated in the data collection. Additional sites are currently being recruited to participate in the Registry. The time required to enter data is ~ 1 minute/patient. Updates in the data collection tool have facilitated ease of using the collected data for toxicosurveillance. *Conclusion:* The ToxIC registry is a viable tool to identify cases that medical toxicologists see at the bedside at multiple sites. Following identification in the database, access to the case details will provide complete clinical records of consultations seen by medical toxicologists. The development of this registry provides a novel toxicosurveillance source for research, education, and improved public health. Such a registry could be expanded to international collaborators.

161. Characteristics of Toxic Alcohol and Glycol Poisoning in the UK

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Objective: Enquiries regarding poisoning with ethylene glycol or methanol are frequently referred to a consultant clinical toxicologist in the UK, because of diagnostic difficulty, severe toxicity or inconsistent availability of specific assays and antidotes. This prospective study was undertaken to investigate the epidemiology of systemic exposures reported to the National Poisons Information Service (NPIS), use of antidotes and their adverse effects. *Methods:* Details of systemic exposures to products containing toxic alcohols and glycols reported to NPIS were collected from 1 January 2010 to 30 June 2010 as part of an ongoing 12 month study and cases of significant exposure were followed up to obtain information on antidote use and patient outcome. *Results:* There were 244 enquiries about toxic alcohols over the 6 month period. One hundred and forty-nine (61%) enquiries originated from hospitals. Sixty-one per cent of patients were male and 8% were under 5 years of age. Exposures were mainly by ingestion (95%), occurred mainly at home (89%), with 55% of cases being accidental and 36% intentional. The most common products were surgical spirits, antifreeze and screen-wash products with ethylene glycol identified as the most common ingredient. At the time of the enquiry 78% of patients had no or minor symptoms and 19% moderate/severe symptoms using the Poisons Severity Score. One hundred and three cases met the criteria for case follow up. Of the 60 cases where the outcome is known, 57 made a complete recovery and 3 had sequelae. Details of monitoring and treatments were available for 70 cases. Fomepizole was administered in 17 cases, ethanol 18 cases and both antidotes in 3 cases. Adverse reactions to the antidotes were reported in 3 cases where ethanol had been administered. Haemodialysis/filtration was instituted in 12 patients. *Conclusion:* Serious poisoning with toxic alcohol and glycols occurs infrequently although the incidence in the UK cannot be determined as some cases may not result in an enquiry to NPIS. Exposures are predominantly acute ingestions involving ethylene glycol and occur more frequently in males. The majority of patients show few symptoms at the time of the enquiry. Ethanol and fomepizole are used in similar numbers of patients without any differences in outcome. *Acknowledgement:* Submitted on behalf of the UK National Poisons Information Service.

162. National Poison Data System: Methadone 2000–2010

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Objective: National Poison Data System (NPDS) provides national real-time data with the potential to assess regulatory or enforcement interventions. We previously reported NPDS 40-mg methadone temporal patterns from 2000–2008 as related to a Drug Enforcement Administration (DEA) dispensing rule change. As of 1-Jan-2008, manufacturers of methadone 40-mg tablets voluntarily agreed to limit wholesale distribution to DEA-registered opioid detoxification and maintenance facilities and hospitals. Retail pharmacies and other healthcare providers would not be able to purchase methadone 40-mg tablets. NPDS data showed 40-mg methadone exposures decreased. Drug ID Calls increased, then decreased. All three signaled a response. We wanted to see if this change was associated with a reciprocal change in the 2.5, 5, or 10-mg methadone dose forms. *Methods:* We studied all 40-mg and 2.5, 5, and 10-mg (low-dose) methadone drug identification (Drug-ID) and human exposure cases (Exposures) from NPDS for 2000 - 12-Nov-2010 to evaluate the impact of this intervention. 40-mg methadone has been available in 7 products from 6 manufacturers and low-dose in 12 products from 8 manufacturers. NPDS was queried for Exposures and Drug-ID case data on these products by day and examined by week, month and year. Each measure was examined by linear and 2nd order (quadratic) least squares regression and piecewise before and after 1-Jan-2008. Time to max (T-max) was determined for the quadratic regressions. Results discussed herein describe the analyses of the by-month data. *Results:* A total of 1,915 40-mg and 3,835 low-dose Exposures and 10,165 40-mg and 97,061 Drug-ID calls were reported. Both 40-mg and low-dose Exposures showed a relatively smooth quadratic pattern (concave down) with a T-max of 2006.1 for 40-mg and 2008.1 for low-dose. In contrast, both 40-mg and low-dose Drug-IDs showed a distinct discontinuity at 1-Jan-2008. For 40-mg the slopes of the linear regressions were 10.2 before and -5.26 calls/month after and low-dose slopes were 178 calls/month before and -152 calls/month after. *Conclusion:* The temporal patterns for the 40-mg and low-dose Exposures show similar patterns with 40-mg peaking ~2 years earlier than low-dose without reciprocal change. Drug-ID calls outnumber Exposures 18.6:1 and both 40-mg and low-dose changes reflect the DEA's 40-mg intervention in 2008.

163. Live Birth Rate as a Predictor of Human Exposures Reported to US Poison Centers

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Objective: The National Poison Data System (NPDS) represents a comprehensive aggregate of calls made to United States (US) poison centers and is the largest available dataset of poisonings in the US. The value of NPDS as a real time national public health surveillance tool relies on a number of assumptions, including validation that NPDS represents a consistent and reliable sampling of the US population. Previous work showed the population with the greatest risk was children <6 years of age. We examined the relationship between US live births and exposures reported to NPDS. *Methods:* Retrospective comparison of annual poisonings with live birth rates using: 1) NPDS annual count of human exposure cases (Exposures) for 2000 through 2009 accumulated through 20 age windows (0–5 by year, 6–12, 13–19, adults by decade through 90 y/o, +4 unknown categories); and 2) US Census Bureau; annual live birth counts (Live-births) from 1978 through 2009 shifted 0 through 19 years (time lag) across the 10 sample years by linear least squares regression. *Results:* the highest positive correlation was Exposures for cumulative ages 0–5 y/o versus Live-births with a 4 year shift ($r = 0.937$, $N = 10$, $p < 0.0001$). Annual live birth rates correlated closely with human exposures reported to poison centers (both positive and negative directions) with a best fit using a 4 year time lag. *Conclusion:* Changes in the number of poisonings reported to US poison centers closely reflect changes in the live birth rate in the US, with a 4 year time lag. With the decrease in live births noted over the last two years (2008 and estimated 2009), US poison centers may expect to observe a similar decline in human exposures. We believe our analysis further supports the validity of this dataset as a public health surveillance tool.

164. Evaluation of Age-Based Risk for Poisoning in the United States

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Objective: The National Poison Data System (NPDS) represents a comprehensive aggregate of calls made to United States (US) poison centers and is the largest available dataset of poisonings in the US. We evaluated the age-based poisoning risk in the US population across nine age windows. *Methods:* Retrospective comparison of annual poisoning rates in 9 age windows (0–5 by year, 6–12, 13–19, adults 20 and older). The data sources used were 1) NPDS; annual count of human poisoning cases (Exposures) for 2000 through 2009; and 2) US Census Bureau; annual live birth (Live-births) counts 1978 through 2009 and death rates (2004–2007) to estimate population at risk (PAR) by age group. We calculated mean exposures per 1000 PAR and change in Exposures per 1000 PAR per year (Slope) for each age group using linear least squares regression. *Results:* There is a clear difference in mean exposures per 1000 PAR across the 9 age groups (ratio of 2 y/o to Adults = 32.2) and a statistically significant change over time (Slope) in 6 of the 9 age groups (Table 1). Both the highest risk and the largest increase over time (Slope) occurred in the 2 year old group. *Conclusion:* These results provide the first quantitative assessment of the age-based risk rates for NPDS Exposure data and demonstrate the value of Live-birth data to estimating the population at risk.

165. Do Older Siblings Enable their Younger Brothers and Sisters?

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Background: Parents commonly find young siblings gathered together near open bottles of medications. Often it is difficult or even impossible to know which sibling is at higher risk for a serious exposure. This study was undertaken to assess the hypothesis that the younger sibling would be at higher risk for a serious exposure due to encouragement by the older sibling. This was assumed based on the theory that the older child would be more likely to model parents administering medication. *Methods:* The notes section from approximately 18,000 acetaminophen exposures sent to a health care facility, spanning the years 2000–2009,

Table 1. Evaluation of age-based risk of poisoning in the US

Population Age Group	2005 PAR (millions)	Mean Exposures/ 1000 PAR	Slope (Exp/ 1000 PAR/yr)	P-value for slope
<1 y/o	4.14	32.3	−0.4965	0.0083
1 y/o	4.08	94.5	0.2447	ns
2 y/o	4.06	96.5	1.2542	0.0005
3 y/o	3.99	42.4	0.6290	0.0006
4 y/o	3.98	20.2	0.3252	0.0002
5 y/o	4.01	11.7	0.1757	0.0002
Child (6–12 y/o)	27.22	5.50	0.0195	ns
Teen (13–19 y/o)	27.23	6.10	−0.0358	ns
Adults (>20 y/o)	268.52	3.02	0.0385	0.0184

from a statewide poison center database were screened using a word search function. Terms used in the search included sibling, brother, and sister. Cases in which positive acetaminophen levels were obtained in both siblings were included. Cases with negative results were excluded. Comparison of acetaminophen levels between older and younger siblings was performed. *Results:* 24 siblings or 12 pairs were included in the study. The average age of the younger sibling was 2.06 years. The average age of the older sibling was 3.58 years. The average acetaminophen level in the younger group was 70 mg/L. The average acetaminophen level in the older group was 49 mg/L. One large exposure in the younger age group significantly contributed to the difference in results. *Conclusion:* Significantly higher acetaminophen levels were found in the younger sibling when there is a co-ingestion between two children. This may be due to the older child being more likely to mimic medication administration by parents. Larger studies are necessary to confirm this data.

166. A One-Year Observational Study of Fatal Poisonings in Ekaterinburg, Russia

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Objective: There is a lack of prospective studies on poisoned patients comparing the mortality inside and outside hospital. *Methods:* A one-year prospective, observational study of all acute poisonings in Ekaterinburg, Russia (population: 1,343,900, of whom 1,145,000 were ≥16 years) between 2009 and 2010. Patients ≥16 years of age who were in contact with any part of the health care system (ambulance service, hospitals, or the Forensic Institute) were included. The fatalities are presented here. *Results:* There were 572 patients who died from poisoning during the period, giving an annual mortality rate of 50/100,000 inhabitants. Of those, 503 (88%) were found dead on scene, 5 (1%) died in the presence of an ambulance, and 64 (11%) died in hospital. Mean age among the fatalities was 45 years (range 17–91); 75% were males. The most frequent agents causing death were found to be ethanol (44%), opiates (29%), carbon monoxide (14%), and acetic acid (4%). Pharmaceutical agents resulted in 30 deaths (5%), of whom 16 died in hospital. The most frequent pharmaceutical agent causing death on scene was drotaverine (4 cases). The majority of the poisonings were accidental (63%), and drug overdoses (29%). Among the dead in hospital, acetic acid (20%), opiates (16%), and ethanol (17%) were most frequently found. Suicides were considered the cause of poisoning in 35% inside hospital, as compared to 4% outside hospital. *Conclusion:* Mortality rate was unexpectedly high (18.4% of all poisonings, 3.3% in hospital), with ethanol poisonings found dead on scene as the main contributor.

167. Pandemic Hand Hygiene Recommendations Increased Inquiries Related to Alcoholic Hand Sanitizers in Children Under 6 Years

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Objective: During the A(H1N1) pandemic many recommendations concerning hand hygiene were issued. People were told to wash their hands with soap and water and to use alcohol-based hand sanitizers regularly. Alcohol can be toxic to small children. The purpose of the study was to investigate whether the instructions and increased availability influenced children's exposures to alcoholic hand disinfectants. *Methods:* Data was collected from the Poison Information Centre (PIC) database and all inquiries about exposures to alcohol-based hand sanitizers were included from January 2005 to December 2010. Inquiries from January 2009 until the end of June 2010 were analyzed in more detail on a monthly basis (Pandemic declared in June 2009). Symptoms reported were assessed according to Poison Severity Score.[1] *Results:* The number of inquiries related to exposure to alcohol-based hand sanitizers rose from 70 in 2005 to a peak of 377 in number of calls, beginning in April 2009 and reaching the highest number in December 2009 followed by a return to normal level again in April 2010. During the year 2009 233 and in the first 6 months of 2010 102 children under 6 years were exposed to alcohol based hand sanitizers. Of the exposures 197 and 89 were oral, 36 and 14 eye, and 3 and 3 dermal. Some of the patients were exposed through more than one route. Of the children only 18 and 17 were symptomatic and all of the symptoms were classified as minor. Home observation was recommended in 222 and 98 cases while 11 and 4 cases required medical attention. *Conclusion:* Recommendations to improve hand hygiene by using alcohol based hand sanitizers also increased children's toxic exposures to these products. Most of the exposed children showed no signs of toxicity, and only a few showed minimal toxicity requiring medical attention. Retailers of alcohol-based sanitizers should remind consumers that these products should be kept out of children's reach. *References:* 1. Persson H, Sjöberg G, Haines J, et al. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol 1998; 36:205–13.

168. Overdose Profile of Antipsychotic Agents

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Objective: Evaluation of the safety profile of traditional and atypical antipsychotics in overdose. *Methods:* Intoxications were analyzed on the basis of data gathered from telephone consultations and medical reports forwarded to the National Toxicological Information Centre (NTIC) in Bratislava from the whole area of Slovakia during the period 1999–2008. All patients who consulted the NTIC because of nonpresribed use or overdose of antipsychotics were included in the group for analysis. The severity of poisonings was classified in accordance with the Poisoning Severity Score. *Results:* During the 10-year period 1090 antipsychotic intoxications were the subject of enquiries to the NTIC. Since 1999 the number has increased by 220%. Annually there is an increase in the number of intoxications by atypical antipsychotics, together with their rising prescription. The highest number of intoxicated patients (181) was in the age group 15 to 19 years. Suicidal intoxications were more frequent - in 875 cases (80.3%) and had a more serious clinical course. Clinical symptoms of intoxication were manifested in 951 patients (90.2%) of the observed group. We registered just 103 cases (9.7%) in which no symptoms of intoxication were manifested after non-prescribed use or overdose. The most frequent (in 657 cases) were moderate symptoms (sleepiness, dizziness, gastrointestinal distress, mild extrapyramidal symptoms, hypotension) that subsided in 24 hours. In 217 patients we observed symptoms of serious and in 71 patients symptoms of severe intoxication. Severe intoxications in 6 patients resulted in death. Financial costs of the treatment increased along with the severity of intoxication and the length of hospital stay. The consequence of our findings is that there is no significant difference in severity or the length of hospital stay between intoxications by atypical and traditional antipsychotics. *Conclusion:* Our analysis shows that an early consultation with the NTIC contributes to essential reduction of hospitalization and severity of symptoms and in this way to the reduction of the treatment costs of intoxicated patients. It also significantly reduces the necessity of a medical facility visit and reduces costs of the health care.

169. Role of the Poison Control Centre of Morocco in the Reduction of Mortality Associated with Poisoning: The Example of Paraphenylendiamine Poisoning

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Objective: The objective of this work is to illustrate the role of the Poison Control Centre of Morocco in the management of poisonings that have a high mortality rate. For this, we describe the epidemiological situation of paraphenylendiamine (Takaout Roumia) poisoning in Morocco. *Methods:* This is a retrospective study of the number of cases and the fatality rate of Takaout poisoning during the period 1980 to 2007 reported to the Poison Control Centre of Morocco. *Results:* Takaout poisoning was the cause of 384 cases of poisoning between 1980 and 2007. It was responsible for 80 deaths. It has the second cause of fatalities (21%) after *Atractylis gummifera L* (28%). Several actions were undertaken. They were completed by organizing a national day during which all stakeholders were committed to the restriction of sales and to providing physicians with standardized support. The number of poisoning cases has been reduced to 13 cases in 2005 and the deaths reduced from 12 cases in 2003 to one case in 2005. *Conclusion:* We can conclude that the role of the Poison Control Centre of Morocco in the collection of epidemiological data concerning the various poisons helped compile a list of poisons with high fatality rate, and helped to direct and control activities thus reducing the mortality rate associated with these poisons.

171. Caustic and Household Detergent Exposures in Emergency Medicine

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Objective: Children younger than 6 years are under risk of poisoning by caustics and other household products.[1,2] The aim of this study was to analyse the caustic and household detergent exposures admitted to Emergency Medicine at Dokuz Eylul University Hospital (EMDEU) between 1993 and 2008. *Methods:* Our retrospective data were transferred into a Statistical Package for Social Sciences for Windows 15.0 (SPSS 15.0). Age, sex, reason of exposure, clinical signs, rate of endoscopy in oral exposures, treatment attempts, length of hospital stay and outcome were evaluated. A chi-square test was used to analyse statistical differences. *Results:* Caustic exposures accounted for 8.5% (1160 cases) and 4.1% (1988 cases) of all poisonings in children and adults, respectively. Female/male ratio was 0.8. Most of the exposures were unintentional (158, 86.8%). Intentional exposures were common in cases between 19 and 29 years old ($\chi^2 = 25.685$, $p < 0001$). The most common caustic substance was alkaline (106, 58.3%) followed by acidic (47, 25.8%) and other household detergents (28, 15.4%). Vomiting (35.7%) nausea (14.8%) and sore throat (13.1%) were the most common clinical signs in oral exposures. Endoscopy was performed in 38.3% ($n = 38$) of symptomatic and 10.6% ($n = 8$) of asymptomatic patients. In patients who had endoscopy, the most frequent finding was first degree damage (58.7%). A 48 year old man died from intentional hydrochloric acid ingestion. *Conclusion:* Children were more susceptible to caustics than adults in our retrospective study. While unintentional caustic exposures were common in children under 6 years old, intentional exposures were

common in young adults. Because of the large number of unintentional caustic exposures in children, parental education is very important to prevent caustic exposures.[3] *References:* 1. Sawalha AF. Poison Control and the Drug Information Center: the Palestinian experience. Isr Med Assoc J 2008; 10:757–60. 2. Villa A, Cochet A, Guyodo G. Poison episodes reported to French poison control centers in 2006. Rev Prat 2008; 58:825–31. 3. Ertekin C, Alimoglu O, Akyildiz H, et al. The results of caustic ingestions. Hepatogastroenterology 2004; 51:1397–400.

172. Epidemiologic Analysis of Intoxications in the Italian Region Emilia Romagna

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Objective: The Department of Pharmacy of the University Hospital of Ferrara (AOUFE) activated a project called "Monitoring and implementation of the Centre of Reference for antidote stocks". Its development follows the correct allocation of available antidotes in the Centre of Reference of the Region Emilia Romagna (RER). An epidemiological analysis to identify different types of intoxication and their respective treatments has been carried out as well. *Methods:* All the 17 Hospitals of the RER were asked to provide information about intoxications registered from 1/1/2005 to 31/12/2009 as well as their respective antidote therapies.[1] Required data were: year, type of intoxication and toxic substance, patient's features, type of antidote used and treatment period. *Results:* 16 hospitals took part in the analysis. 8154 intoxications were registered and they are grouped as follows: 1707 intoxications in 2005 (20.93% over the whole 5-year period); 1523 in 2006 (18.68%); 1593 in 2007 (19.54%); 1560 in 2008 (19.13%); 1771 in 2009 (21.72%). Categorization by toxic substance showed the following: 24% caused by drugs; 17% caused by ethanol; 4% by opioids; 3% by carbon monoxide; 3% by food; 1% by sodium hypochlorite and derivatives; 38% by non classifiable intoxications; 10% by various intoxications. In 13.90% of cases the following antidotes were used: 22.28% (254/1140) activated charcoal associated with gastric lavage; 15.79% (180/1140) activated charcoal; 8.42% (96/1140) activated charcoal associated with $MgSO_4$; 15% (171/1140) flumazenil; 14.30% (163/1140) hyperbaric oxygen; 13.86% (158/1140) naloxone; 5.70% (65/1140) metadoxine; 4.65% (53/1140) benzodiazepines. *Conclusion:* Drug and ethanol poisonings were the most frequent; non-specific treatments were the most frequently performed, followed by the use of specific antidotes such as flumazenil and naloxone. Epidemiological analysis shows that the frequency of intoxications in RER is 3.82 per 10000 inhabitants/year. *References:* 1. Repetto MR. Epidemiology of poisoning due to pharmaceutical products, Poison Control Center, Seville, Spain. Eur J Epidemiol 1997; 13:353–6.

173. Acute Poisoning in Children - Children's Hospital Zagreb, Period 1982–2009

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Objective: To present the results of observing hospitalized children in the Department of Clinical Toxicology and Pharmacology of Children's Hospital Zagreb in period between 1982–2009 (28 years) in order to understand the frequency and causes of acute poisoning in children in the Republic of Croatia, which are not well known. *Methods:* Tracking of total number of children hospitalized due to acute poisoning, percentage of intentional poisonings, breakdown by type of agent that led to poisoning, age and gender. *Results:* During the observed period 6001 patients were hospitalized due to acute poisoning, of which 92% were accidental. Most frequent were drug poisonings (51%), followed by poisonings with alcohol (26%), chemicals (13%), pesticides (5%), inhalation agents (3%), herbs and others (2%). The average age of accidentally poisoned patients was 5 years, excluding poisoning with alcohol where the average age was 15 years. Fifty-five per cent of all accidentally poisoned patients were boys. The average age in the group of intentional poisonings was 16 years, of which 82% were girls. *Conclusion:* Acute poisonings in children involve a complex set of different factors in health and social issues. It would seem useful to extrapolate particular measurable epidemiology features for the purpose of consideration of the problem and for planning preventative measures.

176. Perceived Benefits of Electronic Poisons Information for the Emergency Department

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Objective: Consideration has been given to widening international access to the New Zealand National Poisons Centre's poisons information database: TOXINZ. In an effort to assess clinical perception of this type of clinical decision support system, a survey was administered to identify whether Emergency Department staff in the Australasian region believe that access to an electronic poisons information resource would lead to clinical benefit. *Methods:* A preliminary survey tool was developed and presented to staff in one emergency department for comment and validation. Following revision, six emergency departments in both New Zealand and Australia each received ten of the resulting questionnaires - a total of 60 to each country. The survey was commenced on 14 April 2008 and closed on 30 June 2008. *Results:* The survey achieved an 81.67% (n = 49) and 61.67% (n = 37) response rate in New Zealand and Australia respectively. Seventy percent of New Zealand and 86% of Australian responders were doctors, with the remaining replies from nursing staff. Responders overwhelmingly supported the view that there was a range of benefits in the clinical application of electronic poisons information resources. Results are outlined in Table 1. *Conclusion:* Australasia Emergency Department staff consider that access to a good electronic poisons information resource will lead to a range of clinical benefits. This supports the wider distribution of access to this type of clinical decision support tool.

177. Nine Years of TOXBASE® in Ireland: The Impact of an Online Poisons Database

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Objective: In 2001, TOXBASE®, the UK online poisons information database was made available in Ireland, initially mainly to Emergency Departments (EDs). TOXBASE® usage in Ireland and its impact on telephone enquires to the National Poisons Information Centre (NPIC) were reviewed. *Methods:* Session (logons) data was extracted from the TOXBASE® server. Information on the most frequently accessed products by Irish TOXBASE® users was also extracted. NPIC use of TOXBASE® was excluded from the data. The total number of telephone enquiries for each year was recorded by NPIC. *Results:* By the end of December 2001 there were 22 registered users (16 EDs) in Ireland. This more than tripled to 79 users (38 EDs) by the end of 2009. The number of TOXBASE® sessions (logons) increased nearly 7 fold from 1865 in 2001 to 13,052 in 2009. In the same period the total number of telephone enquiries to NPIC dropped by 39.4%, from 16,241 in 2001 to 9838 in 2009 (Table 1). The most frequently (top 10) accessed products on TOXBASE® changed over the 9 years; however paracetamol remained the most frequently accessed. *Conclusion:* Provision of an online poisons information database in Ireland has reduced the NPIC call load, but increased the overall access rate in EDs to poisons information sources.

Table 1. Do you believe a good electronic poisons information resource would?

	Totally Agree	Agree	Undecided	Disagree	Totally Disagree	No Answer
Save you time						
New Zealand	94%	2%	2%	2%	0%	0%
Australia	70%	19%	8%	0%	3%	0%
Enable better triage						
New Zealand	67%	10%	12%	4%	6%	0%
Australia	49%	22%	19%	8%	3%	0%
Improve patient management						
New Zealand	80%	14%	6%	0%	0%	0%
Australia	62%	22%	14%	3%	0%	0%
Support your clinical decision making						
New Zealand	82%	0%	16%	2%	0%	0%
Australia	62%	22%	16%	0%	0%	0%
Better integrate hospital management						
New Zealand	61%	14%	16%	4%	4%	0%
Australia	24%	43%	24%	5%	0%	3%
Allow more efficient patient management						
New Zealand	78%	22%	0%	0%	0%	0%
Australia	41%	38%	22%	0%	0%	0%
Allow your department to provide a better service						
New Zealand	82%	12%	4%	2%	0%	0%
Australia	49%	22%	22%	8%	0%	0%

Table 1. TOXBASE® usage and telephone enquiries to NPIC in Ireland 2001-2009

		2001	2002	2003	2004	2005	2006	2007	2008*	2009
TOXBASE	Emergency Department users	1822	4141	6826	7260	8149	9029	10,312	14,108	12,955
	Other users	43	40	61	109	75	46	83	118	97
	Total	1865	4181	6887	7369	8224	9075	10,395	14266	13,052
NPIC	Telephone enquiries	16,241	14,620	14,661	13,360	12,655	11,905	11,011	10,494	9838

*TOXBASE® data is for financial year 2008–9.

178. Introduction of Web-based Nursing Guides for Toxicology

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Objective: Nurses involved in triaging patients are the first point of contact in Emergency Departments. To encourage best practice and empower staff dealing with poisoned patients a clear and concise nursing management guide to aid nurses was designed to be available through TOXBASE®. We report overall access for the individual agents from hospitals in the UK and access patterns for these guides 1st April 2009–31st March 2010. *Methods:* The specialist toxicology nurses within the clinical toxicology unit, Royal Infirmary of Edinburgh (RIE) produced nursing management plans for the top 25 poison presentations to the RIE over 3 years. The guides were derived from TOXBASE® monographs and included information on: type of product/specific drug; key clinical features; initial assessment; care of asymptomatic and symptomatic patients. Access to guides is directly from the specific TOXBASE® product entry, and a dedicated web-link for nursing. *Results:* The first guides (G) went live in January 2009 as part of a continuous roll-out programme. The total number of TOXBASE® hits (H) for agents with guides was 254,133 with 7,635 guides downloaded during 2009/10. The top five were: benzodiazepines (H = 28,958 G = 846), NSAIDs (H = 30,042 G = 774), zopiclone (H = 15,336 G = 560), antipsychotics (H = 23273 G = 527) and tricyclic antidepressants (H = 13,661 G = 525), all five guides were available for the 12 months examined. In contrast selective serotonin re-uptake inhibitors (available January 2009) was accessed far fewer times (H = 40,425 G = 168). The most common agents had an access rate of 3.1% but drugs of abuse had much higher accesses (amfetamine H = 3063 G = 413; cocaine H = 4612 G = 245; GBH/GBL H = 1539 G = 295) with an overall rate of 13.75%. *Discussion:* Nurse guides are a way to improve the initial management of poisoned patients. These data suggest these guides are accessed and therefore used by the target group. These data also suggest familiarity with an agent may influence staff accessing the guides. Further audit of their effect on care is required. *Conclusion:* 33 nurse guides are now available via TOXBASE®. They are regularly accessed and have the potential to improve patient care. Further work is required to quantify their effect on patient outcome.

179. Legal Highs: Analysis of the Use of National Poisons Information Service Resources and Newspaper Coverage

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Objective: To analyse usage of UK National Poisons Information Service (NPIS) data for new 'legal highs' that appeared in the UK in 2009, and to analyse the relationship between newspaper coverage of these drugs and enquiries to the NPIS. *Background:* The NPIS provides information to UK health professionals via its clinical toxicology database, TOXBASE®, and over the telephone, often in more severe cases of suspected poisoning. We have analysed TOXBASE® usage and numbers of calls to the NPIS for four 'legal highs' (mephedrone, naphyrone, Ivory Wave, Benzo Fury), and compared these data to newspaper coverage of the drugs. *Methods:* For each drug, the number of TOXBASE® accesses and calls to the NPIS were retrospectively calculated per week from 05/01/2009-30/09/2010. Lexis Nexis[1], an online news resource tool, was used to find all articles from UK newspapers mentioning the drug names. *Results:* Totals for each drug are shown in Table 1. The majority of calls, accesses and articles regarding Ivory Wave occurred in August and September 2010; the peak in calls preceded the peak in articles by two weeks. *Conclusion:* The NPIS provides valuable information upon the appearance of new drugs of abuse. Use of NPIS resources peaked before or concomitantly with peak newspaper coverage of the drugs, suggesting that newspaper coverage did not significantly positively influence legal high use. Newspaper coverage is generally after usage increase as reflected in enquiries. News outlets may not be the optimum way of tracking trends in drug use. *References:* 1. http://www.lexisnexis.com/uk/nexis/ accessed 19/10/2010.

Table 1. Total calls to NPIS, TOXBASE® accesses and UK newspaper articles regarding legal highs from 05/01/2009-30/09/2010

	Mephedrone (% of total)	Naphyrone (% of total)	Ivory Wave (% of total)	Benzo Fury (% of total)	Total
Calls to NPIS	377 (74.2%)	55 (10.8%)	40 (7.9%)	36 (7.1%)	508
TOXBASE® Accesses	5842 (84.7%)	779 (11.3%)	163 (2.4%)	112 (1.6%)	6896
UK Newspaper Articles	1606 (90.5%)	86 (4.8%)	75 (4.2%)	8 (0.5%)	1775

180. Severity of Iron Poisoning Reported in Telephone Enquiries to the National Poisons Information Service in the UK

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Objective: A retrospective analysis of telephone enquiries to the National Poisons Information Service (NPIS) in the UK was performed to investigate the severity of iron poisoning enquiries. *Methods:* All telephone enquiries received by the NPIS are entered into the United Kingdom Poisons Information Database (UKPID). UKPID call data relating to all types of iron exposures between 01/09/2007 and 01/09/2010 were analysed. *Results:* 1651 enquiries involved iron; 1181 iron only exposures were analysed further. Six hundred and ninety-two (59%) related to persons aged ≤15 years (80% of which were aged ≤5 years), 468 (40%) related to ≥16 years (57% of which were aged 16 to 25 years). In enquiries relating to those ≤15 years the ratio of male to female patients was even, whereas 80% of all enquiries that related to persons aged ≥16 years involved females. Iron ingestions, (97% of enquiries), were examined for: type, circumstances and poisoning severity scores[1] (Table 1). Serious toxicity, coma (6), haematemesis (7), hepatic dysfunction (14), melaena (21) somnolence (23) and acidosis (49), was relatively uncommon. Severity was greater in adults (Table 1). *Conclusion:* The majority of iron poisoning enquiries in this study were accidental ingestions in children and resulted in low toxicity. *References:* 1. Persson HE, Sjöberg GK, Haines JA, et al. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol 1998; 36:205–13. *Acknowledgement:* The authors express their gratitude to the NPIS for providing the data analysed herein.

Table 1. Exposure type, circumstances and poisoning severity scores for telephone enquiries involving iron ingestions Sept 2007–Sept 2010

	≤15 years (683)	≥16 years (448)
Exposure type		
Acute	626	341
Acute on therapeutic	31	55
Chronic	3	11
Staggered	10	12
Sub acute	12	18
Unknown	1	11
Circumstances		
Accidental	538	24
Intentional	86 (83 >11 yrs)	329 (233 16–25 yrs)
Therapeutic error	51	78
Other/Unknown	8	17
Poisoning Severity Score		
None	538	239
Minor	97	149
Moderate	11	21
Severe	7	4
unknown	30	35

181. Contribution of a Poison Centre in the Detection and Identification of a Delayed Food Borne Dysgeusia after the Consumption of Pine Nuts Contaminated by Non-Edible Pine Species

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*Introduction:*The detection of food borne outbreaks suffers from high latencies between the outbreak identification, identification of the contaminant and the formulation of an adequate response. In the case of "pine mouth syndrome", this contamination went largely unnoticed for years. *Objective:* To emphasise the role of poison control centres in the detection and identification of a food chain contamination. *Methods:* Epidemiologic data were collected through the poison centres' information system. Suspected pine nut samples were analyzed by GLC, which allows the determination of the botanical origin, based on the fatty acid profile.[1] *Results:* Following a first episode of 7 isolated cases of pine mouth syndrome between August 1998 and June 1999, we published an abstract describing delayed taste disturbances caused by Chinese pine nuts.[2] No external contamination was identified and there was no analytical

method to identify the pinus species involved. The cause of the syndrome remained unknown. The problem virtually disappeared only to reappear in 2009, triggering an urgent message to the EAPCCT-forum in September 2009. At the provisional peak of the second outbreak in the fall of 2010, we registered 40 to 50 cases per month. Concurrently, over 3400 cumulative cases have been reported in France.[3] During the second outbreak, 16 suspected samples were collected and analysed. *Pinus armandii* nuts were identified in all the samples pure or in mixture with *Pinus koraiensis* nuts. To further unravel the pine nut mystery, the Belgian poison centre is currently collaborating with the "Sensory Science and Eating Behaviour" department at Wageningen University in the Netherlands. *Conclusion:* Poison control centres may play an important role in the alert to and the identification of food borne threats. *References:* 1. Destaillats F, Cruz-Hernandez C, Giuffrida F, et al. Identification of the botanical origin of pine nuts found in food products by gas-liquid chromatography analysis of fatty acid profile. J Agric Food Chem 2010; 58:2082–7. 2. Mostin M. Taste disturbances after pine nut ingestion. Eur J Emerg Med 2001; 8:76. 3. Autosaisine du Comité de Coordination de Toxicovigilance (CCTV). Pignons de pin et dysgueusie retardée. Rapport final [Online]. 2010 October [cited 2010 Nov 10]. Available from: http://www.centres-antipoison.net/CCTV/Rapport_CCTV_Pignons_de_pin_2010.pdf

182. A Targeted Effort to Improve the Documentation Quality of Inquiries to the Danish Poison Information Centre. A Quality Assurance Project

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Objective: The Danish Poison Information Centre (DPIC) registers all inquiries in structured records in order to 1. undertake a correct and consistent individual risk assessment, 2. document the sequence of events, and 3. detect and validate adverse events related to toxic exposures (toxicovigilance). In 2008 the DPIC's quality assurance board conducted an audit, evaluating the documentation quality of the telephone inquiries. This audit revealed significant shortcomings.[1] Most significant were the high frequencies of records in which the exposed persons were unidentified (19%) and the exposure (time, amount and/or type of poison) was not clearly described (47%). Furthermore, in 23% the sequence of events was unclear and in 32% no local guidelines for the handling of the exposure existed. The purpose of the present project was to evaluate whether a targeted effort could improve the documentation quality. *Methods:* Based on the audit results, the documentation of the received inquiries was made an area of targeted effort in 2009 and the following interventions were carried out: 1. Senior staff members reviewed all records daily and addressed shortcomings at morning conferences and in training sessions. 2. The stock of treatment guidelines was increased according to the most frequent inquiries. A new audit procedure was planned for autumn 2010. Four monitors evaluated a total of 200 DPIC records, 100 drug and 100 non-drug exposures, randomly chosen from the DPIC database. The quality of these records was assessed according to 16 previously described quality markers.[1] *Results:* The number of records in which the exposed persons were not clearly identified decreased from 19% to 10%. The number of records in which the exposure was not clearly described decreased from 47% to 25%. The number of records in which the sequence of events was ambiguous decreased from 23% to 4%. Finally, the number of records where no local guidelines existed decreased from 32% to 18%. *Conclusion:* A targeted effort can improve documentation quality. An optimized and uniform documentation is an important precondition for consistent risk assessment and the possibility to use PIC data for toxicovigillance. *References:* 1. Jürgens G, Dalhoff KM, Hansen NB, et al. The Use of Record Markers to Evaluate the Quality of Documentation of Inquiries to the Danish Poison Information centre. An Audit Procedure. Clin Toxicol 2010; 48:272.

183. The Effect of Legislation on Synthetic Cannabinoid Abuse in Ireland

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Objective: To investigate telephone enquiries regarding synthetic cannabinoids to the National Poisons Information Centre (NPIC) Dublin and relate this to Irish legislation banning head shop drugs. *Background:* The Irish Criminal Justice Bill on Psychoactive Substances introduced on 11th May 2010 included a ban on synthetic cannabinoids. Prior to this synthetic cannabinoids such as "Spice", "King B" and "Magic Gold" were sold in Irish head shops as "legal highs". *Methods:* A retrospective study was undertaken to investigate telephone enquiries to the National Poisons Information Centre regarding synthetic cannabinoids from Jan 2008 to July 2010. Telephone enquiries were documented by the Poisons Information Officers. Data recorded included demographics, number of enquiries, agent consumed, enquiry source, and symptoms experienced. Symptoms were graded on the Poisoning Severity Score. A timeline comparing poison enquiries with Irish legislation banning synthetic cannabinoids was analysed. *Results:* Over the study period, the NPIC received 31 telephone calls about synthetic cannabinoids concerning 33 patients (21 male, 12 female). The majority of enquiries (67%) involved young adults under the age of 20 with only one enquiry regarding a patient over 40. 76% of enquiries were from hospitals, 18% from general practitioners and only 3% from members of the public. The number of enquiries increased 12 fold from 2008 to 2010 with a peak in March and May 2010. Irish Legislation banning synthetic cannabinoids was introduced on the 11th May 2010. There was only one enquiry to the NPIC regarding synthetic cannabinoids after this date. The most common symptoms consisted of sympathomimetic effects such as palpitations (26.5%), tachycardia (20.6%), agitation (7.6%), mydriasis (14.7%) and tremor (8.8%). Other symptoms included dyspnoea (11.8%), gastrointestinal upset (11.8%), chest pain (8.8%), syncope (5.9%) and cold extremities (2.9%). The majority of symptoms were graded as moderate (54%) with only one patient graded as severe. No patient died as a result of taking synthetic cannabinoids. *Conclusion:* Irish legislation was effective in reducing the number of calls to the NPIC regarding synthetic cannabinoid abuse. This coincided with a 3 fold reduction in the number of operating head shops in Ireland.

