Anniversary Symposium 50 Years Tox Info Suisse

CLINICAL TOXICOLOGY THROUGH THE AGES

Programme
11th November 2016
Aula of the University of Zürich
Kol G 201, Rämistrasse 71, 8006 Zürich
Part 1: Humans and Animals  
Chair: Hugo Kupferschmidt

12:15 Opening  
Hugo Kupferschmidt, Director Tox Info Suisse

12:20 Differing aspects in human and veterinary toxicology  
Hanspeter Nägeli, Zürich

12:55 Food poisoning today - current research to target old problems  
Martin J. Loessner, Zürich

13:30 Venomous animals in Switzerland  
Jürg Meier, Basel

14:05 Coffee break

Part 2: Hips, Pain Killers and Mushrooms  
Chair: Michael Arand

14:35 Welcome address  
Michael O. Hengartner, President UZH

14:45 Fatal shoot from the hip: News of heavy metal poisoning  
Sally Bradberry, Birmingham UK

15:20 Old and new aspects in paracetamol poisoning  
D. Nicholas Bateman, Edinburgh

15:55 Amanita phalloides poisoning  
Thomas Zilker, München

16:30 A silent threat - chronic intoxications  
Michael Arand, Zürich

17:05 Coffee break

Part 3: From Critical Care to the Opera  
Chair: Martin Wilks

17:35 Management of severe poisoning-induced cardiovascular compromise  
Bruno Mégarbane, Paris

18:10 Chemical terrorism: New and old chemical weapons and their countermeasures  
Horst Thiermann, München

18:45 Novel psychoactive substances: How much a threat in public health?  
Alessandro Ceschi, Lugano

19:20 Poisons in the opera  
Alexander Campbell, Birmingham UK

19:50 Conclusion

20:00 Apéro riche

21:30 Closure
Hanspeter Nägeli  
Institute of Veterinary Pharmacology and Toxicology, University of Zurich

Differing aspects in human and veterinary toxicology
Veterinary toxicology is a difficult, yet fascinating subject as it deals with multiple species and a wide variety of poisons of very diverse origins. The management of poisonings in animals is complicated by differences in exposure, variations in xenobiotic metabolism as well as the changing sensitivity of distinct species to toxicants. To provide a valuable aid to veterinary practitioners, since many years we offer a user-friendly decision support system (www.CliniTox.ch) for the clinical management of poisonings. This user-friendly online support is equipped with several multiparametric search functions to allow for a straightforward and fast retrieval of the information needed. The system is permanently updated and linked to the databases on veterinary medicinal drugs and products. Also, the decision support system for clinical toxicology is accompanied by a very popular database on poisonous plants (www.Giftpflanzen.ch). These information systems in the area of veterinary toxicology have been established in tight collaboration with Toxi Info Suisse.

Congratulations on the 50th anniversary! We thank Toxi Info Suisse for the very fruitful collaboration over the last decades and hope that this important Institution will continue to thrive and flourish in the future. We wish all the best and much success for the next 50 years!

Professor Hanspeter Naegeli, D.V.M.

is Professor of Toxicology and Director of the Institute of Veterinary Pharmacology and Toxicology at the University of Zurich. He studied veterinary medicine in Zurich, where he also graduated, and continued his scientific training at the Stanford Medical Center in Palo Alto, California, and at the Southwestern Medical Center at Dallas, Texas. His current research interests include DNA repair and nanotoxicology. Hanspeter Naegeli is a member of the Swissmedic Veterinary Medicine Expert Committee and Chair of the GMO Panel at the European Food Safety Authority.

Martin Loessner
Institute of Food, Nutrition and Health
Department of Health Science and Technology
ETH Zurich
Switzerland

Food poisoning today - current research to target old problems
The problems associated with what is commonly referred to as food poisoning have actually not changed very much over the past years. However, food-borne infections are much more common than intoxications, and it remains a difficult task to further reduce the frequency of food contamination by pathogens such as Salmonella, Listeria, Campylobacter, E. coli, and others. While
technological developments such as modified atmosphere packaging and generally high hygienic standards contribute greatly to improved food safety, increasing consumer demands for fresh and minimally processed foods represent major challenges.

The presentation will highlight some of the current trends in modern food microbiology, such as the use of bacteriophages and their proteins for specific detection and targeted biocontrol of Gram-positive and Gram-negative pathogenic bacteria in foods, and the challenges that need to be overcome.

