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**ABSTRACT BOOK**  
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## THE IMPORTANCE OF THE NATIONAL POISON CONTROL CENTRE IN THE HEALTHCARE SYSTEM IN THE REPUBLIC OF SERBIA

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### Abstract

**Introduction:** The National Poison Control Centre (NPCC) is the only referential institution in Serbia for prevention, diagnosis and treatment of poisoning. It provides the latest poisons information to the general public and specialized toxicology advice to health professionals on the identification of toxic agents, diagnosis and the management of poisoned patients. On request of different ministries and other relevant institutions in the country, the NPCC provides toxicological reports and expertise in the process of registration of chemicals, plant protection products, drugs, etc. Expert advice of the NPCC is also provided in any type of public health emergency and especially in mass chemical accidents. The only pregraduate and postgraduate education in clinical toxicology in the country is available at the NPCC which is the educational base for the Medical Faculty Military Medical Academy, University of Defense. It also liases with poison control centres and other relevant international organization in the world in maintaining training, medical education and toxicovigilance.

**Objective:** To present the role, activities and annual results of the NPCC. **Results:** From January 1 to December 31, 2016, in the Department for reanimation and triage of the NPCC, 4584 patients with acute poisoning were treated. The main cause of poisoning in was alcohol (52,2%), followed by drugs (27,4%), and substances of abuse (7,7%). In the group of 662 hospitalized patients drugs, corrosive agents, pesticides and substances of abuse were predominant cause of poisoning. The reduced number of hospitalization follows the trends and recommendations registered in European PCC. According to the Law on health protection in Serbia, NPCC is responsible for collecting of data on acute poisoning in the country, their analysis with necessary measures in health protection. According to the collected data from 16 medical institutions in different regions of the country, additional 2265 patients with acute poisonings were treated.

The Department of toxicological chemistry NPCC, which is referential in Serbia, has performed over 13304 toxicological analyses, mainly for the Ministry of Defense, but also other health

institutions, different ministries and companies. Over 30 toxicological reports and expertise have marked the work of the Experimental toxicology and pharmacology NPCC. As toxicovigilance and prevention of poisoning are one of main tasks of the PCC, in 2016, on monthly or even daily bases, NPCC has informed and warned the general public and medical doctors on new psychoactive substances and other public health situations.

**Conclusion:** NPCC has a very important and specific place in Serbian health system with the main role in diagnosis and treatment of poisoning, providing relevant information for medical institutions and general public in Serbia, collecting and analysis of data on poisoning in the whole country in order to protect human health and society in general. Beside that, NPCC has a task in risk assesment and providing reliable informations about the effects of toxic chemicals on human health and environment, modality of treatment, education, evaluation of antidotes and constant communication through mass media or intitutions in order to increase awareness about the public health threats and emergencies.

**Key words:** public health, national poison control centre

## **Environmental Pollutants (Cadmium and Polychlorinated Biphenyls) and Thyroid Gland Function**

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### Abstract

Endocrine-disrupting chemicals (EDCs), which are chemicals of special concern that may belong to a variety of chemical classes, can exert their effects through a number of different mechanisms. Some of them interfere with thyroid function, thus causing adverse effects on development, but can also affect metabolism and physiology of adults. Human and wildlife populations all over the world are exposed to more than 800 endocrine disrupting chemicals, cadmium (Cd) and polychlorinated biphenyls (PCBs) being among them. The aim of this experimental study was to evaluate the effects of prolonged, relatively low cadmium (Cd) exposure and exposure to polychlorinated biphenyls (PCBs), on serum triiodothyroxine (T3), and thyroxine (T4), as biomarkers of thyroid function. These two chemicals were chosen since they are persistent and global environmental pollutants that can enter the food chain and as chemicals of high toxicity that pose a threat to human health. Moreover, the effect of co-treatment of Cd and PCBs on thyroid function was also investigated, having in mind that we are not exposed to a single chemical in the real world, but to the mixtures of chemicals. Thus, we investigated the

effect of 28-days oral treatment of rats with six different doses of Cd or PCBs (ranging from 0.3-10 mg Cd/kg b.w. or 0.5-16 mg PCBs/kg b.w.), while nine groups were treated with different dose combinations of Cd and PCBs (1.25, 2.5 or 5 mg Cd/kg b.w./day with 2,4 or 8 mg PCBs/kg b.w./day).