184. Identification of Mushrooms after Exposures Reported to the Norwegian Poisons Information Centre

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Objective: Exposures to mushrooms are common emergency enquiries to the Norwegian Poisons Information Centre (NPIC). The identification of the mushroom is essential in the assessment of the severity of the poisoning and determining suitable treatment. To assist the staff on call the NPIC has employed the service of a company, which has expert knowledge in identifying mushrooms by telephone. They aid the NPIC in the identification of mushrooms involved in possible poisonings 24 hours a day all year round. This study aims to assess the exposures to mushrooms reported to the NPIC in 2010 and describe the system of identification of mushrooms with the aid of biologists. *Methods:* We reviewed the exposures to mushrooms reported to the NPIC from June through October 2010. Patient and exposure characteristics were recorded at the time of the call with completion of a follow-up questionnaire by telephone on the identification procedure, symptoms, severity and outcome. *Results:* The NPIC received 811 calls from health care professionals and the public after acute exposures to mushrooms during the period. One hundred and fourteen calls were included in the follow-up study of which 90 (79%) were referred to mushroom experts for identification. The biologists were able to establish the exact mushroom species in 73 (81%) of the cases and rule out the 5 most poisonous mushrooms in the Norwegian flora (*Cortinarius rubellus*, *Cortinarius orellanus*, *Amanita virosa*, *Amanita phalloides* and *Galerina marginata*) in 16 (18%) of the cases. Photos (mobile phone MMS or e-mail) were used to aid in the identification in 69% of the cases. In the 89 cases where identification was certain or the 5 most poisonous mushrooms ruled out, 97% of the cases could be observed at home. *Conclusion:* Mushroom experts are a valuable resource in the identification of mushrooms by telephone. With their aid NPIC is able to give the caller correct advice and prevent unnecessary medical treatment.

185. Concurrency Between Advice Given by the Danish Poison Information Centre and Information in Hospital Discharge Letters

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Objective: To evaluate the risk assessment performed by the Danish Poison Information Centre (DPIC). All inquiries about poisonings in children (<15 years old) were reviewed and compared with information from hospital discharge letters. *Methods:* All incoming hospital discharge letters from 1.1.2009 to 27.9.2010 were collected and the following information was registered: duration of hospitalization, transfer to Intensive Care Unit, final outcome (no consequences, no initial consequences (e.g. follow-up visits in outpatients), consequences). These data were compared with the following DPIC data: age, gender, toxic agent, and risk assessment (RA-I no risk, RA-II transient risk without any need for treatment, RA-III need of treatment, RA-IV life threatening, RA-V unqualified). *Results:* 276 discharge letters were received from hospital admissions (M/F 138/138). The majority of children were 2–3 years old (29%). The toxic exposures were divided into 3 groups: drugs (group A; $n=167$), chemicals (group B; $n=103$) and substances of abuse (group C; $n=5$). In group A 27/167, in group B 2/103 and in group C 1/5 were transferred to the ICU. According to information in the discharge letters, 79% of the poisonings did not result in any further complications. In 20% of the poisonings, the children needed a second clinical check-up or a follow-up laboratory test after discharge. In only 2 cases did the poisoned patients developed complications (one patient was transferred for plastic surgery after exposure to a corrosive drain cleaner, and one patient was transferred for continuous gastroscopic controls after exposure to an industrial detergent). In 237 cases, DPIC categorized the poisonings as RA-III (189), RA-IV (25) or RA-V (23). In 13% of RA-III and in 16% of RA-IV assessments, the patients were transferred to the ICU (0 in both RA-I and RA-II). There was a significant relationship between the duration of hospitalization (median days) and the risk categorisation performed by the DPIC (RA-I 0.01, RA-II 0.11, RA-III 0.59 and RA-IV 0.92 days). *Conclusion:* There was a close association between the severity of the DPIC RA score and referral to ICU. Furthermore, there was a significant relationship between the RA and the resulting severity of the poisoning according to the duration of hospitalization.

186. Unintentional Overdose with Vitamin D

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Objective: This study evaluates the calls due to overdose of vitamin D (cholecalciferol) in children. The prophylactic dose of vitamin D to avoid rickets is 500 IU p.o. daily during the first year of life. This dose is equivalent to 1 drop of Vigantol. Vitamin D intoxication may cause hypercalcemia. *Methods:* A retrospective analysis of the calls due to overdose of vitamin D was performed, using the electronic records database from January 1 to December 31, 2009. The outcome was evaluated based on the telephone inquiries and discharge reports of hospitalized patients. *Results:* 105 calls (50.5% of all inquiries due to vitamins in 2009) concerned vitamin D. Only children aged 0–3 years were involved, of whom 66.6% children were younger than 1 year. There were 46 boys (43.8%) and 59 girls (56.2%). The most common incorrect dose in 51 children was 5000 IU (about 10 drops) of vitamin D, administered to the mouth directly from the dropper. Nine children older than 1 year ingested approximately 100,000 IU of vitamin D from the bottle. Only 5 children received vitamin D repeatedly in a dose of 5000 IU for 10 days, due to a misunderstanding of the prescription. Serum calcium level was measured in 27 children; in 5 patients it was increased to 2.70–2.95 mmol/L 15–24 hours later (2x 40,000 IU, 3x 100,000 IU). Twenty-two children were hospitalized for 2 days. *Conclusion:* A high percentage of parents did not follow the instructions on the package to give one drop in a meal or on the spoon. About 33.4% of the ingestions were caused by incorrect storage. Nevertheless, overdose up to 100,000 IU did not cause any symptoms, and only in 5 of 105 cases was a mild increase of serum calcium level found. Physicians should carefully educate parents about the correct method of providing the prophylactic treatment and the parents should be more cautious about the storage of drugs. *Acknowledgements:* MSM0021620807.

187. Lead Exposure in the Danish Population as Seen from an Open Poison Centre

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Objective: Exposure to lead has declined significantly over decades.[1] Simultaneously the lowest level of health effects from lead has decreased.[2,3] In the present case series we described lead exposure in a post-industrial society. *Case series:* All contacts to the Danish Poison Information Centre where lead was stated as the toxic agent were identified in the centre's database and the records evaluated. The time frame was from the poison centre opening to the public on August 1st, 2006 to October 31st, 2010. Information on lead source, exposure circumstance, demographic characteristics and, if available, blood-lead level was extracted. Thirty-one cases exposed to lead were identified. Ten were five years or younger and all had eaten lead objects. Six were 5–14 years old and except for one with mixed exposure, all had oral exposures. Among those 15 years or older, four had been exposed by inhalation, two orally, one by a gun shot, five by more than one route and four by unknown route. Exposure at work was the setting for 5 cases, two with inhalation, one with mixed and two with undetermined exposure. Blood lead measurements (BLLs) were available for six cases and ranged between 0.17 and 2.73 micromol/L. Three 14-years old boys had peak BLLs at 1.99, 2.68 and 2.73 micromol/L after having eaten a lead based glass colour and two of these had chelation treatment. *Conclusion:* Although rare, lead exposure occurs in modern society. In some instances with toxicologically significant blood lead levels as a consequence. Thus know-how on the subject should not be neglected. *References:* 1. Nielsen JB, Grandjean P, Jørgensen PJ. Predictors of blood lead concentrations in the lead-free gasoline era. Scand J Work Environ Health 1998; 24:153–6. 2. Menke A, Muntner P, Batuman V, et al. Blood lead below 0.48 micromol/L (10 microg/dL) and mortality among US adults. Circulation 2006; 114:1388–94. 3. Gilbert SG, Weiss B. A rationale for lowering the blood lead action level from 10 to 2 microgr/dL. Neurotoxicology 2006; 27:693–701.

188. The Role of the Slovenian Poison Control Centre in the Prevention of Chemical Poisoning in Children

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Objective: Prevention of poisoning, especially in children, is one of the most important tasks of our National Poison Control Centre (PCC). In the late childhood period (age 11–18 years) drugs of abuse and suicide attempts predominate. In contrast, poisonings of children in the early period (age 0–10 years), are unintentional and as such accessible for poisoning preventative measures. *Methods:* We analysed the calls register of our 24-hour information and consultation service for the period 2001–2003. In children, age 0 to 10 years, poisonings with chemicals represent 48.9% (n = 832). Among dangerous chemicals, pesticides (20.8%), organic solvents (14.6%), corrosives (10.8%) and gases (3.8%) predominate. Among non-toxic chemicals, soaps/detergents (23.5%) and others (26.5%) predominate. In 2004 the preventative action plan for children was established in collaboration with Institute for Public Health of the Republic of Slovenia, Ministry of Health and Ministry of Education. The action plan includes an education program for target groups (parents, carers and teachers) as well as collaboration on the legalisation level. The action plan was adopted well; its effectiveness was evaluated by comparison with another analysis for the period 2007–2009. *Results:* Poisonings with chemicals in this period represented 47.5% (n = 863). Poisoning with pesticides was reduced by 47.1%, with organic solvents 39.7%, with corrosives 43.5% and with gases 35.7%. We registered an increase of exposures in children to non-toxic chemicals: by 24.7% for soaps/detergents and 58.5% for others. *Conclusion:* Co-ordinated efforts and collaboration between the National PCC and the above mentioned institutions resulted in effective preventative programs which are reflected in the considerable decline in poisonings in children with dangerous chemicals. However, the percentage of exposures to chemicals remained at the same level due to increased exposure to non-toxic chemicals. In the future we have to pay more attention to reducing the children's exposure to non-toxic chemicals, which should be in accordance with good practice of general chemical management. Our special aim for the near future is also to achieve a restriction of concentrated corrosives used as household products.

189. The Effect of Active Poison Information Education on the Call Volume and Structure

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Objective: To describe the effects of active poisons information education on the awareness of the population of 1.34 million inhabitants to the poisons information centre without an expensive media campaign and to discuss the influence of awareness on the structure of calls. *Method:* All calls answered in the Estonian Poisons Information Centre (EPIC), published articles and lectures about poisonings and their prevention were analysed via a time-line from the 1st of October, 2008 to the 30th of September 2010. The goal of the published articles and lectures was to prevent poisonings and create poison centre awareness. The goal of primary intervention was to prevent poisonings and secondary education was defined as reducing morbidity and mortality by creating poison center awareness. All calls concerning general information about health and diseases, poisonings and other questions were classified as general questions (GQ). Only calls concerning acute exposure to poisons were defined as poisoning questions (PQ). Since EPIC's telephone lines opened for the general public in October, 2008 the monthly number of calls was compared. *Results:* During the analysed period in total 768 calls were answered. The structure of the calls was as follows: 2008 90 calls: 37(41.1%) GQ, 53(58.9%) PQ; 2009 331 calls: 127(38.4%) GQ, 204(61.6%) PQ; 2010 347 calls: 86(24.8%) GQ, 261(75.2%) PQ. In 2008 3 lectures were held and 2 articles were published; in 2009 9 lectures and 8 articles; in 2010 6 lectures and 6 articles. As a result, the median monthly call volume increased from 30 in 2008 to 38.6 in 2010 (22.2%), the number of PQs increased from 17.7 in 2008 to 29 in 2010 (39%). *Conclusion:* Active and systematic poisons information education increases the awareness of the population to the poison information centre without an expensive media campaign and has a positive impact on the volume of poisoning calls handled by the centre. The educational programmes did not have an immediate effect on the call volume and structure but had a positive effect from a longer perspective. As earlier published articles described, combining primary and secondary poison prevention in one initiative may have a small but positive impact on poison centre call volume.

190. How to Use the Internet and the Media to the Benefit of Public Health? The Norwegian Poison Information Centre's Experiences Shared

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Objective: Until 2003 the means the Norwegian Poison Information Centre (NPIC) used actively to reach the public were brochures, posters and a website with limited information. In 2003 we changed direction in order to reach the public in different ways, and not only at their initiative. Our goals are to reach as many as possible who are in need of our service, educate the public, and to prevent poisonings, wrong treatments and unnecessary anxiety. *Methods:* The poison information website is updated regularly. It presents correct and easily comprehensible information on poisons and first aid information for the public and the media. Some topics are emphasized according to seasonal changes, whereas others are highlighted when incidents of public interest occur. Over the last few years efforts have been made to increase the visibility of our website on different search engines. The poison information centre also administers a website especially targeting health-care personnel, "The Library of poisonings", with treatment guidelines for acute intoxications. This was opened in 2007. Every year we draw up a media plan with 2–3 topics that we want published. The chosen topics are selected related to trends in society or issues we know to occur time and again. Press releases are issued regularly. Through public relations campaigns in the media NPIC issue warnings and advice related to the given subject. When the media report on toxicological topics we also respond to this. *Results:* Over the last two years we have had an explosive increase (nearly 200%) of unique viewers on our website. "The Library for poisonings" shows a similar pattern. We also observed that the media refer to us more often than before. *Conclusion:* This proactive work has increased knowledge about NPIC and our services. At minimal cost we also reach those who do not deliberately seek information. This will prevent poisonings and reduce both the risk of incorrect treatment and unnecessary anxiety. If a situation arises, those involved will then know where and how to reach us. We have become the acknowledged source of updated and reliable information on toxicology for the public, healthcare personnel and the press/media.

191. Sufficient Product Information Without Exhausting the Poisons Information Centre's Resources?

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Objective: To describe the current system regarding product information in the Norwegian Poisons Information Centre (PIC), including the Product Information Bank (PIB). *Results:* A PIC needs immediate access to product information on any product they are asked about. However, maintaining an updated database of all products is too time-consuming for most PICs. The Norwegian PIC used to have a database of about 4000 datasheets, but not the resources to keep it properly updated. Also, this system forced us to spend time registering products we rarely have enquiries about. In 2009 most of our datasheets were transferred to PIB. Companies who want the PIC to have access to their material safety data sheets (MSDS) are asked to register them in PIB. PIB is a public website (www.pib.no) run by the Norwegian Product Register (governmental). An offline copy of PIB is made available in the PIC to ensure continuous accessibility. The PIC has been involved in the development of PIB from the beginning. PIB's vision is to be an official website for efficient exchange of information about chemical products in Norway. It is therefore vital that most products are included and that the information is up-to-date. As yet it is not mandatory and thus, far from all companies are willing to devote resources to registering their products in PIB. The number of MSDS in PIB per November 2010 is 5111. In addition to the MSDS, the PIC has online access to The Product Register's database with complete composition of about 25,000 products. However, time consuming security measures means that this database is only sporadically used in emergency situations. For most enquiries our general knowledge of products and chemicals and/or information from datasheets is sufficient. *Conclusion:* Despite a limited number of MSDS available in PIB it is useful to the PIC. The PIC can devote attention to the products that are most relevant to its work. Even though PIB is our current solution, we follow closely and with great anticipation the ongoing work regarding CLP article 45.

192. The Federal Institute for Risk Assessment Human Case Report Database For Poisonings - Standardization of Case Reports, Improvement and Examination for Subject-Specific Access

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Background: The Federal Institute for Risk Assessment (BfR) Documentation and Assessment Centre for Poisonings (BfR-DocCentre) is part of the German toxicological network. German Physicians and Poison Centres (PCs) report human data of poisonings to the BfR. Every case is assessed on the chemical product involved with the distinct formula provided by BfR product database, which contains notifications of the German industry. Data on human poisonings is condensed in a harmonized and standardized data file for analysis. In addition cases of special toxicological and scientific interest (e.g. rare poisonings, high-/low-dose exposures, cases with unexpected clinical course, substances of special interest etc) are prepared for standardized case reports. For better retrieval of human toxicological data a bilingual case report database has been implemented. *Methods:* The cases are documented in a standardized form (accident/situation of poisoning/age/gender/symptoms/signs/exposure data/clinical course/assessment/remarks), indicated by the substance/product involved and supplemented with important references. After co-checks for correctness, completeness and readability, the German text is translated into English and transferred to the database. In addition, selected case reports from literature were transferred as pdf-files to the same database. *Results:* Since July 2002 more than 500 cases have been selected, prepared and processed with additional data for case reports. The case reports were written down in uniform documents, provided with keywords and additional information, finally assigned to index words. Starting in 2004, the documents were recorded in a prototype database driven by MS-Access, from 2006 onwards the case record database was transferred to an Informix 9.2 database in web-browser technology. At present, the BfR-case database has been provided with additional staff. The BfR is in consultation with specialists in data protection to ask whether the BfR case record database can to be opened in the future for specialists. *Conclusion:* In the assessment of poisonings and for e-learning there is a great interest in case reports. The BfR intends in future to offer its case reports on poisoning via its Internet portal for subject-specific access.

193. From Bedside to Bench: Calcium Gluconate is an Effective Treatment in Hydrofluoric Acid Skin Burns and Reverses Fluoride Induced Vasoconstriction *In Vitro*

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Objective: We studied the efficacy and safety of intra-arterial infusion of calcium gluconate on hydrofluoric acid (HF) skin burns treatment as well as on fluoride effects in rabbit aortic ring contraction *in vitro* and in modulation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in vascular derived smooth muscle cells in culture. *Methods:* HF lesions could be hypothesized to be mediated by fluoride which was previously identified as a GTP binding proteins activator leading to inositol-phosphate accumulation and increase in $[Ca^{2+}]_i$. Calcium gluconate either topical or in intra-arterial infusion is considered the most effective clinical therapeutic approach. In this study, we examined a case series of patients with severe HF burns admitted to the Toxicology Unit of Careggi Florence Hospital, between 2005/2009 and treated with calcium gluconate both in local dermal application and in intra arterial infusion. Moreover, fluoride effects on rabbit aortic ring contraction *in vitro* and on modulation of $[Ca^{2+}]_i$ in vascular derived smooth muscle cells in culture were evaluated. *Results:* Five patients were admitted to the Toxicology Unit of Careggi Florence Hospital with a diagnosis of HF skin burns. They were treated with local dermal application and intra-arterial infusion of calcium gluconate. In all cases there was a complete *restitutio ad integrum*, with a maximum latency of two months and an average hospitalization time of six days. In *in vitro* experiments, sodium fluoride (10–30 mM) induced a contraction of rabbit aortic ring preparations ($167 \pm 25\%$, $n = 4$, $p < 0.05$ one tailed t test) when compared to a standard contraction stimulated by KCl 80 mM. Calcium gluconate (50–100 mM) was able to decrease sodium fluoride induced contractile response ($38 \pm 17\%$, $n = 4$, $p < 0.05$ one tailed t test). Similar results were obtained on sodium fluoride increase in $[Ca^{2+}]_i$ in vascular derived smooth muscle cells in culture. *Conclusion:* Intra-arterial infusion of calcium gluconate was confirmed as a safe and effective therapeutic approach for wound healing and pain relief in HF skin burns. Calcium gluconate was also shown to be effective in reversing fluoride induced *in vitro* vasoconstriction. Thus, vasoconstriction may be suggested as a possible mechanism of HF induced skin damage.

194. Benzydamine: Recreational Misuse of a Non Recreational Drug

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Objective: Benzydamine hydrochloride is an indolic non steroidal anti-inflammatory drug available as mouthwash, vaginal douche, aerosol and pills. Being an over the counter drug it can be easily obtained and its recreational use has been described amongst street youth in developing countries. We describe an acute recreational benzydamine intoxication following voluntary ingestion of a commercially available vaginal douche and its clinical management. *Case report:* A 35 year old woman affected by a nutritional disorder and previous chronic ethanol abuse, detained in jail, was admitted to the Toxicology Unit of Careggi Florence Hospital, for hallucinations and altered mental state following benzydamine ingestion. On arrival the patient reported the recreational use of 10 sachets of a commercially available vaginal douche (benzydamine 500 mg, per sachet) diluted in water. The patient was confused, agitated with mild tachycardia (96 bpm) and hypertension (135/95) with hallucinatory vision and muscle weakness. Toxicological screenings were negative for alcohol and common drugs of abuse. ECG showed QT interval prolongation. Treatment was symptomatic (diazepam i.v.) and supportive. The hallucinations lasted for almost six hours. ECG normalized after 24 hours. The patient remained in hospital for 6 days due to psychiatric comorbidity and was discharged in good health. *Conclusion:* Benzydamine has structural similarity to dimethyltryptamine and for this reason could cause severe acute central nervous system toxicity. Although the exact mechanism of benzydamine hallucination is still unknown, multiple pharmacological interactions could be hypothesized.

195. Successful Reversal of Life Threatening Cardiac Effect Following Dosulepin Overdose Using Intravenous Lipid Emulsion

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Objective: In addition to its use as a nutritional component in parenteral nutrition, intravenous lipid emulsions (ILE) have been suggested in the management of poisoned patients following a lipophilic drug overdose.[1] ILE therapy is not standard therapy in human cyclic antidepressant overdose cases and few case reports including intentional cyclic antidepressant drug overdoses have been described.[1] To our knowledge no previous case reports of the beneficial effect of ILE on human tricyclic antidepressant dosulepin (also named dothiepin) intoxication exist. This case reports a successful acute reversal of a potential life threatening condition following dosulepin overdose using ILE. *Case report:* A 36 year-old female intentionally ingested 5.25 g of dosulepin. On submission the QRS complex was 120 milliseconds and the QT interval was 348 milliseconds, HR 113 beats/min. Her level of consciousness was deteriorating and the patient had 2–3 episodes of seizures each lasting 10–30 seconds, which were treated with propofol, 20–50 mg. The patient received bicarbonate, 200 mmol, and assisted ventilation. Ninety minutes following submission the QRS complex was 158 milliseconds and the QT interval was 422 milliseconds, HR 91 beats/min. Supraventricular or ventricular arrhythmias were not observed. In order to treat the intoxication intravenous lipid emulsion 20% was dosed as 1.5 mL/kg (100 mL) in 5 min. followed by 400 mL in 20 min. Blood pressure was immediately stabilised and the monitored QRS complex narrowed and QT interval became shorter. *Conclusion:* Cyclic antidepressants affect the cardiac conduction system and the myocardium. The exact mechanism of action from ILE may not be determined from the data presented. ILE was in this case dosed due to the severe symptoms and the

acknowledged lipophilic nature of dosulepin; log P (octanol/buffer pH 7.4) 2.8. The obtained effect does not rule out the supposed effects of alkalinization and supported ventilation. However, the effects of the treatment of the severe dosulepin intoxication support the theory of ILE creating an intravenous lipid sink for lipophilic drugs. *References:* 1. Jamaty C, Bailey B, Larocque A, et al. Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies. Clin Toxicol (Phila) 2010; 48:1–27.

196. Bidirectional Tachycardia During Treatment of Metoprolol Overdose

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Objective: Bidirectional tachycardia is an unusual arrhythmia characterized by beat-to-beat alternation of the morphology and the axis of the QRS-complexes. It is most commonly linked to digitalis toxicity, certain channelopathies, cardiomyopathies, seldom in case of pheochromocytoma, myocarditis. We report the first case of bidirectional tachycardia associated with administration of atropine and dopamine in metoprolol overdose. *Case report:* A 33-year-old female presented to our department 8 hours after intake of 1500 mg metoprolol. On arrival her vital signs were: BP 93/57 mmHg, HR 67 bpm, GCS 15/15. Electrocardiogram displayed sinus rhythm with normal PR, QRS and QTc interval. After 8 hours she became drowsy, an electrocardiogram was notable for third degree atrioventricular block and her blood pressure dropped to 70/40 mmHg. She was given a bolus of 1 mg atropine and infusion of dopamine (8 micrograms/kg/minute). Ten minutes later the patient complained of retrosternal chest pain. The ECG revealed a bidirectional tachycardia at 160 bpm with QRS of 88/121 ms which lasted for 2 minutes with spontaneous return to a sinus tachycardia at 100 bpm. The subsequent ECG showed ST-segment elevation in lateral leads. Dopamine infusion was stopped and colloid infusion was administered. The patient's BP went to 86/62 mmHg. Cardiac troponin was moderately elevated. An echocardiography was carried out showing no regional wall motion abnormalities with an ejection fraction of 38% (by Simpson method). Cardiac MR performing next day revealed anterolateral hypokinesis and an ejection fraction of 48%. Chest pain lasted for 10 hours and ST-segment elevation for 3 days. A second echocardiography performing 5 days after ingestion showed an ejection fraction of 60% with no wall motion abnormalities. The patient refused coronarography. Stress test was normal. *Conclusion:* In our case dopamine (together with administration of atropine after ingestion of a large amount of metoprolol) seemed to cause: 1. bidirectional tachycardia (perhaps triggered by a burst in the sympathetic tone) 2. myocardial stunning (resulting perhaps from coronary artery spasm).

197. The Role of Urgent Esophagogastroduodenoscopy in Prognosis of Acute Caustic Poisonings

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Introduction: Ingestion of corrosive substances causes severe lesions to the upper gastrointestinal tract that are manifested with destructive changes of the mucosa and muscle layer and even perforation of the esophagus and the stomach in more severe cases. The gold standard for determination of the grade and extent of the lesion, which at the same time helps in deciding on the therapeutic approach, is urgent esophagogastroduodenoscopy. The aim of this paper was to present our clinical experience with the 4-grade endoscopic classification of post-corrosive injuries in prognosis of the outcome in acute caustic poisonings. *Methods:* This was a retrospective study comprising 33 patients with grade II B and III injury hospitalized at the University Clinic for Toxicology in Skopje, FYROM in the period 2008–2009. The grade of injury was determined with urgent esophagogastroduodenoscopy performed in the first 12–24 hours after admission and the post-corrosive injuries were classified according to the four-grade classification recommended by Kikendall. After treatment the patients were followed for a minimum of six months. *Results:* A total of 33 patients were analyzed. At the time of hospital admission post-corrosive injuries of grade III predominated ($n = 22$, 66.67%), whereas the remaining patients had post-corrosive injuries of grade II B ($n = 11$, 33.33%). After 6 months of clinical follow-up, the most common late post-corrosive complications of the esophagus were stenosis of the esophagus ($n = 19$, 57.58%) while normal finding of the esophagus was found in 14 (42.42%) patients [($p < 0.01$** $p < 0.001$***) (N.sig.)]. The most common post-corrosive damages of the stomach were: antro-pyloric stenosis ($n = 10$, 30.30%), pyloric stenosis ($n = 6$, 18.18%) and antral stenosis ($n = 3$, 9.09%), whereas in 14 (42.42%) patients a normal finding of the stomach was found [($p < 0.05$* $p < 0.01$** $p < 0.001$***) (Sig.)]. *Conclusion:* Urgent esophagogastroduodenoscopy has to be done in all acute caustic poisonings in the first 12–24 hours and they are to be classified according to Kikendall's four-grade classification. Patients with confirmed post-corrosive lesion of grade III show a high percentage of morbidity. The classification in four grades of post-corrosive injuries to the upper gastrointestinal tract might help in therapeutic approach and prognosis of the outcome.

198. Mortality Rate in Glycol and Methanol Intoxications in Poland in the Year 2009

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Background: Glycol and methanol poisoning is not common but can be a life threatening condition. In Poland most of patients intoxicated with those alcohols are admitted to the hospitals at a late stage, with profound acidosis and multiorgan failure. Because of this, the majority of them must be treated in Toxicological Units (TUs) and Intensive Care Units (ICUs). *Objective:* The aim of our study was to compare the mortality rate among patients treated because of glycol and methanol poisonings in 2009 in all TUs and ICUs in Poland. *Methods:* All medical interventions provided in TUs and ICUs, in which the main diagnosis was coded as T51.1, and T52.3 according to ICD-10, and all those codes recorded as co-morbidities and positively verified by two toxicologists were included in our study. The state of health as well as the age of both groups were similar. *Results:* There were 192 patients in Poland in 2009, including 23 methanol and 105 glycol patients hospitalized in TUs, and 20 methanol and 44 glycol patients treated in ICUs. Intoxications with those alcohols were the main cause of death among all acute poisonings in all TUs and ICUs in Poland in 2009. In the methanol group the mortality rates in TUs and ICUs were 39.1%, and 55.0% respectively, while in glycol group the mortality rates in TUs and ICUs were 20.9%, and 56.8% respectively. The overall mortality rate in both groups was 24.2% in TUs, and 56.2% in ICUs. The much higher mortality rate in ICUs needs further and exact investigation, however, to some extent, this problem may be connected to delayed diagnosis of intoxication; prolonged supportive treatment; too low dose of intermittent haemodialysis (iHD), and the usage of Continuous Renal Replacement Therapy (CRRT), which is the standard procedure carried out in ICUs, but for which the clearance is much lower than for iHD. *Conclusions:* There is a strong need for postgraduate toxicological education. Every Polish district should have its own Toxicological Unit. It is necessary to produce diagnostic and treatment protocols for intoxicated patients in Poland. *References:* 1. Bayliss G. Dialysis in the poisoned patient. Hemodial Int 2010; 14:158–67.

199. Impact of Direct Admissions to a Poisons Treatment Ward

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Objective: To evaluate the benefits of direct admission to a specialist treatment ward compared to transfer following initial triage in an Accident and Emergency department (A&E). *Background:* The poisons treatment ward, part of the Welsh National Poisons Unit, is an eight-bedded ward opened in 1983 dedicated to the care of poisoned patients; the only specialised treatment ward of its type in the UK. In April 2005 a policy was introduced to allow patients with uncomplicated paracetamol poisoning to be admitted directly to this ward; previously they would have required triage in A&E and then transfer across the city by ambulance, a distance of 6 miles. Later that year this policy was extended to allow all uncomplicated poisoning cases with a GCS of 14 or above to be admitted directly. *Results:* Following these changes, the number of direct admissions increased from 6.5% to 50% of total admissions. The policy was revised again in 2008 to allow all overdoses with a GCS above 8 to be directly admitted; currently direct admissions account for 75% of all patients admitted to the ward. *Conclusion:* The overwhelming benefit of direct admission is to the patient who has immediate access to specialist care; additional advantages include a reduction in waiting times, inevitable in a busy accident unit. This is particularly important in a group of patients that have self-harmed and tend to readily self-discharge. The ward ensures that all patients have access to early psychiatric assessment - also important as a significant proportion (30%) of patients is discharged within 24 hours. Currently 71% of all patients admitted to the ward are psychiatrically assessed prior to discharge. The calm environment of the ward is conducive to the specialist care required by poisoned patients with trained doctors, nurses and psychiatric staff ensuring a high standard of effective care. Other obvious and quantifiable benefits of direct admission to the poisons ward include reduced pressure on the busy A&E department and a decrease in inter-hospital ambulance transfers; the cost savings are appreciable with 1207 direct admissions in 2009 that would have otherwise utilised considerable human and financial NHS resources.

200. Effective Methotrexate Elimination using High-Flux Haemodialysis

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Background: Methotrexate is a chemotherapeutic agent used to treat cancer (breast, gastric, bladder, lymphoma and sarcoma) as well as psoriasis and rheumatoid arthritis. In overdose, toxic effects can be severe, symptoms can include vomiting, diarrhoea, mucositis, haemorrhagic enteritis, renal failure, hepatotoxicity and bone marrow suppression leading to leucopenia, thrombocytopenia and anaemia. Standard treatment is symptomatic and supportive together with folinic acid or glucarpidase therapy but response can be variable. Enhanced elimination of the drug by haemodialysis is generally considered to be ineffective. We report a case in which serum methotrexate concentrations were effectively and rapidly reduced using high-flux haemodialysis. *Case report:* A 23-year old female patient on treatment with high dose methotrexate for lymphoma was admitted with renal failure. Her serum methotrexate concentration was 81.9 μmol/L upon presentation. She was started on folinic acid therapy and also haemodialysis using an FX 100 high-flux dialyser. Following a

Table 1. Methotrexate (MTX) concentrations before and after dialysis

	MTX μmol/L	Dialysis	MTX μmol/L	Dialysis	MTX μmol/L
Day 1	81.9	6 hours	67.6	6 hours	11.2
Day 2	24.0	"	4.2	"	2.7
Day 3	3.75	"	0.98		
Day 4	1.26	"	0.45		
Day 5	0.48	"			
Day 6	0.2				

6-hour dialysis session, a break of 2 hours and a further 6-hour session, the methotrexate concentration fell to 11.2 μmol/L. The following day this had rebounded to 24 μmol/L, following a further 2 sessions of dialysis this was reduced to 2.7μmol/L. Six-hourly sessions of dialysis/day for the following 3 days reduced circulating methotrexate concentrations to 0.2 μmol/L (Table 1). Each morning there was evidence of a rebound in concentrations. *Conclusion:* Methotrexate toxicity can be severe and deaths have occurred. In this case high-flux dialysis rapidly decreased circulating concentrations. The use of this means of elimination should be considered in cases of life-threatening toxicity not responding to conventional treatment.

201. Coagulation Tests as Predictive Parameters of Acute Liver Toxicity in Phalloides Syndrome: Thrombin Time and Activated Partial Thromboplastin Time

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Objective: Phalloides syndrome is an urgent toxicological issue demanding early treatment. In countries where measurement of amanitin is not available, estimation and rechecking of the coagulation blood tests in the early phases of poisoning is imperative for making treatment decisions. Prothrombin time (PT) is accepted as an early and prognostic parameter but the activated partial thromboplastin time (aPTT) and thrombin time (TT) can also be considered as valuable markers of acute toxic hepatitis. *Methods:* The coagulation tests in 6 patients with incubation period of more than 10 hours and prominent gastroenterocolitis were analyzed. Admittance at the Clinic was after 17.6 $\pm$ 6.02 hours of having the mushroom meal with developed gastroenterocolitis and dehydration. The prothrombin time (PT), activated partial thromboplastin time (aPTT) and thrombin time (TT) were measured on admission. *Results:* During the stay the patients underwent symptomatic and active treatment with haemoperfusion and haemodialysis with ALT values maximally found to be 3520 $\pm$ 2009 U/l and AST 2383 $\pm$ 1589 U/L. TT and aPTT were prolonged before PT. aPTT showed significant correlation with outcome (death/survive) ($r = -0.97$, $p = 0.008$), while PT ($r = 0.50$, $p = 0.31$) and TT (r-0.50, $p = 0.31$) showed a weaker association with the outcome. The comparison of the correlation coefficient for the test/outcome association, showed strong and significant difference between aPTT and PT (Z st -3, 23, $p = 0.0012$). The differences between correlations of the test with the outcome, aPTT and TT ($Z = -1.89$, $p = 0.058$) and PT with TT ($Z = 1.34$, $p = 0.17$) were not significant. *Conclusion:* In case of inaccessibility to amanitin estimation in biological materials, coagulation tests may be useful parameters of early decision for aggressive and active treatment in phalloides syndromes and prognosis. TT and aPTT are early signs of acute liver toxicity while aPTT can be used as a more predictive sign of the clinical outcome.

202. Intralipid Treatment of Sedative Hypnotic Drug Overdose: A Case Series

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Objective: Intralipid Emulsion Therapy (ILE) has been advocated as a possible treatment for sedative hypnotic drug ingestion such as quetiapine in addition to ILE's accepted role in local anaesthetic toxicity and possible role in cardiotoxic poisoning. In 2009 our regional toxicology service introduced a clinical protocol to allow the use of intralipid in sedative hypnotic drug overdoses where endotracheal intubation was imminently required or considered likely. Intralipid 20% solution (Fresenius Medical Care Ltd.) was administered into a peripheral vein via a wide bore cannula in a dose of 500 mL over 20 minutes in suitable cases after discussion with the clinical toxicologist. Methods: A retrospective chart review was conducted to review the outcomes of this protocol in October 2010. Data collected included demographic details, drug(s) ingested, need for intubation, time for which ventilation was required and length of stay (LOS). *Results:* During the 12 month period from November 2009 till October 2010, ILE was used in nine cases. Of these 2 (22%) were male and median age was 32 years old (IQR 27–43). Intubation was required in 7 (78%) cases, 5 (71%) of whom received ILE prior to intubation. The median time to intubation was 19 minutes (IQR 13–80) from ILE administration. Median length of ventilation was 31 hours (IQR 28–49h). Median LOS for all 9 cases was 88 hours (IQR: 60–93h). Of the 2 cases that did not require intubation one required a nasopharyngeal airway for several hours and had no significant increase in GCS over this period. Quetiapine was the main ingestant in 6 cases (67%) with 2 cases (22%) due to baclofen and 1 due to carbamazepine (11%). Coingestants were mirtazapine, olanzapine, amisulpride and benzodiazepines. All drugs ingested were lipid soluble with the exception of baclofen. *Conclusion:* ILE did not appear to have a dramatic effect in this case series with intubation avoided in 2 cases one of whom still required other airway intervention and GCS remained low sometime after ILE administration. A larger study is required to further evaluate the effect of ILE in sedative drug overdose.

203. A Tale of Two Overdoses

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Introduction: Tricyclic antidepressants are known to cause haemodynamic instability and seizures primarily due to their sodium channel blocking effect. It has a rapid onset of action and needs to be treated early. We report a case which demonstrates the benefit of early gastrointestinal decontamination and supportive management. *Case report:* A 31 year old woman, who weighed 90 kg, presented to the Emergency Department, an hour after ingesting 5000 mg of amitriptyline. On arrival she walked in but soon dropped her GCS to 8, HR = 150, BP = 100/60 and QRS width = 160 ms. She was rapidly managed with intubation and gastrointestinal decontamination and tablets were aspirated via the nasogastric tube. She had an uneventful course in intensive care and was extubated after 34 hours. Two weeks later she took a further overdose of 5000 mg of amitriptyline, while on day leave from the psychiatric unit. She notified staff in the psychiatry unit within half an hour of ingestion, but due to the time delay for transfer to the intensive care unit, definitive management was delayed for three hours. On arrival to intensive care she had a GCS = 3, HR = 140, BP = 140/80 and QRS width = 100 ms. She was intubated and given activated charcoal. On this occasion no tablets were able to be aspirated from the nasogastric tube. Six hours post ingestion she had two episodes of pulseless ventricular tachycardia and seizures. She became haemodynamically unstable with widened QRS on ECG. She required in total 550 mmol of intravenous sodium bicarbonate, hypertonic saline and noradrenaline infusion to maintain haemodynamic stability. Her condition stabilised 12 hours post ingestion and she was extubated after 48 hours. *Conclusion:* These two episodes of amitriptyline overdose of the same dosage in the same patient illustrate the importance of early decontamination and supportive management. On her first presentation she was treated with early intubation and decontamination and had an uneventful course. In contrast there was a delay in decontamination and supportive treatment by 3 hours on her second visit which led to recurrent pulseless ventricular tachycardia, seizures and haemodynamic instability.