**Professor Martin J. Loessner, Ph.D.**

Martin Loessner received his undergraduate degree in Biology from Albert-Ludwigs-University of Freiburg, Germany. He continued his education at Wayne State University, Michigan, USA, earning an MSc degree in Biology, and in 1991 received his PhD from the Technical University of Munich, Germany. He continued his career at TU Munich, established an independent research group, and eventually was appointed Assistant Professor for Microbiology. Martin was a visiting researcher at the University of Nottingham, UK, the Ben-Gurion-University, Israel, the University of California, Berkeley, USA, and Stanford University, Palo Alto, USA. Since 2003, Martin Loessner is Professor and Chair of Food Microbiology in the Institute of Food, Nutrition and Health at the Swiss Federal Institute of Technology (ETH), Zurich, Switzerland. He has been Head of the Institute of Food Nutrition and Health, and currently serves as Director of Studies for the Food Science curriculum offered by the Department of Health Sciences and Technology.

The research in Martin Loessner’s laboratory is focused on the molecular biology of foodborne pathogenic bacteria and their specific bacteriophages, with a focus on the biological functions of the Gram-positive cell wall and its interaction with phage and the environment. State-of-the-art technology is also employed for development of novel and innovative applications for detection and control of various pathogens, including Listeria, Staphylococcus and Salmonella. The scientific output is reflected in more than 180 research papers, book chapters, reviews, and more than 20 patents, and has received several awards and prizes. The group has many active international research collaborations, and maintains fruitful contacts with industry.

**Jürg Meier**

University of Basel
Switzerland

**Switzerland – a hell of venomous animals?**

Every house, every garden, every forest in Switzerland contains a multitude of venomous animals. However, these species, dangerous as they are for their surrounding animal life, are of no medi-
When dealing with venomous animals of medical importance, only venomous snakes are of medical importance from a toxicological point-of-view. Of course the medically most important venomous animals also in Switzerland are insects of the order Hymenoptera (bees and wasps) with 3-4 fatal cases observed every year. However, fatality may be the endpoint of anaphylactic reactions due to strong allergens present in hymenopteran venoms. Focusing on snakebite in Switzerland, two findings have to be taken into consideration. Firstly, envenomation following the bite of the two indigenous venomous snake species, the Common viper (Vipera berus) and the European asp or Aspic viper (V. aspis) during outdoor leisure activities. Secondly, envenomation following the bite of exotic venomous snakes kept at home by pet keepers. Indeed, an estimated number of some 2,000 specimens of venomous snakes is present in Swiss households. Whereas snakebite cases with indigenous vipers every year may lead from moderate to severe envenomations, the last fatality occurred some 50 years ago. Also envenomation by exotic snakes normally can be treated in a manner to prevent fatality. Venomous snake pet keepers need a permission of the cantonal veterinary office and their animal husbandry is regularly controlled for both animal protection and security reasons. In contrast to e.g. Germany, where the keeping of venomous snakes is already forbidden in an increasing number of federal states, it is preferred to allow husbandry of venomous snakes in Switzerland. Real life experience shows that a ban of venomous snake husbandry only provokes the illegal keeping of these animal in a totally uncontrolled manner. Tox Info Suisse plays an important role with advisory services in snakebite emergencies and in the coordination of “Antivenin.ch”, the network of eight antivenin hubs established throughout Switzerland.

Professor Jürg Meier, Ph.D.

is a Professor of Zoology at the University of Basel, Switzerland, European registered toxicologist, President of the mutual ethical commission on experimental animals of the Swiss cantons Basel-City, Basel-Countryside and Argovie and Controller of private venomous snake and dangerous animal husbandries for the veterinary office of the Swiss canton of Zurich. He is the owner and managing director of Jumeba, a consulting company active in leadership, quality management and toxicology.
He is author and co-author of several books and of more than 100 scientific publications on venomous animals and animal venoms, respectively.

**Fatal shoot from the hip: News of heavy metal poisoning**

Hip reconstruction is an extremely common orthopaedic procedure, some 80,000 such operations being carried out each year in the UK alone. This may involve complete replacement of the hip joint using metal, ceramic or polyethylene components or resurfacing of the weight bearing areas with a metal coating. All metal components in replacements and resurfacings are made of cobalt/chromium alloys.

Wear and tear of hip prostheses is a significant problem, 1 in 8 requiring revision within 10 years. Polyethylene is particularly liable to wear while metal is much more durable. Having both the head and cup components made of metal, so called metal-on-metal (MoM) replacements and resurfacings offers greater durability. This led to a surge in popularity of MoM prostheses particularly during 2003 – 2010. However, friction between metal surfaces generates nanoparticulate cobalt and chromium debris, particularly in poorly functioning implants, and this is associated with increased blood cobalt and chromium concentrations. Severe, even life threatening systemic cobalt poisoning has occasionally resulted.