The results show that oral 28 days treatment of rats with 6 different doses of Cd induced dose-dependent decrease of T3 while statistically significant reduction of T4 was observed for doses  $\geq 1.5$  mg Cd/kg b.w. revealing that T3 hormone is more sensitive to Cd than T4. This finding suggests that Cd interferes with thyroid function predominantly at extrathyroidal level. Applied doses of PCBs, on the other hand, induced more pronounced reduction of T4 than T3: significant decrease of T4 was observed for all applied doses and was dose dependent while T3 levels were significantly reduced for doses  $\geq 2$  mg PCB/kg, indicating that PCBs predominantly induce direct effect on thyroid gland. The results on the effects of co-exposure to Cd and PCBs on T3 and T4 hormones, analyzed using methodology based on the differences in slopes of dose-response curves, indicated synergistic interactions between these two chemicals for the effects on thyroid function, i.e. levels of thyroid hormones in serum.

Further intensive scientific work is needed to improve our understanding of the impacts of thyroid disruptors on human health and thus decrease the rise of thyroid-related diseases and disorders.

**Keywords: Endocrine-disrupting chemicals, cadmium, polychlorinated biphenyls, T3 and T4 hormones.**

## **POISONOUS PLANTS AND THEIR TOXIC COMPONENTS**

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### Abstract

More than half a million plant species are known today, and one plant in ten is poisonous. Only about 1,000 species, however, have been studied in detail for ingredients. There are about 50 plants families with poisonous species in Europe. The toxicity of poisonous plants is graded as: extremely poisonous – milligram quantities may have life-threatening effects (*Colchicum autumnale* – “mrazovac”, *Conium maculatum* – “kukuta”, *Laburnum anagyroides* – “zanovet”, *Hyoscyamus niger* – “bunika”, *Nerium oleander* – “oleander”, *Convallaria majalis* – “đurđevak”, *Thuja occidentalis* – “tuja”, *Aconitum napellus* – “jedić”, very poisonous – severe

signs of poisoning (*Veratrum album* – “čemerika”, *Taxus baccata* – “tisa”, *Rhododendron sp* – “rododendron”, *Chelidonium majus* – “rusa”, and poisonous (*Ranunculus acris* – “ljutić”, *Prunus laurocerasus* – “lovor-višnja”, *Evonymus europea* – “mašljika”, *Narcissus pseudonarcissus* – “narcis”).

The poisonous substances of plants are divided into alkaloids, triterpene glycosides, cyanogenic glycosides, and other poisonous substances and commonly, poisonous plants contain several of these substances.

Many accidents of human and animal poisoning by plants in the past century were caused by consumption of pyrrolizidine alkaloids. In Uzbekistan, Afghanistan and India, some 6,000 people have died in massive poisoning accidents by consuming poisonous plants, which caused heightened public interest. Such poisonings have often been caused by cereals or bread contaminated by seeds of various poisoning plants, such as *Heliotropium* (“posunac, sunčac”) and *Crotalaria species*. Medicinal plants in the genera *Senecio* (“kostriš”) and *Crotalaria* have also often been the cause of poisoning.

Every year in the world around 20.000 to 60.000 cases of poisoning plants and their products are registered. According to the statistics from the The Swiss Toxicological Information Centre in Zurich for the period of 2004. to 2014. years records, 75 to 85 percent of poisoned patients are children. Frequent cause of poisoning are poisoning plants *Lonicera* (crveno pasje grožđe, plotoplet), *Taxus* (tisa), *Solanum* (razvodnik) and *Convallaria* (đurđevak). In the National Poison Control Center, MMA annually from 10 to 20 patients with plants poisoning are treated. Besides accidental poisoning with *Colchicum autumnale* (mrazovac), for purposes of abuse, young people commonly used *Datura stramonium* (tatula) and *Hyosciamus niger* (bunika). Different methods for the detection and quantification of individual alkaloids from biological materials will be reviewed in the paper. Reliable and sensitive methods are liquid chromatography with mass and ultraviolet detection which give us the ability to compare the obtained spectra with Spectra library. Also, the Department of Toxicological Chemistry NPCC has developed HPLC/PDA and LC/MS method for determination of content of plant toxic compounds, isolated from biological materials. Introduced methods are used in routine analysis. Detection of glycoside is more complex. Extremely low concentrations can be detected by immunological-polarization fluorescent method. Detection of tissue organs after death can be performed by liquid chromatography with ultraviolet detection.