204. Massive Overdose of Meprobamate Treated with Continuous Venovenous Hemodiafiltration

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Objective: Meprobamate is an old sedative and anxiolytic drug. Overdose with this substance still occurs and may be potentially life-threatening due to cardiovascular collapse and severe CNS depression.[1] We present a case of severe intoxication in a suicide attempt with meprobamate in a 45 year-old woman treated with continuous venovenous hemodiafiltration. *Case report:* The clinical course was complicated by profound CNS depression, respiratory failure, and prolonged hemodynamic instability despite aggressive fluid resuscitation and administration of vasopressors. Orotracheal intubation was performed and multiple dose activated charcoal was administered. Because of the serious clinical condition, continuous venovenous hemodiafiltration (CVVHDF) was begun in order to enhance meprobamate elimination. Pharmacokinetics during CVVHDF could be described by first order kinetics. The elimination half-life ($t_{1/2}$) was 6.6 hours, total plasma clearance (CL_{tot}) was 87 mL/min and clearance by CVVHDF (CL_{HDF}) was 64 mL/min (74% of CL_{tot}). After 36 hours of CVVHDF, extracorporeal assistance was stopped and the patient made an uneventful recovery. *Conclusion:* CL_{HDF} was clearly limited by the dialysate flow rate and it could be concluded that meprobamate was readily dialyzable and filterable, in accordance with the physico-chemical properties of meprobamate. *References:* 1. Charron C, Mekontso-Dessap A, Chergui K, et al. Incidence, causes and prognosis of hypotension related to meprobamate poisoning. Intensive Care Med 2005; 31:1582–6.

205. Predictors of Mortality in Verapamil Overdose: Usefulness of Serum Verapamil Concentrations

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Objective: Verapamil poisoning may result in life-threatening cardiovascular morbidities and fatalities. To date, prognosticators of mortality have been poorly investigated and the use of serum verapamil concentration for prognosis remains unclear. We aimed to evaluate the ability of usual clinical and laboratory parameters including serum verapamil concentrations measured on admission to predict outcome (survival versus death) in verapamil poisoning. *Methods:* We reviewed the medical records of all intentional and

Table 1. Comparison of parameters on ICU admission according to the patient's final outcome

Parameters on ICU admission	Survivors (N = 61)	Fatalities (N = 4)	*p*
Verapamil ingested dose (mg)	2,400 [1,680–4,920]	7,200 [6,000–10,800]	**0.02**
Systolic blood pressure (mmHg)	93 [77–110]	23 [0–48]	**0.001**
Heart rate (/min)	72 [57–86]	38 [35–52]	**0.006**
Serum glucose (mmol/L)	8.0 [5.7–12.0]	15.7 [12.6–23.6]	**0.01**
Serum lactate (mmol/L)	2.3 [1.8–5.7]	13.4 [7.8–14.6]	**0.01**
Serum creatinine (μmol/L)	98 [79–135]	139 [128–237]	**0.04**
Alanine aminotransferase (IU/l)	18 [13–30]	438 [83–1,547]	**0.02**
QRS enlargement (s)	0.08 [0.07–0.10]	0.130 [0.112–0.178]	**0.02**
QTC (s)	0.40 [0.36–0.44]	0.50 [0.47–0.56]	**0.007**
SAPS2	27 [18–49]	88 [63–93]	**0.004**
Serum verapamil (μmol/L)	1.65 [1.22–3.30]	6.88 [5.55–8.93]	**0.002**
Serum norverapamil (μmol/L)	1.42 [1.13–1.78]	2.11 [1.73–2.49]	**0.08**

symptomatic verapamil poisonings admitted over eight years to two medical intensive care units (ICU). Clinical and laboratory parameters were measured in 65 patients and final outcomes of survival or death recorded. A multivariate analysis was conducted to evaluate the prognostic values of recorded parameters. *Results:* Life-threatening complications of verapamil poisoning included shock (62%), atrioventricular block (24%), sinoatrial block (20%), acute respiratory distress syndrome (19%), and cardiac arrest (11%) resulting in death (8%). Verapamil concentrations measured on ICU admission were the only independent factors associated with mortality ($p = 0.01$). Comparison of serum verapamil (A), norverapamil (B), and verapamil + norverapamil (C) concentrations measured on admission according to the patient's final outcome in the intensive care unit are shown in Table 1. The optimal verapamil cutoff point was 5.0 μmol/L (100% sensitivity, 91% specificity), which conferred a 2.8-fold increase in odds of fatality. *Conclusion:* Cardiovascular monitoring and assessment of organ failure are vital in symptomatic verapamil poisoning. The serum verapamil concentration has excellent prognostic ability for predicting fatality in verapamil overdose.

206. Clinical Aspects of Genomics in Poisoning Situations

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Objective: Pharmacogenetics aims to explain the genetic variability in drug response and adverse drug effects. Despite large variability between individuals, in many fields of drug therapy standard dosages are used. Treatment is rather oriented towards diseases instead of individual patients. However, the one-dose-fits all principle has come into question in many fields of drug therapy since we know, for many therapeutic areas, that large variability in drug exposure between subjects is leading to sometimes fatal overdosing and serious adverse effects. *Discussion:* Drug poisoning depends on many factors, among which variability in drug exposure may be one of the most important. Pharmacogenetic variants in drug metabolizing enzymes lead to differences in pharmacokinetic parameters. In the common case when an active drug is inactivated by a polymorphic enzyme, genetic differences in drug clearance may lead to higher drug exposure and poisoning due to slow metabolism. Less commonly, such as when activation of a prodrug depends on a polymorphic drug metabolizing enzyme, serious adverse events have been experienced in individuals with a high drug metabolizing activity. Differences in drug clearance often correlate with surrogates for insufficient drug therapy such as differences in drug tolerance, time to dose finding, and the number of drug switches or therapeutic attempts. Typically, the role of a genetic polymorphism is not apparent unless additional factors are present. There are only a few studies on the impact of genotype-context interactions on therapeutic outcome. Some examples illustrate the importance of the context, such as the CYP2D6 ultrarapid metabolizer genotype in codeine treatment which led to fatal overdosing with morphine only in conditions where additional factors were present such as a lack of drug glucuronidation capacity in a newborn child. The importance of additional factors in clinical practice may be studied more in detail in the future by exploiting the huge potential of electronic patient records to depict clinical reality. *Conclusion:* The clinical application of pharmacogenetics for prevention of toxic drug effects may be expanded in the future by improved knowledge of the functional effects of genetic polymorphisms in patients as well as a broad capture of data on the patient's context.

207. Genomic, Transcriptomic and Metabolomic Tools as Biomarkers of Paracetamol Hepatotoxicity

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Introduction: The history of research on paracetamol toxicity is an excellent example of the evolution of investigation aims and tools in clinical toxicology in the last few decades. The ability of paracetamol as a potent hepatotoxic producing hepatic cytolysis and, eventually, acute hepatic failure was described in adults and children and led to extensive research on the implied toxic mechanism and the antidotes to be used. In 1975 a treatment nomogram was the result of the study of a large number of cases and established different hepatotoxicity risks for different populations. The basic mechanism of cell lesion was described as follows: at toxic doses paracetamol undergoes an oxidative metabolic pathway, mediated by a member of the Cyt P450 family, producing a reactive metabolite, NAPQI able to be conjugated with glutathione. Following glutathione depletion, NAPQI links covalently to macromolecules, impairing its function and producing cell death. This was a neat and elegant explanation which allowed, on the one hand, the definition of risk populations, such as patients having a history of contact with substances (mainly alcohol), causing probable P450 induction, or with nutritional deficiencies, and, on the other hand, the development of antidotes such as glutathione precursors. *Discussion:* Nevertheless, many gaps remained to be filled at the molecular level. Many of them have been dealt with in the last decade by means of basic Omic's tools. We will review some of them: 1.- Genetic and genomic inter individual differences in metabolic pathways: The existence of glutahione transferase and Cyt P450 2E1 polymorphisms and its influence in paracetamol metabolism have been described in the 90s.[1,2] Nevertheless much more attention has been focused on the enzymatic induction of the oxidative metabolic pathway. The CYP450 isozyme, currently identified as CYP2E1, was purified and characterized early in the 80s. The enzyme expression in the cell is regulated by transcriptional activation, mRNA stabilization, and increased translatability and protein stabilization.[3] One of the main CYP2E1 inducers is ethanol. Some studies have suggested that ethanol protects CYP2E1 from cytosolic degradation through the ubiquitin-proteasome proteolytic pathway,[4] others mention a two-step mechanism related to BAC (Blood Alcohol Concentration): a first step associated with low BACs appears to be post-transcriptional by stabilization and a second step is associated with high BACs and attributed to increased CYP2E1 gene transcription.[5] Recent studies suggest that CYP3A ethanol induction can also play a role in raising acute paracetamol toxicity.[6] It seems that not only CYP2E1 but also CYP1A2 and CYP3A11 play an important role in NAPQI generation from paracetamol. A transgenic mouse line expressing the human CYP2E1 gene has been developed to study the role of CYP2E1 in acetaminophen hepatotoxicity. This model will be also useful as an *in vivo* tool for predicting drug metabolism and disposition and drug-drug interactions of chemicals that are substrates for human CYP2E1.[7] Up to now P450 induction needs to be inferred from the patient's antecedents from previous exposures. Real time polymerase chain reaction, enzyme-linked immunosorbent assay, and CYP2E1-dependent enzyme activity could be performed in peripheral blood allowing to define, in an objective way, the risk populations. Therefore CYP2E1 over expression could be considered as a biomarker of susceptibility. 2.- Intracellular targets and pathogenic pathways: In the last decade some of the paracetamol intracellular targets and lesional mechanisms have been studied in detail. Besides the role of NAPQI, glutathione depletion by itself gives way to free oxygen reactive species increasing oxidative stress which causes mitochondrial permeability transition and loss of the ability of the mitochondria to synthesize ATP and cellular necrosis.[8] In search of sensitive and specific biomarkers for drug-induced liver injury, it has been suggested that a transcriptomic "signature" produced by paracetamol can be found in peripheral blood related to immune and inflammatory pathways.[9] In experimental animals it increases the intrahepatic expression of interleukin (IL)-1 alpha, IL-1 beta, and IL-1 receptor antagonist (IL-1ra), Compared with wild-type (WT) mouse-derived hepatocytes, IL-1ra-deficient (IL-1ra KO)-derived hepatocytes exhibit more resistance against paracetamol with depressed intrahepatic expression of CYP1A2, CYP2E1, and CYP3A11, impairing paracetamol metabolism.[10] *Conclusions:* Transcriptome and metabolomic methods have shown characteristic down regulation of genes involved in oxidative phosphorylation and mitochondrial function in peripheral blood, positively correlated with the production of NAPQI, and a concurrent increase in serum lactate after non-toxic and toxic doses of paracetamol. Those changes could be considered as biomarkers of effect. Both types of biomarker, of effect and susceptibility, can supply very useful information to be taken into account together with the classical exposure biomarker, i.e. paracetamol blood concentration. *References:* 1. Ueshima Y, Tsutsumi M, Takase S, et al. Acetaminophen metabolism in patients with different cytochrome P-4502E1 genotypes. Alcohol Clin Exp Res 1996; 20:25A-28A. 2. Josephy PD. Genetic variations in human glutathione transferase enzymes: significance for pharmacology and toxicology. Human Genomics and Proteomics. Volume 2010, Article ID 876940, 14. doi:10.4061/2010/876940. 3. Koop DR, Tierney DJ. Multiple mechanisms in the regulation of ethanol-inducible cytochrome P450IIE1. Bioessays 1990; 12:429–35. 4. Roberts BJ, Song B., Soh Y, et al. Ethanol induces CYP2E1 by protein stabilization. J Biol Chem 1995; 270:29632–5. 5. Hu Y, Ingelman-Sundberg M, Lindros KO. 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208. The Use of Genotyping in a Specific Oncology Patient Population to Avoid Drug Toxicity

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Discussion: Pharmacogenetics covers the genetic variations that affect pharmacokinetics and -dynamics, in genes and proteins involved in drug absorption, metabolism, excretion, cellular transport, targets and target pathways, and their influence on drug-response phenotypes. In childhood acute lymphoblastic leukemia (ALL) pharmacogenetics has in the recent years become a major field of research. The genetic variation includes insertions, deletions, and variations in gene copy numbers, and not least an estimated 15 million single nucleotide polymorphisms with a minor allele frequency of at least 1%. This genetic variation is of particular importance for drugs with a very narrow therapeutic index such as anticancer agents. Many public databases (e.g. hosted by National Center for Biotechnology Information (NCBI), the International HapMap project, and The Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) offer information on single nucleotide polymorphisms (SNPs), including their unique dbSNP ID number, their location in a specific gene, whether they are haplotype-tagged, and for example whether they are synonymous (confer no amino acid change) or non-synonymous (changes the amino acid). The therapeutic outcome for any disease is determined by the interaction between the host, the disease, and the therapy. Previously the focus was primarily on the effect of a specific treatment on the disease, and treatment failures (not least within oncology) were in general regarded to represent resistant disease. However, numerous studies have strongly indicated that for sensitive diseases, such as childhood leukemia, host variations in drug disposition determined by inherited genetic variants may, as frequently as truly resistant disease, lead to treatment failures. Unfortunately, few studies have actually explored this in depth, and many potential obstacles burden the journey. In oncology, most patients are treated to the limit of acceptable toxicity due to the relatively steep dose-response relationship for most anticancer agents, and a significant fraction of the patients are treated beyond this limit and experience serious late effects (e.g. reduced auditory or kidney function) or even deaths due to toxicities, mostly life-threatening infections. In children above the age of 1.0 year cancer is the most common medical cause of death in the industrialised countries, and ALL is the most common cancer in childhood. Over the last decades the outcome for children with ALL has changed dramatically from being an almost universally fatal disease to 80% cure rates by first-line therapy. However, to obtain these cure rates most of the patients receive up to ten different drugs that target DNA synthesis (i.e. the antimetabolites, typically methotrexate, 6-mercaptopurine, cytarabine) or induce DNA-damage (e.g. antracyclines, cyclophosphamide, epipodophyllotoxins), and post-transcription drugs that target amino acids (i.e. asparaginase) or specific proteins (e.g. Vinca alkaloids) or induced lymphoid apoptosis or involution (the glucocorticosteroids). In addition, as first or second line therapy for selected subsets of patients, the pediatric oncologist has in the armamentarium a wide range of specific antibodies (e.g. CD20 antibodies), hemapoietically targetted drugs (e.g. Myelotarg), small molecules (e.g. tyrosine kinase inhibitors), and nucleoside analogues (e.g. nelarabine, clofarabine). Is it at all possible in the crowded field of players to dissect out which drugs are crucial and which genetic variants are critical? Can any single variant be expected to carry any independent significance, or are only wide profiles of interest? And if predictive and prognostic variants can be identified, how can this knowledge become integrated into daily clinical practice in treatment response and pharmacokinetics/dynamics. To promote this implementation into the clinic at least ten different issues must be addressed, and within oncology this has so far not been the case for any genetic variant: i) The diversity in response should be predictable by host genomics. This is the primary focus of most genotype-phenotype association studies but is insufficient for personalised medicine. ii) The risk of unacceptable toxicity must be regarded to outweigh the chances of cure, or the risk of relapse must be regarded to outweigh the risk of toxicity, thus leaving clinical room for dose adjustments. iii) Individualized treatment adjustments by host genomics should have predictable effects in individual patients. This has at least been demonstrated with therapeutic drug monitoring, but not with genotyping. iv) Individualised dose adjustments must be superior to adjustments by toxicity (this has not been shown, but at least indicated in a few studies). v) Reducing toxicity or increasing efficacy by host genomic based dose adjustments must not be upset by "reverse" events (i.e. less efficacy or more toxicity) (this certainly remains to be explored). vi) To convince clinicians to use genetic markers in their treatment strategies, such host genomic based treatment guidelines must be defendable statistically (including confirmation in independent data sets) and be biologically understood. This is rarely the case with new associations found through genome-wide association studies. vii) Useful alternative therapeutic approaches must be available. This is often not the case. We may be able to identify individuals at risk for a specific toxicity, but how to treat these outliers is often less obvious. viii) The overall burden of therapy should not be increased, i.e. both upward and downward dose adjustment should be possible within a given patient cohort. This is of course a soft criterion, and this requirement will differ from disease to disease depending on the cure rates and rates of toxicities. ix) The overall risk of a specific toxicity in the total population (e.g. renal failure) should be significantly reduced if this is the target. Many studies report hazard ratios for a specific toxicity associated with a genotype, but even if this hazard ratio is high (e.g. 4.0) the impact of changing therapy for such patients will have a limited overall impact on the toxicity risk among the total population, if this high-risk genotype is rare. Thus, clinicians may feel that the complexity of genotyping and subsequent dose adjustment is too troublesome, unless the toxicity in question is clearly unacceptable. x) Finally, any approach needs to be tested in randomised trials. *Conclusion:* In conclusion, personalised medicine will certainly change the way we treat our patients, but for most diseases and treatments we have a long way to go before this is widely integrated into daily practice.

209. Opioid Receptor Polymorphism Associated with Drug Overdose Severity: Pilot Results

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Objective: Genetic variations in the mu-opioid receptor mediate individual differences in the human response.[1] A common mu-opioid receptor single nucleotide polymorphism (SNP) A118G has been associated with enhanced drug abuse behavior; however its association with overdose severity in humans is unknown. We evaluated the relationship between the A118G SNP and overdose severity in patients presenting to the emergency department (ED) with acute drug overdose. *Methods:* In an observational cohort study at an urban teaching hospital, we evaluated consecutive adult ED patients presenting with suspected acute drug overdose over a 5 month period for whom discarded blood samples were available for analysis. Demographics, clinical variables, urine toxicology screens, and adverse outcomes were collected by an abstractor prior to SNP analysis. In-hospital severe outcomes were defined as any of the following: respiratory arrest (mechanical ventilation); cardiac arrest (loss of pulse); and mortality. Blinded high-resolution melt genotyping of the A118G SNP was performed after standard DNA purification (Qiagen QIAamp DNA Blood mini kit) and whole genome amplification (Qiagen REPLI-g). Patients were classified as either wildtype (A/A), heterozygous (A/G), or homozygous mutant (G/G) using LightCycler 480 v1.5 software (Roche). *Results:* We have to date evaluated 54 patients (43% female, mean age 41, 12 A/A, 40 A/G, 2 G/G). Urine toxicology was positive in 39%, of which there were positives for 8 opiates (8 A/G), 5 methadone (5 A/G), 10 cocaine (3 A/A, 7 A/G), 12 benzodiazepines (3 A/A, 9 A/G), 5 barbiturates (5 A/G). During hospitalization there were 5 respiratory arrests (5 A/G), 3 cardiac arrests (3 A/G), and 2 died (2 A/G). *Conclusion:* These pilot data show very high prevalence of the A118G mu opioid receptor SNP in ED patients with acute drug overdose, with no severe outcomes in wildtypes. Future studies will test larger populations and other mutations for overdose vulnerability. *References:* 1. Shabalina SA, Zaykin DV, Gris P, et al. Expansion of the human mu-opioid receptor gene architecture: novel functional variants. Hum Mol Genet 2009; 18:1037–51.

210. Relevance of Transport Systems in Clinical Toxicology

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Discussion: Pharmacokinetics has been defined over the past several decades as the study of drug absorption, distribution, metabolism and excretion (ADME) when the drug is introduced into a biological system such as the human body. This definition can also be extended to toxicokinetics in overdosed or intoxicated patients. Pharmacokinetics are now challenged by the growing importance of transporters, a relatively new and potentially major factor in xenobiotic ADME. The drug transporters in the membranes of cells and organelles of mammalian tissues are members of two superfamilies. Those of the ABC (ATP-binding cassette) superfamily are responsible for primary active transport, while the members of the SLC (solute carrier) superfamily are involved in secondary active transport. The ABC transporters are encoded by 48 genes in humans, only about 9 of which influence drug kinetics. P-glycoprotein (P-gp; ABCB1), several isoforms of the multidrug resistance associated proteins (MRPs; ABCCs) and the breast cancer resistance protein (BCRP; ABCG2) efflux their substrates from cells to the extracellular space. In contrast, 362 genes are presently known to encode SLC transporters, and the number is still growing. Several SLC families, classified by their substrate specificity, like the transporters of organic anions (OAT), organic anion polypeptide (OATP), and organic cations (OCT), mediate the influx or efflux of substrates with complex modes of transport requiring voltage or/and ion gradient co-transport. About 30 of these proteins are involved in drug kinetics. The recent intrusion of drug transporters means that there is no single mechanism by which drugs permeate through the membranes. All these transporters have polyspecific transport properties. A wide range of drugs and metabolites, from conventional organic anions, cations and zwitterions to oligopeptides, can be simultaneously transported by one or more transporters. These transporters are also ubiquitous within the cells of all mammalian organs, including the intestine, liver and kidney, where they play key roles in the absorption and elimination of drugs. Their presence at all physiological blood-barriers make them critical components for regulating the tissue distributions of drugs. The presence at membranes of transporters modulates the traditional theory of "diffusional pharmacokinetics" towards "vectorial pharmacokinetics" in which ADME processes are more deterministically governed. For example, the hepatic uptake and biliary excretion of numerous xenobiotics

can be mediated by specific transporters expressed either in the basolateral membrane of the hepatocytes or in the bile canalicular membranes, respectively. In a similar way, renal reabsorption and secretion are highly dependent on the expression of multiple transport systems in both the basolateral and apical side of the proximal tubular cells. Drug transporters are also clinically important. They can modulate the pharmacological activity of drugs by affecting their intracellular concentrations and causing toxicity in specific organs due to intracellular drug accumulation. Hepatotoxicity, nephrotoxicity, neurotoxicity can be induced by the active transport of toxins inside the cells and transport systems can be considered as a biological target for developing antidotal strategies. Like the drug metabolizing enzymes the expression of transport systems can be induced or inhibited by the toxin itself or the co-ingested toxins. The recent discovery of the pathways regulating their transcription and of multiple mutations affecting their transport function introduces significant new factors influencing the way responsiveness to drugs varies from one person to another. Lastly the toxin interaction with transport systems can have specific impacts in clinical toxicology. Depending on the ingested dose of toxins, the transport can be saturated if the dose overpasses its transport capacity or when polyintoxications occur. *Conclusion:* Transport systems have to be considered as a key player of the toxicokinetic-toxicodynamic relationship and a possible actor for helping clinicians in the therapeutic management of the patient. *References:* Scherrmann JM. Transporters in absorption, distribution and elimination. Chem Biodivers 2009; 6:1933–42.

211. Decreasing Absorption and Increasing Elimination of Ingested Modified-Release Preparations: An Evidence Based Approach

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Objectives: To review the evidence base for modified-release (MR) preparations delaying the onset of, and prolonging, clinically significant symptoms following overdose; to define the role of activated charcoal (AC) and whole bowel irrigation (WBI) in decreasing the absorption of MR drugs; to describe the role of AC in increasing the elimination of MR preparations. *Modified-release preparations:* These include delayed- and extended-release systems for oral administration and oral delivery systems designed specifically to modify the release of poorly water-soluble drugs. In contrast to immediate release drugs, MR formulations release active drug into the body gradually and usually predictably over a 12- to 24-hr period to maintain plasma concentrations within a therapeutic range, in order to minimize adverse effects. With most MR preparations there is a prolonged absorption phase, so that the onset of symptoms is delayed (as late as 16–20 hr[1]), which leads to a delayed time to maximum plasma concentration (Tmax).[1] The release of drug from the formulation may be further prolonged due to the formation of a concretion of tablets (pharmacobezoar) in the stomach or intestine. *Impact of single doses of AC:* There is evidence from volunteer studies that AC 25 g administered 1 hr post dosing can reduce significantly ($p < 0.001$) the absorption of MR preparations of carbamazepine (200 mg), theophylline (200 mg) and verapamil (120 mg).[2] AC 1 g/kg (with sorbitol) administered 1 hr after theophylline MR 10 mg/kg to five children resulted in a 61% reduction ($p < 0.01$) of the AUC 0–12.[3] *Impact of multiple doses of AC:* In other limbs of this study[3], AC 1g/kg administered either at 3 hr, 6 hr, 9 hr, 12 hr ($n = 5$) or at 6 hr, 9 hr, 12 hr ($n = 5$) reduced the AUC 0–12 by 38% ($p < 0.02$) and by 18% (NS) respectively. AC 20g administered at 6 hr, 7 hr, 8 hr, 10 hr and 12 hr after theophylline MR 1200 mg/70 kg body weight to 9 volunteers decreased serum theophylline concentrations significantly.[4] In another study, the administration of AC at 1 hr (50 g), 5 hr (25 g) and 9 hr (25 g) after theophylline MR 600 mg in 12 volunteers reduced theophylline absorption by 91.2%.[5] The AUC of theophylline in the control group was 152.8 ± (SD) 1.44 mg/L/hr and in the AC group was 13.4 ± 2.3 mg/L/hr. In the same study[5] AC was given at 6 hr (50 g), with further doses at 10 hr (25 g) and 14 hr (25 g). The AUC of theophylline in the AC group was 65.3 ± 1.33 mg/L/h, a reduction of 57.3%. No statistical calculations were undertaken. It is not known whether the impact of AC in the second part of the study was on increasing elimination alone, which it is known to do,[6] or partly on decreasing absorption. *Impact of WBI:* WBI commenced 1 hr after the administration of lithium MR 0.8 mEq/kg to 10 volunteers reduced the AUC by 67% ($p < 0.0005$) and significantly decreased the mean serum lithium concentration ($p < 0.03$).[7] Aspirin 2,925 mg was administered to 10 volunteers.[8] WBI, commenced 4 hr after dosing, reduced significantly ($p < 0.01$) the AUC and peak salicylate concentrations; it was also superior to AC and sorbitol ($p < 0.05$). WBI started after the administration of AC to volunteers dosed with MR preparations of carbamazepine, theophylline and verapamil did not decrease absorption more than AC alone and in the case of carbamazepine decreased its efficacy.[2] Clinical studies: No controlled clinical studies have been performed, though case reports and case series have been published, at least in regard to WBI,[9] which are problematic to interpret. *Conclusion:* Ingestion of MR preparations may result in a delay in the onset of symptoms and presentation. Pharmacobezoar formation, may further delay release of drug. In volunteer studies, administration of a single dose of AC up to 1 hr after drug dosing has been shown to reduce absorption. Multiple doses of AC, even when commenced at 6 hr post dosing, have reduced plasma drug concentrations significantly in some studies but not others. It is not known whether this is the result of increased drug elimination or reduced absorption. WBI has been shown in volunteers to reduce the absorption of MR preparations significantly. *References:* 1. Buckley NA, Dawson AH, Reith DA. Controlled release drugs in overdose. Clinical considerations. Drug Saf 1995; 12:73–84. 2. Lapatto-Reiniluoto O, Kivistö KT, Neuvonen PJ. Activated charcoal alone and followed by whole-bowel irrigation in preventing the absorption of sustained-release drugs. Clin Pharmacol Ther 2001; 70:255–60. 3. Lim DT, Singh P, Nourtsis S, et al. Absorption inhibition and enhancement of elimination of sustained-release theophylline tablets by oral activated charcoal. Ann Emerg Med 1986; 15:1303–7. 4. Goldberg MJ, Spector R, Park GD, et al. The effect of sorbitol and activated charcoal on serum theophylline concentrations after slow-release theophylline. Clin Pharmacol Ther 1987; 41:108–11. 5. Minton NA, Henry JA. Prevention of drug absorption in simulated theophylline overdose. J Toxicol Clin Toxicol 1995; 33:43–49. 6. Vale JA, Krenzelok EP, Barceloux DG. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. American Academy of Clinical Toxicology, European Association of Poisons Centres and Clinical Toxicologists. J Toxicol Clin Toxicol 1999; 37:731–51. 7. Smith SW, Ling LJ, Halstenson CE. Whole-bowel irrigation as a treatment for acute lithium overdose. Ann Emerg Med 1991; 20:536–9. 8. Kirshenbaum LA, Mathews SC, Sitar DS, et al. Whole-bowel irrigation versus activated charcoal in sorbitol for the ingestion of modified-release pharmaceuticals. Clin Pharmacol Ther 1989; 46:264–71. 9. Tenenbein M, Seger DL, Meulenbelt J. American Academy of Clinical Toxicology and European Association of Poisons Centers and Clinical Toxicologist position paper: gastrointestinal decontamination. J Toxicol Clin Toxicol 2004; 42:237.

212. A Survey on Forensic Cases Related to Dextropropoxyphene and Tramadol in the Context of the Withdrawal of Medicines Containing Dextropropoxyphene from the French Market

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Objective: Following a European Medicines Agency review concerning the risk of fatal overdoses in the wake of withdrawal of marketing authorisations in the UK and Sweden in 2005, the European Commission decided in June 2010 to withdraw dextropropoxyphene-containing drugs (DXP) within 15 months. In France, DXP has been extensively used from 1964 without any pharmacovigilance signal and rare fatal overdoses. In June 2009, the Agence française de securité sanitaire des produits de santé (Afssaps) put in place risk minimisation measures and specific follow-up on adverse reactions, overdoses and deaths related to DXP and tramadol. *Methods:* Afssaps monitored the evolution of the sales of DXP and tramadol in 2009. Data related to tramadol or DXP cases in 2009 were obtained from 22 forensic toxicological laboratories (about 80% of the total) and the two periods, before and after June 2009, compared. Post-mortem peripheral DXP and tramadol blood concentrations were considered as toxic if >1 µg/mL and lethal if >2 µg/mL. *Results:* Sales of DXP decreased by about 40% from June 2009 and were replaced with paracetamol, tramadol or codeine. A comparison of the 2 periods showed the following results before vs. after 1 July 2009: the total number of forensic cases analysed was 2948 vs 2939. DXP was detected in 66 cases vs. 45 with 6 vs. 10 cases >1µg/mL and 5 vs. 8 cases >2 µg/mL. Tramadol was detected in 63 vs. 60 cases with 17 vs. 13 cases >1 µg/mL and 16 vs. 21 cases >2 µg/mL. A chi-square test indicated that the observed decrease in the proportion of toxic deaths with DXP was not significant but close to the threshold ($p = 0.06$). *Conclusion:* There was no change in the proportion of toxic deaths with tramadol ($p = 0.87$) between the 2 periods. The decrease of the sales of DXP does not seem correlated with a change in the number of deaths related to DXP and tramadol. Following a survey (http://www.centres-antipoison.net/CCTV/index.html) on the toxicity of tramadol compared to DXP, Afssaps concluded that a sudden withdrawal of DXP was contra-indicated and that a progressive action would allow switching patients to safer alternatives. The survey of the deaths linked to DXP and/or tramadol should be continued even after the withdrawal of DXP.

213. Epidemiology of Poisoning in Pregnancy as Reported to the UK Teratology Information Service over a 5 Year Period

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Objective: The clinical consequences of poisoning in pregnancy are uncertain for many substances. Ongoing collection of pregnancy outcome data is important to monitor the risks associated with maternal poisoning and associated treatments. The UK Teratology Information Service (UKTIS) provides information on all aspects of the toxicity of drugs and chemicals during pregnancy and collects data on pregnancy outcomes for surveillance purposes. This study was performed to describe available pregnancy outcomes after episodes of maternal poisoning reported to UKTIS. *Methods:* Computer records for the 5 year period up to 1st September 2010 were reviewed to analyse the numbers and types of poisoning in pregnancy as reported to the UKTIS. The pregnancy outcome data collected prospectively during this period was also examined. *Results:* During this 5 year period UKTIS has provided fetal risk assessment for 25,153 pregnancies. Of these, 1328 (5.3%) involved overdose, other types of poisoning or drug abuse. The most frequent types of substances involved were pharmaceuticals (62.9%), household products (12.1%) and drugs of abuse (10.3%). Information on pregnancy outcome was requested for 905 pregnancies, but only provided by the healthcare provider in 224 cases (25%). The

reported outcomes included 171 live-born infants, 37 elective terminations, 13 spontaneous abortions and 3 intrauterine deaths. There were 4 infants with congenital malformations reported (3 major, 1 minor malformation). The incidence of congenital malformations amongst the live-born infants was within the expected range for the unexposed population (4/171, 2.3%: 95% CI 0.75–6.26). *Conclusion:* Poisoning during pregnancy makes up a small but important proportion of calls taken by UKTIS. The low rate of successful follow up limits the ability of teratology information services to advise on the risks of adverse pregnancy outcomes. The limited data collected over the last 5 years, however, do not indicate substantially increased fetal risks. Improved methods of follow up are needed if adequate information is to be made available to support management and provide advice to the women affected.

214. Paediatric Overdose with Cough and Cold Medicines: The Irish Experience

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Objective: To describe cases of poisoning with cough and cold medications in children reported to the National Poisons Information Centre (NPIC) over a 4 year period. *Methods:* The records of telephone enquiries to the NPIC from 2005–2008 inclusive were retrospectively reviewed to identify enquiries about paediatric (0–14 years old) cases of poisoning with cough and cold medicines. The agents included in the review were brompheniramine, dextromethorphan, guaiphenesin, doxylamine, pseudoephedrine, oxymetazoline, phenylephrine, pholcodine, triprolidine, xylometazoline, diphenhydramine, or methoxyphenamine. Data collected included month of exposure, source of enquiry, circumstances, patient gender and age group, poisoning severity score, treatment advice and agents ingested. *Results:* The NPIC received 475 enquiries about suspected paediatric poisoning concerning these drugs between 2005 and 2008. Two hundred and two enquiries were from general practice/primary care, 137 from members of the public, 131 from hospitals and 5 from others. Enquiries peaked in March (64 enquiries) and troughed in June (28 enquiries). Most of these children (86.7%) were less than 5 years old and 253 (53.3%) were male. The majority of cases (96.8%) were the result of accidental overdose or therapeutic errors although 10 patients (all aged 13–14 and females), had taken an intentional overdose. Many preparations contained multiple ingredients. Products containing pseudoephedrine (302 cases) and/or triprolidine (127 cases) were most frequently ingested. One hundred and thirty-three (28.0%) children did not require treatment, 134 (28.2%) were referred to the emergency department, 19 (4.0%) were referred to their General Practitioner, 73 (15.4%) callers were advised to seek medical attention if the child became symptomatic, supportive management was advised for 90 (18.9%) patients and other treatment for 26 (5.5%). Overall, 90 (18.9%) children were symptomatic when the NPIC was called, but only 7 of these had moderate features and none was severely poisoned. *Conclusion:* Only 18.9% of children who had taken excessive doses of these medications were symptomatic and most of these had minor features only. Severe poisoning from cough and cold medicines was not seen in this study.

215. Acute Poisonings Treated at the Outpatient Accident and Emergency Clinic in Oslo, 2008

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Objective: Treatment of acute poisonings at an outpatient around-the-clock accident and emergency clinic (EMA) is common in Oslo. In 2003, the number of patients treated at the EMA equalled that of the five hospitals in Oslo seen as whole. There is a tendency for poisonings by drugs of abuse to be treated at the EMA, while pharmaceutical poisonings are treated in hospitals. Our objectives were to study the poisoning pattern with regards to the intention behind the poisoning, treatment and follow-up. *Methods:* All acutely poisoned adults (≥16 yrs) treated at the EMA during one year were included consecutively in a prospective study design. A standardized form was completed by the treating physician, covering the aims of the study. *Results:* There were 2401 cases during the year. Of these, 1588 (66%) were males and the median age was 35 years. The most frequent main agents were ethanol (44%), opiates (22%), and carbon monoxide/fire smoke (10%). Of the patients, 83% received no further treatment than observation, 9% received antidote(s), mainly naloxone, and 2% received activated charcoal. The median observation time for discharged patients was 3.6 hours. None developed sequelae or died. Sixty per cent were discharged without follow-up and only 17% were transferred to hospitals. Predictors for hospitalization were pharmaceutical poisonings, respiratory depression, and a suicidal intention behind the poisoning. Poisonings with ethanol or opiates were predictors for discharge. The attending doctors assessed 72% of the poisonings as accidental overdoses with drugs of abuse, 15% as other accidents and 11% as suicide attempts. Of the suicide attempts, 13 (4.8%) were discharged without follow-up. *Conclusion:* The majority of poisonings were substance abuse related. Outpatient treatment of acute poisonings was both efficient and safe. Whether short and long-term mortality rates are affected by the low referral rate of follow-up is, however, uncertain and needs further study. It is concerning that some of the suicide attempters were discharged without follow-up. The poisoning pattern was largely unchanged compared to the 2003-study, but the number was increased by two-fold in only five years, which calls for concern. We have no single explanation for this increase. Further studies should focus on possible explanations.

216. The Use of Extracorporeal Techniques in Acute Acetaminophen (Paracetamol) Poisoning

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Objective: Although acetaminophen (APAP) can be removed by extracorporeal removal (ECR) techniques such as hemodialysis, the safety and efficacy of N-acetylcysteine usually make the risks of ECR unjustified in APAP poisoning. However, some authors still recommend ECR in select APAP poisonings. Furthermore, a recent review of 20 years of data from the American Association of Poison Control Centers (AAPCC) demonstrated a surprisingly high, and rising, reported use of ECR in APAP poisoning.[1] We sought to investigate the true reasons that ECR was used in APAP poisoning. *Methods:* All APAP exposures receiving ECR were eligible for the study. Cases were obtained from the AAPCC database from 1993 through 2005, inclusive. Poison center information was obtained for each case, and the poison center directors were contacted to retrieve their individual cases. A structured survey was administered to confirm correct coding and to establish whether ECR was used to remove APAP or to treat other toxin effects or medical conditions. *Results:* 341 cases were identified for inclusion; 21 were eliminated because the poison centers had closed and their records were lost. Of the remaining 320 cases, 15 centers representing 109 cases did not respond to our requests. Of the remaining 211 cases, 145 were retrieved and analyzed. ECR was used for one or more of the following indications: correction of acidosis (76) and renal failure (89); removal of a co-ingestant (39); or treatment of rhabdomyolysis (18). Only 11 cases were interpreted to have employed ECR specifically for APAP removal; 7 came from a single center where Hemacleanse DT was routinely employed. None of these cases documented APAP clearance rates. *Conclusion:* Despite the increased use of ECR in cases of APAP poisoning as reported in AAPCC data, it is rarely used for drug elimination. When used, data are not systematically collected to allow determination of the efficacy of elimination. We suggest either abandoning use of ECR to remove APAP or systematically collecting data to confirm its safety and efficacy. *References:* 1. Holubek WJ, Hoffman RS, Goldfarb DS, et al. Use of hemodialysis and hemoperfusion in poisoned patients. Kidney Int 2008; 74:1327–34.