Since monitoring of blood cobalt concentrations has become routine for many patients with a MoM prosthesis, clinical toxicologists are increasingly being asked to interpret results and advise on the associated risk of systemic cobalt poisoning. It is important that we know how to assess this risk and how to recognise and manage systemic cobalt toxicity.

**Dr. Sally M. Bradberry, M.D. BSc MD FRCP FAACT FEAPCCT** is Director of the National Poisons Information Service (Birmingham Unit) and West Midlands Poisons Unit, City Hospital, Birmingham, UK and Honorary Senior Lecturer, School of Biosciences, University of Birmingham, UK. She has over 20 years’ experience as a practising clinical toxicologist and has published widely in many aspects of the speciality with over 200 peer-reviewed journal articles and book chapters. She has given some 50 invited keynote addresses. Her special interests include the management of patients with poisoning due to metals and pesticides.
Old and new aspects in paracetamol poisoning

Paracetamol was introduced into clinical practice in the 1950s. In 1966 the first cases of paracetamol poisoning were reported in Scotland. Within 10 years of this event concentration risk nomograms had been constructed, and an antidote, acetylcysteine, developed and tested in clinical trial. The increase in mortality from paracetamol overdose that had been exponential in the UK to this point was then halted.

Subsequent measures to address paracetamol overdose were focused initially on pack size reduction, although the effectiveness of these is debated.

There was, however, the increasing recognition that adverse events were more common with acetylcysteine than previously thought, and that anaphylactoid reactions were a particular problem in patients with lower concentrations of paracetamol. As some regulators moved to lower thresholds for treatment with acetylcysteine in an attempt to reduce mortality rates from paracetamol this problem was exacerbated.

These observations led to the revision of the standard intravenous protocol of acetylcysteine by our group in Edinburgh with encouraging clinical outcomes in terms of adverse effects. This regimen is also somewhat shorter than existing protocols and therefore offers a potential to identify “at risk” patients earlier in the clinical course.

Present treatment protocol nomograms were all developed based on the clinical end point of a rise in ALT. This measure lacks specificity, particularly in the context of multiple ingestions, and alternative indicators of patients at risk are required. Over the past five years our group and others have identified a range of novel biomarkers that appear to offer earlier and more precise identification of patients who are likely to develop severe liver injury from paracetamol. They also may offer targets for novel therapeutic interventions in targeted groups.

The next development will be to link use of these markers to shorter safer treatment protocols, thus reducing both the numbers of patients treated who are unlikely to develop liver injury, and the time needed to be spent by most patients in hospital.

Professor D. Nicholas Bateman, M.D. BSc MBBS MRCS MD FRCP FRCP(E) FBPhS FBTS FAACT FEAPCCT

is honorary professor of clinical toxicology at the University of Edinburgh. He has worked in the field of clinical pharmacology and clinical toxicology for 40 years. He is a former editor-in-chief of Clinical Toxicology and former president of the EAPCCT. He was
Management of Amanita Poisoning

Poisonings by amatoxins containing mushrooms is still a life-threatening disease. Amatoxins are extremely toxic by blocking transcription within the nucleus of the cell. They are enriched in the liver cells by a special transporting system OATP1B3 thus leading to hepatotoxicity and acute liver failure. In some cases only liver transplantations can save the lives of the mushroom eaters. Many antidotes were tried in the past. Their efficacy could never be proven. Two of them work by blocking the transport of amatoxins into the liver cells: Penicillin and Silibinin. Two studies of our Toxicological Department in Munich will be presented. First the indication for liver transplantation after amanita poisoning, second comparing Penicillin plus Silibinin treatment to Silibinin treatment of its own. Liver transplantation is indicated if coagulopathy is severely impaired and nephrotoxicity becomes obvious. Silibinin alone seems to be a better therapy than the combination of the old antidote Penicillin and the new antidote Silibinin together. It is very important to start antidotal therapy as early as possible and not to lose time by trying to secure the diagnosis. If a patient after a mushroom meal develops gastroenteritis with a latency of more than six hours therapy has to be commenced and can be stopped if no signs of hepatopathy emerge within the following two days.

Professor Thomas Zilker, M.D.

has been the director of the Toxicology Department including the Poisons Control Centre in Munich from 1993-2012. He is specialized in Internal Medicine. His secondary specializations are in endocrinology, environmental medicine, psychotherapy and clinical toxicology (GfKT). He worked at the Klinikum rechts der Isar in Munich which is the University hospital of the Technical University Munich (TUM). He took a sabbatical in Cambridge in 1980 and at the Swiss Toxicological Information Centre in 1988.