**Key words: plant, toxicity, components**

## Development and enhanced possibilities of laboratory support at University Clinic for Toxicology Skopje

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Diagnosis in toxicology is based in great part on laboratory research and findings. As a result of the changes that occurred in the last eight months in the Toxicology Laboratory of the University Clinic for Toxicology in Skopje, in order to maintain and continuously improve the work and enhance the quality of the laboratory, we focused on the progress. The process of modernization of the toxicology laboratory started with the expansion of the pallets for analysis, upgrading the analytical methods and automating the instruments. With the introduction of LIS on entire laboratory instrumentation, we started organizing the processes of laboratory performance, enabling the implementation of ISO standardization and accreditation according to ISO15189. A sophisticated, modern toxicology laboratory is the goal and the best support of the diagnostic procedures of the specialists in our Clinic.

**Key words: Laboratory support, poisonings**

### ЕПИДЕМИОЛОШКИ ПРОФИЛ НА АКУТНИ ТРУЕЊА РЕГИСТРИРАНИ НА КЛИНИКА ЗА ТОКСИКОЛОГИЈА, СКОПЈЕ, ВО ПЕРИОДОТ 2010-2017 ГОДИНА

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**Вовед:** Акутните труења со медикаменти, хемикалии, алкохоли, ПАС и други токсични субстанции се значаен медицински и социјален проблем. Цел на студијата е да ги прикаже акутните интоксикации регистрирани на ЈЗУ УК за Токсикологија во периодот од 2010-2017 год. според демографски обележја, етиологија, вид на средство и застапеност на амбулантски/хоспитално лекувани интоксикации.

**Метод:** ретроспективна студија која вклучува акутни интоксикации кај 10756 пациенти, забележани во Регистарот на труења на Клиниката за токсикологија. Податоците се собирани според истории на болест, медицинските дневници и извештаи од ургентната

амбуланта на Клиниката за токсикологија и пријавените акутни интоксикации на Клиниката по електронска или редовна пошта.

**Резултати:** Во периодот 2010-2017 год на Клиниката за токсикологија се регистрирани вкупно 10756 акутни труења со медикаменти, хемикалии, психоактивни супстанции, растенија и артроподи. Најголем број на труења се регистрирани во 2013 год (1492 пациенти). Од сите регистрирани интоксикации, најзастапени се труења во возрасната група (20-74 год) со највисока партиципација во годишниот збир во 2015 год (86,2%). Суицидалните идеи се најчест мотив за реализација на акутните труења во сите години, но најмногу се застапени во 2015 год (57,2%). Половата дистрибуција покажува незначајна разлика во партиципацијата на машкиот и женскиот пол (49,5% мажи vs. 50,5% жени) во вкупниот број на пациенти. Повеќе од половина од третираниите пациенти се амбулантски лекувани, со највисока застапеност на амбулантско лекување во 2016 год (68,9%), а најмногу хоспитално третирани интоксикации се во 2011 год (54,9%) Најчесто застапени во сите обсервирани години се труења со медикаменти (42,9%) со највисок процент на учество во вкупниот годишен број на интоксикации во 2011 год (51,1%). Бензодијазепините се и понатаму најчесто употребуван фармацевтски препарат (54,46%) од сите медикаментозни интоксикации со најголема застапеност во 2015 год (67,9%). Акутни алкохолни интоксикации во периодот 2010-17 год се на второ место според својата средна застапеност од 26,31%, а најголема застапеност во вкупниот број на труења се забележува во 2014 год. (35,1%). Хемикалиите се на третата позиција според фреквенцијата на јавување (25,1%) и тоа најчести се корозивните труења, со средна застапеност од 51,9% во вкупниот број на труења со хемикалии. Предозираност од ПАС и несакани ефекти од употреба на ПАС се регистрирани кај 1,1% од случаите со намалување на предозираност од хероин, но пораст на регистрирани случаи на несакани ефекти од употреба на кокаин и марихуана, вклучително употребата на марихуана со медицинска индикација, амфетамини и МДМА.

**Заклучок:** Медикаментозните интоксикации се и понатаму најчести интоксикации но и бројот на акутни интоксикации со корозивни средства останува значаен проблем во секојдневната пракса. Акутните алкохолни интоксикации го одржуваат својот тренд на застапеност и покрај превентивните мерки превземени од државата; истовремено се забележува пораст на бројот на третирани пациенти поради употреба на кокаин, марихуана, амфетамини и МДМА.