217. The Utility of Paracetamol Concentrations Prior to Four Hours Post-Ingestion in Acute Paracetamol Overdose

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Objective: Risk assessment for possible hepatotoxicity and requirement for antidotal treatment with N-acetylcysteine following acute, non-staggered paracetamol overdose involves plotting the plasma paracetamol concentration (PPC) taken at ≥4 hours post-ingestion on the paracetamol treatment nomogram. The ability of PPC taken <4 hours post-ingestion to determine risk is unknown and current nomograms do not enable their interpretation. The aim of this study was to determine, using a convenience sample of patients in whom a pre-4 hour paracetamol concentration had been taken during routine clinical management, the utility of a pre-4 hour PPC in predicting risk as determined by a subsequent ≥4 hour PPC plotted on the treatment nomogram. *Methods:* Data on all paracetamol-poisoned patients (April 2005-September 2010) was extracted from a purpose-designed electronic toxicology database used to prospectively collect data on all poisoned patients presenting to an inner city teaching hospital. Inclusion criteria: adult patients presenting with acute non-staggered paracetamol ingestion with a detectable PPC 0–3.75 hours post-ingestion and a subsequent 4–12 hour post-ingestion PPC. *Results:* Of 1812 paracetamol-related presentations, 43 fulfilled inclusion criteria (initial pre-4 hour PPC range 11–352 mg/L, time post-ingestion range 0.6–3.7 hours). Five presentations required antidotal therapy based on a subsequent ≥4 hour PPC plotted on the non-high risk UK "200-line" treatment nomogram (initial pre-4 hour PPC range 98–352 mg/L, time post-ingestion 0.6–3.0 hours). Eight presentations developed ≥4 hour post-ingestion PPCs between 50–100% of the UK non-high risk "200-line" nomogram (initial pre-4 hour PPC range 104–320 mg/L, time post-ingestion 1.4–3.7 hours). Forty presentations developed ≥4 hour post-ingestion PPCs between 0–50% of the UK non-high risk "200-line" nomogram (initial sub-4 hour PPC range 11–105 mg/L, time post-ingestion 1.9–3.4 hours). No pre-4 hour PPC less than 78 mg/L (n = 29; 67% of all pre-4 hour samples, PPC range 11–77 mg/L, time post-ingestion range 1.4–3.7 hours) was associated with a ≥4 hour PPC requiring antidotal treatment based on UK non-high risk "200-line", and only 3/29 (10.3%) of these presentations developed ≥4 hour PPCs that would require antidotal treatment based on the UK high-risk "100-line". *Conclusion:* This pilot study suggests it may be possible to define a sub-4 hour post ingestion PPC threshold that would exclude the requirement for further >4-hour "risk-assessment" PPC measurements following acute, non-staggered paracetamol overdose enabling earlier medical discharge of patients with sub-toxic paracetamol ingestions.

218. Can AST/ALT Ratio Indicate Recovery after Acute Acetaminophen Poisoning?

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Background: Acetaminophen (APAP) is the leading cause of pharmaceutical poisoning in the US and Europe. Elevations in [AST] and [ALT] indicate hepatic toxicity. [AST] and [ALT] rise in similar proportions but later decline at different rates, with [AST] falling more rapidly than [ALT]. *Objective:* To determine whether the [AST]/[ALT] ratio can indicate assured recovery after APAP poisoning. *Methods:* In this retrospective, IRB approved study, we identified cases of patients hospitalized for acute APAP poisoning by querying the pharmacy database of all patients treated with N-acetylcysteine (NAC) from 2001 to 2009. We included all patients with severe APAP poisoning, defined as [AST] or [ALT] > 1000 IU/L. We reviewed all charts to exclude NAC given for other indications. We then recorded paired [AST] and [ALT] concentrations measured at the same time from the same specimen. We classified each pair as clearly post-peak [AST] or not (the non-post-peak values included values before or at the observed peak [AST]). We calculated the [AST]/[ALT] ratio for each pair of values until both [AST] and [ALT] were < 100 IU/L. We compared different thresholds of [AST]/[ALT] in increments of 0.1 to find the optimal value that reliably indicated resolving transaminases. *Results:* We identified 1634 patients who received NAC during the 9-year study period. Of these 292 received NAC for suspected poisoning by APAP and/or other substances. After excluding patients without hepatotoxicity, patients with peak [AST} and [ALT] < 1000 IU/L, and patients without confirmed history or laboratory evidence of APAP ingestion, we had 14 evaluable patients with severe hepatotoxicity after acute APAP overdose with 164 evaluable pairs of AST and ALT. The sensitivity of [AST]/[ALT] was 84% at a cut-off of 1.0, 94% at 0.8, 96% at 0.6, 99% at 0.5, and 100% at 0.4. *Conclusion:* [AST]/[ALT] ratio </= 0.5 following severe hepatoxicity from single acute APAP overdose appears highly predictive of recovery in patients treated with NAC. This has potential to be an indicator of safe termination of NAC treatment.

219. Respiratory Injuries After Oral Ingestion of Cleaning and Cosmetic Products Containing Surfactants. First Results from a Prospective Multicentre Study in Germany

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Objective: Cleaning and cosmetic products containing anionic and nonionic surfactants are considered widely as minimally toxic. Exposure generally causes limited cutaneous, ocular and gastrointestinal irritant effects. Most common symptoms are nausea, vomiting and diarrhoea. However, aspiration may result in considerable respiratory distress. One objective of this study was to evaluate the frequency and severity of respiratory events. *Methods:* Prospective analysis of acute ingestions from three German poison centres during a six month period. After a confirmed oral exposure of manual dishwashing detergents, soaps, shampoos, general purpose cleaners or laundry detergents, a follow-up call at least 48 h after ingestion was performed. Additional data and follow up information were collected with a structured telephone-interview based on a detailed questionnaire. The interviews were conducted by trained Poisons Information Centre staff. *Results:* 604 patients were covered. Age groups: 540 children, 40 adults, 24 elderly persons. Respiratory symptoms developed in 99 patients (90 children, 2 adults, 7 elderly persons), most frequently cough (90). Other minor symptoms were transient mild laboured breathing (2), transient shortness of breath (1). In 5 cases cough persisted for more than 6 hours without further respiratory symptoms. Pulmonary aspiration with hospitalisation on intensive care units was reported 5 times. Bronchial airway obstruction (2), tachypnoea (2), oxygen desaturation/hypoxemia (4) were reported in 4 cases (1 toddler, 3 seniors). Mechanical ventilation because of respiratory failure was reported once (94 year old woman). *Conclusion:* After ingestion of surfactant containing products, pulmonary injury occurred rarely in this study. In spite of initial cough in 15 percent, only 1 percent developed respiratory symptoms requiring emergency health care. Mainly elderly persons suffered from aspiration pulmonary injury with hospitalisation (17% of elderly people after ingestion of surfactant containing products) while only one child out of 540 suffered prolonged respiratory symptoms with the need of hospitalisation and supportive medical therapy (0.2% of all children). Elderly patients have an increased risk of respiratory injury after ingestion of anionic and non ionic surfactants.

220. Acute Pneumonia after Accidental Fuel Hydrocarbon Ingestion in Adults: A Prospective Study

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Objective: The pulmonary toxicity of hydrocarbons is well-known, and the ingestion of one swallow of fuel hydrocarbons (FH) (gasoline, diesel, fuel mixture) is a frequent cause of admission to emergency departments (EDs). Studies in the medical literature are generally inhomogeneous, and no prospective studies are available focusing exclusively on acute accidental FH ingestion in adults. We investigated (i) the incidence of acute pneumonia, and (ii) the correlation with some risk factor in patients who ingested one swallow of automotive FH. *Methods:* A prospective study of adult patients referred to Pavia Poison Center in a two-year period (July 2008-June 2010) has been performed. Inclusion criteria were (i) accidental ingestion of one swallow of FH, and (ii) admission to EDs within 8 hours after ingestion. All the patients were observed for at least 8 hours in hospital; a chest X-ray was performed at the 8th hour after ingestion. A telephone follow-up was performed at day 3 and 7 after discharge. Informed consent was obtained from all the enrolled patients. The lack of the results of the X-ray was considered an exclusion criterion. Patients included were evaluated for (i) type of FH (gasoline, diesel, fuel mixture), (ii) modality of ingestion (from glass/bottle or during siphoning), (iii) acute symptoms, and (iv) development of acute pneumonia. *Results:* Among 250 cases of accidental FH ingestion referred to PPC in the studied period, 116 patients were included in the study. Thirteen patients (11.2%) developed acute pneumonia within 8 hours (X-ray confirmed), and seven of them were asymptomatic at admission. We found a statistically significant correlation between acute pneumonia and siphoning (12/13, $p = 0.03$), but not between acute pneumonia and vomiting after ingestion ($p = 0.54$). Among the 103 patients discharged with negative X-ray, follow-up at day 3 (available for 78/103 patients) and at day 7 (70/103 patients) revealed no occurrence of pulmonary symptoms. *Conclusion:* Acute pneumonia after accidental FH ingestion in adults is a frequent event and can occur even in the absence of respiratory symptoms at admission. In our cases all the acute pneumonia occurred within eight hours, mostly after ingestion by siphoning.

221. Work-Related Rhinitis and Asthma due to Detergents and Disinfectants: the Role of Ethylenediaminetetra-acetic Acid

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Objective: Detergents and disinfectants are an emerging cause of work-related rhinitis and asthma. The components responsible for these effects are not well known. This study discusses the role of ethylenediaminetetra-acetic acid (EDTA) which is frequently found in cleaning products. *Methods:* In our unit occupational rhinitis cases were explored using nasal provocation tests (NPT) with substances used in the workplace. The cases of 28 patients who received NPT with EDTA (tetrasodium salt) between January 2002 and July 2010 were reviewed and analysed. The criterion for a positive test was a doubling of nasal resistance measured by posterior rhinomanometry. *Results:* Twenty-eight patients who presented with a work-related rhinitis had a nasal provocation test (NPT) with EDTA. Ten tested positive for EDTA concentrations of 1% ($n = 6$), 2% ($n = 3$) or 4% ($n = 1$). Eighteen patients tested negative with EDTA concentrations of 1% ($n = 10$), 2% ($n = 7$) and 4% ($n = 1$). Of the patients who had a positive NPT, seven were female and three were male. Their median age was 46 years (38–63 years). In 8 cases, asthma was associated with rhinitis. These 10 patients were mostly cleaners ($n = 5$) or health professionals ($n = 4$). EDTA concentration in the incriminated products was 0.02% to 12% (median: 2.5%). In all cases, these products were sprayed by their users. Nine out of the ten patients had NPT also with other substances (quaternary ammonium compounds, amines, aldehydes, sulfites). One patient had 2 other positive NPT (with didecyldimethyl ammonium 0.2% in water and with N-lauryl-N,N-dimethylamine 0.5% in water). Two patients had one other positive NPT (with alkyldimethylbenzyl ammonium 0.1% in water and with didecyldimethyl ammonium 0.2% in water). *Conclusion:* EDTA is present in numerous detergent and disinfectant sprays To our knowledge, this report is the first to document cases of EDTA-related rhinitis and asthma. The mechanism of these respiratory diseases is not clear: both allergic and pharmacological mechanisms may be involved. An investigation strategy is needed to clarify this point.

222. Metformin Toxicity - Poison Centre Experience Versus Cochrane Reports

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Objective: Metformin is promoted as first line treatment in type-2-diabetes. This is in spite of indications that the substance can cause lactic acidosis both in overdose as well as in recommended therapeutic doses. In a recent Cochrane report based on more than 70,000 patient-years of exposure, it is stated: "There is no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with increased risk of lactic acidosis".[1] The aim of this study is to evaluate the occurrence of lactic acidosis associated with metformin treatment from a Poisons Centre (PC) perspective and compare the situation with findings from pooled therapeutic trials. *Methods:* A retrospective survey was performed based on telephone inquiries and case reports received by the Swedish PC during the ten-year period 2000 to 2009. *Results:* The prescription rate of metformin in Sweden has increased from 17.5 million defined daily doses (DDD) year 2000 to 57.1 million DDD in 2009, and the annual inquiries to the PC concerning metformin has increased tenfold. During this period (2000–2009), the PC was consulted by Swedish hospitals concerning 158 metformin intoxications in adults. Eighty-eight patients had taken an acute overdose while the remaining 70 cases were caused by therapeutic use of metformin. In the latter group 66 patients (94 percent) developed severe lactic acidosis (lactate > 10 mmol/L, pH < 6.95 or BE < 15) due to accumulation of metformin. The most common precipitating factor was temporary renal insufficiency owing to a few days of vomiting and/or

diarrhea with subsequent dehydration. Eighty-two percent of the patients with acidosis (54 cases) underwent dialysis (hemodialysis and/or CVVHD) in an intensive care setting. Among the patients that took an acute overdose only nine percent in this series developed severe lactic acidosis. *Conclusion:* The risk of developing severe lactic acidosis during long-term treatment with metformin is not insignificant and due to the nature of the circumstances leading to this condition, it is unlikely to be revealed in controlled treatment studies. A multitude of case reports in the literature also supports this experience. *References:* 1. Salpeter S, Greyber E, Pasternak G, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010; (1):CD002967.

223. Surveillance of Toxic Exposures to Plant Protection Agents and Biocidal Products in Europe

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Introduction: Pesticides are a heterogeneous group of biologically active substances designed to control pests such as insects, fungi, weeds, rodents, nematodes, algae, bacteria, and viruses. Due to their toxicological properties, pesticides have the potential for causing adverse effects on human health and the environment. Nevertheless, these chemicals serve many useful purposes and, as a consequence, are widely used in agriculture, other occupational settings, and at home. Considering their large availability for consumers as well as their toxicity, The International Code of Conduct on the Distribution and Use of Pesticides (hereinafter the Code of Conduct) calls for actions to reduce health and environmental risks. Among these actions the Code of Conduct specifically encourages governments to develop reporting systems designed to identify incidents of acute human health effects related to pesticides exposure.[1] The main intent of this contribution is to highlight how the European legislation on pesticides complies with this specific commitment. Furthermore, an overview of available data on pesticide poisonings in Europe is provided and, on that basis, prospects for a European programme for surveillance of toxic exposure to pesticides are discussed. *Methods:* Directives and Regulations on pesticides were searched in order to identify the articles requiring collection and reporting of acute health effects. Composite reports of the European Commission containing data on pesticide poisonings were reviewed as well as publications presenting national sources of data and surveillance systems. *Results:* According to the European legislation, preparations containing pesticides are classified in two main categories of use: plant protection agents and biocidal products (definitions reported in Regulation (EC) No 1107/2009 and Directive 1998/8/EC, respectively). Directive 2009/128/EC, establishing a framework for Community action to achieve the sustainable use of pesticides (hereinafter the Directive), requires that Member States (MSs) shall adopt National Action Plans (NAPs) aimed at reducing risks and impact of pesticides on human health and the environment and at developing alternative approaches and techniques to reduce their use. Among the objectives and measures to carry out, NAPs shall include the implementation of systems for gathering comparable information on pesticide acute poisoning incidents (Art. 7). The Directive also specifies that these systems should operate according to the indications that will be provided in 2012 by a strategic guidance document developed by the Commission, in cooperation with MSs. In agreement with the Directive, Regulation (EC) No 1107/2009, concerning the placing of plant protection products on the market, specifies that MSs shall set out provisions concerning the collection of information and reporting on suspected poisonings related to plant protection agents (Art. 68). With reference to biocidal products, Directive 1998/8/EC requires that MSs forward a report to the Commission every three years to document the activities undertaken to control the products on the market and to provide information on any case of poisoning. European data on pesticide poisoning exposures are presently very scanty and there is limited information on surveillance systems active at national level in MSs. In the second Composite Report in accordance with Directive 1998/8/EC, covering the period December 2003-November 2006,[2] 15,539 cases of toxic exposures to active substances were gathered. However, the Commission pointed out that the information on poisonings collected by MSs did not always allow for clear distinction between biocidal products and plant protection agents or other types of dangerous agents, nor could the available data be merged and analysed to provide integrated figures of poisonings and biocidal products involved. As a matter of fact, MSs have performed their own collection and transmission of data without sharing a standard case definition and classification scheme. In this context, Poisons Centres (PCs) are indicated by most of MSs as the available source of information. With reference to plant protection agents, a preliminary effort to harmonise collection of European data was performed using paraquat as a model substance. Several limitations of this experience have been pointed out, however.[3] A recent study carried out in UK evaluated the feasibility and practicalities of establishing permanent arrangements to collect data on pesticide related illness in Primary Care.[4] Another recent study used the National Poisons Information Service as source of information to characterize UK childhood exposure to pesticides, demonstrating the relevance of this type of service for surveillance activities.[5] In Italy, a national program for surveillance of acute pesticide-related illnesses (SAPRI-Program) was implemented in 2001.[6] This program identifies about 2,800 cases of pesticide exposures each year, including about 1,300 cases exposed to plant protection agents and 1,500 to biocidal products for pest control (group 3 according to Directive 1998/8/EC). About 90% of these cases are notified to the System by national and regional PCs, and the remaining 5% by Local Health Units. About 50% of cases exposed to plant protection agents and 30% of those exposed to biocidal products for pest control are classified as pesticide-related poisonings according to the standard definition provided by CDC.[7] *Conclusion:* The primary objective of surveillance of toxic exposure to pesticides (STEP) is to alert the health authorities about the risk that pesticides my pose to human health under certain conditions and to provide information to the regulatory authorities about the need for risk mitigation measures.[1,7] PCs represent a critical source of data for STEP implementation at national and international level[1,7] and their use is recommended when resources are limited.[3] On that basis, a special effort should be undertaken in Europe in order to develop a harmonised minimum set of data about exposures to pesticides documented by PCs. *References:* 1. International Code of Conduct on the distribution and use of pesticides. 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Available: www.iss.it (accessed 2 December 2010). 7. CDC. NIOSH. 2005. Pesticide-Related Illness and Injury Surveillance. How-to guide for state-based injury surveillance. Available: http://www.cdc.gov/niosh/docs (accessed 2 December 2010).

224. How will Poisons Centres be Affected by new Developments in Chemicals Legislation?

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Objective: In the last 5 years, the chemicals legislation of the European Union (EU) was rigorously updated. The REACH regulation (EC) No 1907/2006 and the CLP regulation (EC) No 1272/2008 completely renew the rules on (risk) management of substances and mixtures and will gradually replace various chemicals directives, including the substances directive 67/548/EEC and the preparations directive 1999/45/EC. The Cosmetic products regulation (EC) No 1223/2009 will replace Directive 76/768/EEC on cosmetic products. As these new EU legislations are 'regulations' instead of 'directives', they apply directly in the same way in every EU member state after coming into force. For poisons centres, the changes in chemical legislation predominantly affect the notification of product information by companies to competent authorities or poisons centres. Both the CLP regulation and the Cosmetic products regulation contain articles on the notification of hazardous mixtures and cosmetic products, respectively. The European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) is recognised as an important stakeholder and is actively involved in the discussions on these legislative developments. *Methods:* To participate in the discussions, the EAPCCT Board has activated the 'Working group on Poisons Centres Activities/European Regulatory Issues'. Various EU poisons centres are represented in this working group and, in subgroups, take part in the projects of the European Commission (EC) on the notification of hazardous mixtures and on the notification of cosmetic products. *Results:* In the CLP regulation, paragraphs 1–3 of article 45 describe the notification of information on hazardous mixtures to appointed bodies. However, it does not exactly describe what information is required and how it should be notified. At a late stage in the development of the CLP regulation, under the pressure of all stakeholders, this shortcoming was recognised and corrected with paragraph 4. It states that, before January 20th 2012, the EC shall review the possibility to harmonise product notification to the appointed bodies in the EU, including the establishment of a data exchange format. And the final result may be adopted by the EC and added as an Annex to the CLP regulation. In 2010 the EC organised two meetings with the EAPCCT working group and representatives of competent authorities to discuss the requirements for the notification of product information. The starting document for the discussions was the EAPCCT guideline on product information requirements from 1989. A new updated version of the guidelines was established and endorsed by the EAPCCT Board. Important parts of the new EAPCCT guideline are the requirements on the composition of a product and the concentration of its substances. The newly defined health hazard classes and categories of the CLP regulation were individually discussed. Based on poisons centres experience, a selection was made for which health hazard classification and category of a substance an exact concentration is required. Selected were acute toxicity (oral, dermal, inhalation) categories 1, 2 and 3, specific target organ toxicity (single and repeated exposure) category 1 and 2, skin corrosion category 1 and eye damage category 1. In addition, the existing rules, on the notification of the full composition (without the use of thresholds) and on the use of defined concentration ranges for other substances, still apply. These are the minimum requirements for poisons centres. The notification of exact concentrations for all substances in a mixture is preferred. In a similar manner, other requirements on product information and

company information were addressed and integrated into the new EAPCCT guideline. In November 2010, the EC organised a workshop, where all stakeholders were invited and the poisons centres' point of view was presented and discussed. It became clear that stakeholders had different views on the required quality of the product information. Nevertheless, they all favoured working together in an effort to realise harmonisation of product notification to appointed bodies. In 2011, the EC will organise two meetings with all stakeholders to identify the differences and how they can be resolved. After these meetings the EC will end the review with a report describing whether harmonisation of product notification can be reached and how. Of interest for the developments of the CLP project is another project by the EC that is establishing a Cosmetic Products Notification Portal (CPNP). In article 13 of the new Cosmetic products regulation it is prescribed that companies have to notify, by electronic means, (clearly defined) product information to the EC and that the EC shall make the product information electronically available to poisons centres and competent authorities. The EC is currently developing this central database to which cosmetic product information can be uploaded by companies. Poisons centres and competent authorities can search, view and download the available product information. The EAPCCT working group, together with other stakeholders, takes part in the discussions on the development of CPNP. The current planning of the EC is to bring CPNP into production at the beginning of 2012. *Conclusion:* At the workshop of the CLP project, EAPCCT and poisons centres had for the first time the opportunity to present to a broader audience of stakeholders their requirements on product information necessary to perform their tasks. It is the starting point for further discussion among stakeholders to realise a harmonised notification of product information in EU member states. In the CPNP project, poisons centre requirements on information quality and format are brought into the discussion and, where possible, into the design of the CPNP. Both these EC projects develop along different paths and have different timeframes. EAPCCT and poisons centres do not favour the development of these projects into different electronic data exchange formats. For all stakeholders involved it would be best if only one electronic data exchange format can be established that suits the notification of all (hazardous) mixtures.

225. New EAPCCT Guideline on Required Product Information

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Objective: Based on article 45 (4) of Regulation (EC) No 1272/2008, the European Commission (EC) currently explores the possibility of harmonising the notification of product information to appointed bodies (Poison Centres and governmental authorities). The EAPCCT, recognised as an important stakeholder, is taking part in this review and has developed a new guideline on required product information. *Methods:* Poison Centre representatives from various EU countries evaluated the recent developments in European legislation and the consequences these might have for Poison Centres in the EAPCCT working group on European Regulatory Issues. A subgroup is involved in the discussions with the EC on the harmonisation of product notification. Members of this subgroup developed a new version of the guideline on the required product information, which was recently endorsed by the EAPCCT Board. *Results:* The new guideline describes the product information that should be notified by companies besides the Safety Data Sheet (SDS) in order to facilitate the possibility for Poison Centres to perform an adequate risk assessment after exposure to a product. Most important is a detailed product composition. The guideline requires the mention of all substances in a mixture (whatever their toxicity). Actual concentrations are required for substances classified as acute toxicity (oral, dermal, inhalation) category 1–3, specific target organ toxicity (STOT) single/repeated exposure category 1–2, skin corrosion category 1ABC and serious eye damage category 1, according to Regulation (EC) No 1272/2008. For all other substances defined concentration bands are accepted: 0–0.1%, 0.1–1%, 1–3%, 3–10%, 10–20%, 20–30%, 30–50%, 50–75%, >75%. If available, CAS- and EC-numbers (EINECS/ELINCS) are required. Furthermore, information on the categorisation, classification, packaging and physical/chemical characteristics of a mixture must be notified. If a mixture is reformulated, the guideline describes when a renewed notification is necessary. Toxicological information is expected to be included on the improved SDS according to REACH. *Conclusion:* The new EAPCCT guideline on required product information is an important step towards harmonisation of product notification and will be the start of discussions with industry and EU member state representatives. In the near future the results of this discussion will be incorporated by the EC in an Annex to Regulation (EC) No 1272/2008.

226. The NPIS Pesticide Surveillance Project 2004–2010: Acute Pesticide Poisoning in the Older Person (≥65 years)

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Objective: To describe pesticide exposures in patients aged ≥65 during the 6.5 years of the NPIS TOXBASE® pesticide surveillance project. *Methods:* The National Poisons Information Service Edinburgh Unit (NPISE) monitors pesticide exposures following Internet (TOXBASE®) or telephone enquiries. All patient related accesses to pesticides on TOXBASE® between 1/4/2004 and 1/10/2010 were notified electronically to NPISE, and followed up using on-line, email or paper questionnaires. All NPIS telephone enquiries from 1/9/2009 were also followed up. Enquiries from outside the UK and those where symptoms were deemed not related were excluded. Exposures were analysed for circumstances and symptoms in patients aged ≤64 and ≥65 years using Fisher's exact test as appropriate. *Results:* Since 2004 5211 pesticide exposures have been reported to NPISE. Children (<13y), cases without age and chronic exposures were excluded (2878). Patients ≥65 comprise 18.8% of acute adult reports (438). Accidental poisonings in those ≥65 frequently occurred while the pesticide was in use; 278 (69.1%). The majority of exposures involved amateur products (313, 77.9%). Agents reported following accidental exposures were similar in patients ≥65 and ≤64, glyphosate and permethrin predominating. Deliberate self-harm (DSH) was less frequent in patients ≥65 (8.2%) compared to patients ≤64 (23.0%) ($p = <0.001$). DSH exposures in patients ≥65 most frequently occurred between ages 65–71 years, 23 of 36 exposures (63.8%). Few DSH exposures occurred over 85 years (2, 5.6%). This reflects findings from previous work on suicide in the elderly.[1] In patients ≥65 rodenticides were involved in 5 DSH cases (13.9%), ≤64 rodenticides were the most frequently reported agent (158, 36.3%, $p = <0.006$). Poisoning Severity Scores (PSS) grades for accidental exposures appeared similar for patients ≥65 and ≤64 (60% minor, 7% moderate and 1% severe for both). Eye, skin, mouth and respiratory irritation were frequently reported following accidental exposure in patients ≥65. *Conclusion:* Older patients comprise a significant proportion of pesticide exposures. Findings in accidental poisoning are similar to those in younger patients. In the ≥65 group DSH is less common and the products used differ. *References:* 1. De Leo D, Padonai W, Socco P, et al. Attempted and completed suicide in older subjects: results from the WHO/EURO Multicentre Study of Suicidal Behaviour. Int J Geriatr Psychiatry 2001; 16:300–10.

227. Cytokine and Chemokine Profiles in Acute Carbon Monoxide Poisoning: Marked Elevation of Interleukin-6 in Cerebrospinal Fluid

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Background: We reported that early elevation of interleukin-6 (IL-6) concentration in the cerebrospinal fluid (CSF) may be a predictive marker of delayed encephalopathy (DE) due to acute carbon monoxide (CO) poisoning.[1] However, cytokines other than IL-6 in CSF after CO poisoning had not been determined. *Objective:* To investigate the relationship between outcome of CO poisoning and profile of cytokine/chemokine level in blood and CSF, in order to find any prognostic markers for prediction of the outcome. *Methods:* We measured 17 cytokines/chemokines in the CSF of 39 acute CO poisoned patients who manifested unconsciousness in their course. The CSF and blood were obtained within 24 hours after the last CO exposure. The cytokines/chemokines in their CSF and sera were determined by the microbeads assay method. All patients were observed for at least 3 months, and classified into two groups according to their clinical outcomes. Patients who revealed delayed neuropsychological syndrome or persistent vegetative state were classified into the encephalopathy group (Group E, n = 9), and patients who had no delayed symptoms were classified into the no complication group (Group N, n = 30). The relationship between clinical outcome and levels of cytokines/chemokines was examined by statistical analysis. *Results:* The CSF levels of interleukin (IL)-1-beta, IL-4, IL-6, IL-8, IL-10, IL-12, granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, interferon-gamma, monocyte chemoattractant protein-1, macrophage inflammatory protein-1-beta and tumor necrosis factor-alpha were significantly elevated in group E. In that group, the serum levels of IL-6 and granulocyte colony-stimulating factor were also significantly elevated. The difference in CSF IL-6 was the most significant among them. *Conclusion:* There are differences in cytokines/chemokines profiles of the two groups in CO poisoning. Cytokines/chemokines analysis of CSF is more useful than that of serum, and the most useful biomarker among these analytes was CSF IL-6 for prediction of encephalopathy. *References:* 1. Ide T, Kamijo Y. The early elevation of interleukin 6 concentration in cerebrospinal fluid and delayed encephalopathy of carbon monoxide poisoning. Am J Emerg Med 2009; 27:992–6.

228. Population Pharmacokinetics and Pharmacodynamics of Escitalopram in Overdose and the Effect of Activated Charcoal

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Objective: We have previously shown that citalopram overdose causes QT prolongation and that single dose activated charcoal (SDAC) reduces the risk of this occurring.[1] This study aimed to investigate the pharmacokinetics and pharmacodynamics of escitalopram (S-enantiomer of citalopram) overdose to describe the time-course of QT interval prolongation and determine the effect of SDAC on the relative risk of

an abnormal QT developing. *Methods:* The data set included 78 escitalopram overdose events (median dose 140 mg [10–560 mg]). SDAC was administered 1 to 2.6 hours after 12 overdoses. A fully Bayesian analysis was undertaken in WinBUGS 1.4.3, first for a population pharmacokinetic analysis of 34 admissions with plasma concentration data followed by a pharmacokinetic-pharmacodynamic (PKPD) analysis of data for all 78 patients. The developed PKPD model was used to predict the probability of having an abnormal QT based on the QT nomogram.[2] *Results:* A one-compartment model with first-order input and first-order elimination described the pharmacokinetic data, including uncertainty in dose and a baseline concentration for patients taking escitalopram therapeutically. SDAC reduced the fraction absorbed by 31% and reduced the individual predicted area under the curve adjusted for dose [AUC_i/dose]. The absolute QT interval was related to the observed heart rate with an estimated individual heart-rate correction factor [$\alpha = 0.35$]. The heart-rate corrected QT interval was linearly dependent on predicted escitalopram concentration (slope = 87 ms/mg^{-1}, between-subject CV = 70%) using a hypothetical effect-compartment (half-life of effect-delay = 1.0h). Administration of SDAC significantly reduced QT prolongation and was shown to reduce the risk of having an abnormal QT by approximately 35% for escitalopram doses above 200 mg. *Conclusion:* The pharmacokinetics of escitalopram in overdose were similar to citalopram. Escitalopram was associated with a delayed lengthening of the QT interval in a dose-related way. SDAC resulted in a moderate reduction in fraction of escitalopram absorbed and reduced the risk of an abnormal QT occurring. *References:* 1. Friberg LE, Isbister GK, Duffull SB. Pharmacokinetic-pharmacodynamic modelling of QT interval prolongation following citalopram overdoses. Br J Clin Pharmacol 2006; 61:177–90. 2. Chan A, Isbister GK, Kirkpatrick CM, et al. Drug-induced QT prolongation and torsades de pointes: evaluation of a QT nomogram. QJM 2007; 100:609–15.

229. Toxicity Profile of Desvenlafaxine

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Background: Very limited toxicity data exists on the serotonin and noradrenaline reuptake inhibitor desvenlafaxine (Pristiq® - extended release tablets). It is the major active metabolite of venlafaxine (Efexor®) and toxicity may be similar (e.g. seizures, serotonin toxicity and dysrhythmias). *Objective:* This study aims to describe the toxicity profile of desvenlafaxine for both accidental paediatric ingestions and deliberate self-poisoning. *Methods:* Cases were recruited through calls to the NSW Poisons Information Centre (PIC) from September 2009 - November 2010. A 2 page clinical research form was used to collect information from hospital-based calls and was faxed at the time of the initial call. A copy of the patient's medical record for the admission was also requested retrospectively. A follow-up call for accidental ingestions was attempted within 72 hours of the initial call. *Results:* A total of 31 cases of desvenlafaxine poisoning with outcome information was collected through the PIC. The patients were classified as follows: i) Accidental paediatric exposures (n = 3): 24 month male ingested 50 mg and experienced 2 episodes of vomiting and mild drowsiness shortly after ingestion, the child was observed in hospital for 4.5 h. Two further cases in 2 year olds with estimated doses of 5 mg and 50 mg remained asymptomatic. ii) Deliberate self-poisoning (n = 28): 13 cases involved desvenlafaxine only (alcohol involved in 6 cases) and of these, 10 (77%) were symptomatic (estimated median dose: 900 mg; range: 200–2100 mg): nausea (n = 7), tachycardia (n = 4), drowsiness (n = 4; alcohol possible cause in 2 cases; lowest GCS was 14), hyperreflexia (n = 2), hypertension (n = 2; max SBP: 159 and 168 mmHg), vomiting (n = 2; in the only two patients given charcoal), tremor (n = 1), clonus (n = 1), ocular clonus (n = 1), mydriasis (n = 1). Two cases (ingesting 1400 and 2100 mg) met the Hunter Serotonin Toxicity Criteria for serotonin toxicity but both were mild-moderate and received no active treatment. No seizures or QRS/QT widening was recorded in association with single drug ingestions of desvenlafaxine. Three patients remained asymptomatic (dose: 600–700 mg). *Conclusion:* In this limited series, no serious toxicity was noted from desvenlafaxine in accidental paediatric ingestions of up to 50 mg (estimated) and deliberate self-poisoning of up to 2100 mg. Further surveillance is required, particularly with larger doses.

230. The P-glycoprotein Activity of Drugs Highly Associated with Torsade de Pointes

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Objective: To evaluate the role of an efflux transporter, P-glycoprotein (P-gp), in drug-associated torsade de pointes (TdP). *Methods:* We analyzed the product labels of drugs withdrawn because of association with TdP (cisapride, terfenadine, and astemizole) to identify contraindicated concomitant drugs that have P-gp activity. We identified other drugs that have been associated with TdP by data mining the FDA's Adverse Event Reporting System (AERS) database using the safety data mining Multi-item Gamma Poisson Shrinker (MGPS) method. We analyzed individual drugs with top Empirical Bayesian Geometric Mean (EBGM) values for TdP. We also used MGPS to identify drug-drug pairs having the top EBGM values for TdP that could not be explained by the association of their individual drug components with TdP. The top drug pairs by EBGM values were assessed to determine if the drug pair included drugs that were P-gp substrates and/or P-gp inhibitors. *Results:* The drugs contraindicated for concomitant use with cisapride, terfenadine, and astemizole are almost all known P-gp inhibitors. Data mining of postmarketing drug safety reports identified drugs associated with TdP. The drugs ranked here in descending order (by EBGM value) are ibutilide (236), levacetylmethadol (107), bepridil (96), sotalol (68), disopyramide (47), methadone (44), quinidine (42), pentamidine (39), cisapride (32), erythromycin (32), terfenadine (30), droperidol (28), astemizole (27), and pimozide (25). Nine of these 14 drugs are known P-gp substrates and seven are also known P-gp inhibitors (3 drugs lack literature reports of P-gp activity). The drug pairs most highly associated with Tdp were cisapride-erythromycin, erythromycin-terfenadine, sulfamethoxazole/trimethoprim-methadone, itraconazole-terfenadine, amiodarone-voriconazole, ketoconazole-terfenadine, atazanavir-methadone, methadone-ritonavir, fluoxetine-trazodone, flurazepam-methadone, amiodarone-loratadine, ciprofloxacin-sotalol, methadone-nelfinavir, fluoxetine-ondansetron, methadone-voriconazole, and sertraline-sotalol. With the exception of pairs that included sotalol each of these drug pairs included a P-gp substrate that prolongs the QT interval and a P-gp inhibitor. Many of these drug pairs included drugs that were both P-gp substrates and inhibitors. *Conclusion:* Further research is needed to evaluate a potential role for P-glycoprotein (drug efflux) inhibition increasing the intracellular levels of drugs that prolong the QT interval, thereby precipitating TdP.

231. Prognostic Factors in Methanol Poisoning: A Multi-Center Study

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Objective: Prognostic parameters in methanol poisoning are reported from time to other, but reports with a high number of patients with a complete acid-base status on admission are scarce. No comparative studies on prognosis with ethanol vs. fomepizole exist. In order to study the prognostic factors in methanol poisoning with a special focus on antidote, we collected material from four different countries where a blood gas was analyzed on admission, and outcome was known. Inclusion criterion was a history of methanol poisoning or a positive S-methanol. In only one outbreak was fomepizole the antidote of choice (n = 51). *Methods:* The material was collected from two different outbreaks in Norway (1979 and 2002–2004), one outbreak in Estonia (2001), one in Tunisia (2003/2004), as well as material from one referral center in Iran (2004–2009). The patients were separated into three groups: Group I: Survivors without sequelae, Group II: Survivors with sequelae, Group III: The patients who died. Data included age, sex, consciousness on presentation, serum potassium/creatinine, methanol level and blood gas analysis on admission. *Results:* A total of 302 patients were included in the study. ROC-curves were used to validate how strongly the different parameters correlated with death. Student's T-tests were used to separate the different admission parameters. *Results:* The ROC-curve showed a strong correlation between death and pH (0.888), base deficit (0.851) and coma (0.813). There was a significant difference in ROC-value between the patients where fomepizole was used and the rest for pH (0.942 vs. 0.883), coma (0.909 vs. 0.794), and PCO_2 (0.868 vs. 0.533). There were a significant difference between the two antidotal treatment groups regarding the pH in the dying patients ($p = 0.011$). *Conclusion:* The high number of patients with thorough sampling of admission data made it possible to compare prognostic parameters for the two antidote groups. Overall, in spite of different confounders, there seemed to be a leftward shift in morbidity and mortality between the two groups. When fomepizole was the antidote used, more patients seemed to survive with sequelae instead of dying, and patients surviving with sequelae seem to avoid the sequelae to a certain extent.