A silent threat - chronic intoxications

The assessment of acute toxicity of a compound in question is - in general - a straight forward process. In such case, the immediate...
response to a toxic stimulus facilitates the establishment of a causal relationship. In contrast, chronic toxicity poses a much greater problem. Issues that add to the complexity are, among others, adaptive responses to the exposure, higher sensitivity to confounding factors and simply the length of the required observation period, compromising the completeness of data sets. On the level of the individual person, the lack of an immediate adverse effect results in a failure to develop an appropriate avoidance behaviour. Instead, the personal belief what is "good" or "bad" for oneself forms the basis for respective decisions. With a few examples (arsen, broccoli, tobacco) the presentation will address the difficulties to detect and evaluate chronic toxicity and highlight some discrepancies between personal perception and scientific evidence.

Professor Michael Arand, Ph.D.
is Professor of Toxicology and Pharmacology at the Institute of Pharmacology and Toxicology/University of Zurich and is a European-registered Toxicologist. He is the president of the Swiss Commission for Setting Occupational Exposure Limits of Hazardous Compounds (MAK Commission) and a member of the Swissmedic Human Medicines Expert Committee. Michael Arand is the delegate of the University of Zurich in the foundation council of Tox info Suisse.

Management of severe poisoning-induced cardiovascular compromise

Objectives: Despite significant improvement in critical care, drug-induced cardiovascular failure remains a leading cause of death. Among the 2,686,673 exposures in adults reported to the American Association of Poison Control Centers in 2012, cardiovascular drugs were involved in 3.87% of the cases but accounted for 12.18% of the fatalities. Calcium-channel blockers (CCB) and beta-blockers (BB) accounted for 35% of cardiovascular drug exposures, while CCB represented the first cause and glycosides the second cause of cardiovascular agent-related death.

Methods: This presentation will review the predictive factors for failure of the pharmacological treatments of drug-induced cardiovascular failure and define the place of ECMO in poisonings.

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

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

Professor Bruno Mégarbane, M.D., Ph.D.
Bruno Mégarbane is professor of critical care medicine at Paris-
Diderot University and directs a research team at INSERM UMRS-1144. He is the head of the Department of Medical and Toxicological Critical Care at Lariboisière Hospital, Assistance Publique – Hôpitaux de Paris, in Paris, France. He is the current President of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT). He conducted several clinical and experimental studies in clinical toxicology, mainly regarding mechanisms of opioid-related respiratory toxicity, prognostic factors of life-threatening poisonings, and management of refractory cardiotoxicant poisonings using ECMO. He is a member of the EXTRIP group and an associate editor for Clinical Toxicology.

Horst Thiermann  
Bundeswehr Institute of Pharmacology and Toxicology, Munich, Germany

Chemical Terrorism: New and old chemical weapons and their countermeasures

It is a great success that 192 State parties participate in the Chemical Weapons Convention, prohibiting production, storage and use of chemical warfare agents. In spite of all efforts, in Syria and Iraq use of nerve agents and sulphur mustard was confirmed recently. These events clearly point to an ongoing threat by such compounds and other toxic substances, e.g. chlorine. Hence, effective medical measures are necessary to avoid huge numbers of fatalities as occurred during the Sarin attacks in Syria in 2013.

Nerve agents as Sarin or VX are until now regarded as the most serious threat. These compounds exert life threatening cholinergic crises. The toxic mechanism is quite similar for all highly toxic nerve agents and hundreds of pesticides. Due to different chemical and physical properties of the individual compounds, however, the course of poisoning, e.g. time to onset and duration of signs and symptoms may vary significantly. Additionally, especially highly toxic nerve agents call for self-protection of medical personnel in order to avoid life threatening secondary contamination.

Since decades, administration of atropine, an oxime, and a benzodiazepine has been recommended. Meanwhile, it is discussed to use an optimized treatment protocol suggesting a more aggressive atropinisation, adequate dosing of oximes and benzodiazepines as well as on-site ventilatory support. Moreover, alternative therapeutic approaches e.g. small molecule scavengers, and modulators of nicotinic receptors are a matter of research.

Although the first use of sulfur mustard occurred 100 year ago this alkylating agent still has to be considered as an extremely dangerous chemical warfare agent. Enhanced analytic capabilities nowadays allow verification of poisoning, however, treatment is still symptomatically. New therapeutic approaches refer to chemosensors, e.g. TRP-channels and the use of stem cells.
In addition to the compounds listed in the chemical weapon convention, other toxic industrial materials, e.g. chlorine can be used especially by terrorists or other none state actors. Such substances have to be considered as a new upcoming threat.