**Клучни зборови:** епидемиологија, интоксикации, регистар



## Mechanism-based approaches to drug toxicity assessment

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The use of any drug beyond the beneficial properties may be associated with a spectrum of adverse effects. In this respect, toxicology is an integrative part of medical education combined with pharmacology. Regrettably, toxicity is a main cause of late-phase failures in drug discovery. Adequate knowledge in mechanisms of drug toxicity may be helpful to define an overall safety profile. The causes of drug toxicities include mechanism-based (on-target) toxicity, off-target toxicity, bioactivation and production of toxic metabolites, immune hypersensitivity, idiosyncrasy, mutagenesis and carcinogenesis and teratogenicity. Understanding of these mechanisms of toxicity influences both the decision to develop and the risk assessment of drugs. Both pre-clinical (*in vitro* tests using cells/cell lines and *in vivo* testing in animals) and clinical trials associated with a drug are of importance to describe potential for toxicity. Evaluating toxicity and assessing risks of a new drug require comprehensive experimental testing against a broad spectrum of toxicity endpoints. Traditional toxicology approaches are relatively slow, directed toward individual elements of toxicity, and not necessarily relevant to human issues if done with experimental animals. Development of more useful biomarkers and short-term assays for rapid screening of drug toxicity early in the drug discovery is an imperative. Some progress has been made with “omics” technologies (genomics, proteomics, metabolomics) and “the metabolome” (variation in the profiles of endogenous metabolites) to describe new predictive biomarkers. *In vitro* toxicogenomics based on gene expression pattern could be done in a human cell line and be predictable for humans. *In vivo* predictive toxicogenomics evolving rapidly into a system toxicology that will be able to describe all the toxicological interactions and using the knowledge of toxicogenomic responses in certain species predict the modes of action of similar drugs in other species. *In silico* methods are applicable to predict toxicity ranging from acute toxicity or carcinogenicity to predictions of the underlying mechanisms of toxicity development, e.g. the identification of targets involved in adverse drug reactions and toxic effects. These methods comprise statistical models based on quantitative structure–activity relationships (QSAR) and machine learning algorithms trained on compounds with known toxic activity and so-called expert systems which incorporate human knowledge and expert toxicity rules such as structural alerts. *In silico* predictive toxicity methods represent an ultimate progress not only enabling the reduction of the associated time, costs and animal experiments, but also facilitate the designing of drugs with low toxicity while retaining the functionalities.

In conclusion, the integration of recent innovations like computational modeling and simulation studies, bioinformatics, high throughput screens, toxicokinetic and toxicogenomic tools with other necessary tests in experimental animals and appropriately designed clinical trials will undoubtedly bring significant advances in predicting drug toxicity.

**Key words: drug development, drug toxicity, toxicity assessment, predictive toxicology**

## Plant Toxicology and Risk Assessment

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Various plant species provide novel bioactive compounds which contribute significantly to the prevention and treatment of numerous diseases. In industrialized countries, up to 50% of the population regularly use herbal products with a continuously growing interest for further utilization among patients, predominantly because of less severe adverse effects compared to synthetic agents. Besides their anti-inflammatory, antibacterial and antioxidant properties, many plant species have been found to possess toxic potency as well. Ongoing plant research strives to explore the possibilities in utilizing their toxic properties for therapeutic purposes in terms of discovering novel cytotoxic agents from natural origin. Therefore, the aim of this study is to investigate the cytotoxic potential of selected aromatic herbs: *Allium ascalonicum* L. (AAR), *Allium cepa* L. (ACR), *Allium sativum* L. (ASR), *Nigella sativa* (NSS), *Orchis mascula* (L.) L. (OMT), *Ocimum basilicum* L. (OBH) and *Trigonella foenum-graecum* L. (TFGS).

The toxic bioactivity of plant extracts was examined by employing a rapid and cost-efficient screening method with *Artemia salina* species model system. Brine shrimp lethality assay is frequently conducted as alternative *in vivo* model, because of the good correlation demonstrated with toxicological studies on higher animals, giving baseline information of the plant species for therapeutic purposes. The method evaluates the mortality of *Artemia salina* larvae by exposing them to the examined plant extracts. Dead shrimps are counted after 24 hours of exposure and the percentage of mortality is calculated. Using probit regression analysis, LC<sub>50</sub> values are calculated from the percentage of mortality and the concentration of extract. The cytotoxic potential of the extracts is evaluated with Meyer's scale and Clarkson's scale based on their LC<sub>50</sub> values.