232. Correlation of Blood Lead Levels and Soil Lead Levels in Pediatric Patients in Sub-Saharan Africa

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Objective: The objective of this study was to determine if community Soil Lead Levels (SLL) and resident Blood Lead Levels (BLL) are correlated in a heavily contaminated area in sub-saharan Africa. Pediatric patients in 12 periurban communities were studied. SLLs versus BLLs were compared for correlation. *Methods:* Venous blood lead levels were collected and analyzed by using LeadCare™ B-Pb assay. Surface soil samples were collected and analyzed by inductively-coupled plasma atomic emission spectroscopy (ICP-AES). Descriptive statistics were used to characterize the variables. *Results:* A total of 990 venous BLL were collected from 12 communities and compared to SLL in these same communities. The mean age of participants was 4.8 years (range 1–12). The mean venous blood level for the entire population was 19.275 μg/dL (range 7.3–44.6). SLLs collected in the communities ranged from 500 to >2500 ppm. There was a log-linear correlation between BLL and SLL. Data showed an increase in mean BLL as mean soil lead levels increased. This correlation existed for communities with SLL below 1000 ppm. Among communities with SLLs above 1000 ppm, mean BLLs are high however they seemingly plateau and do not

continue to increase as SLL increases. *Discussion:* There is a curvilinear relationship between community SLLs and mean resident BLLs in the children providing samples. Although this seemingly plateau effect has been observed at lower BLLs in the past, it is unclear as to why BLLs plateau even as the soil levels continue to rise. *Conclusion:* In a heavily contaminated area of sub-Saharan Africa, community SLL and mean resident BLL levels in pediatric patients follow a curvilinear relationship with a plateau in BLL at a SLL of approximately 1000 ppm.

233. A European Survey on the Availability of Antidotes

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Objective: Antidotes may be a critical component in the care of poisoned patients. This study aims to examine the degree of availability of essential antidotes in Europe. *Methods:* A questionnaire was sent to 62 poison control centers (PCCs) from 31 different countries in Europe. The questions concerned availability of 21 selected antidotes, organization of antidote stocks, financing, and possible problems involved in the management of these drugs. The chosen antidotes were: acetylcysteine, activated charcoal, atropine sulphate, botulism antitoxin, calcium disodium EDTA, calcium gluconate (antidote gel), deferoxamine, digoxin-specific antibody fragment, ethanol, flumazenil, folinic acid, fomepizole, glucagon, hydroxocobalamin, methylene blue, naloxone, octreotide, physostigmine, protamine sulphate, sodium thiosulphate and silibinin. *Results:* The questionnaire response rate was 60% (37 answers from 24 countries, meaning that 77% of the different countries responded). The results are based on all PCC responses, representing the following countries: Austria, Belarus, Belgium, Bulgaria, Czech Republic, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Sweden, Switzerland, UK and Russia. Approximately one third of the PCCs were lacking availability of five or more of the 21 essential antidotes, and more than half of the PCCs were not satisfied with the antidote stock that they had access to today. Seven PCCs (19%) were lacking seven or more of the important antidotes. One fourth of the PCCs reported lack of regular collaboration with other PCCs or health care providers concerning purchasing of antidotes or routines for bilateral cooperation in case of urgent need for a specific antidote. The four antidotes with the lowest availability rate at the PCCs were botulism antitoxin (54%), silibinin (62%), fomepizole (65%) and hydroxocobalamin (70%). The digoxin-specific antidote was available at 28 of the PCCs (76%). The most commonly reported reasons why a certain PCC was lacking a specific antidote were "too expensive" or "problems with import from other countries". *Conclusion:* Appropriate storage of antidotes is a problem in many European countries. Regional unavailability of antidotes and lack of financing seem to be critical factors. An intensified and better organized European collaboration concerning storage and supply of antidotes would possibly improve the situation.

234. Euthasol Overdose with Cardiac Arrest Resuscitated with Intravenous Lipid Emulsion

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Objective: Veterinary euthanasia solutions commonly contain barbiturates, neuromuscular blockers, anticonvulsants, or sedatives. Due to widespread use, overdose by humans occurs occasionally. We report a case in which lipid emulsion therapy successfully reversed severe toxicity following an overdose of a euthanasia solution containing pentobarbital. *Case report:* A 20 year-old healthy man was found unresponsive in a veterinarian's office. Bystander cardiopulmonary resuscitation (CPR) was initiated for apnea and pulselessness. Emergency Medical Services (EMS) noted the presence of pulseless electrical activity (PEA). The patient had a tourniquet on his left arm and a 100 mL bottle of Euthasol (pentobarbital 390 mg/mL and phenytoin sodium 50 mg/mL) with 90 mL missing was discovered near-by. CPR was initiated and was continued for 30 minutes in the ED. The poison center recommended an intravenous bolus of 1.5 mL/kg of Intralipid while CPR continued which was given soon after. Spontaneous circulation returned 10 minutes following the bolus. The patient remained in intensive care unit for one week but was neurologically intact upon extubation. The serum pentobarbital concentration was 7.8 micrograms/mL (therapeutic concentration, 1 to 5 micrograms/mL) prior to the infusion of lipid emulsion with a positive phenytoin concentration. *Conclusion:* Parenteral pentobarbital produces rapid onset respiratory depression and subsequent cardiovascular collapse. The treatment of pentobarbital poisoning is primarily supportive, but this is not generally successful once cardiac arrest has occurred. The Log P of pentobarbital is 2.10 and bupivacaine is 3.64 which is similar and may explain why lipid emulsion was successful in this case. In this case of massive overdose and a nonperfusing cardiac rhythm, intravenous fat emulsion therapy was associated with rapid recovery.

235. Analysis of Antidote Stocks in the Hospitals of the Italian Region Emilia Romagna

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Objective: The Department of Pharmacy of the University Hospital of Ferrara (AOUFE) has been appointed Regional Centre of Reference for the supply of some antidotes by the Region Emilia Romagna (RER).[1] In order to assess their availability, a qualitative-quantitative analysis of antidotes available in regional hospitals has been carried out. We paid particular attention to antidotes supposed to be used within 30 minutes, namely the A-type,[2] and which should be available in all hospitals. *Methods:* All 17 regional hospitals were asked for information about the kind and the quantity of stocked antidotes. The number of potentially intoxicated users has been calculated according to the maximum dosage. *Results:* All 17 regional hospitals provided the required information with the following results. Among the 27 A-type antidotes we analyzed, the stock for the maximum treatment of a patient was the following: 2 antidotes (ipecacuana, naloxone) were available in all hospitals; 2 antidotes (calcium gluconate and activated charcoal) were available in 5 hospitals, and 5 antidotes (atropine sulphate, dantrolene, physostigmine, sodium thiosulfate, protamine sulphate) were available in 15 hospitals. Seven A-type antidotes (fomepizole, $MgSO_4$, Fuller's earth, hydroxocobalamin, digoxin-specific antibodies, polyethylene glycol 4000 and ethyl alcohol 96°) were available in less than 10 hospitals. The availability of antidotes to be used within 2 hours (B-type) was limited: Prussian blue was found in 5 hospitals with dimercaprol and pralidoxime in 8. *Conclusion:* Quantities of some antidotes available in regional hospitals are not sufficient to treat a single patient. This is the case for fomepizole, digoxin-specific antibodies and Fuller's earth among A-type antidotes, and of Prussian blue, dimercaprol and pralidoxime among B-type ones. Therefore, the need to provide many regional hospitals with higher stocks of antidotes is recognized. *References:* 1. S. Bianchi, Zoppellari R, Scanavacca P. Transfer of antidotes to other hospitals carried out by a regional antidote reference centre. Clin Toxicol 2009; 47:477. 2. Resolution CEE 90/C; 3/12/1990 90/C 329/03. http://www-3.unipv.it/reumatologia-tossicologia/cav/doc/GU_allegato3.pdf

236. A Decade of Cyanide Antidote Administration at an Urban Tertiary Care Center

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Background: Cyanide (CN) is a mitochondrial poison found as a byproduct of structural fires or as an industrial compound that can be intentionally ingested. Two CN antidotes exist, hydroxocobalamin and sodium thiosulfate, although the international medical community lacks consensus about which antidote to use first-line.[1] In order to clarify factors involved with CN antidote choice, we reviewed all CN antidote administration at a large academic tertiary care center to determine: (a) the indication cited and (b) the effects on mortality, if any. *Methods:* A retrospective review of all hospital affiliated medical records was performed over 10 years of consecutive potential CN poisonings presenting to a single large academic tertiary referral center from January 2000 to November 2010. The study was performed using an extensive electronic data warehouse by searching for the following terms: "cyanide", "thiosulfate" and "hydroxocobalamin". Medical record abstraction included the following data: baseline demographics (age, gender, race); indication for CN poisoning (burns, smoke inhalation, ingestion) versus non-CN related (ulcers, vitamin deficiency); medical history; blood gas and chemistries. The primary outcome was in-hospital mortality, while the secondary outcome was indication for CN antidote administration. *Results:* Of 60 patients yielded by the search, 43% were female, the average age was 34.9 years, 45% were under 18 years of age, and subjects were racially diverse (33% Caucasian, 27% Hispanic/Latino, 20% African American). Overall 7/60 (12%) died during hospital admission and 8/60 (13%) patients were suspected of CN poisoning. Of the 8 patients suspected of CN poisoning, only 1 (12.5%) was treated. *Conclusion:* In the rare cases of CN antidote administration over the past decade at an urban tertiary care center, the minority of indications were to treat suspected CN poisoning. In patients with suspected CN poisoning, the rate of antidote administration was poor and precluded analysis of mortality benefit. Future studies should focus on elimination of barriers to CN antidote administration. *References:* 1. Hall AH, Saiers J, Baud F. Which cyanide antidote? Crit Rev Toxicol 2009; 39:541–52.

237. Death After Flumazenil Use

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Objective: To report a case of death as consequence of flumazenil use in a pregnant woman. *Case report:* An eight weeks pregnant woman, 19 years-old, intentionally ingested an estimated dose of 50 to 300 mg of clonazepam, two and a half hours before first being seen at a local ER. She presented sleepy and with nausea. Gastric lavage was performed despite the long period since ingestion, and was obviously unsuccessful. Two hours later, the ER team called our Poison Control Center (PCC) asking for orientation on the use of flumazenil, as the patient remained sleepy. They were told not to use it as she could have ingested other CNS depressors, like tricyclic antidepressants and carbamazepine that could induce dangerous and refractory seizures after flumazenil administration. Seven hours later our PCC was contacted again, asking for our agreement about the use of flumazenil as the patient continued to be sleepy. Information about the low risk of problems for the patient and the baby was then given, with information about the baby's and mother's

cardiac monitoring to be performed and continuing with the supportive care. Four hours later the PCC was informed the patient had developed respiratory depression, when she was intubated, and died after receiving 0.2 mg of flumazenil, which triggered a series of recurrent seizures proceeding to cardiac arrest resistant to all reanimation measures. After that the patient's mother reported that she found an empty 50 pill pack of carbamazepine at home, adding that the patient was a regular carbamazepine user. *Conclusion:* Benzodiazepine (BZD) intoxications are rarely fatal when not associated with other CNS depressants, in which case severe CNS depression with apnea, coma, and cardiovascular complications can occur, and should be treated accordingly. Flumazenil is a competitive BZD receptor antagonist restoring consciousness but not reversing respiratory depression induced by BZD. It may trigger withdrawal syndrome in BZD dependent patients. It can be used very cautiously in BZD isolated overdoses, but its potential to induce refractory convulsions in concurrent carbamazepine and tricyclic antidepressants intoxications can lead to catastrophic outcomes, as seen in the present case. *References:* 1. Seger DL. Flumazenil - treatment or toxin. J Toxicol Clin Toxicol 2004; 42:209–16.

238. Fomepizole - Availability in Welsh Hospitals

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Objective: To establish the location, stock levels and availability in Welsh acute hospitals of the ethylene glycol antidote - fomepizole. *Methods:* A questionnaire was sent to 21 hospitals in Wales with accident and emergency departments requesting information on the availability of fomepizole (according to the NPIS recommendation); whether it was available immediately, within 1 hour, or greater than 1 hour and whether the recommended stock was held (25 × 20 mL ampoules 5 mg/mL). If the drug was not stocked at the hospital, the nearest source and estimated time of delivery was also requested. *Results:* The survey was concluded in November 2010 and completed questionnaires were received from all 21 hospitals. Only 3 hospitals had the antidote immediately available and one of these did not hold the recommended amount of stock. Seven hospitals confirmed that they would have access to fomepizole within 1 to 2 hours of request. One hospital confirmed availability 'some time' the same day and another could access it within three days. Nine hospitals reported that they had no known access to fomepizole and recorded no information regarding nearest source or time within which it could be made available. *Conclusion:* Results of the survey indicate that the availability of fomepizole in Welsh hospitals is generally limited - this is of concern given that the National Poisons Information Service currently advises that fomepizole, a potent competitive inhibitor of alcohol dehydrogenase, is the antidote of choice in ethylene glycol poisoning. Use of the alternative antidote, ethanol infusion, requires constant monitoring of blood alcohol levels - not always available in smaller hospitals. There is a likelihood of reduced consciousness, and its use usually necessitates monitoring of the patient in a HDU/ITU setting. In children there is a risk of hypoglycaemia and it is contra-indicated in the first trimester of pregnancy. Fomepizole may also be preferable to use of ethanol in patients who have co-ingested drugs causing CNS depression. Accidental and deliberate ingestions of ethylene glycol-containing products are not infrequent in Wales and the ready availability of an effective and safe antidote in all accident and emergency departments should be encouraged.

239. Agranulocytosis after Massive Benzene Ingestion - A Case Report

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Objective: Toxic effects of benzene ingestion are well recognized and primarily include signs and symptoms of CNS depression, gastrointestinal irritation and cardiac arrhythmias. We report a unique case of agranulocytosis after massive benzene ingestion. *Case report:* A 52-year old female with a history of depression ingested almost 1000 mL of pure benzene used as a solvent in a biochemical laboratory. At admission, 3–4 hours after ingestion she presented with staggering gait, somnolence, agitation, tachycardia, vomiting and profuse diarrhea. The initial blood analysis revealed WBC $36.2 \times 103/mm^3$, RBC $5.6 \times 106/mm^3$, hemoglobin 15.8 g/dL, hematocrit 45%, and platelets $247 \times 103/mm^3$. BUN was 9.2 mmol/L, creatinine 64 μmol/L, sodium 136 mEq/L, potassium 3.9 mEq/L, glucose 9.2 mmol/L, AST 63 u/L, ALT 41 u/L, CK 204 u/L, LDH 847 u/L. Urine analysis revealed a high concentration of phenol (320 mg/L). A few hours later she developed nodal tachycardia characterized by a heart rate of 150–170 per minute, with multifocal ventricular extrasystoles. Arrhythmia was successfully treated with lidocaine, so the next day heart rate normalized. Severe diarrhea with incontinence gradually resolved within a week. However, on the skin in the thoracic and gluteal area which was in contact with vomitus and stool, extensive grade II chemical burns developed. Complete blood count monitoring revealed the fall in neutrophils with minimal number of $0.232 \times 103/mm^3$ twenty days after ingestion. Bone marrow biopsy revealed lowering of granulopoietic precursor cells number and increased number of eosinophils, lymphocytes and plasma cells. The patient received filgrastim for 11 days until normalization of neutrophils in peripheral blood. *Conclusion:* Chronic benzene exposure has been associated with hematologic disorders (thrombocytopenia, aplastic anemia, pancytopenia, and acute myelogenous leukemia). Acute toxicity of benzene inhalation to hematopoietic precursor cells is demonstrated in experimental animals. This report indicates a similar mechanism of toxicity in a human after a single exposure to an extremely high dose.

240. The Toxicity of Liquid Detergent Capsules (Fabric Cleaning Liquid Tablets)

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Objective: To ascertain the toxicity of liquid detergent capsules. *Methods:* Between 1 March 2008 and 30 April 2009 the UK National Poisons Information Service collected prospectively 647 telephone enquiries relating to liquid detergent capsules. *Results:* The majority of enquiries (96.1%) concerned children five years of age or less. Exposure to these products occurred mainly as a result of ingestion alone (n = 518; 80.1%), with eye contact alone (n = 61; 9.4%), and skin contact alone (n = 7; 1.1%) being less common; 9.4% (n = 61) of enquiries involved multiple routes of exposure. The most common features reported following ingestion alone were vomiting (n = 124) followed by coughing (n = 21) and nausea (n = 18). Nine patients developed drowsiness and nine a rash, possibly due to topical contact with the capsule. Features that developed following ocular exposure were conjunctivitis with or without eye pain (n = 64), eye pain alone (n = 13) and keratitis (n = 4). Follow up was attempted in all these cases and to the best of our knowledge ocular damage resolved in all. Seven patients aged three or less were exposed via the dermal route alone and developed rash (n = 4), irritation (n = 2), chemical burn (n = 2) and paraesthesiae (n = 1). *Conclusions:* This is the largest study reported to date and confirms that ocular exposure may lead to conjunctivitis and keratitis, findings reported previously[1–3] and from which recovery is to be expected. Ingestion may also result in drowsiness; CNS depression has been observed previously[4] though the mechanism is unclear. Parents have a vital role to play in ensuring that these products are stored safely at all times. *References:* 1. Horgan N, McLoone E, Lannigan B, et al. Eye injuries in children: a new household risk. Lancet 2005; 366:547–8. 2. Fayers T, Munneke R, Strouthidis NG. Detergent capsules causing ocular injuries in children. J Pediatr Ophthalmol Strabismus 2006; 43:250–1. 3. Mathew RG, Kennedy K, Corbett MC. Wave of paediatric eye injuries from liquid detergent capsules. Br Med J 2010; 340:c1186. 4. Wood KL, Thompson JP. Liquitabs - a thorough and comprehensive review of the UK national data. Clin Toxicol 2009; 47:459.

241. Toxicity of Household Products in the UK

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Objective: To ascertain the toxicity of current UK household products. *Methods:* Between 1 March 2008 and 30 April 2009 the UK National Poisons Information Service collected prospectively 5939 telephone enquiries relating to household products, approximately 12% of all telephone enquiries. *Results:* The majority of enquiries (65.5%) concerned children five years of age or less and were received predominantly from hospitals (32.1%), general practitioners (29.8%) and NHS Direct/NHS 24 (28.5%). The majority of exposures occurred at home (97.6%); most exposures were accidental (93.6%). Liquid detergent capsules were most commonly involved (n = 647) followed by bleach (n = 473), multipurpose cleaners (n = 408), descalers (n = 397) and disinfectant/antiseptic/sanitiser liquids (n = 270). Intentional exposures were more likely to involve bleaches, multipurpose cleaners and disinfectant/antiseptic/sanitiser liquids. Exposure to household products occurred mainly as a result of ingestion (75.8%), with eye contact (8.4%), inhalation (6.9%) and skin contact (3.1%) being less common; 5.1% of enquiries involved multiple routes of exposure. The most commonly reported features were vomiting (ingestion), pain (eye contact), dyspnoea (inhalation) and burn (skin contact). In 5840 of 5939 enquiries the Poisoning Severity Score was known at the time of the enquiry. The majority of patients (70.5%) were asymptomatic, 28.0% had developed minor features, 75 patients had developed moderate features and nine patients had developed serious features (PSS 3). Five of these nine patients made a complete recovery, though two developed severe complications and two others died from poisoning with drain cleaner and PVC solvent cleaner; the outcome in two is unknown. *Conclusions:* Household product exposures are common in the UK, in other parts of Europe[1] and in the US[2], though they rarely result in severe sequelae. *References:* 1. Rauber-Lüthy C, Kupferschmidt H. Household chemicals: management of intoxication and antidotes. In: Luch A, ed. Molecular, Clinical and Environmental Toxicology. Volume 2: Clinical Toxicology. Basle, Switzerland: Birkhäuser Verlag, 2010:339–63. 2. McKenzie LB, Ahir N, Stolz U, et al. Household cleaning product-related injuries treated in US emergency departments in 1990–2006. Pediatrics 2010; 126:509–16.

242. Dimethylfumarate Exposure: A New Series of 123 Cases Notified to the French Toxicovigilance System and the REVIDAL GERDA Network

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Objective: In France, from October 2008 to January 2009, more than 100 cases of serious skin disorders were reported, following contact with dimethyl fumarate (DMFu) contaminated sofas or shoes, mostly imported from South-East Asia. Despite the European ban on these products at the end of 2008 and the removal of contaminated items from their homes, some people were still reporting health effects. So, a second survey of DMFu exposure cases was conducted between January 2009 and February 2010. *Methods:* The French toxicovigilance system and the REVIDAL GERDA network (a surveillance system in dermatology) were requested to collect new symptomatic cases potentially related to supposed DMFu contaminated items. A careful analysis of each reported case was carried out by a toxicologist and a dermatologist. Independently, each physician achieved a causal link assessment based on a specific method using chronological clinical and bibliographical criteria like the French pharmacological method. *Results:* 123 cases were collected, mainly related to exposures to seating (in 45 cases) and shoes (in 61 cases). Contact irritative dermatitis and/or allergic dermatitis were reported in 113 cases. Respiratory symptoms without further examinations were reported in 8 cases, 6 of them associated with dermatitis. According to the imputability method, 6 cases were classified as highly likely, 11 as likely, 45 as plausible and 29 cases remained doubtful. Thirty-two cases were considered without relevant link. All dermatological lesions resolved after removal from exposure to the suspected item. Respiratory symptoms persist in 3 patients. One-third of cases occurred before January 2009, but were reported after. For the remaining case, the start of exposure or information regarding the date of purchase or first use remains somewhat unclear. *Discussion:* Cases of dermatitis, possibly linked to DMFu contaminated items, were reported after the European ban, which may be explained by late distribution of contaminated items or illegal import. Persistence of some clinical signs after removal of contaminated items may be related to secondary pollution of adjacent clothes or pieces of furniture, as shown in a recent French study conducted by The French Agency for Food, Environmental and Occupational Health & Safety (ANSES). Non dermatological symptoms deserve further investigations and should be carefully searched in patients with contact dermatitis.

243. Investigation of Dimethylfumarate Contamination in 14 French Dwellings

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Objective: In France, from October 2008 to January 2009, more than 100 cases of serious skin disorders were reported following contact with dimethylfumarate contaminated sofas or shoes,[1] which were forbidden on the French market in December 2008. This ban was extended to all products containing dimethylfumarate in Europe in March 2009.[2] Despite the removal of suspected or contaminated products from their homes, some people are still reporting health problems. An updated review of French dimethylfumarate exposure cases notified to the French toxicovigilance system was achieved between 2009 and 2010. In order to assess dimethylfumarate concentrations in these dwellings, environmental measurements were carried out in 2009 by the French Agency for Food, Environmental and Occupational Health Safety (Anses). *Methods:* Dwellings were selected following 4 criteria, the inhabitants had to: (i) be members of one of the two French dimethylfumarate victims' associations, (ii) declare the previous presence of a sofa suspected to contain dimethylfumarate in the dwelling, (iii) have reported acute dermatological symptoms possibly related to dimethylfumarate exposure, (iv) still complain about health problems. Different textile materials in direct contact with contaminated sofas, or located in the same room, were sampled as well. Dimethylfumarate was extracted with ethanol and quantified by gas chromatography-mass spectrometry. The quantification limit was 0.1 mg/kg and the detection limit was 0.02 mg/kg. *Results:* 74 textile samples in 14 dwellings were analysed. Dimethylfumarate was quantified in 16 samples from 6 dwellings. Measured concentrations comprised between 0.1 and 0.6 mg/kg for materials in direct contact and between 0.2 and 1.4 mg/kg for the other materials. Dimethylfumarate was detected but not quantified in 6 other samples. *Discussion:* These results suggest that removed contaminated sofas could have been the source of dimethylfumarate contamination of the tested textile materials. Other explanations such as a previous contamination of these materials before their introduction in the dwellings cannot be excluded. No conclusion can be made on the link between residual dimethylfumarate contamination and persistent adverse health effects. *References:* 1. Flesch F, Lefranc A, Cochet A, et al. Contact dermatitis to dimethyl fumarate in seats or shoes: 118 Cases Notified to the French Toxicovigilance System. Clin Toxicol 2010; 48:256–7. 2. Commission Decision 2009/251/CE.

244. 2-Chloroethanol Intoxication: Analysis of Cases

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Objective: 2-Chloroethanol (ethylene chlorhydrin, CAS 107-07-3) is a solvent commonly used in industry and noted to be highly toxic in animals and humans. In Taiwan, farmers apply 2-chloroethanol to grapevines to accelerate sprouting, and put themselves at risk of accidental intoxication. Severe intoxication presenting with hypotension, respiratory failure, seizure, coma or mortality can occur even after only skin or inhalational exposure.[1] *Case series:* We reviewed the medical charts of 2-chloroethanol intoxication cases from four hospitals in the region of grape cultivation. Chronological data, exposure histories and clinical presentations were recorded and analyzed. *Results:* From 1993 to 2010, 36 cases in total with more complete records were analyzed. There were 17 lethal cases (mortality rate 47.2%) with older age (average age 60.7 $\pm$ 10 years vs. 45 $\pm$ 15.6 of survivors), 82% (14 cases) with oral exposure who only survived by 13.6 $\pm$ 7.9 hours. Most of the patients presented initially with gastrointestinal symptoms and mild somnolence, but deteriorated rapidly to refractory hypotension in lethal cases. Fomepizole had been used in 9 cases for 1–6 days with seven survivals. *Conclusion:* 2-Chloroethanol is highly toxic to farmers. 2-Chloroethanol is a halide alcohol and might be metabolized to more toxic metabolites by alcohol dehydrogenase, and, therefore, the enzyme antagonist fomepizole might play a potential and crucial role in 2-chloroethanol intoxication.[2] *References:* 1. Deng JF, Yang CC, Tsai WJ, et al. Acute ethylene chlorohydrin poisoning: experience of a poison control center. J Toxicol Clin Toxicol 2001; 39:587–93. 2. Chen YT, Liao JW, Hung DZ. Protective effects of fomepizole on 2-chloroethanol toxicity. Hum Exp Toxicol 2010; 29:507–12.

245. A Case Report Concerning Monochloroacetic Acid

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Objective: To report a case of acid injury after ingestion of a wart remover containing monochloroacetic acid. *Case report:* A 2.5 year old boy ingested about 1 mL of a wart remedy containing 50% monochloraocetic acid, a corrosive also causing systemic toxicity. Initially he vomited at least 5 times, but there were no other signs or symptoms. He was taken to hospital by ambulance helicopter. On admission 90 min after the accident he was awake and stable. Blood pressure was 89/61, pulse 110, SaO_2 99%, RF 32/min. He had four small ulcerations around his mouth; the inside was pale with moist mucous membranes without lesions. Gastric decontamination was not performed. In the ICU he was given N-acetylcysteine IV, 850 mg in 500 mL in 5% glucose over 4 hours, in addition to metoclopramide, cefuroxime and omeprazole. He was not allowed to eat or drink. Except for a lowered pO_2 (9.2–10.7 kPa) and elevated ALAT (57 U/L), all blood tests were normal. The next day he had blisters on his lower lip and tongue. An endoscopy performed under general anesthetic was uncomplicated, and demonstrated significant superficial acid-injuries over the entire length of his esophagus. There were no deeper lesions, and no bleeding or damage to the stomach. IV omeprazole and N-acetylcysteine were continued, sucralfate was added, and he was allowed to take fluids. Two days after the accident he was discharged. A control endoscopy 5 weeks later was normal, but swallowing was still painful. *Conclusion:* Monochloroacetic acid has caused several deaths after skin exposure or swallowing.[1,2] Ingestion of 5 mL wart remover in a comparable case was lethal.[1] Our case had a favourable outcome, probably due to a small amount of acid and early vomiting. Although the burn lesions were extensive, they were superficial. No evident systemic effect was seen, as opposed to other cases. *References:* 1. Rogers DR. Accidental fatal monochloroacetic acid poisoning. Am J Forensic Med Pathol 1995; 16:115–6. 2. Kulling P, Andersson H, Boström K, et al. Fatal systemic poisoning after skin exposure to monochloroacetic acid. J Toxicol Clin Toxicol 1992; 30:643–52.

246. Diversely-Sized Particulate Matter Air Pollution (PM2,5, PM10–2.5) is Associated with Different Acute Manifestations of Diseases in the Emergency Department

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Objective: Particulate matter (PM) air pollution has been associated with cardiovascular and respiratory disease.[1,2] Recent studies have also proposed a link with venous thromboembolism.[3,4] This study aimed to investigate the relationship between diversely-sized particulate matter air pollution and different acute manifestations of disease in Emergency Department, focusing on thromboembolic disease. *Methods:* We have collected data about Emergency Department (ED) accesses for cardiovascular or respiratory disease, as well as environmental data about daily levels of PM10, PM2.5, temperature, humidity and atmospheric pressure in the period between May 1st 2007 and June 30th 2009. Coarse PM (PM10–2.5) was calculated by subtracting PM2.5 from PM10. *Results:* During the considered period a total number of 7,076 diagnoses of respiratory and cardiovascular acute diseases were observed. In a multiple regression model adjusted for other atmospheric parameters daily levels of PM2.5

presented a positive correlation with chronic obstructive pulmonary disease (COPD) exacerbation (beta-coefficient = 0.217; P = 0.003), while those of PM10–2.5 were correlated with heart failure (beta-coefficient 0.151; P = 0.002) and venous thromboembolism (beta-coefficient = 0.237; P = 0.020). During the days with levels of PM10–2.5 higher that the 75th percentile, there was an increased risk of observing ED accesses for venous thromboembolism (OR 1.69 with 95% CI 1.13–2.53). On the other hand, no significant association was found with cardiovascular or cerebrovascular disease. As regards venous thrombosis risk, interestingly, in a subgroup of subjects without active thrombosis and without anticoagulant therapy (n = 103) an inverse correlation between PM10–2.5 and prothrombin time was found (R = −0.226; P = 0.022). *Conclusion:* This study suggests that diversely-sized PM air pollution may be associated with different acute manifestations of human diseases (COPD, heart failure and venous thromboembolism). In particular, PM10–2.5 may be related with thrombophilia and venous thromboembolism risk. *References:* 1. Brook RD, Rajagopalan S, Pope CA 3rd, et al. Particulate matter air pollution and cardiovascular disease. An update to the scientific statement from the American Heart Association. Circulation 2010; 121:2331–78. 2. Stieb DM, Szyskowicz M, Rowe BH, et al. Air pollution and emergency department visits for cardiac and respiratory conditions: a multi-city time-series analysis. Environ Health 2009; 8:25. 3. Dales RE, Cakmak S, Vidal CB. Air pollution and hospitalization for venous thromboembolic disease in Chile. J Thromb Haemost 2010; 8:669–74. 4. Pope CA 3rd. The expanding role of air pollution in cardiovascular disease: does air pollution contribute to risk of deep vein thrombosis? Circulation 2009; 119:3050–2.

247. Peripheral Neuropathy and Encephalopathy Associated with Residential Exposure to Roofing Solvents

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Background: Organic solvent exposure can be associated with peripheral neuropathy and encephalopathy. Neurological disabilities in association with residential exposure to roofing adhesives have not been reported. *Case report:* A 38 year old man was in prior good health and employed as an educational psychologist with good performance evaluations. He took no medications, used neither alcohol, nor tobacco, nor drugs, and denied solvent abuse. There was neither personal nor family history of diabetes. He lived with his wife on the top floor of a residential apartment building. Roofing work was undertaken using adhesives containing hexane, heptane, toluene, and xylene. Noxious chemical odors in the apartment forced his wife to leave for a five day period until the work was completed. The man remained in the apartment due to an approaching deadline for completing a doctoral dissertation requiring access to his computer and data. When his wife returned, she found her husband confused. She described strong chemical odors in the apartment. The Health Department was contacted and performed air sampling after the roofing work was completed and after the apartment was 'aired out' for four days. Toluene levels were 10 ppm. Xylene levels were 20 ppm. After the exposure, the man developed a complex illness with irritability, difficulty with memory and concentration, weakness, fatigue, insomnia, irritant rhinitis, muscle shaking and cramping, and extremity weakness. Nerve conduction studies found evidence of a chronic polyneuropathy affecting predominantly distal nerves, described as a dying back neuropathy. Neuropsychological testing found mild to moderate deficits in learning, memory, attention, and mental flexibility, with pronounced slowing of psychomotor speed and impaired manual dexterity. Electro-vestibular and electro-ocular tests were abnormal, with both central and peripheral abnormalities. He lost the ability to read due to difficulties with short term memory, was terminated from his job for poor job performance though all pre-morbid evaluations were good, and was unable to complete his doctoral dissertation. *Conclusion:* Exposure to roofing adhesive solvents in a residential apartment building was associated with onset of peripheral neuropathy and encephalopathy. Careful monitoring should be instituted when roofing solvents are used with precautions to protect occupants.

248. Poisonings Caused by "Chumbinho", an Illicit Rodenticide Used in Brazil

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Objective: To describe the profile of poisonings caused by "chumbinho" (cholinesterase inhibitors) followed by the Campinas PCC. *Methods:* A descriptive, transversal study based on data collected prospectively from 07/2009 to 06/2010. Variables analyzed included demographics, circumstances of exposure, clinical manifestations, length of hospital stay (LOS), treatments performed, identification of pesticides (LC/MS), cholinesterase activity (at admission and after 24 h and 48 h; Elman's method) and classification of severity using the Poisoning Severity Score (PSS; 0–4) based on the overall clinical course. *Results:* Seventy-six patients were poisoned with "chumbinho" over a 12 month period. Age ranged from 2 to 74 years (median = 36 years), and 53.9% were male. Circumstances of poisoning included: suicide attempt (92.1%), attempted homicide (5.3%), accidental ingestion (2.6%). Most of the patients (96.1%) were symptomatic, with predominantly cholinergic muscarinic manifestations and an average LOS of 7.4 days. Atropine was given in 82.9%, and mechanical ventilation used in 46.1%. Table 1 summarizes the gastrointestinal decontamination procedures. Plasma toxicological analysis (n = 59) revealed: aldicarb (55), carbofuran (2), aldicarb with carbofuran (1) and undetected (1). In 14 patients with sequential cholinesterase measurements, partial and uniform recovery of enzymatic activity was observed every 24 h, consistent with carbamate poisoning. The cases were classified as asymptomatic (5.3%), mild (11.8%), moderate (35.5%), severe (43.4%) and fatal (4%) (PSS, mean ± SD = 2.3 ± 0.9). *Conclusion:* Most exposures to "chumbinho" were due to suicide attempts, were severe and were caused by aldicarb, with a fatality rate of 4%. Gastrointestinal decontamination did not affect the LOS and outcome.

Table 1. Gastrointestinal decontamination procedures after poisoning with "Chumbinho"

Subgroups, time after ingestion/ gastrointestinal decontamination	Gastric lavage, N (LOS; PSS)*	Activated charcoal, N (LOS; PSS)*
≤1 h	24 (3.0; 2.0)	14 (4.0; 2.5)
>1 h	24 (3.5; 2.0)	11 (4.0; 2.0)
not determined	14 (5.5; 3.0)	12 (6,5; 3.0)
not performed	14 (4.0; 2.0)	39 (3.0; 2.0)
p (LOS; PSS)[#]	0.268; 0.796	0.272; 0.115

*Median values. LOS = length of hospital stay (days); PSS = Poisoning Severity Score (Persson *et al.,* 1998). [#]Kruskal-Wallis nonparametric test for independent samples.

249. Intratesticular Injection of Printer Ink: A Case Report

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Background: Inkjet cartridge injection is rarely described in medical literature.[1] Inkjet printer inks have generally low toxicity, but they may contain potentially harmful ingredients like p-anisidine, organic solvents or lead which may be more dangerous in cases of parenteral administration. *Case report:* A 29 year old male, drug addict, was admitted to hospital due to injection of 10 mL of ink from inkjet printer cartridge into his right testicle. Injection occurred after three days of alcohol and metamphetamine binge. According to anamnesis one year earlier, acting under the influence of alcohol and metamphetamine, the patient removed his left testicle with a knife. On admission to the hospital tremor of hands and tongue was present. The patient complained also of nausea, epigastric and muscle pain. Initial ultrasound demonstrated presence of fluid in the right testicle and gas bubbles in the scrotum. Whole blood count revealed mild leukocytosis of 15.1 G/L. Surgical revision demonstrated puncture of the testicle and no ink inside the scrotum. The examination of patient's semen performed a week after injection showed black color of ejaculate, sperm count of 1.2 million/mL, with 88% of dead, and only 1% of mobile sperms. The black color of urine was observed for nine days after the event. Other laboratory tests were within normal range. Control ultrasound made ten days later demonstrated persisting fluid reservoir in the right testicle. The patient was discharged home and the next follow up was scheduled to be done in a month. *Conclusion:* Intratesticular injection of printer ink resulted in no significant systemic toxicity, however, semen examination showed severe impairment of sperm viability. The clinical symptoms observed in our patient were mainly connected with drug intoxication, and disappeared after diazepam injection. Further examinations must be done to evaluate late toxicity of injected ink. *References:* 1. Heden F. [Case report. Ink intoxication - a man colored blue] [Article in Swedish]. Lakartidningen 2001; 98:2719–20.