In conclusion, improvement of existing therapeutic protocols by more specific recommendations should be possible. New and encouraging approaches are under investigation which may improve treatment of chemical weapon poisoning on the long term.

Colonel (MC) Professor Dr. Horst Thiermann, M.D.

is the director of the Bundeswehr Institute of Pharmacology and Toxicology. He specialized in Pharmacology and Toxicology as well as in Clinical Pharmacology and has been appointed Professor at Technical University, Munich.

Colonel (MC) Prof. Dr. Thiermann is vice-chairman of Bundesinstitut für Risikobewertung (BfR) Committee for the Assessment of Intoxications, member of the board and scientific committee of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) and past president of Clinical and Translational Toxicology Specialty Section (CTTSS) of the Society of Toxicology (SOT).

Alessandro Ceschi
Division of Clinical Pharmacology and Toxicology
Ente Ospedaliero Cantonale
Lugano, Switzerland

Novel psychoactive substances: How much a threat in public health?

In recent years there has been a dramatic increase in the availability and use of novel psychoactive substances on the recreational drug scene worldwide. Many of these substances, which are products of rational drug design with the aim to evade existing laws but to retain the psychoactive properties of the parent compound, pose a significant burden on public health in Europe.

PD Dr.med. Alessandro Ceschi

As a physician board certified in clinical pharmacology and toxicology and general internal medicine, Dr. Ceschi is the Deputy chief physician and Head of the Division of clinical pharmacology and toxicology and the President of the Drug and therapeutics committee at Ente Ospedaliero Cantonale, Lugano, Switzerland. He is also a consultant at the Department of clinical pharmacology and toxicology of the University Hospital Zurich and a senior lecturer in clinical pharmacology and toxicology at the Faculty of medicine of the University of Zurich. He gives also lectures in clinical toxicology at the Department of pharmaceutical sciences of the University of Basel. Dr. Ceschi is a member elected by the Federal Council as the representative of the Swiss Medical Association at the Federal
drug commission. He serves as a board member at the Swiss Society of Clinical Pharmacology and Toxicology (SSCPT). A focus of his research activities was on the investigation of the acute toxicity of substances acting on the central nervous system, such as psychotropic prescription and illicit drugs.

**Alexander Campbell**

**Poisons in the Opera**

Poisoning happens in the most unlikely settings; opera houses being one of the more unusual locations, one not generally prominent in poisons centre data! Comprehensive analysis of operatic poisonings has been undertaken revealing that poisonings are both accidental and intentional, with adult intoxications predominant and an unacceptably high mortality rate from the bizarre range of toxic substances to which opera singers and characters can be exposed. Certain sub-populations (sopranos) appear more vulnerable, and generally medical interventions in these cases appear inadequate. It is clear that poisons information services need to improve their "performance" and raise their vocal profiles in this theatre of activity.

**Alex Campbell**

started his toxicological career in November 1988 when starting work as a Specialist in Poisons Information for the UK National Poisons Information Service (NPIS) at its London unit. Whilst at the London unit, before its closure, he initiated the UK Veterinary Poisons Information Service which he directed for 20 years until 2012. He has written and lectured extensively on veterinary toxicology. In 2012 he was awarded the Blaine award and honorary life membership of the British Small Animal Veterinary Association for his services to veterinary medicine. Despite the veterinary focus Alex always remained active in human toxicology / poisons centre work. He has been on the Board of the EAPCCT since 2000, serving as its General Secretary from 2002-2006, its Treasurer from 2008-2012, and its President from 2014-2016. He is a fellow of both the EAPCCT and AACT. His current role is as Manager of the NPIS's Birmingham Unit under the directorship of Dr Sally Bradberry.
**Venue and Access**

The Anniversary Symposium is taking place in the grand auditorium (Aula, Kol G 201) of the University of Zurich, City Centre Campus, Rämistrasse 71, 8006 Zurich (Google Maps).
Public transport: The most near tram stop is ETH/Universitätsspital served by lines 6, 9, and 10. Tram line 6 connects to the main train station (in 7 minutes), line 10 to the Zurich airport (in 30 minutes).

By car: Parking slots near the venue are very rare. Participants coming by car need to use one of the public city parking garages (fee CHF 2.00 to 5.00 per hour):

- Parkhaus Rämibühl
  Zürichbergstrasse 10
  8044 Zürich
- Parkhaus Careum
  Pestalozzistrasse 7
  8032 Zürich
- Parkgarage am Central
  Seilergraben
  8001 Zürich
- Parkhaus Hohe Promenade
  Rämistrasse 22a
  8001 Zürich
- Parkplätze USZ Süd
  Gloriastrasse
  8006 Zürich
  (occupied most of the time!)