250. Cardiac Dysrhythmia Induced by Perchloroethylene - Acute Poisoning - Case Report

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Objective: The majority of cases of perchloroethylene (PCE) intoxication are due to chronic inhalation. However, the acute effects of PCE vapor inhalation are also possible and associated with cardiac, hepatic, and renal involvement.[1,2] A few deaths have even been reported.[3,4] We describe a rare case of acute PCE poisoning (first case in last 15 years), presenting with signs of cardiac toxicity and with favorable outcome. *Case report:* A 45 year old female was admitted to the Clinic of Toxicology after one hour's exposure to PCE vapor with unknown concentration, because of a defect of the dry cleaning machines. The patient was conscious, tachypneic, with blood pressure 160/100 mm Hg, Signs of eye and upper airway irritation were present: swollen and erythematous palpebrae, lacrimation, rhinitis, cough. Nausea, dizziness, malaise, headache, tremor and impaired coordination were present. Laboratory monitoring did not show signs of hepatic or renal involvement. Blood gas analyses showed compensated respiratory alkalosis and pH 7.419. EEG was normal. X-ray of the lungs did not show pathological changes. Also, there was no clinical or echocardiographic evidence of heart disease. Endoscopy of the upper gastrointestinal tract showed erosive gastritis and duodenal ulcer with positive CLO test. ECG at admittance: nodal rhythm, frequency 60/min, horizontal electrical axis, monomorphic ventricular extrasystoles (VEs). Third day ECG: sinus rhythm, frequency 57/min, horizontal electrical axis. The patient

was discharged on the seventh day without signs of CNS stimulation/depression and without any dysrhythmia. *Conclusion:* PCE acute poisonings may present with signs of CNS irritation and different types of dysrhythmias, including nodal rhythm, without hepatic or renal involvement. ECG monitoring for possible induction of arrhythmias should be carried out in all patients exposed to perchloroethylene. *References:* 1. Abedin Z, Cook RC Jr, Milberg RM. Cardiac toxicity of perchloroethylene (a dry cleaning agent). South Med J 1980; 73:1081–3. 2. Choi YH, Kim N, Seo YS, et al. ARF requiring hemodialysis after accidental perchloroethylene ingestion. Am J Kidney Dis 2003; 41:E11. 3. Gamier R, Bedouim J, Pepin G, et al. Coin-operated dry cleaning machines may be responsible for acute tetrachloroethylene poisoning: report of 26 cases including one death. J Toxicol Clin Toxicol 1996; 34:191–7. 4. Lukaszewski T. Acute tetrachloroethylene fatality. Clin Toxicol 1979; 15:411–5.

251. Hepatic Dysfunction Following Acetic Acid Ingestion

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Objective: Acetic acid ingestion may result in corrosive injury to the upper gastrointestinal tract. Searching Medline, we have found only a few reports of hepatic failure in intentional acetic acid poisoning. We present a case of hepatic injury in accidental acetic acid poisoning. *Case report:* A 50-year old woman was admitted to a regional hospital half an hour after an accidental ingestion of approximately 50 mL of 80% acetic acid. Upon admission she was alert, with signs of respiratory distress (tachypnea, 87% hemoglobin oxygenation). Her blood pressure was 144/80 mmHg, heart rate 55/min. She had perioral and oral burns, dysphagia with odynophagia and was drooling extensively. Upper gastrointestinal endoscopy showed extensive corrosive injury with oral, pharyngeal, esophageal and gastric necroses and isolated areas of gastric bleeding. She was transferred to our centre and was put on infusion of crystalloids, analgesics and a proton pump inhibitor. Initial laboratory tests showed abnormal liver tests: aspartate aminotransferase 4.6 μkat/L (normal values <0.58 μkat/L), alanine aminotransferase 1.07 μkat/L (normal values <0.74 μkat/L) and lactate dehydrogenase 4.54 μkat/L (normal values <3.2 μkat/L). The next day the signs of hepatic injury were at their highest: aspartate aminotransferase 12.01 μkat/L, alanine aminotransferase 13.96 μkat/L, lactate dehydrogenase 20.10 μkat/L. Creatinine, urea, creatine kinase, alkaline phosphatase, gamma-glutamyltransferase and bilirubin levels, as well as INR, all remained normal. Abdominal ultrasound showed a moderately enlarged liver with what appeared to be diffuse parenchymal changes. We ruled out other toxic and viral causes of hepatic dysfunction. Enzyme levels returned to their normal in course of the next couple of days and further recovery was uneventful. *Conclusion:* Accidental acetic acid ingestion may present early with hepatic failure beside corrosive injury to the upper gastrointestinal tract.

252. Phosphoric Acid Poisoning: A Case Report

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Objective: To present a rare case of poisoning characterized by serious cutaneous burns and gastrointestinal irritation as a result of a suicidal attempt. *Case report:* A 52-year-old-man ingested and spilled an unknown amount of a solution containing 50% phosphoric acid down his front. Clinical examination revealed chemical burns of 2nd and 3rd degree on 30% and 10% of body surface (head, trunk and arms), respectively. Skin and ocular decontamination was performed with large irrigation of saline. Ocular lesions appeared particularly severe. An esophagogastroscopy performed during the initial evaluation showed widespread hemorrhages, erosions and transmucosal ulcerations, with a grade 2B esophageal injury. Gastric tube was not inserted. Laboratory results were: metabolic acidosis (pH 7.10 units), hyperphosphatemia (3.87 mmol/L, normal values: 0.81–1.61), hypocalcemia (1.54, n.v. 2.02–2.6), severe hypoglycemia and a lengthened clotting time (INR 6.97, n.v. 0.8–1.2). Hypotension required dopamine and generous filling: in the acute phase we infused crystalloids, colloids, red blood cells and plasma. Electrolyte correction was performed. The main systemic symptoms and signs were due to central nervous system involvement (shiver, spread, excitement). Prolonged sedation and three weeks of mechanical ventilation were necessary. The patient had a good systemic recovery except for a serious sight impairment because of the severe cataract he developed. *Conclusion:* Chemical burns caused by phosphoric acid are uncommon and data about specific treatment are few. Phosphoric acid spilling or ingestion can quickly lead to death. Double exposure forced us to very aggressive therapy that fortunately has been successful. Early recognition of affected areas and adequate resuscitation are fundamental.

253. Methemoglobinemia due to Local Treatment of Skin with Gunpowder: A Case Report

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Objective: Methemoglobinemia is a disorder characterized by the presence of a higher than normal level of methemoglobin in the blood. Methemoglobin is an oxidized form of hemoglobin that has almost no affinity for oxygen, resulting in almost no oxygen delivery to the tissues. When its concentration is elevated in red blood cells, tissue hypoxia can occur. Gunpowder is a mixture of sulfur, charcoal and potassium nitrate. Compounds containing nitrates can cause methemoglobinemia. This case report presents clinical and laboratory changes (methemoglobin levels) due to local treatment of skin with gunpowder in patients with psoriasis. *Case report:* We report a 58 year old woman with acquired methemoglobinemia, hospitalized in the Toxicology Clinic, MHATEM "Pirogov". The patient arrived at the hospital after repeated local treatment of skin with gunpowder on the occasion of psoriatic changes - for self-treatment. She complained of severe headache, general weakness, muscle aches, dizziness, nausea, vomiting, abdominal pain, shortness of breath. She had cyanosis of the skin and the lips. She reported a history of psoriasis and diabetes mellitus. Vital signs were: pulse rate 78/min, RR 110/70 mm Hg, respiratory rate 18/min. On physical examination the patient was conscious, but sleepy and relaxed, she had central and peripheral cyanosis without tachypnea or tachycardia. Skin and mucous membranes were cyanotic. The pupils were normally broad. Lungs - clear vesicular breathing bilaterally. Cardiovascular system: heart - rhythmic activity without added noise. The abdomen was soft. Hepatosplenomegaly was not detectable. Extremities were without edema, but with cyanosis to the end-phalanges of the upper and lower limbs. Laboratory data: hematology studies, biochemical parameters, acid alkali equilibrium - in the reference values. Arterial blood gas analysis (ABG) showed hypoxia with normal pH. Her methemoglobin levels (in dynamic) were: 31.7%, 23.5%, 7.80%, 4.80% and 2%. (Normal = 0–2%). Treatment consisted of infusion of fluids; corticosteroids, large doses of ascorbic acid, oxygen. The patient remained in hospital for five days. *Conclusion:* Acquired methemoglobinemia is a treatable condition that causes significant morbidity and even mortality. Severe and moderate degrees of intoxication can be caused by nitrate compounds, penetrating the human body through the skin.

254. Healthy Homes for Healthy Children: Preventing Accidental Kerosene (Paraffin) Ingestion in Children in Developing Countries

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Background: Besides house and road accidents, in accidental poisoning in children within the house itself, kerosene poisoning is a major problem. In particular in developing countries, where kerosene is still used daily on a large scale for different purposes such as cooking, lightning and for rural medicine. Over the past 15 years, data from Egypt to Sri Lanka have shown that risk. Kerosene accounts for about 60% of pediatric poisonings in Kenya and South Africa. *Methods:* Analysis of available information and literature in order to: 1. find the main causes for accidental kerosene ingestion and 2. prepare a framework for the prevention of accidental kerosene ingestion in children from developing countries. To obtain a deeper view about the most recent or current scenarios in different parts of the developing world several 'International Program on Chemical Safety' (IPCS) offices and Poison Centers in South-East Asia and the African region were contacted. *Results:* Kerosene was found as the most common cause of accidental poisoning in children among household poisonings. Mortality was found to be low, but morbidity was high. Children aged 1–3 years were most likely to be involved in accidental kerosene poisoning. Improper storage of kerosene was detected as the main contributory factor for these accidents. Kerosene was found to be stored in jars, bottles or containers previously used for beverages and juices and these were in easy access of children and mistaken by children for something to drink. *Conclusion:* Accidental kerosene ingestion is a public health issue in the developing world, because children are innocent and parents are not aware and careful enough about storage of kerosene. There is a need for education and increased awareness regarding the poisonous effects of kerosene. Active interventions such as campaigns in schools and local hospitals, performing dramas on the street especially in rural areas, should educate people about safe storage practices. Also they could be provided with safety information (flyer, stickers, symbols etc) and printed information on the back of the pay receipt each time they buy kerosene. Illegal and unsafe kerosene sale has to be stressed.

255. Thermal and Chemical Skin Burns in the Republic of Benin: An Underestimated Cause of Avoidable Mortality in the Developing Countries

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Introduction: Burns represent a worldwide public concern with a special issue in the developing countries due to persistent high-rate mortality. The recently funded Senegalese Poison Centre in Dakar was mandated to develop a prevention policy to limit the consequences of thermal and chemical skin burns among the poorest rural population, including in neighboring African countries. To date, epidemiological data on burns are missing in Benin. *Methods:* We conducted a retrospective descriptive study during a 3-year period (2007–2010) including all cases of skin burns admitted into a rural hospital in Benin. Circumstances, clinical, and outcome data were collected. Results are given as median (25–75th percentiles). Comparisons according to outcome were performed using Chi-2 and Mann-Whitney tests. *Results:* We collected 37 cases (age: 5 years [2–25];

sex ratio: 18M/19F), suffering from thermal (31/37), chemical (5/37), and electrical burns (1/37). Burns were related to domestic (23/37), traffic (7/37), and work accidents (5/37) or assault (2/37). Burns were superficial second degree (22/37), deep second degree (13/37), deep third degree (1/37), and superficial first degree (1/37). Burns involved skin with Wallace scores of 54% [36–72]. Additionally an ocular burn was noted in only one case. Delay to hospital admission was 1 hour [0.5–2.6]. Management included washing with sterile isotonic saline (36/37), non-opioid (29/37), opioid analgesics (8/37), and rehydration (37/37, volume: 1,250 mL [1,000–2,000]. All patients received antibiotics, including penicillin M/metronidazole combination (24/37), 3rd generation cephalosporins/metronidazole (3/37), penicillin M/aminoglycoside (3/37), penicillin M/macrolide (1/37). Only 7/37 patients received anti-tetanus serum. Care included vigorous cleaning (15/37) and bandages (8/37). Seventeen patients died, 8/37 returned home despite advice, 1/37 developed hospital-acquired infection, and 11/37 presented successful outcome on follow-up. The parameters significantly associated with death were age ($p = 0.03$), Wallace score ($p = 0.0007$), burn depth ($p = 0.005$), and severity of dehydration ($p = 0.01$). *Conclusion:* Skin burns still represent a serious concern in developing countries, particularly in Benin, with an elevated mortality rate among young people. Efficient prevention is required, based on the identification of compounds and behaviors at risk.

256. Criminal Poisoning with Aldicarb

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Objective: To report a case of cholinergic toxidrome induced by aldicarb and review the current literature. *Case report:* Ten minutes after ingesting coffee in the break room, four paramedics simultaneously developed a cholinergic toxidrome involving blurred vision, muscle weakness, sweating, nausea, vomiting and profuse diarrhoea. Clinical examination revealed miosis, but no bradycardia or salivation. Toxicological analysis of the coffee revealed the presence of aldicarb, an insecticide, nematicide and acaricide of the carbamate class. Blood analysis carried out at different times after presumed absorption showed neither aldicarb nor its metabolites however plasma pseudocholinesterase was reduced. Clinical improvement occurred within three hours with symptomatic treatment without atropine or pralidoxime. *Discussion:* Aldicarb, whose marketing has been prohibited in the EU since 30 April 2007, is a reversible inhibitor of cholinesterase. Toxic effects appear at doses below 0.01 mg/kg with a very steep dose-response curve.[1] Biology shows a transient decrease of plasma pseudocholinesterase. In severe intoxications serum aldicarb level from 850 to 900 ng/mL and concentrations of 250 to 1000 ng/mL in 24 hour urine have been reported.[2] Concentrations for mild poisoning have not been recorded. Symptoms are of short duration due to spontaneous hydrolysis of the AChE-carbamate linkage. The antidote of choice is atropine. The indication for plasma cholinesterase reactivators seems controversial. *Conclusion:* This case series shows that possible criminal contamination of a beverage with the acutely toxic carbamate aldicarb can cause symptoms of cholinesterase inhibition despite the absence of measurable levels of the compound or its metabolites in blood. This apparent low ingestion appears responsible for the favourable clinical outcome. *References:* 1. Rotterdam Convention - Operation of the prior informed consent procedure for banned or severely restricted chemicals - Draft decision guidance document for aldicarb. November 24, 2008; p 10–15. 2. Jarlet E, Bédry R, Berthommier JM, et al. Incidence and characteristics of severe methomyl intoxications (a carbamate insecticide) on Reunion Island. Réanim Urgences 2000; 9:177–84.

257. Lactate and pH Value as a Measure of Severity of Metformin Overdose: An ICU Italian Experience

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Objective: Metformin, a common oral antidiabetic drug of the biguanide class, is sometimes associated with hazardous lactic acidosis and high mortality rate. The aim of our study was identify a correlation between pH, lactate levels, time to normalization, treatment and mortality in patients with metformin overdose, in comparison with a recent review.[1] *Methods:* We performed a retrospective observational study, selecting 10 diabetic patients admitted to ICU for metformin overdose. We considered for each patient: outcome; pH at admission (IpH); nadir of pH (NpH) lowest pH; blood lactate level at admission (ILac) and peak lactate (pLac); days in hospital; time (inflection day) of the normalization of pH and lactate; treatment with continuous renal replacement therapy (CRRT); intercurrent disease; and APACHE II. *Results:* We identified 10 patients, 8 females and 2 males, mean age 67.2 ± 9.6 years and a mortality of 10%, all except one treated by CVVH (continuous veno-venous hemofiltration). In the group of survivors the average pH was 7.11 ± 0.17 and NpH 7.05 ± 0.18; lactates were 18.04 ± 6.55 for ILac and 18.67 ± 6.97 for the pLac. In the only fatal case IpH was 6.95 and NpH was 6.93; ILac and pLac were equal to 32 mmol/L. Lactacidemia and pH normalized in all cases within the 3rd day of hospitalization. *Conclusion:* Non survivors with metformin overdoses have lower values of NpH and pLac higher than survivors. NpH and pLac were confirmed as useful indicators of survival, in particular high levels of pLac. The average NpH (7.11) and pLac (18.67) in survivors was very different than those of the reference work. In contrast, the value of pLac in the non-survival patient was close to that of 35 mmol/L found by Dell'Aglio in non-survivors. The paucity of patients does not allow us to affirm the validity of the inflection day; early use of CRRTs might explain the low mortality, but their impact on survival cannot be determined with certainty. *References:* 1. Dell'Aglio DM, Perino LJ, Kazzi Z, et al. Acute metformin overdose: examining serum pH, lactate level, and metformin concentrations in survivors versus nonsurvivors: a systematic review of the literature. Ann Emerg Med 2009; 54:818–23.

258. Severe Cobalt Intoxication due to Metal-on-Ceramic Pairing in a Hip Arthroplasty

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Objective: The essential heavy metal cobalt is toxic at high exposures. Severe cobalt intoxication after surgery with metal-on-ceramics hip replacement is described. Slow abrasion of the metal by ceramic particles has led to a serious toxicity. *Case report:* A 56-year-old man underwent total hip prosthesis (ceramics-on-ceramics); 3 years later his ceramic inlay had broken. During a revision of the hip, ceramic fragments were carefully removed and the wound was repeatedly cleaned; then a metal head was used. Alloys in metal implants contained cobalt, chromium, titanium, and aluminum. The patient was admitted 20 months later due to the luxation of the hip head. An extraordinary amount of metallic mass was observed during the surgery. In addition, cardiomyopathy with large pericardial exudate, severe sensimotor polyneuropathy, hypothyreosis, and severe hypacusis were found. Cobalt serum level reached 506 (N lower than 0.9) micrograms/L, chromium 14.3 (N lower than 0.5) micrograms/L. Concentration of cobalt and chromium in pericardium punctate was 930, and 29.6 micrograms/L; in liquor 8.5 and 0.96 micrograms/L; in urine 138.6 (N lower than 1.0) and 18.8 L (N lower than 0.5) micrograms/L, respectively. Unithiol increased urine cobalt and chromium elimination from 291 to 458 and from 35.1 to 50.6 micrograms/24 h. Plasma cobalt level decreased to one half within 3 months, and the symptoms gradually improved. *Conclusion:* Metal-on-ceramics arthroplasty should be avoided as cobalt intoxication may result from abrasion of the metallic head by small residues of the previous hip ceramic implant. The patient's condition improved after symptomatic and antidotal treatment. The effect of Unithiol is difficult to evaluate, as a successful recovery at similar cobalt level without the antidote has been seen.[1] On the other hand, cobalt concentrations up to 50 times higher compared to controls were found even 4 years after surgery.[2] Unithiol may be considered in life-threatening cobalt intoxications. *References:* 1. Oldenburg M, Wegner R, Baur X. Severe cobalt intoxication due to prosthesis wear in repeated total hip arthroplasty. J Arthroplasty 2009; 24:825. 2. Lhotka C, Szekeres T, Steffan I, et al. Four-year study of cobalt and chromium blood levels in patients managed with two different metal-on-metal total hip replacements. J Ortop Res 2003; 21:189–95. *Acknowledgements:* MSM0021620807.

259. Acute Hepatotoxicity Caused by Deliberate Ingestion of Gold Potassium Cyanide with Quantitative Determination of Gold in Serum and Urine

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Objective: Poisoning with oral ingestion of gold potassium cyanide is rarely reported. We describe a case of deliberate ingestion of potassium dicyanoaurate by a patient who developed severe cholestatic hepatitis. We additionally provide kinetic data of gold in serum and urine. *Case report:* A depressive 33-year-old male goldsmith deliberately ingested about 80 mL of an electroplating solution containing potassium dicyanoaurate, equivalent to about 1 g of gold. Soon after, he vomited and was admitted to hospital. Here, vital signs were stable, physical examination was unremarkable and routine clinical chemistry showed only slightly elevated lactate (3.1 mmol/L), normal transaminases but an increase in γGT (64 U/L) and leucocytes (13.2 G/L). Toxicological analysis at admission revealed a serum ethanol level of 1.58 g/L and a cyanide-level lower than 0.1 mg/L. The patient did not present symptoms and signs of cyanide intoxication. However, the next day, about 20 h after ingestion, laboratory pointed to a leading cholestatic hepatic injury (AST 526 U/L, ALT 480 U/L, AP 135 U/L, γGT 1498 U/L, bilirubin 7.4 mg/dL). An elevation of alpha-amylase, creatine kinase and LDH was also evident. A normal cystatin C, cystatin-clearance, serum creatinine and glomerular filtration rate (GFR) did not point to renal injury. Blood count and coagulation parameters were normal. Cholestatic parameters peaked 26 h after ingestion and decreased slowly but still were elevated (bilirubin 1.5 mg/dL, γGT 727 U/L, AST 48 U/L, ALT 221 U/L) at day 8 when the patient was finally transferred for further psychiatric evaluation. Other reasons for cholestatic hepatitis were excluded. Gold in EDTA-plasma 2.5 h after ingestion was 3787 µg/L, peaked at 4571 µg/L some 29 h after ingestion and decreased according to a one-phase exponential decay function with a terminal half-life of 31 h. Within the first 5 days, cumulative urinary excretion of gold was less than 3 mg and therefore negligible. *Conclusion:* Dependent on the composition of gold containing electroplating solutions, toxicity is primarily gold-related rather than being associated with cyanide poisoning. Gold-induced hepatotoxicity that can appear

delayed seems to be the primary manifestation of toxicity and may be fatal in large overdoses. Treatment is mainly supportive.

260. Blood Lead Levels in 6-year-old Sudanese Children

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Objective: To conduct the first ever pediatric blood lead surveillance study in Sudan, the geographically largest nation in Africa with a population of 40 million. Sudan has a growing petrochemical industry, and leaded gasoline was used nationwide until 2000. *Methods:* A cross-sectional survey of blood lead level (BLL) was undertaken in convenience samples of healthy 6 year old children attending well-child visits at outpatient clinics of hospitals in two urban centers, Khartoum and Omdurman, and the rural town of Aldiwaim. Capillary blood samples were analyzed for lead using the ESA Lead Care II system. Lower limit of quantification (LLQ) was 3.4 micrograms/dL. Statistical analysis was done by SigmaStat (version 3.5). A questionnaire on demographic and potential exposure factors was administered to subjects' parent(s) and in further analysis we will explore association between lead concentration and demographics to identify potential risk factors for lead exposure. Participation was by voluntary informed consent in accordance with a protocol approved by the research and ethical committee of the Federal Ministry of Health of Sudan. *Results:* In this survey of 209 Sudanese children, BLLs exceeded 5 micrograms/dL in more than 50% of both urban and rural subjects (Table 1), a significant elevation compared to developed countries such as the United States, where less than 5% of children have BLLs >5 micrograms/dL.[1] *Conclusion:* Further investigation of potential sources of exposure is warranted. *References:* 1. Centers for Disease Control and Prevention. Fourth National Report on Human Exposure to Environmental Chemicals. Atlanta, USA. CDC 2009. http://www.cdc.gov/exposurereport/pdf/FourthReport_ExecutiveSummary.pdf [accessed 24 November 2010].

261. Hemolytic Anemia After Taking Lead Containing Herbal Medicines: A Case Report

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Background: Lead intoxications had been reported in patients who took alternative medicine, but in adults, hemolytic anemia attributable to lead intoxication after taking Chinese herbal medicines has been rarely reported in the literature. *Case report:* A 45-year-old woman visited a local hospital complaining of anorexia and fatigue. Her blood work was significant for a normocytic anemia (hemoglobin 7.9 g/dL, mean corpuscular volume 96 fL), positive Coomb's test with an elevated bilirubin (total: 2.1 mg/dL, direct: 1.0 mg/dL), alanine aminotransferase, aspartate transaminase, alkaline phosphatase and gamma-glutamyltransferase. Autoimmune hemolytic anemia was suspected, and she received two-month steroid therapy. She came to our medical center due to persistence of symptoms. Follow-up blood tests showed hemoglobin 10.8 g/dL, with basophilic stippling, mean corpuscular volume 104 fL, platelet 119,000/cumm, and negative Coomb's test. A blood lead level was obtained, with a value of 75 μg/dL (reference range: <10 μg/dL). On further query, the patient had consumed lead containing Chinese Medicine for five months prior to becoming ill. Chelation therapy was started with succimer (2,3-dimercaptosuccinic acid). However, she developed itching and skin eruption. Use of another chelating agent, ethylene diamine tetraacetic acid (EDTA) successfully lowered the blood lead level and improved the anemia. *Conclusion:* This case is presented to emphasize the importance of medication histories, including alternative medicine, while approaching patients with hemolytic anemia.

262. Quantification of Blood Concentration of Mercury and Arsenic in the Healthy Population in Aragon (Spain)

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Objective: Despite their long toxicological history, arsenic and mercury are still a matter of environmental and public health concern. Their ubiquitous presence in food and water produces their persistence in the human body. Their effects at low blood concentrations and their precise threshold in non exposed populations are still contentious. In the particular case of mercury, its presence in the human environment (dental amalgams, vaccines, batteries, light bulbs, thermometers) and the biased publicity, readily reaching people through the media and the Internet, are leading to frequent analytical demands whose results can give way to misunderstandings and further demands for useless and even dangerous treatments. Therefore, we think we need to maintain an accurate profile of arsenic and mercury blood concentrations in the current healthy population that can significantly fluctuate among different regions and different alimentary habits. *Methods:* We have obtained 121 blood samples from healthy blood donors (87 men and 34 women). Epidemiological data obtained from the donors were: age, sex, race and postal code. Mercury and arsenic blood concentrations were analyzed by means of inducible coupled plasma mass spectrometry (ICP-MS). *Results:* The mean Hg concentration was 7.6 micrograms/L ($\pm$4.7) and the mean arsenic concentration was 3.3 micrograms/L ($\pm$3.5). By sex the mean mercury concentration in men was 7.7 micrograms/L ($\pm$4.6) and the mean arsenic concentration was 3.5 micrograms/L ($\pm$3.8); in women, the mean mercury concentration was 7.3 micrograms/L ($\pm$5.02) and the mean arsenic concentration was 3.0 micrograms/L ($\pm$2.2). In relation to the residential area we have found mean values very similar for arsenic concentrations in urban (3.3 ± 3.4) and rural areas (3.6 ± 3.8) and mean values of mercury slightly higher in rural (9.5 ± 4.2) than in urban areas (7.5 ± 4.7) without statistical significance. It is remarkable that 26.4% of subjects had a mercury blood concentrations above the current standard reference levels (<10 micrograms/L). *Conclusion:* It is necessary to maintain a periodic control of the concentrations of mercury and arsenic in healthy populations in order to be able to revise, if needed, the standard levels for the supposed non exposed population to avoid unfounded public alarm.

Table 1. Blood lead concentrations in Sudanese children

Site	Number of subjects			Blood Lead Concentration (mcg/dL)			
	Total	M	F	Median	Range	% $\geq$5	# of readings $\leq$ LLQ
Khartoum	129	78	51	5.30	3.4–17.9	54.26	11 (8.5%)
Omdurman	42	20	22	5.40	3.6–12.7	59.52	3 (7.1%)
Aldiwaim	38	21	17	5.40	3.4–14.4	52.23	4 (10.5%)

263. Occupational Poisoning in Spain as Observed in the Emergency Departments and in the Toxicology Information Service

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Objective: Acute occupational poisoning is a human toxic issue difficult to survey due to the different possible organizations involved and the dispersion of the cases among different settings. The aims of the Spanish Program for Toxicosurveillance (TSP) focus on the surveillance of acute poisoning by chemicals attending hospital Emergency Departments (EDs). One of the involved groups comes from the occupational field. Another source of information was the Spanish Information Toxicology Service (SIT). We have analyzed the characteristics of the occupational cases in the TSP and their particularities versus the total chemical cases. We have also compared the occupational data from the TSP and the SIT sources to assess the differences between them. *Methods:* We compared the cases' frequency, sex, chemical agent involved, route of entry and main clinical symptoms in the total and occupational TSP cases in ten years and the occupational SIT cases in one year. *Results:* TSP has accumulated 6,012 chemical cases between 1999 and 2008, of which 1,042 are occupational cases (17%). Among the total SIT 78,210 in one year, 1,095 (1.4%) were occupational cases. Both TSP and SIT cases are evenly distributed by sex (50%) but occupational cases from both sources of data are more frequent in men (73% and 63%) than in women (27% and 30%) ($p < 0.05$). The main differences from both databases are: a higher proportion of cases by toxic gases (17% versus 2%) and irritant gases (22% versus 10%) in the TSP than in the SIT cases ($p < 0.05$) and a lower proportion of cases by pesticides (12% versus 22%) and detergents (2% versus 9%) in the TSP than in the SIT cases ($p < 0.05$). A higher proportion of respiratory and ocular routes of entry and of respiratory symptoms in the TSP cases ($p < 0.05$) have also been detected. *Conclusion:* These sources of data show some slight but significant differences and have to be analyzed together in order to get a broader picture of acute occupational poisoning in Spain.

264. Long Term Lead Exposure and Health Effects

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Introduction: Lead is a poison that affects virtually every system in the body. It has been suggested that the nonspecific symptoms of inorganic lead intoxication are related to the effects of the blood lead level. *Methods:* A total of 503 battery recycling workers with long-term exposure to inorganic lead between the ages of 36 and 45 years in this study filled out a questionnaire of paraclinical symptoms. The SPSS software version 11.5 and STATA version 8 was used for statistical analysis; the chi-square, Fisher's exact

test and the parametric tests were used. Logistic regression modeling was used for multivariable analysis. *Results:* Sub-populations in this study consisted of 285 (56.6%) with BLL >40 μg/dL and 218 (43.4%) with BLL <40 μg/dL. The mean age was 41.7 years with mean job experience of 13 years and mean BLL was 43.3 μg/dL. The most prevalent symptoms were: lower limb pain (p-value = 0.007), memory loss (p-value = 0.02), depression (p-value = 0.04), pyrosis (p-value = 0.08); no effects on blood pressure, triglyceride, cholesterol, low density lipo protein, high density lipo protein, blood urea nitrogen, creatinine were seen. *Conclusion:* This study showed that more prevalent symptoms have started near BLL = 40 μg/dL. The earliest symptom was lower limb pain and the latest symptom was sleep disorders. The frequency of symptoms was related to blood lead levels especially greater than 40 μg/dL and also the symptoms were more prevalent in new workers with BLL than long time exposed workers with higher BLL. Strategy for regular health monitoring in industry is mandatory. *References:* 1. Candela S, Ferri F, Olmi M. Lead exposure in the ceramic tile industry: Time trend and current exposure levels. [Article in Italian]. Ann Ist Super Sanita 1998; 34:137–43. 2. Baker EL, Landrigan PJ, Barbour AG, et al. Occupational lead poisoning in The United States: clinical and biochemical findings related to blood lead levels. Br J Ind Med 1979; 36:314–22.

265. Cytochrome p450 Enzymes and Their Role in Poison Control Centre Information Supply

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Objective: Cytochrome p450 enzymes play a major role in the phase I metabolism of many xenobiotics.[1] Main enzymes involved are CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Their contribution to adverse events and interactions in therapeutic drug use has been extensively studied, but their significance in clinical toxicology is not well known. Antidepressants and antipsychotics are often involved in suicide attempts, and many of these drugs are metabolized by cytochrome p450 enzymes.[1] To investigate if the information supply from Poison Information Centres should be adjusted according to p450 interactions, we investigated to what extent those interactions are suspected. *Methods:* All multi-intoxications of at least one antipsychotic or antidepressant, combined with any other substance, reported to our Poison Information Centre in the year 2009 were included. Ingested compounds were categorized as substrate, inhibitor and/or inducer for the above mentioned enzymes, based on the Flockhart table[2] and the psychresidentonline table[3]. Potential interactions were investigated. *Results:* Of total information requests about 18,169 patients, 3069 patients ingested an antidepressant, and 2224 patients ingested an antipsychotic. Among those patients, 2081 in the antidepressant group and 1545 in the antipsychotic group had a multi-intoxication (n = 2856, overlap in 770 patients). Median ingestion among the 2856 multi-intoxication patients was 3 compounds (range 2–16). Interactions on p450 level were recorded in 1646 out of 2856 patients (57.6%). The order of involvement is CYP3A4 (n = 1331, 46.6%) > CYP2D6 (n = 1034, 36.2%) > CYP2C19 (n = 396, 12.9%) > CYP1A2 (n = 227, 7.9%) > CYP2C9 (n = 88, 3.1%) > CYP2E1 (n = 74, 2.6%) > CYP2B6 (n = 3, 0.1%) > CYP2C8 (n = 1, 0.04%). *Conclusion:* In the majority of cases of multi-intoxications with antipsychotics or antidepressants, interactions on p450 level are suspected, with the genetically polymorph enzymes CYP2D6 and CYP2C19 among the top 3 enzymes. This indicates that their role in clinical toxicology cannot be ignored. However, more research needs to be done to analyze to what extent these interactions influence clinical outcome after intoxications. *References:* 1. Zanger UM, Turpeinen M, Klein K, et al. Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. Anal Bioanal Chem 2008; 392:1093–108. 2. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed 4 October 2010. 3. http://www.psychresidentonline.com/CYP450%20drug%20interactions.htm

266. Laboratory Results - When the Figures Don't Fit the Facts!

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Objective: Information relating to interference in certain biochemistry analyses is readily available in the scientific literature, yet the UK National Poisons Information Service (NPIS) still regularly receives enquiries from clinicians struggling to interpret unexpected results. We report three recent cases that serve to illustrate how erroneous laboratory results can confuse the clinical picture and even lead to misdiagnosis in cases of poisoning. *Case series:* 1. A 19-year old male presented at hospital claiming a deliberate ingestion of methanol. He appeared clinically well but had a markedly raised serum creatinine - 766 μmol/L. He had been admitted 10 days previously with a paracetamol overdose and it was assumed that the elevated creatinine was a consequence of this and his methanol story was disregarded. An NPIS specialist advised that nitromethane in model engine fuel is known to give falsely high results with certain (Jaffé) creatinine assays. This was confirmed and antidotal treatment was commenced for methanol ingestion. 2. A 35-year old male was admitted with acidosis (pH 6.8) and a raised serum lactate concentration of 24 mmol/L. A preliminary diagnosis of cyanide poisoning was made and antidote considered. An NPIS specialist advised that certain Point of Care blood gas analysers have been reported to provide falsely elevated blood lactate concentrations when ethylene glycol metabolites are present. Blood lactate was measured on a different instrument and shown to be within normal limits. Antidotal therapy was commenced for ethylene glycol ingestion - a diagnosis subsequently confirmed by blood ethylene glycol measurement and a markedly raised osmolar gap. 3. A 3-year old girl was admitted with a 3-day history of vomiting. She was obtunded, acidotic (pH 6.9) and had a serum salicylate concentration of 50 mg/L, although there was no history of aspirin ingestion. Supportive treatment was initiated and a search at home for possible sources of salicylic acid made. A suggestion by NPIS to the clinician that metabolic disorders such as Maple Syrup Urine Disease can cause acidosis and give false positive salicylate results was later confirmed to be the case. *Conclusion:* The possibility of assay interference should be considered when the figures don't fit the facts.

267. Development and Validation of a Fully Automated Toxicological Liquid Chromatography-Mass Spectrometry Screening System in Urine Using Online Extraction with Turbulent Flow Chromatography

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Objective: Liquid chromatography-mass spectrometry (LC/MS) is a powerful tool widely used for forensic targeted drug screening. However, the quality of LC/MS data collected is largely affected by sample preparation methods. Offline solid phase extraction (SPE) and liquid liquid extraction (LLE) are the most often used sample preparation methods. These methods are often quite time consuming. Here we will present an automatic online sample preparation method for the screening of more than 400 acidic, neutral and basic drugs in urine with LC/MSMS. *Methods:* Sample preparation was performed by an online sample extraction method utilizing the TurboFlow technology. Two TurboFlow columns (Cyclone, C18XL) were connected in series and used for sample extraction. Urine samples were run both natively and after enzymatic hydrolysis. The eluent was then transferred to the LC column (Betasil Phenyl-Hexyl, 100 × 3 mm, 3 μm) for separation. A 30 mn gradient from 1% to 98% organic was employed for separation of the analyte with flow rates of 300 μL/minute. All samples were then analyzed on a LXQ ion trap mass spectrometer (Thermo Scientific) with the APCI source and a scan-dependent polarity switching method was used for data acquisition. MS2 and MS3 spectra were acquired. *Results:* The method using on-line extraction has been fully validated. A minor matrix effect (suppression < 5%) was observed for over 98% of the compounds. 90% of the substances showed a recovery of more than 90%. The limit of identification (LOI) was below 10 ng/mL for 60% of the substances and 90% could be identified at a concentration of 100 ng/mL. 103 patient samples were analyzed. A total of 451 substances could be identified using the combination of both established methods (GC/MS and LC/MS specific methods on a triple stage mass spectrometer) and the new on-line extraction method. When using only the established methods, 354 substances (78%) could be identified. With the new method, 404 substances (89%) could be identified. *Conclusion:* The online TurboFlow method with the LXQ ion trap mass spectrometer allows the identification of more than 400 compounds with LOIs of 10 ng/mL for the majority of the compounds.

268. Retained Drugs in the Deceased

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Objective: Since gastrointestinal (GI) decontamination is controversial and there is a trend toward less intervention we sought to evaluate the presence of undissolved drugs in the GI tract of fatal overdoses and define factors that might contribute to continued drug presence. *Methods:* Autopsy reports from the New York City Office of the Chief Medical Examiner were reviewed from 01/01/2009 to 12/31/2009. Inclusion criteria were: deceased of all ages, whose cause of death was established as "overdose" or "intoxication," from ingestion of drugs in the tablet form. Exclusion criteria were: cause of death attributed solely to drugs in a non-tablet form, or traumatic death. *Results:* 623 cases were reviewed; 355 cases met inclusion criteria. Dissolved and partially dissolved tablets were present in the stomach of 24 cases (6.7%). Actual tablets were identified as Oxycontin® in 2/24 cases, and not identified in 22/24 cases. Opioids were present in 12/24 cases, and anticholinergics in 16/24 cases and remained uncertain in other 2/24. Modified release venlafaxine was confirmed in one case. Salicylates were present in one case. The time from ingestion was challenging to determine, since 23/24 patients were dead at presentation. *Conclusion:* Dissolved and partially dissolved tablets were found on autopsies of 24/355 (7%) people, with 22/24 cases (91.6%) containing drugs that slow gut motility such as opioids and anticholinergics, and drugs that may have delayed absorption such as salicylates and modified-release preparations. Patients with severe toxicity may have retained drugs in their stomach which may undergo further absorption, suggesting consideration for GI decontamination in selected patients.

269. Potential Utility of Plasma Butyrylcholinesterase and RBC Acetylcholinesterase Determinations as Rule-Out Testing in the Setting of Nerve Agent or Organophosphate Mass Exposure

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Objective: Cholinesterase determinations have been used to identify organophosphate exposed patients and guide duration of oxime therapy, and may distinguish patients with mild organophosphate/nerve agent exposure from those who are manifesting stress reactions.[1,2] An Institutional Review Board (IRB)-approved study to determine a U.S. population range of butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE) evaluated relationships to a number of demographic variables. *Methods:* 976 patients ranging in age from 0–95 years in 3 hospital settings underwent a standard questionnaire and determination of cholinesterase activities by spectrophotometric analysis using a variety of instruments. *Results:* The mean (SD; instrument) plasma BuChE was 7 Units/mL (1.6; Ortho DT60); AChE 15.4 Units/mL (3.1; COBAS Integra 800). Although trends were present for age and underlying chronic medical conditions, none of these were predictive for individuals. AChE determinations were independent and were not predicted by low or high BuChE. *Conclusion:* A large hospital-based population sample of U.S. residents demonstrates Gaussian distribution of cholinesterase activities, consistent with reports of other geographically and ethnically distinct populations.[3–5] A low normal BuChE cannot distinguish a mildly poisoned individual from one with a stress reaction in the setting of an organophosphate/nerve agent exposure. However, the finding of a normal range AChE would be reassuring; and in concert with continued clinical evaluation, could allow better utilization of medical resources including oxime therapy. While our sample over-represents certain chronic conditions, these results are likely applicable to the general population. *References:* 1. Worek F, Koller M, Thiermann H, et al. Diagnostic aspects of organophosphate poisoning. Toxicology 2005; 214:182–9. 2. Wu AHB, Smith A, McComb R, et al. State-wide hospital clinical laboratory plan for measuring cholinesterase activity for individuals suspected of exposure to nerve agent chemical weapons. Clin Toxicol (Phila) 2008; 46:110–6. 3. Mohammad FK, Alias AS, Ahmed OAH. Electrometric measurement of plasma, erythrocyte, and whole blood cholinesterase activities in healthy human volunteers. J Med Toxicol 2007; 3:25–30. 4. Simpson NE. Factors influencing cholinesterase activity in a Brazilian population. Am J Hum Genet 1966; 18:243–52. 5. Calderon-Margalit R, Adler B, Abramson JH, et al. Butyrlcholinesterase activity, cardiovascular risk factors, and mortality in middle-aged and elderly men and women in Jerusalem. Clin Chem 2006; 52:845–52.

270. Beta-hydroxybutyrate, Glucose and Lactate in the Postmortem Diagnosis of Alcoholic and Hyperglycemic Ketoacidosis

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Objective: The aim was to evaluate the importance of beta-hydroxybutyrate (BHB), glucose and lactate in the post mortem diagnosis of alcoholic versus hyperglycemic ketoacidosis as the possible cause of death. *Methods:* Evaluation of toxicological results in death cases identified in our institute in the study period 2006–2010 with an *ante mortem* history of alcohol use, without an anatomical or pathological cause of death, and in which BHB, glucose, and lactate were determined in blood, urine, and/or vitreous humor post mortem. *Results:* Four males and three females (21–59 years) were identified in the study period. At autopsy, no anatomical or other cause of death could be detected. Toxicological analysis of alcohol, drugs-of-abuse and prescription drugs did not reveal a toxicological cause of death: alcohol was detected in blood in three cases (0.03 to 1.8 g/L), in urine in four cases (0.06 to 2.4 g/L), and drugs detected were found in non-fatal concentrations. Acetone was detected in blood and/or urine in all cases. Based on the combined glucose and lactate levels in vitreous humor, hypoglycemia was concluded in one case (glucose < 0.3 mmol/L; lactate 14 mmol/L) and hyperglycemia in two other cases (glucose: 6.6 and 55 mmol/L; lactate: 47 and 21 mmol/L, respectively). Acetoacetate which is quickly decarboxylated in the body was detected in one case only, in a low concentration. BHB concentrations were elevated or high in all cases: 1 to 14 mmol/L in blood, and 1 to 31 mmol/L in vitreous humor. In the literature, BHB concentrations in vitreous humor below 0.5 mmol/L are considered to be normal, from 0.5 to 2.5 mmol/L considered to be elevated, and concentrations higher than 2.5 mmol/L are considered as pathological. Based on the combined BHB, lactate, and glucose concentrations, it was concluded that alcoholic ketoacidosis was the likely cause of death in five cases and hyperglycemic ketoacidosis the likely cause of death in two cases. *Conclusion:* BHB, glucose, and lactate are important parameters to differentiate between alcoholic and hyperglycemic ketoacidosis as the likely cause of death in forensic cases with an *ante mortem* history of alcohol use.

271. Blood Ethanol Concentrations in Traumatic Emergencies

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Objective: Alcohol consumption is becoming a major problem in Bulgaria. The purpose of our study is to examine the relationship between alcohol use and traumatic emergencies among patients hospitalized in the Emergency Medicine Institute "Pirogov". *Methods:* 154 traumatic emergencies as a result of traffic accidents (TAs), domestic accidents and assaults (DAAs) or work-related accidents (WRAs) over a one year period (01/01/08-31/12/08) were studied. Blood samples for determining blood ethanol concentration (BEC) were drawn at the time of hospitalization in all trauma cases. Samples were analyzed by using the HS-GS-FID method. All values above 0.05 mg/mL were considered positive. Types of trauma and their relationship to alcohol consumption and BEC were analyzed. *Results:* Overall samples for 50% of patients ($n = 77$) were positive for BEC. Average BEC was 1.89 mg/mL [0.05–5.42 mg/mL]. From all male trauma patients 52% were positive for alcohol, while only 33% of female trauma casualties were positive. The highest number of positive cases was registered for the age 18–25 years (56% of all patients from this age group were positive for alcohol). 74% of all trauma patients, admitted to hospital between 0:00 a.m and 6:00 a.m had positive BEC. Alcohol was related to 64% of the DAAs, 56% of the TAs and 15% of the WRAs. The highest average BEC is registered in TAs (2.13 mg/mL), followed by DAAs (1.84 mg/mL). A statistically significant difference was found in comparison with cases of WRAs ($p < 0.0001$), where the average BEC was 0.52 mg/mL. Cases with polytraumatic injuries and brain injuries were the groups most frequently related to alcohol consumption - 42% positive cases. Among all BEC positive cases, poly-traumas were with highest frequency (29.9%), followed by brain injuries (19.5%). The highest mean BECs was seen in patients with brain injuries (2.28 mg/mL), in samples drawn between 06:00 pm and 0:00 a.m., and in the age group 46–65 years. *Conclusion:* Alcohol intake provokes various traumas, complicates therapy and worsens prognosis. Early determination of BEC is very important, particularly in patients with brain injuries, for differentiation between toxic and traumatic central nervous system depression. In every single case of trauma, information about presence of ethyl alcohol in blood is needed for forensic practice.

272. Influence of Blood Sampling on Concentration of Ethyl Alcohol in Blood

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Objective: Blood sampling for measuring alcohol is not standardized in Bulgaria. The aim of our study is to determine whether type of blood sampling tube (BST) will change blood ethanol concentrations (BECs) and influence clinical interpretation. *Methods:* Variances in BECs in samples collected from one subject in different BSTs were determined. BECs of 8 volunteers were measured. Four samples at a single point were collected from each: two in BSTs without anticoagulant/preservative (red top), and two in tubes with anticoagulant/preservative (gray top). Effects of some procedures on blood samples, collected in two types of tubes on initial BECs were investigated. Eighteen blood specimens of patients with acute alcohol intoxication were analyzed. Half of the samples were taken in red top tubes, the rest in gray top tubes. Initial BEC was compared to concentrations measured: at triple opening/closing; after staying open for 90 minutes; after storing closed for 24/48 hours at room temperature. *Results:* In each grey top tube sample, BEC was lower than that in red top tubes. Mean difference was $11.9 \pm 4.2\%$ (tubes with over 50% filling) and $15.5 \pm 5.5\%$ (with less than 50% filling). Largest deviations were observed in red top tube samples, with high air chamber, stored open at about 30°C. During simultaneous influence of these factors, the average percentage of ethanol recovery was $77.5 \pm 7.9\%$. In red top samples with smaller air chamber, stored at normal temperature, average percentage of ethanol recovery was $95.2 \pm 2.1\%$. In all grey top samples the percentage of ethanol recovery was above 95.5%. *Conclusion:* Depending on the type of BST and method of processing, BEC vary considerably. These differences do not influence clinical assessments. However such deviations are inadmissible for forensic practice and can influence judicial rulings. A standard protocol for sampling for BEC determination has been prepared for legalization in the country.

273. Respiratory Failure Following Inadvertent Administration of Methylergonovine in a Neonate

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Objective: Medication errors can have substantial effects on morbidity and mortality in the hospitalized pediatric patient. We report a case of a newly born neonate with respiratory failure after receiving a 0.1 milligram dose of methylergonovine. *Case report:* A full-term female infant (1,814 grams) was inadvertently given methylergonovine intramuscularly, instead of a hepatitis B vaccination 1 hour post-delivery. Shortly after medication administration, the patient's extremities became cyanotic and displayed "rhythmic" movements which were interpreted to be seizure-like. The patient was immediately transferred to the neonatal intensive care unit and resuscitated with intravenous fluids. After fluid resuscitation, her symptoms resolved; the patient remained hemodynamically stable and continued to produce urine. Within hours, the patient began to hypoventilate and was endotracheally intubated. Twenty-four hours later she was successfully extubated without further sequelae. Upon review, the

patient received 0.5 milliliters (0.1 milligram) of methylergonovine in lieu of 0.5 milliliters (5 micrograms) of the hepatitis B vaccine; both vials were found to have similar appearing labels. *Conclusion:* Medication errors in the pediatric population can lead to profound morbidity and mortality; resulting in a prolonged hospitalization, and a significant increase in medical expenses.[1] This case illustrates the need for increased awareness, amongst healthcare professionals, in regards to labeling similarities that may exist between different medication classes; thereby, facilitating errors in the correct setting. *References:* 1. Hicks RW, Becker SC, Cousins DD. MEDMARX® Data Report: a Chartbook of Medication Error Findings from the Perioperative Settings from 1998–2005, 2006, Rockville, MD, United States Pharmacopeia Center for the Advancement of Patient Safety. http://www.usp.org/products/medMarx/ (accessed 10 January 2011).

274. Therapeutic Error as a Cause of Unintentional Poisoning in Children

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Objective: To determine how often therapeutic error is the cause of unintentional poisoning in children under six in New Zealand. *Methods:* A retrospective review was undertaken of all calls to the New Zealand National Poisons Centre (NPC) for unintentional poisoning in children aged 0–6 years during the period 1 January - 30 June 2010 (397 calls). Calls were categorised as therapeutic error if they involved an unintentional deviation from a proper therapeutic regimen that resulted in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance. *Results:* A total of 211 calls were identified as being therapeutic error over this period. Therapeutic analgesics were the most common agent involved in therapeutic errors (36%), with incorrect dose being cited as the most common cause of the error (78.7%). Therapeutic errors accounted for 3.33% of all childhood poisoning exposure enquiries to the NPC. This compares to the 2006 AAPCC Annual Report[1] where therapeutic errors comprised 10% of exposures. *Conclusion:* Therapeutic errors are a small but significant cause of unintentional poisoning in children under 6 years of age. Creation of an awareness programme of the dangers of incorrect therapeutic dosing could potentially reduce injury and harm to children. *References:* 1. Bronstein AC, Spyker DA, Cantilena LR Jr, et al. 2006 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS). Clin Toxicol (Phila) 2007; 45:815–917.

275. Ingestion of Benzydamine-Containing Vaginal Preparations Before and After a TV Advertising Campaign

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Objective: To provide a preliminary description of therapeutic errors due to misunderstanding of the correct instructions for use of vaginal preparations containing benzydamine hydrochloride (Tantum Rosa) observed in Italy before and after a TV advertising campaign. *Methods:* The database of the national Poison Control Centre (PCC) of Milan was searched retrospectively and prospectively in order to identify all cases of exposure to Tantum Rosa vaginal preparations occurring between January 1 2004 and December 20 2009, before a TV advertising campaign was launched in Italy, and in the following months, between December 21 2009 and August 31 2010. The ratio observed/expected (O/E) and 95% confidence intervals (95% CI) were estimated assuming a Poisson's process in the occurrence of the events. The main characteristics of cases observed in the two periods were compared using Pearson's χ^2 test. *Results:* Altogether, 201 cases were identified. Of these, 95 were exposed in the pre-advertising period and 106 in the following one. All cases were accidentally exposed. In both periods the most frequently found preparation was Tantum Rosa in 500 mg granular form single-dose packets to be dissolved in water, reported altogether in 185 cases. The ratio O/E in the post-advertising period was 9.8 (95% CI = 8.6–11.8, $p < 0.001$). In comparison with the pre-advertising period, the following period was characterised by a higher percentage of female (92% vs. 77%, $p < 0.05$) subjects exposed for therapeutic error due to oral ingestion of the drug (70% vs. 14%, $p < 0.001$); subjects with clinical effects associated to exposure (53% vs. 26%, $p < 0.001$). Altogether, 82 cases were classified as poisonings. Among these, severity of poisoning was low for 73 cases, including 24 cases occurring in the pre-advertising period and 49 in the post-advertising one. For 9 cases severity of poisoning was moderate. All but one of them occurred in the post-advertising period. Signs and symptoms most frequently reported were: vertigo (24 cases), oesophageal irritation and abdominal pain (18 cases, respectively), vomiting (17 cases), nausea (11 cases), hallucinations and pharyngeal pain (6 cases, respectively), dizziness (3 cases). *Conclusion:* PCCs can be used to evaluate the impact of direct-to-consumer-advertising on drugs misuse and to support prevention strategies.

276. Medication Prescribing Errors in the Prehospital Setting and in the Emergency Department

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Objective: To describe the incidence and characteristics of medication errors in adults during pre-hospital emergency treatment, and in the emergency department (ED), and to identify risk factors for medication errors in those settings. *Methods:* A retrospective study of adult patients transferred by Emergency Medical Services to the ED of a University-affiliated hospital in Israel. The drugs administered in the mobile intensive care unit (MICU) and in the ED were reviewed by two reviewers, who independently decided whether an error had occurred. The primary outcome was the number of drug errors per patient. Secondary outcomes were the type and severity of the errors and variables associated with increased incidence of drug errors. *Results:* During the study period 1,837 patients were brought to the ED by MICU vehicles. Five hundred and thirty-six (29%) patient charts were randomly selected for review; 65 (12.12%) charts could not be found, thus 471 charts were reviewed. In the MICI 188 patients (45.63%) received medications; of those 12.76% (24 patients) were subject to a medication error. The number of drugs administered and long evacuation times were associated with higher risk for an error, $P < 0.01$ and $P = 0.011$ respectively. The presence of a doctor in the MICU did not alter the risk of an error (CI = 0.998–11.350). In the ED 332 patients received medications (72.6%). Of those, medication errors occurred in 120 patients (36.1%). The more medications administered, the higher the risk of error ($P < 0.01$). Fewer errors occurred in trauma patients. ($P = 0.041$; CI = 1.031–4.566). Errors occurred in 36.1% of the patients treated in the ED compared with 12.76% of the patients treated in the mobile ICU ($p < 0.001$). *Conclusion:* More medication errors occur in the ED than in the emergency vehicle. Patients treated with multiple medications are more prone to medication errors.

277. Dosing Errors with Infacol Wind Drops (Simethicone)

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Background: Infacol Wind Drops (simethicone) have been available in Australia for many years for the treatment of infant wind. Recently, the manufacturer introduced a new dosing device using an unusual syringe design. This study aimed to investigate dosing errors with Infacol. *Methods:* A retrospective review of calls made to the NSW Poisons Information Centre during 1 January 2004 to 15 July 2010 involving therapeutic errors with Infacol Wind Drops. *Results:* There were 567 therapeutic errors matching the search criteria: 73 in 2004, 52 in 2005, 87 in 2006, 73 in 2007, 103 in 2008, 120 in 2009 and 59 until mid-2010. The median age was 2 months (interquartile range: 1–3 months; range: 5 days–3.5 years). The median dose given in error was 1.5 mL and the most common erroneous dose was 2 mL (range: 0.2–8 mL), instead of the recommended dose of 0.2 mL for under 2 years, and 0.4 mL for over 2 years. Sixteen infants were brought to hospital following ingestion and three parents consulted a general practitioner. There were no cases of toxicity requiring hospitalisation. *Conclusion:* The most common dosing error was 10 times the recommended dose. Although there have been no reports of serious toxicity associated with simethicone, considerable distress occurs when incorrect doses are given to infants. This research highlights the importance of smart dosing device design and labelling to minimise the risk of dosing errors and the importance of trained sales staff ensuring carers are confident in choosing and delivering the correct dose.

278. Chemical Submission: Results of Toxicological Tests in Sexual Assault Victims

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Objective: Victims of sexual assault frequently refer to mental confusion and amnesia, which are sometimes attributed to the inadvertent introduction of pharmaceuticals or drugs mixed with a drink to facilitate the assault (chemical submission). The aim of this study was to evaluate the presence of xenobiotics in alleged rape victims. *Methods:* During the period May 2009 to July 2010, people attending the emergency department of our hospital due to alleged sexual assault who might have been victims of chemical submission were systematically investigated for the presence of alcohol in the blood and pharmaceuticals (benzodiazepines, methadone, morphine, methylphenidate, scopolamine) or drugs (cocaine, heroin, cannabis, amphetamines, liquid ecstasy [GHB], ketamine) in the urine by immunoassay and gas chromatography coupled with mass spectrometry (GC/MS). *Results:* Eighty-four cases were included. Toxicological analysis was positive for xenobiotics in 45 cases (53.6%). The most-frequently identified substance was ethyl alcohol (48% positive in cases tested). Mean blood alcohol level was 1.48 g/L (range 0.06–5.70 g/L). Other xenobiotics detected were cocaine (17.9% of samples tested), benzodiazepines (15.3%), cannabis (12.9%), amphetamines (3.5%) and opiates (2.3%). No patient tested was positive for GHB, ketamine, methadone, methylphenidate or scopolamine. *Conclusion:* The presence of pharmaceuticals, drugs of abuse and, especially, ethyl alcohol, is common in patients reporting sexual assault with alleged chemical submission. We did not detect GHB, ketamine, methadone, methylphenidate or scopolamine in the urine of our patients. However, delayed collection of urine samples meant that some negative results could not be evaluated.

279. Myeloperoxidase Changes in Serum of Subjects Exposed to Irritant Factors Released During Uncontrolled Fire

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Objective: Evaluation of the concentration of myeloperoxidase (MPO) in serum from 40 patients hospitalized in the Toxicology Unit due to inhalational exposure to smoke from a fire. *Methods:* 40 patients, hospitalized in the Toxicology Unit after exposure to toxic factors released during an uncontrolled fire participated in the project as a study group. They underwent: spirometry, chest x-ray, arterial blood gases evaluation, basal biochemistry tests: full blood count, urea and creatinine level. The MPO concentration was measured in their serum samples at first day (day of admission), the second day and the day of discharge. The MPO concentration was also measured in the serum of blood samples from 10 unexposed, healthy persons (the control group). *Results:* The average age of patients exposed to toxic factors released during the uncontrolled fire was 49.75 years. The most frequent symptoms in the study group were complaints associated with lower airways pathology - declared by 21 (52.5%) patients, pharynx or nose related symptoms occurred in 14 patients (35%), whereas symptoms suggestive of conjunctivitis occurred in 9 (22.5%) patients. Statistically significantly higher levels of carboxyhemoglobin, thiocyanates, C reactive protein were revealed in comparison with the control group on the first day. On the same day of observation, the concentration of MPO measured in the serum samples from the study group was 364.28 nanograms/mL, while in the samples from the control group 323.59 nanograms/mL with $p > 0.05$. No statistically significant changes in MPO levels were found within the study group of 40 patients between the first day and other analyzed days of hospitalization. Spirometry at rest revealed significantly lower values of FVC, FEV1 and FEF25–75% within the study group, compared to controls, with $p < 0.05$. *Conclusion:* Presented outcomes did not reveal the usefulness of MPO determination as a biomarker of exposure to toxic factors released during uncontrolled fire.[1] *References:* 1. Wagner JG, Roth RA. Neutrophil Migration Mechanisms, with an Emphasis on the Pulmonary Vasculature. Pharmacol Rev 2000; 52:349–74.

280. Clara Cell Protein Changes in Serum of Subjects Exposed to Irritant Factors Released During Uncontrolled Fire

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Objective: Evaluation of concentration Clara Cell Protein (CC 16) in serum from 40 patients hospitalized in the Toxicology Unit due to inhalational exposure to smoke from a fire. *Methods:* 40 patients, hospitalized in the Toxicology Unit after exposure to toxic factors released during an uncontrolled fire participated in the project as a studied group. They underwent: spirometry, chest x-ray, evaluation of arterial blood gases, basal biochemistry tests: full blood count, urea and creatinine level. The CC 16 concentration was measured in their serum samples at first day (day of admission), the second day and the day of discharge. The CC 16 concentration was also measured in the serum of blood samples from 10 unexposed, healthy persons (the control group). *Results:* The average age of patients exposed to toxic factors released during uncontrolled fire was 49.75 years. The most frequent symptoms in the studied group were complaints associated with lower airways pathology - reported by 21 (52.5%) patients, pharynx or nose related symptoms occurred in 14 patients (35%), whereas symptoms suggestive of conjunctivitis occurred in 9 (22.5%) patients. Statistically significantly higher levels of carboxyhemoglobin, thiocyanates, C reactive protein and CC 16 were revealed in comparison with the control group. CC16 concentrations measured at first day were 18.61 micrograms/L in the serum samples from the studied group and 10.67 micrograms/L in the samples from control group with $p < 0.05$. Significantly higher CC16 concentrations at the first day were also noted within the group of patients complaining of at least one symptom - 19.65 micrograms/L - in a comparison with the asymptomatic patients. Spirometry at rest revealed significantly lower values of FVC, FEV1 and FEF25–75% within the studied group, comparing to controls, with $p < 0.05$. *Conclusion:* The outcomes presented may indicate the usefulness of CC 16 protein as a biomarker of exposure to toxic factors released during uncontrolled fire.[1] *References:* 1. Halatek T, Opalska B, Swiercz R, et al. Glutaraldehyde inhalation exposure of rats: effects on lung morphology, Clara-cell protein, and hyaluronic acid levels in BAL. Inhal Toxicol 2003; 15:85–97.

281. Risk of Venothromboembolism Associated with Asians using Immunomodulatory Agents

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Objective: Venous thromboembolism (VTE) in patients receiving immunomodulatory agents (iMiDs) like thalidomide and lenalidomide is believed to be uncommon in Asian patients with haematology malignancies.[1] With limited evidence postulating a negligible risk, VTE prophylaxis is commonly omitted. In this study, we evaluate the incidence and risk factors of drug induced VTE in these patients. *Methods:* Patients with confirmed diagnosis of VTE were obtained from a Multiple Myeloma registry maintained in a tertiary institution. Their characteristics and exposure to iMiDs and anti-platelets agents (APA) were compared against other patients in the registry. Thromboprophylaxis was not mandated in this patient population. *Results:* Among 320 consecutive and previously untreated patients entered into the registry, and prospectively followed for 12 years, 18 VTE events (5.6%) were diagnosed. 232 patients (72%) were exposed to an iMiD. Risk of VTE was not associated with patient or disease characteristics at presentation. Exposure to an iMiD was found to be a significant risk factor (17/18 patients developed VTE during or immediately after treatment) giving an iMiD-associated VTE risk of 7.4%. The median time to VTE was 16 months. The cumulative incidence of VTE among patients exposed to iMiDs at 5.6 years (median overall survival) was 12%. *Conclusion:* VTE risk in Asian patients, especially those with haematology malignancies, is substantially higher than postulated and confers a significant morbidity and mortality risk. Events appear to occur later in the course of the disease and were significantly influenced by the cumulative exposure to iMiDs. As iMiDs are essential for the treatment of such patients, physicians should be cognizant of this potential complication. They should also recommend thromboprophylaxis for our Asian patients. *References:* 1. Shyu VB, Wang PN, Chu PH. Low incidence of venous thromboembolism in Asian myeloma patients treated with thalidomide plus dexamethasone. APJOH 2010; 2:41–7.

282. Internet Accessibility and Quality of Product Declarations of Ephedrine Containing Products

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Objective: The illegal trade of ephedrine containing products is an unsolved problem for the Danish health services. A retrospective survey of inquiries to the Danish Poison Information Center[1] indicated careless consumer behavior with intentional intake of large doses for the purpose of weight loss and training enhancement. We wanted to investigate the accessibility of ephedrine containing products for Danish consumers on the Internet, in order to evaluate to what extent poor product declarations could contribute to mislead consumers to believe that these products are harmless. *Methods:* We conducted a one day search on the Internet, using Google as a search engine, with the Danish search terms: Vægttab [weight loss], efedrin [ephedrine] and efedrin produkter [ephedrine containing products]. Limits were set to only include websites in Danish. Pages were only included if it was possible to "go to the cash register". *Results:* 12 websites (519 hits) offering a total of 101 ephedrine containing products were found. Although we performed our search in Danish, only a minority continued in Danish all the way to "cash register". None informed about the illegal import to Denmark. 79% stated the amount of ephedrine per serving, ranging from 10–75 mg ephedrine (mean 24.5 mg $\pm$ SD 12.75). 55.4% warned against potential adverse effects and patients at risk, none in Danish. 83% had information about recommended dose, 12% in Danish. Only 12% of the websites, giving more specific product information were in Danish. In only 13% could the producer be identified. *Conclusion:* Illegal ephedrine products are easily accessed on the Internet by Danish consumers. Only a minority revealed relevant medical information and most declarations were in English. These products do not fulfill the requirements of declaration for medical products and are easily accessible to a group of people who are not medically screened. Therefore, consumers may be at risk of serious adverse effects. Misleading sales slogans, such as "all natural, beneficial to your health, no side effects, scientifically proven" give a false sense of security and may enhance careless and risky consumer behavior. *References:* 1. Kjærgaard CT, Skanning PG, Jürgens G. Retrospective review of ephedrine exposures. An observational case series. Clin Toxicol 2010; 48:262.

283. Postgraduate Education in Clinical Toxicology: 17 Years Experience

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Objective: In many countries clinical toxicology is not a specific medical speciality. In 1994, we started a yearly postgraduate educational course in clinical toxicology. We report the results of 17 years' experience. *Methods:* The education programme started in 1994 with a certification in clinical emergency toxicology. From 2000, we included 2 other options: industrial-environmental toxicology and pharmacovigilance. The programme comprises 5 theoretical courses or modules of one week each [30 hours: (1) Basis and general aspects of toxicology, (2) Acute toxicity of drugs, plants, (3) Acute toxicity of industrial products, (4) Occupational and environmental toxicology, (5) Pharmacovigilance]. Each option includes 3 modules: 1-2-3 for clinical emergency toxicology, 1-3-4 for industrial and environmental toxicology, 1-2-5 for pharmacovigilance. Twenty-six professors or teachers are involved in the programme. All presentations (PowerPoint) are distributed to the students. Each course is evaluated by the students with a grading from 1 (poor) to 5 (excellent). The annual examination includes multiple choice questions, written questions and a dissertation (20–40 pages) with an oral presentation. The official certification is delivered by the university. The course is open to all graduates with a university degree in medicine or pharmacy. *Results:*

Between 1994 to 2010, 272 applicants were registered: 264 were MD and 8 PhD, working in Poisons Centres (22%), Emergency units (35%), Intensive care units (12%), Occupational medicine (27%). Two hundred and nine students were present at the exam and 188 (90%) obtained the certification: 156 in clinical emergency toxicology, 62 in industrial and environmental toxicology and 12 in pharmacovigilance. The mean number of certifications awarded per year was 7 up to 1999 and 14 from 2000. The mean evaluation rating of the courses was 3.9. *Conclusion:* Because clinical toxicology is not a speciality in our country, there is no national education programme and/or certification. However, there is a need for education in clinical toxicology for MDs and PhDs working in units where knowledge of toxicology is mandatory. Although, clinical toxicology is not officially recognised, the number of students attending the courses and the number of certifications justify the continuation of this education programme.

284. Methemoglobinemia is not Associated with Intentional Carbon Monoxide Poisoning

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Introduction: Suicide attempts often involve the inhalation of motor vehicle exhaust. These exhaust fumes are associated with a number of dangerous combustion products such as carbon monoxide (CO), cyanide, nitrogen oxides, and methemoglobin. CO is the predominant toxin associated with suicide attempts from motor vehicle exhaust. A less commonly reported toxicity associated with this type of exposure is methemoglobinemia (MetHmg). *Objective:* To determine the incidence of MetHmg in cases of intentional CO poisoning associated with motor vehicle exhaust fumes. *Methods:* Design: A multi-center retrospective emergency department (ED) cohort. Study setting: 23 New Jersey and New York EDs. Subjects: Consecutive patients with the ED diagnosis of CO toxicity and intentional exposure were identified from January 1, 2000 to October 31, 2006. *Results:* Out of 4.2 million consecutive patients in the 23 EDs, 52 ED patients were identified with intentional CO toxicity (0.012% of all ED patients). Mean age was 40.2 yrs and 25% were female. Mean CO levels were 16.7% with the highest level being 84%. No cases of MetHmg were found. The highest level of methemoglobin was 0.9%. *Conclusion:* Methemoglobinemia associated with intentional CO poisoning is uncommon.

285. Delayed Respiratory Distress in an Infant Following Inhalation of Talc-Containing Baby Powder

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Objective: The inhalation of talcum powder, or finely ground magnesium silicate, is associated with severe respiratory complications, including respiratory arrest and death. Despite safe alternatives, talc unfortunately remains a component of commonly available baby powder products. We report a case of severe pneumonitis with a delayed progression of symptoms following inhalation of talc-containing baby powder. *Case report:* A previously healthy 11 month-old boy was brought to the emergency department 20 minutes after inhaling baby powder (81% talc) during his diaper change. His mother described immediate coughing and cyanosis that improved en route to the hospital. Upon arrival, he was crying with a respiratory rate of 40–60/min, an oxygen saturation of 98%, pulse of 104/min, and temperature of 37.1°C. Lung examination revealed clear breath sounds bilaterally, and a CXR was normal. After consultation with the poison center, he was given prednisone and admitted for observation. The following day he was well-appearing without tachypnea, and was discharged home. Less than 24 hours later, the child returned to the same ED with grunting respirations, subcostal retractions, and diffuse crackles on lung auscultation. There was no history of re-exposure. Vital signs were: respirations 60/min; oxygen saturation 92%; pulse 150/min; temperature 39.7°C. A CXR showed increased bronchovascular markings and thoracic hyperinflation, without focal infiltrate. Nebulized albuterol was given without improvement. The patient was admitted to the pediatric intensive care unit, and received intravenous methylprednisolone and empiric antibiotics. His symptoms slowly resolved over the next two days, and he was discharged in stable condition on hospital day 3 to complete a five day course of corticosteroids. *Conclusion:* In 2008, the American Association of Poison Control Centers reported 2,526 exposures to powders made of talc, 87% of which occurred in children under the age of 6 years. Delayed onset of respiratory symptoms is described up to several hours following suspected talc inhalation. This child developed severe pneumonitis presenting more than 36 hours after inhalation of talc-containing baby powder, and following resolution of his initial symptoms. Clinicians should be aware of the possibility of delayed progression of lung injury following acute talc inhalation.

286. Hemodialysis Clearance of Glyphosate Following a Life-threatening Ingestion of Glyphosate-Containing Herbicide

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Objective: Ingestion of glyphosate-containing herbicides can result in renal failure, electrolyte abnormalities, acidosis, and cardiovascular collapse. In severe toxicity the use of hemodialysis is reported, but largely unsupported by kinetic analysis. We report the dialysis clearance of glyphosate following a suicidal ingestion of a glyphosate-containing herbicide. *Case report:* A 62 year-old man was brought to the emergency department approximately 8.5 hours after drinking a bottle of commercial herbicide containing a 41% solution of glyphosate isopropylamine, in polyoxyethyleneamine (POEA) surfactant and water. Upon presentation, he was bradycardic and obtunded with respiratory depression necessitating intubation and mechanical ventilation. Initial laboratory results were significant for: pH 7.11, PCO_2 64 mmHg, PO_2 48 mmHg, potassium 7.8 mEq/L, Cr 291.7 micromol/L (increased from 84.0 micromol/L three months prior), bicarbonate 22 mEq/L, anion gap 18 mEq/L, lactate 7.5 mmol/L, amylase 364 U/L, hematocrit 46.9%, and a glucose of 27.6 micromol/L. Acidosis and hyperkalemia persisted despite fluid resuscitation. The patient underwent hemodialysis 16 hours post ingestion with an Optiflux F160NR membrane (Fresenius) at a blood flow of 200 mL/min for 2.5 hours. A serum glyphosate concentration drawn prior to hemodialysis was 240 mcg/mL, which decreased to 92.6 mcg/mL after dialysis. Pre- and post-filter serum concentrations were 156 mcg/mL and 12.8 mcg/mL, respectively. After hemodialysis the acidosis and hyperkalemia resolved. The patient remained hemodynamically stable, had improvement in mental status, and was discharged from the intensive care unit in stable condition on hospital day 3. *Conclusion:* The pre- and post-filter serum glyphosate concentrations correspond to an extraction ratio of 91.8%. The hemodialysis clearance was calculated to be 97.5 mL/min. While hemodialysis has been previously employed as therapy for patients with severe toxicity from glyphosate-containing herbicides, this is the first demonstration of the successful clearance of glyphosate by hemodialysis, which corresponded to clinical improvement in a patient who presented with several poor prognostic factors (advanced age, large volume ingested, impaired consciousness). The effect of hemodialysis on the surfactant compound is unknown as it could not be measured. Hemodialysis should be considered when severe acidosis and renal failure complicate ingestion of glyphosate-containing products.

287. The NPIS Pesticide Surveillance Project 2004–2010: Fly and Wasp Killer Exposures

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Objective: To describe fly and wasp killer exposures in patients reported during the 6.5 years of the NPIS TOXBASE® pesticide surveillance project. *Methods:* The National Poisons Information Service Edinburgh Unit (NPISE) monitors pesticide exposures following Internet (TOXBASE®) or telephone enquiries. All patient related accesses to pesticides on TOXBASE® between 1/4/2004 and 1/10/2010 were notified electronically to NPISE, and followed up using on-line, email or paper questionnaires. All NPIS telephone enquiries from 1/9/2009 were also followed up. Enquiries from outside the UK and those where symptoms were deemed not related were excluded. Exposures were analysed for circumstances and symptoms. *Results:* Since 2004 5211 pesticide exposures have been reported to NPISE. One hundred and eighty-nine (3.6%) of these involved accidental exposure to fly and wasp killer products. These products are normally sold as aerosol sprays but occasionally as powders or foams for use on nests. The majority of exposures involved adults (141, 74.6%) and were acute (184, 97.4%). Just over half of patients were male (100, 52.9%) and accidental poisonings frequently occurred while the pesticide was in use; 99 (52.4%). Exposure occurred while in use by another person in 27 (14.3%) cases and after application in 24 (12.7%). Most products were for amateur use: 155 (82.0%). Top agents reported were tetramethrin (91), permethrin (44) and d-phenothrin (36). Route of exposure: inhalation (68, 36.0%); ingestion (30, 15.9%), eye contact (27, 14.3%); skin (17, 9.0%), multiple (47, 24.9%). Commonly reported symptoms were: nausea/vomiting (28); mouth/throat irritation (21); eye irritation (18); skin irritation (17); headache (12); dyspnoea (11); chest pain (10); cough (8); abdominal pain (6); oral paraesthesia (6); unpleasant taste (6); diarrhoea (5); dizziness (5). Poisoning Severity Score (PSS) grading: none (51, 26.9%); minor (123, 65.1%), moderate (10, 5.3%); uncertain (5, 2.6%), no serious poisonings or deaths reported. Moderate cases involved 6 patients with prolonged symptoms, 2 with corneal abrasions, 1 collapse and 1 haematemesis (probably unrelated). *Conclusion:* Accidental exposures to fly and wasp killers account for a small proportion of pesticide exposures overall, however 70.4% reported symptoms. Most of these symptoms were minor but moderate severity did occur. Many symptoms reported may relate to propellants in aerosol products, such as butane and petroleum distillates.

288. Slug Killers: A Common UK Enquiry

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Objective: To describe exposures to slug killers reported to a poisons service pesticide surveillance project. *Methods:* As previously reported, the National Poisons Information Service, Edinburgh (NPISE) monitors pesticide exposures in the UK. All patient related accesses to pesticides of interest on TOXBASE® (Internet poisons database) between 1/4/2004 and 31/08/2010 were notified electronically to NPISE, and were followed up using on-line, email or paper questionnaires, together with all Scottish telephone

enquiries. Enquiries where symptoms were deemed not related to the exposure were excluded. Slug killer enquiries were analysed for products, circumstances and symptoms in adults and children. A Poisoning Severity Score (PSS) score[1] was assigned to each incident by information staff. *Results:* Information on 8832 incidents involving pesticides was collected. Of these 406 (4.6%) involved slug killers (predominantly pellets). Two hundred and sixty incidents involved unidentified slug pellets, 137 metaldehyde, 6 ferric phosphate and 3 aluminium sulphate. Where gender was known (404) the male:female ratio was 1:0.6. Where recorded (394) the median age was 2 years (average 9.5 years; range <1–88 years). Where circumstances were known, in 14 cases the patient was using the product themselves; in 33 cases someone else was using it; 173 incidents occurred after application; 27 due to unsatisfactory storage; and 5 were occupational exposures. For children aged <=12 years (325) PSS0 - 282; PSS1 - 27 (mainly gastrointestinal upset and/or rash/irritation); PSS2 - 1 (prolonged vomiting); uncertain - 15. Seventy cases involved patients >12 years; 33 were the result of deliberate self-harm (PSS0 - 18; PSS1 - 7; PSS2 - 3; PSS3 - 1; uncertain - 4); 36 were accidental (PSS0 -20, PSS1 - 14, PSS2 - 2 (of which one of uncertain connection)). Occupational exposures (5) resulted in no more than minor features. The single severe case involved a deliberate ingestion of a liquid metaldehyde preparation resulting in ITU admission. *Conclusion:* Although slug killers are a common query in the UK, accidental exposure in children seldom results in more than minor features. Deliberate ingestion of liquid preparations may be more serious. *References:* 1. Persson HE, Sjöberg GK, Haines JA, et al. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol 1998; 36:205–13.

289. Acute Poisoning with Imazapyr Herbicide: Taiwan Poison Center Study

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Background: Imazapyr is an imidazolinone herbicide. The herbicidal activity is derived from its ability to disrupt an enzyme (found only in plants) necessary for protein synthesis, and which interferes with cell growth and DNA synthesis in plants. It is thought to be of low toxicity to humans. However, information about clinical effects and fatality in human poisoning is not well known. *Methods:* We retrospectively analyzed all imazapyr exposures reported to the Taiwan National Poison Center between July 1985 and June 2009. *Results:* A total of 59 patients were analyzed. Most exposures (92%) involved suicidal ingestion. Ten out of 54 patients with oral exposure were asymptomatic, while the others developed gastrointestinal (48%), neurological (33%), cardiovascular (17%), respiratory symptoms (11%) and miscellaneous effects. Six patients developed severe toxic effects and three patients died. Case fatality rate from ingestion was 5.6%. Profound shock, coma, respiratory insufficiency and aspiration pneumonia were associated with severe or fatal effects. *Conclusion:* Imazapyr exposure usually causes mild or insignificant effects. However, coma, cardiovascular insufficiency, aspiration pneumonia, or even mortality may occur. Management for imazapyr poisoning is decontamination and supportive treatment, especially respiratory monitoring and ventilatory support, if needed.

290. Aldicarb: A Case Series of Watermelon Borne Carbamate Toxicity

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Background: Aldicarb poisoning has occurred from ingestion of watermelons and cucumbers illegally sprayed with this carbamate insecticide known to be absorbed by watermelons and cucumbers. Despite prohibitions, this dangerous use continues. *Case series:* Seven farm workers presented to a rural hospital with varying degrees of nausea, vomiting, diarrhea, abdominal pain and altered mental status. Symptoms began immediately after sharing a watermelon freshly picked from a field. Toxicology consultation was obtained, a diagnosis of cholinesterase inhibition poisoning was made, and the individuals were empirically treated with atropine and pralidoxime with resolution of symptoms. The remains of the partially consumed watermelon, a second watermelon from the same field, and a watermelon from another source were obtained and frozen at -20 degrees Celsius pending analysis. The Regional Public Health Surveillance Team was contacted and undertook an investigation. Watermelons from the farm were quarantined. Testing of the water source for irrigating was negative. Chemical analysis of the watermelon samples using liquid chromatography and mass spectroscopy revealed contamination with aldicarb, a carbamate insecticide restricted from use on watermelons. The seven farm workers recovered without sequela. Public health actions included: the watermelon patch was tilled under; watermelons were quarantined then destroyed; the farm owner was prohibited from having on site gardens; and workers were educated regarding restricted pesticides and the dangers associated with inappropriate application. *Conclusion:* Despite government regulations, misuse of restricted pesticides such as aldicarb continues to occur. This incident highlights and provides further evidence of the significant health risk associated with consumption of watermelon grown in aldicarb exposed soil.

291. Clinical Experiences of Organophosphate Fungicide Intoxication Patients - Three Cases of Edifenphos and One Case of Iprobenfos

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Background: Patients with pesticide poisoning should be treated as soon as possible, and appropriately, because pesticides have different mechanisms of action. For example, organophosphate fungicides have a different mechanism of action to that of organophosphate insecticides, so, treatment of poisoning with them should be different. However, edifenphos is a kind of organophosphate fungicide which needs the same treatment as organophosphate insecticides. *Case series:* 1. A 46-year-old man was poisoned by an unknown agricultural chemical. His mental status was semicoma with pin-point pupils. There was a large amount of saliva in his mouth. He was treated with pralidoxime and atropine. Later the chemical was identified as edifenphos (organophosphate fungicide). He had SLUDGE (salivation, lacrimation, urination, defecation, gastrointestinal motility, emesis) symptoms with low pseudocholinesterase level (below 200 U/L). 2. A 91-year-old woman was poisoned by an organophosphate fungicide containing edifenphos. She did not have SLUDGE symptoms but did have respiratory failure owing to muscle weakness with low pseudocholinesterase (below 200U/L). She was treated with pralidoxime for 3 days. 3. A 62-year-old man was poisoned by an organophosphate fungicide containing edifenphos. His mental status was semicoma with SLUDGE symptoms and pin-point pupils. He had low pseudocholinesterase level (below 200 U/L). 4. A 74-year-old woman was poisoned by 500 mL of iprobenfos which is also an organophosphate fungicide. Her mental status was alert without SLUDGE symptoms. She was treated conservatively, without using pralidoxime and atropine. *Conclusion:* Both edifenphos and iprobenfos are organophosphate fungicides. Edifenphos inhibits cell wall synthesis by reduction in chitin synthase activity. It also has an inhibiting action on acetylcholinesterase. Iprobenfos, on the other hand, does not have an obvious effect on acetylcholinesterase. Although edifenphos is a kind of organophosphate fungicide, it is the only one having an inhibiting action on acetylcholinesterase. Edifenphos poisoned patients should therefore be treated with pralidoxime and atropine, contrary to the treatment of other organophosphate fungicides. *References:* 1. Din AB, Yarden O. The Neurospora crassa chs-2 gene encodes a non-essential chitin synthase. Microbiology 1994; 140:2189–97.

293. Severe Neurotoxicity Due to Type I Pyrethroid Ingestion in a 19-Month-Old Patient

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Objective: Although pyrethroid exposure is widely reported, severe pyrethroid poisonings are relatively uncommon in the developed world. Pyrethroids are synthetic pyrethrins analogues divided into type-I (without cyano-group) and type-II (with cyano-group). Pyrethroids act on nerve axons, prolonging sodium-channel depolarization and causing hyperexcitation.[1] We describe a 19-month-old patient in whom tonic-clonic seizures and coma occurred after type-I pyrethroids ingestion. *Case report:* A 19-month-old female presented to the emergency department (ED) with recurrent tonic-clonic seizures, bilateral miosis and Glasgow Coma Score 3. Vital signs including blood pressure, oxygen saturation on room air, and body temperature were normal; pulse rate was 130 pulse/minute. A further inquiry revealed that 9 hours before she had accidentally ingested an imprecise amount of Formula-Mayer-Concentrato®, an insecticide containing piperonyl butoxide 7% and type-I pyrethroids (bifenthrin 5%, esbiothrin 3%). Orotracheal intubation, oxygen administration and benzodiazepine infusion were performed. Thiopental sodium up to 18 milligrams/kilogram/hour was intravenously administered to control convulsions. Gastric lavage, activated charcoal and cathartic administration were carried out. During the following 72 hours she became progressively alert; she was extubated six days after admission and discharged asymptomatic 12 days after hospitalization. Bifenthrin and piperonyl butoxide blood levels at 9, 48, 72 hours after ingestion were 500 and 1,640, 95 and 640, 40 and 165 nanograms/milliliter, respectively. Bifenthrin, esbiothrin, piperonyl butoxide were confirmed in gastric aspirate. *Conclusion:* Type-I pyrethroid poisoning is characterized by depression of consciousness, tremors, seizures, paralysis and pulmonary edema.[1] Piperonyl butoxide is an acaricide frequently found in pyrethroid formulations and may increase their toxicity in animals.[2] In our case coma and seizures represented the principal life-threatening features. Supportive therapy and gastric decontamination were performed; benzodiazepines and high doses of thiopental sodium were successfully administered to treat seizures. Bifenthrin and pyperonyl butoxide were confirmed in blood and gastric aspirate samples. In acute pyrethroid poisoning first-aid treatment is therefore of major importance and will include maintenance of an airway and control of muscle fasciculation and seizures. *References:* 1. Bateman DN. Management of pyrethroid exposure. J Toxicol Clin Toxicol 2000; 38:107–09. 2. Goldstein JA, Hickman P, Kimbrough RD. Effects of purified and technical piperonyl butoxide on drug metabolizing enzymes and ultra-

structure of the rat liver. Toxicol Appl Pharmacol 1973; 26:444–58.

294. Atropine Poisoning: Two Severe Clinical Cases Confirmed by Laboratory Analysis

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Objective: To describe two cases of severe anticholinergic poisoning due to atropine ingestion. *Case series:* 1. A 67 year old female pharmacist was brought to the emergency department (ED) with somnolence, rash, mydriasis, hypertension, tachycardia, and hyperthermia. At admission no history was available, and an anticholinergic syndrome was suspected. Gastric decontamination was performed and physostigmine (up to 0.8 mg/kg/hour) was intravenously administered. Later, the daughter found a 1% atropa-extract that the mother had probably drunk in unknown amount. Atropine serum level two hours after admission was 20 nanograms/mL. On day 4 the patient was transferred asymptomatic to a psychiatric ward. Case report 2. An 80 year old retired pharmacist was found in a coma at home, with a bottle of atropine powder nearby. The wife said she had seen him putting a white powder in his coffee. The patient was in chronic treatment with oxycodone, amlodipine and erythropoietin for a multiple myeloma. At ED admission coma, mydriasis, tachypnea, pulse rate 90 bpm, dry skin and mouth were observed. Gastric decontamination was performed and naloxone was administered with slight improvement of neurologic conditions. As symptoms worsened, physostigmine (up to 4 mg bolus) was repeatedly administered. The patient died 3 days later from respiratory arrest. Laboratory screening confirmed atropine in the powder and serum levels of 350 nanograms/mL at admission. *Conclusion:* To our knowledge many cases of anticholinergic poisoning are reported after ingestion of plants containing belladonna alkaloids, some of these also with analytical confirmation.[1] Cases of ingestion of large amounts of pure atropine with laboratory confirmation are less frequently described. In these cases high atropine blood concentrations were detected several hours after ingestion compared to normal levels and half-lives reported.[2] There are still some doubts about the correlation between serum levels and clinical effects. The clinical picture may become severe and not easy to treat even with administration of high doses of physostigmine. *References:* 1. Bogan R, Zimmermann T, Zilker T, et al. Plasma level of atropine after accidental ingestion of Atropa belladonna. Clin Toxicol (Phila) 2009; 47:602–4. 2. Baselt RC. Atropine. In: Baselt RC, eds. Disposition of toxic drugs and chemicals in man. 5th ed. Foster City, USA: Chemical Toxicology Institute, 1999:69–72.

295. A Case of Massive Zonisamide Overdose with a Moderate Clinical Course

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Objective: Zonisamide is an anti-epileptic that acts on voltage-sensitive sodium and calcium channels, with modulatory effect on GABA-mediated neuronal inhibition and inhibitory effect on carbonic anhydrase. Zonisamide overdose data are limited and no case of zonisamide monointoxication has been published to date. A 26-year-old female developed coma, bradycardia, hypotension and respiratory depression after ingesting an overdose of zonisamide and clonazepam.[1] *Case report:* A 25-year-old epileptic female treated with 300 mg zonisamide/d, 5 mg clobazam/d and 150 mg lacosamide/d was brought to the emergency department 8 h after ingestion of 12.6 g zonisamide with suicidal intent. At admission she was obtunded (GCS 9) and vomited repeatedly. ECG showed QRS widening (102 ms) and QT prolongation (QTc 506 ms). Pulse rate was 87 beats/min, blood pressure 103/54 mmHg. The patient was intubated and a single-dose of activated charcoal was administered. Arterial blood gas analysis (ABGA) after intubation showed moderate lactic acidosis (pH 7.28, pCO_2 5.19 kPa, pO_2 20.1 kPa, bicarbonate 28.4 mmol/L, BE -7.3 mmol/L, lactate 5.5 mmol/L). The level of consciousness improved within 8 h and she was extubated. She remained somnolent for another 50 h and transient myoclonus and diplopia occurred. The following day, the ECG was normal (QTc 375 ms). ABGA showed a normal-anion-gap metabolic acidosis with respiratory compensation (pH 7.34, pCO_2 3.7 kPa, pO_2 13.0 kPa, bicarbonate 17.0 mmol/L, BE -9.7 mmol/L, lactate 0.5 mmol/L, chloride 117 mmol/L, sodium 136 mmol/L). This alteration improved over the next 3 days. Polyuria without alteration of other renal parameters was persistent at discharge (day 7). Laboratory analysis at admission revealed a plasma zonisamide concentration of 182 mg/L (therapeutic 10–40 mg/L), therapeutic levels of clobazam and lacosamide and a positive serum toxicological screening for caffeine. The zonisamide plasma concentration one month earlier had been 26.5 mg/L. *Conclusion:* Despite a high plasma zonisamide concentration, the patient showed a moderate clinical course with characteristic symptoms. QRS widening and QT prolongation have not been previously described. Due to the long serum half-life (50–70 h), symptoms can persist for several days, but complete recovery can be expected with supportive care. *References:* 1. Naito H, Itoh N, Nakamura N. Monitoring plasma concentrations of zonisamide and clonazepam in an epileptic attempting suicide by an overdose of the drugs. Curr Ther Res 1988; 43:463–7.

296. Milnacipran Poisoning: A Review of the Cases Notified to the Paris Poison Centre from 1997 to 2009

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Introduction: Milnacipran is a serotonin and noradrenaline re-uptake inhibitor (SNRI) available commercially in France since 1997. Only 4 cases of milnacipran overdosage have been published. We analysed all cases of milnacipran poisoning reported to the Paris Poison Centre. *Methods:* From the Paris Poison Centre database, we identified all milnacipran poisoning cases from 1st June 1997 to 30th November 2009. Iterative milnacipran plasma levels were measured in 4 cases by high-performance liquid chromatography with fluorimetry detection. *Results:* During the study period 112 milnacipran poisoning cases were notified to the Paris poison centre. Of these, 108 were voluntary (18 with milnacipran alone), 4 were accidental. The latter were concerned with children who ingested very small amounts and all were asymptomatic. The milnacipran-only parasuicidal poisoning cases (n = 18; 16 females and 2 males) were aged 14–28 years (median 25 years). The median supposedly ingested dose (SID) was 1250 mg (175–3000 mg). Seven cases were asymptomatic with a median SID of 1125 mg (175 mg-1400 mg). The most frequent symptoms observed were somnolence in 6 cases with a median SID of 1200 mg (450 mg-3000 mg) and gastrointestinal symptoms (nausea, vomiting and abdominal pain) in 6 cases. Nine cases were hospitalised for a median duration of 24 hours (24h-72h). Nine cases had an ECG which was normal in all. Outcome was known in 17 cases and was favourable in all. Most polyintoxication cases (66/90) were symptomatic but signs and symptoms could always be explained by the associated drugs. Plasma milnacipran levels were obtained in four with SID of 4000 mg, 2400 mg, 2800 mg and an unknown dose; calculated elimination half-lives were 5.8, 8.1, 7.6 and 7.9 hours, respectively. *Conclusion:* Our series of milnacipran-only intoxications showed that this molecule is relatively safe as only somnolence and gastrointestinal symptoms were observed. This is in accordance with the 6 cases published in the literature. The elimination half-lives after overdosage were comparable to those reported at therapeutic dosage. This intoxication does not need specific management.

297. Toxicity Profile of Varenicline

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Objective: Limited toxicity data exists on the smoking cessation drug, varenicline (Champix®/Chantix®). This study aims to describe the toxicity profile of varenicline for both accidental paediatric ingestions and deliberate self-poisoning. *Methods:* Cases were recruited through calls to the NSW Poisons Information Centre from September 2009 - November 2010. A 2 page clinical research form was used to collect information from hospital-based calls and was faxed at the time of the initial call. A copy of the patient's medical record for the admission was also requested retrospectively. A follow-up call for accidental ingestions was attempted within 72 hours of the initial call. *Results:* A total of 32 cases of varenicline poisoning with outcome information were collected through the Poisons Information Centre. The patients were classified as follows: i) Accidental paediatric exposures (n = 21; median age: 3; range: 1–6 years), 20 were symptomatic (estimated ingested dose: median: 1 mg, IQR: 1–2 mg; range: 0.25–18 mg): Nausea (n = 17), vomiting (n = 14: 8 involved repeated vomiting), hyperactivity/sleep disturbance (n = 10), pallor (n = 8), lethargy (n = 8), nightmares (n = 2), mydriasis (n = 2), mild hypotension with bradycardia (n = 1), intermittent twitch (n = 1), sweating (n = 1), diarrhoea (n = 1). Eleven were hospitalised for monitoring, the only treatment provided in hospital was IV fluids in 2 cases. One child (5%) remained asymptomatic (estimated ingested dose: 0.25 mg); ii) Deliberate self-poisoning (n = 11), 6 cases involved varenicline only (± alcohol) and of these, 6 (100%) were symptomatic (estimated dose: 7–50 mg): Nausea (n = 6), vomiting (n = 6), salivation (n = 1), sweating (n = 1), mild hypotension (n = 1), drowsiness and confusion (n = 1, no ethanol present). Five other patients coingested drugs which could have explained their symptoms. One patient remained asymptomatic (estimated dose: 8 mg). No seizures or cardiotoxicity was recorded in association with varenicline overdose. The only treatment required was basic supportive care with symptomatic relief provided included anti-emetics, proton pump inhibitors and IV fluids. *Conclusion:* In this limited series of 32 cases, no serious toxicity was noted from varenicline in accidental paediatric ingestions of up to 18 mg (estimated) and deliberate self-poisoning of up to 50 mg. Symptoms are very common in all types of exposures and at any dose. The majority of accidental paediatric ingestions did not require treatment in hospital. Further experience is still required.

298. Angiotensin II Antagonists - An Assessment of Their Toxicity

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Objective: The aim of the study was to assess the toxicity of angiotensin II antagonists in overdose, because there is little information in literature on this topic. *Methods:* In a retrospective study, cases of poisoning by angiotensin II antagonists from seven Poisons Information Centres in Austria, Germany, and Switzerland were analysed. Inclusion criteria were monointoxication, defined dose, and documented follow up. *Results:* In total, 206 cases of poisoning by angiotensin II antagonists were registered (candesartan 94, eprosartan 3, irbesartan 20, losartan 26, olmesartan 16, telmisartan 18, valsartan 29). Patients involved were 150 children (0.8–13 years) and 56 adolescents (15–17 years) or adults (28 -77 years). Dose expressed as a multiple of the maximum daily dose for adults ranged between 0.06–6.5 (median 0.5) in children and 0.5–50 (median 7.8) in adolescents/adults. Most children remained asymptomatic (82.7%), 16.7% developed mild symptoms. Only in one case, hypotension required therapeutic measures after ingestion of the 1.5-fold maximum dose of candesartan by a 2.5-year-old toddler. In adolescents/adults almost half the patients suffered from mild (37.5%) or moderate symptoms (8.9%). Most frequent symptoms were hypotension (48%, usually mild), fatigue (19%), nausea/vomiting (15%), dizziness (12%), and somnolence (10%). In moderate poisonings, collapse, coma or pronounced hypotension were observed in adults after ingestion of a 5–7-fold maximum dose of valsartan or a 20–50-fold maximum dose of eprosartan, irbesartan or telmisartan. *Conclusion:* After ingestion of the maximum daily dose for adults by children, there is no or only mild toxicity. Higher doses may cause moderate poisoning requiring appropriate treatment. In adults, doses from the 5-fold maximum daily dose induced moderate toxicity in several cases. In general, angiotensin II antagonists seem to have a wide therapeutic index. Differences in toxicity within the group of angiotensin II antagonists can not be assessed in this study because the number of cases for most substances was too small.

299. Toxicokinetics of Quetiapine and its Active Metabolite N-desalkylquetiapine During Acute Poisoning

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Objective: Toxicokinetic data on the atypical neuroleptic quetiapine (Q) is relatively sparse. CYP3A4 metabolizes Q to the main active metabolite N-desalkylquetiapine (NDQ). Peak concentrations occurs 2h post-ingestion and $t_{½}$ is 7h. Fatal outcomes have been reported at S-concentrations of 19–48 micromol/L. Toxicokinetic data from a near-fatal case is presented. *Methods:* Q and NDQ were measured by a validated LC MS/MS method. The lower limit of quantification was 0.020 and 0.025 micromol/L for Q and NDQ, respectively. SI-conversion factors for Q and NDQ (micromol/L–mg/L) are 0.384 and 0.296, respectively. *Case report:* A 39-year-old woman ingested unknown (large) amounts of Q. She was somnolent, tachycardic (115 bpm), but otherwise stable. ECG was normal. Gastric lavage and activated charcoal regimen was not performed, as the suspected time of ingestion was >2h. Ten hours after admission, status epilepticus developed, treated with diazepam. Respiratory collapse, hypotension and severe bradycardia with broad QRS-complexes (150 ms) followed, requiring intubation and cardiopulmonary resuscitation. After successful resuscitation, mechanical ventilation, vasopressors, diazepam and valproate infusions were necessary. Acute respiratory distress syndrome (ARDS) rhabdomyolysis, metabolic acidosis and sepsis were treated. Her condition gradually improved, but CCT showed possible hypoxic brain damage. After 39 hospital days, psychiatric follow-up and rehabilitation was initiated. S-concentrations of Q and NDQ peaked 12 and 63 hours post-admission, at 31.81 and 10.34 micromol/L, respectively (Table 1). *Conclusion:* The late peaking S-concentration could be due to large amounts ingested and her circulatory complications impairing gut perfusion; anticholinergic effects have not been reported. As the complications followed the kinetic timeline, a more aggressive decontamination approach might have been beneficial.

Table 1. Quetiapine and N-desalkylquetiapine concentrations after overdose

Hours after admission	Quetiapine (micromol/L)	NDQ (micromol/L)
0	6.81	6.49
12	31.81	7.76
24	8.54	4.02
30	6.75	4.74
38	8.06	5.02
55	4.03	8.12
62	3.04	10.34
64	2.73	8.31
80	1.99	7.16
86	1.63	6.96

300. Reviewing Quetiapine: Implications from Poison Information and Analytical Data

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Objective: Quetiapine is a dibenzothiazepine derivative that has been evaluated for management of patients with the manifestations of psychotic disorders. Since its introduction in 2000 it has gained increasing importance in the treatment of schizophrenia, bipolar disorders and psychosis due to dementia. Intoxications are supposed to be mild to moderate with somnolence and tachycardia as the main clinical symptoms. They typically resolve within several hours. Correlation between symptoms and ingested dose was found to be poor.[1] As the number of intoxications with quetiapine increases, accumulated data from the Poisons Information Centre (PIC) Berlin were reassessed and completed with analytical results of quetiapine intoxications. *Methods:* All human cases of quetiapine poisoning reported to the PIC Berlin between 2003 and 2009 were analyzed. In addition the analytical results from 93 intoxicated patients were checked for serum concentrations and elimination kinetics. *Results:* From 2003 to 2009 Berlin PIC was consulted in 494 (315 m, 146 f, 33 unknown) cases of deliberate self-harm with quetiapine. Numbers of inquiries increased almost linearly from 18 (2003) to 133 (2009). Reported doses ranged from 100 to 30,000 mg. On initial contact 420 patients were already in an ER with 369 of them having signs of intoxication. In 434 cases inpatient treatment was advised. Severity of intoxications was estimated as PSS3 in 88 patients and PSS2 in 106 patients. Mean serum concentration of quetiapine from 93 patients was 3,914 mg/L (608–11,814 mg/L), thus exceeding the upper therapeutic level (350 µg/L) more than tenfold. Elimination half-life calculated from consecutive quantification was 10.4 hours $\pm$ 5.49 hrs with maximum values at 23.7 hrs indicating a significant delay in elimination of quetiapine compared to population kinetics. *Conclusion:* Intoxications occurred more often with quetiapine than with other atypical neuroleptics. A majority of patients had moderate to severe symptoms requiring inpatient treatment. There is a significant risk of prolonged symptoms due to aberrant elimination kinetics. *References:* 1. Hunfeld NG, Westerman EM, Boswijk DJ, et al. Quetiapine in overdosage: a clinical and pharmacokinetic analysis of 14 cases. Ther Drug Monit 2006; 28:185–9.

301. Acute Trimipramine Poisoning: Analysis of Clinical Features and Factors Influencing Severity

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Objectives: Trimipramine is a widely used tricyclic antidepressant and intoxications with this drug are frequently observed. The aim of the present study was to analyse the clinical features of trimipramine poisoning, and to identify a minimum toxic dose and the dose bearing a 50% risk of developing a moderate, severe or fatal outcome. We also investigated the influence of ingested dose, age, gender and weight, and the effect of decontamination measures on the severity of poisoning. *Methods:* A retrospective case study of all acute human trimipramine monointoxications involving adults and reported by physicians to the Swiss Toxicological Information Centre between January 1992 and December 2009. *Results:* There were 170 (73.9%) females and 56 (24.3%) males; the mean age was 35.7 years (range 16–77). Fifteen (6.5%) patients remained asymptomatic, 137 (59.6%) showed mild symptoms, 54 (23.5%) moderate and 21 (9.1%) severe symptoms (Poisoning Severity Score). In 3 (1.3%) cases the outcome was fatal due to refractory cardiovascular collapse. 93% of the cases were suicide attempts or completed suicides. The most common symptoms were central nervous system depression (79.2%), tachycardia (19%), QTc prolongation (13.9%), agitation (12.2%), and dysarthria (10.9%). We found a significant correlation between ingested trimipramine dose and severity of poisoning ($p < 0.001$). The minimum dose for moderate symptoms was 250 mg (median dose 1.2 g) and 850 mg for severe symptoms (median dose 2.7 g). The dose for a 50% risk of developing a moderate, severe or fatal outcome was 5.16 g. In 38 (16.5%) patients early gastrointestinal decontamination was performed. Overall, these patients ingested higher trimipramine doses than the late- or not-decontaminated patients (not significant, $p = 0.226$). The median doses were also higher in the decontaminated group within all severity-categories except in the fatal cases. We found no significant correlation between age, gender and weight, and the severity of poisoning. *Conclusion:* Trimipramine poisonings mainly occurred as a consequence of suicide attempts in young female patients. Moderate trimipramine intoxications can occur after ingestion of doses in the high therapeutic range. Poisoned patients have to be monitored for central nervous system depression, dysrhythmias, and QTc prolongation. Early decontamination might be beneficial.

302. Acute Quetiapine Overdose in Adults - Experience in Sweden

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Objective: Quetiapine was introduced on the Swedish market in 2003 for treatment of schizophrenia and bipolar disorder. The prescription rate of quetiapine has increased and an increase in the number of inquiries related to overdose has been observed. In order to assess the acute toxicity of quetiapine, a retrospective survey of hospital case records received by the Swedish Poisons Information Centre (Swedish PC) was carried out. *Case series:* Since the introduction the Swedish PC has received 493 calls concerning quetiapine overdose in adults and adolescents. During this period 40 cases of pure quetiapine poisoning were available to be analysed in detail by studying hospital case records. The patients were 13 to 90 years old, 28 females and 12 males. The ingested dose ranged from 400 mg to 33 g

(average 6.2 g, median 3.1 g). The reasons for overdosing were self destructive behaviour/suicidal attempt (33/40), therapeutic error (2/40) and unknown (5/40). The severity of poisoning was graded according to the Poisoning Severity Score (PSS). Three patients were asymptomatic (PSS 0), 24 patients developed mild symptoms (PSS 1), 10 patients developed moderate symptoms (PSS 2) and 2 patients developed severe symptoms (PSS 3). The most frequent symptoms were mild to moderate CNS-depression (29/40), tachycardia (20/40), hypotension (7/40), agitation (5/40), prolonged QTc interval (4/40). Other symptoms seen in a few cases were seizures, dry mouth, prolonged QRS interval, coma and miosis. At doses below 3.6 g most patients had mild symptoms. Treatment with gastric lavage and/or activated charcoal was performed in 16/40 patients. There was also one fatal case. A 38-year-old man, with a previous gastric bypass, ingested 24 g slow release quetiapine. He arrived at hospital one hour later asymptomatic, apart from tachycardia. He refused gastric decontamination and charcoal. After six hours he became progressively more sedated, developed frequent seizures and died of circulatory collapse 14 hours after ingestion. *Conclusion:* In this series most cases of quetiapine poisoning were benign. In general, doses below 3.6 g produced minor symptoms. Patients taking a large overdose of slow release quetiapine can be asymptomatic up to six hours after ingestion and then progressively develop severe symptoms.

303. Pediatric Venlafaxine Exposures: Should Current Guidelines be Re-evaluated?

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Objective: There is a paucity of literature about pediatric venlafaxine exposures. While current resources suggest that pediatric ingestions of <5.5 mg/kg can be managed at home, these are based on a small ($n = 14$) sample. We sought to characterize which pediatric exposures reported to a Poison Centre could potentially be managed conservatively. *Methods:* Retrospective chart review of pediatric (ages 0–17 years) venlafaxine exposures reported to our Poison Centre from April 1, 2006-June 30, 2009. Inclusion criteria were: single unintentional ingestion where a mg/kg dose could be calculated (some calculations based on average weight for age) and where medical outcome and the highest level of care was documented. *Results:* 92/188 cases of pediatric venlafaxine ingestion met inclusion criteria. Ages ranged from 7 months to 17 years. The amounts ingested ranged from 17–1500 mg or 1.3–106 mg/kg. Table 1 depicts medical outcomes and highest level of care by dose range ingested. Minor effects included nausea, vomiting, mydriasis, diaphoresis, drowsiness. Major effects included agitation, ataxia, tachycardia, hypertension, tremors, confusion, auditory hallucinations. Major effects were observed only in children ingesting >11 mg/kg. All were asymptomatic within 6–10 hours post exposure. The high number of Emergency Department (ED) visits in the 5.5–11 mg/kg dose range likely reflects existing recommendations. *Conclusion:* Children ingesting <11 mg/kg as a single unintentional ingestion seem less likely to develop significant symptoms and may be candidates for home observation. Further prospective validation is indicated.

Table 1. Medical outcomes and highest level of care by dose range ingested for pediatric venlafaxine exposures

	≤5.5 mg/kg	5.5–11 mg/kg	>11 mg/kg
n	46	19	27
No effect	12	14	19
Minor effect	2	0	5
Major effect	0	0	3
Unknown nontoxic*	32	5	0
Home treatment	41	4	2
ED treatment	4	14	20
Admitted to ward	0	1	5
Unknown	1	0	0

*Unknown non-toxic = not followed up as considered non-toxic so no information on outcome.

304. Hemodialysis for Carbamazepine Removal

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Objective: Severe carbamazepine intoxication with plasma level exceeding 40 micrograms/mL is often associated with coma, seizures, brain edema and shock. Digestive tract decontamination and charcoal hemoperfusion (HP) do not always decrease plasma carbamazepine concentrations significantly. A few cases of successful hemodialysis (HD) usage were published in the last decade.[1,2] *Methods:* Six-hours HD was performed in 20 cases with blood flow rate 200 mL/min and dialysis fluid flow rate 500 mL/min. In 8 other cases HP was followed by HD. The plasma carbamazepine concentration was measured by fluorescent polarizing immunoassay (TDx-FLx Abbot Laboratories). *Results:* All patients were comatose on admission and 17 were ventilated. Mean plasma concentration was 38.4 micrograms/mL in the group treated with HD and 39.5 in the group treated with HP and HD. Level of consciousness evaluated by GCS on admission was 5.2 and 4.9 respectively. The time from admission to start of extracorporeal detoxification was 4.9 hours in the HD group and 6.4 hours in the HP-HD group. Clearance of carbamazepine was 59.8 ± 3.9 mL/min on average and remained stable during 6 hours of the procedure. Concentration of carbamazepine decreased on average from 28.2 ± 2.1 to 20.6 ± 2.4 micrograms/mL ($p < 0.001$). Concentration of carbamazepine in outflow dialysis fluid was from 2.1 to 5.2 micrograms/mL, and decreased towards the end of the procedure. The total amount of carbamazepine which was removed was 600 mg on average, with the range of 533–714 mg. The apparent elimination half-life was 19.2 hours from the admission to the beginning of HD, 11.7 hours during HD and 43.9 hours during the observation time after HD. *Conclusion:* Hemodialysis seems to be an effective method for carbamazepine removal. *References:* 1. Chetty M, Sarkar P, Aggarwal A, et al. Carbamazepine poisoning: treatment with haemodialysis. Nephrol Dial Transplant 2003; 18:220–1. 2. Tapolyai M, Campbell M, Dailey K, et al. Hemodialysis is as effective as hemoperfusion for drug removal in carbamazepine poisoning. Nephron 2002; 90:213–5.

305. Successful Lipid Emulsion Treatment for Generalized Seizures and Cardiac Arrest Following Epidural Lidocaine Administration

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Objective: We describe a case of tonic-clonic seizures and cardiac arrest after epidural administration of lidocaine. The patient was successfully treated with intravenous lipid emulsion. Remarkable was the absence of toxic lidocaine level in serum. *Case report:* An 84-year old female was referred to an orthopaedic outpatient clinic for treatment of chronic lower back pain. Lidocaine 20 mg together with triamcinolone 80 mg was administered epidurally. Approximately two minutes after the administration, generalized tonic-clonic seizures occurred. Another three minutes later, she developed respiratory and cardiac arrest and cardiopulmonary resuscitation (CPR) was initiated by the attending physician. Upon the arrival of the resuscitation team, a further three minutes later, ECG showed bradycardia that quickly progressed to asystole. ACLS was performed, patient required intubation, and received adrenaline 2 mg I.V. and atropine 3 mg I.V. A bolus of intravenous lipid emulsion (Intralipid 20% 100 mL, i.e. 1.5 mL/kg) was given. Seven minutes after CPR initiation return of spontaneous circulation was established. ECG showed sinus rhythm, rate 77/min, right bundle branch block (RBBB; QRS 148 ms), and a QTc of 495 ms. After a renewed episode of pronounced hypotension she was given another I.V. bolus of 100 mL of Intralipid 20%, and was then transferred to the ICU. Within six hours she was alert and responsive. Subsequent laboratory assessment did not explain the cardiac conduction anomalies. Arterial blood gases were normal; there was no methemoglobinemia, nor signs of hepatic impairment or congestive heart failure. A GC-MS analysis of serum sample drawn after the lipid emulsion treatment showed lidocaine level to be lower than 1 mg/L (therapeutic serum range being 2 to 4 mg/L). Next day a 24-hour Holter monitoring showed sinus rhythm with RBBB, with episodes of non-sustained atrial tachycardia and no ventricular ectopic activity. She was discharged five days after the incident without neurological sequelae. *Conclusion:* Our case supports the clinical efficacy of lipid emulsion infusion in local anesthetic toxicity. A matter of interest, which perhaps could help to better understanding of the mechanism of lipid rescue, is the fact that we could not confirm a lidocaine serum concentration which reached toxic levels, thus strengthening the "lipid sink" concept.

306. Accidental Tiotropium Overdose in a Child: A Case Report

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Objective: Tiotropium is a long-acting anticholinergic agent increasingly used via inhalation in the management of chronic obstructive pulmonary disease. Toxicity following oral ingestion of capsules intended for inhalation has not previously been reported, and has been considered unlikely unless large amounts have been ingested because of low oral bioavailability.[1] We describe a case of an accidental oral overdose of tiotropium in a paediatric patient resulting in an anticholinergic toxidrome. *Case report:* The National Poisons Information Service (NPIS) was contacted about a 2 year old female patient following accidental ingestion of 8 capsules (144 micrograms) of tiotropium (Spiriva®) who had presented with features of anticholinergic toxicity including dry mouth, dilated pupils, tachycardia (133 beats/minute) and localised flushing of the cheek. Conservative management was advised with observation for at least 6 hours post-exposure or until asymptomatic. The patient was discharged after observation for six hours by which time all symptoms, except flushing, had resolved. The flushing was clinically deemed to be unrelated to the ingestion. A literature search did not reveal any reports of oral toxicity with tiotropium in any age group. Anticholinergic toxicity due to accidental inhalation has been reported with a dose of 90 micrograms in a 74 year old, who developed tachycardia, urinary retention and dry mouth.[2] Over 5 years the UK National poisons Information Service has received enquiries about 21 episodes of accidental oral ingestion in paediatric patients (0–10 years). The majority were asymptomatic, in spite of ingesting high doses. A 3 year old ingested 216 micrograms with no symptoms reported at 6 hours. A one year old referred to hospital was asymptomatic

after ingesting 180 micrograms. A 4 year old patient was reported to have a dry mouth after ingesting 18 micrograms; this was treated conservatively at home. *Conclusion:* Anticholinergic features can develop after ingestion of tiotropium capsules by children, but this appears uncommon. *References:* 1. Product Information (SPC) Spiriva 18 microgram inhalation powder, hard capsule. Boehringer Ingelheim Limited. http://www.medicines.org.uk/EMC/medicine/10039/SPC/Spiriva+18+microgram+inhalation+powder%2c+hard+capsule/#OVERDOSE (accessed on 9 November 2010). 2. Gregory MD, Mersfelder TL, Jamieson T. Accidental overdose of tiotropium in a patient with atrial fibrillation. Ann Pharmacother 2010; 44:391–3.

307. Pulmonary Hemorrhage in Quinine Toxicity

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Objective: While non-cardiogenic pulmonary edema and acute respiratory distress syndrome are known complications of malaria, the possibility of quinine toxicity causing respiratory failure must be considered. We report two cases of quinine toxicity that resulted in alveolar hemorrhage. *Case series:* Case 1: A 50 year old female with a history of depression and alcoholism presented complaining of vision loss, dizziness, and tinnitus after taking 9100 mg of quinine as a suicide attempt. On examination, her vital signs were normal except a blood pressure of 147/90. She had decreased hearing; her pupils were 7 mm bilaterally and nonreactive, and visual acuity examination revealed only light perception. The remainder of her physical exam was unremarkable. Her EKG was notable for a QRS interval of 120 ms and ST depressions in multiple leads. She received charcoal, sodium bicarbonate, and nimodipine and showed improved vision and hearing. However, 2 days after admission, the patient suddenly developed respiratory failure requiring intubation. Chest x-ray showed bilateral infiltrates, and bronchoscopy revealed alveolar hemorrhage. Case 2: A 35 year old previously healthy female was transferred to our hospital while being treated with quinine for falciparum malaria that was discovered on blood smear. She was transferred due to worsening thrombocytopenia and anemia. At our institution, she was febrile to 39.3 degrees and tachycardic at 122 BPM. Her EKG showed a QTc of 510 ms. Her hemoglobin dropped to 7 g/dL, and her mental status declined, requiring intubation. Her quinine was replaced with a quinidine infusion. She received exchange transfusion and improved after her parasitemia was $<1\%$. However, she failed extubation multiple times with hemoglobin subsequently falling to 5 g/dL. Chest x-ray indicated diffuse alveolar hemorrhage, confirmed with bronchoscopy. *Discussion:* Quinine is used as an antimalarial agent, but toxicity is manifested by cinchonism, dysrhythmia and hematologic disturbances. We propose that quinine toxicity may be unrecognized as a cause of respiratory failure from alveolar hemorrhage because it is used to treat malaria, a disease with its own pulmonary complications. *Conclusion:* Quinine toxicity may be an unrecognized cause of acute respiratory failure from alveolar hemorrhage.