According to the obtained LC<sub>50</sub> values, all extracts manifested certain toxicity to the exposed brine shrimps, with the exception of *Allium cepa* (LC<sub>50</sub> 1445 µg/mL). Additionally, *Allium sativum* (LC<sub>50</sub> 754 µg/mL) and *Allium ascalonicum* (LC<sub>50</sub> 599 µg/mL) were classified as herbal extracts with weak cytotoxic potential on the Clarkson's scale. Moderate cytotoxicity was detected for *Orchis mascula* (LC<sub>50</sub> 313 µg/mL), *Trigonella foenum-graecum* (LC<sub>50</sub> 229 µg/mL) and *Nigella sativa* (LC<sub>50</sub> 203 µg/mL), while *Ocimum basilicum* demonstrated high cytotoxicity with LC<sub>50</sub> value 62 µg/mL.

The cytotoxic potential for *Ocimum basilicum* in the current study is in accordance with results from a series of *in vitro* cytotoxicity studies against several cell lines. Previous research demonstrated that *Ocimum basilicum* methanol extracts possess strong cytotoxic activity against

HCT116 and HepG2 carcinoma cell lines, and the *Ocimum basilicum* essential oil has significant cytotoxic potency against HeLa cells, HEP-2 cells and NIH 3T3 fibroblasts.

Due to the notable cytotoxic potency observed in this study, the examined species present promising sources of bioactive phytochemicals that need to be further assessed for their individual toxic effects and potential synergistic activity. Careful selection and adequate utilization of the aromatic herbs with cytotoxic potential could provide a more favourable approach in cancer prevention. Additionally, their targeted use as adjuvants to conventional therapy may assist cancer management by improving the outcome of the chemotherapeutic agents.

**Keywords: brine shrimp lethality assay; probit analysis; herbal extracts; cytotoxic potential**

## **Importance of Harm Reduction Programs in Macedonia**

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Drug use in contemporary society can be viewed as a cultural, as well as medical, social and economic phenomenon that requires interventions on several levels: creating services, programs and policies that will cover all aspects related to use of drugs, prevention, treatment, harm reduction, re-socialization and rehabilitation.

There are several definitions for harm reduction. The International Harm Reduction Association (IHRA) provides the most encompassing definition:

“Harm Reduction” refers to policies, programmes and practices that aim primarily to reduce the adverse health, social and economic consequences of the use of legal and illegal psychoactive drugs without necessarily reducing drug consumption. Harm reduction benefits people who use drugs, their families and the community.

[http://www.ihra.net/files/2010/08/10/Briefing\\_What\\_is\\_HR\\_English.pdf](http://www.ihra.net/files/2010/08/10/Briefing_What_is_HR_English.pdf)

Based on a behaviorist study and assessment of the number of drug injecting population in Macedonia carried out in 2010, the estimated number of people injecting drugs in Macedonia aged 18 to 45 is 10.900, while the estimated number of people injecting drugs in Skopje, aged 18 to 45 is 3.150, i.e. around 2.650 up to at 4.050 IDUs at most. The study was carried out by the Public Health Institute, in cooperation with HOPS, supported by the Global fund for fight against AIDS, tuberculosis and malaria, and UNAIDS. (Mikikj, V., Kuzmanovska, G., Memeti, Sh., Report from the behavioral research and assessment of the drug injecting population number in Macedonia, 2010, Skopje, 2011).

## Why harm reduction?

- We never, like others, will not have society without drugs;
- Abstention is unacceptable for many drug users;
- Primary prevention and implementation of laws in this field have own limitations;
- People will continue to use drugs, getting sick and die;
- What we can do is to reduce the infections, reduce suffering and death cases and other consequences what people facing;

In the period 1994/95 research on use of drugs in Macedonia was conducted from two experts, Jean Paul Grund and Dusan Nolimil. In the report key findings is that Macedonia facing increase of use of drugs, especially heroin. Name of the report is "Heroin epidemic in Macedonia". Based on the recommendations end of year 1996 organization MASK was established, which in 1997 was transformed to citizen association HOPS. HOPS continue as a one of the three needle and syringe exchange program opened in SEE (South East Europe) together with the opened programs in Slovenia and Croatia.

Why was important these programs to be established in Macedonia?

Effectiveness of harm reduction programs is confirmed in WHO report "Effectiveness of sterile needle and syringe programming in reducing HIV/AIDS among injecting drug users" from 2004. Research was done in 103 biggest cities in the world and confirm that in 36 cities where needle and syringe exchange programs exist HIV prevalence was reduced 18,6%, and in those 67 cities where those programs don't exist HIV prevalence was increased for 8,1%.

First HIV case in Macedonia is registered 1987. From 1987 till 2017 356 HIV cases was registered in the country. Less than 15 cases are injecting drugs related.

In Macedonia from 1996 till today 16 harm reduction programs in 13 cities are established. Those programs giving services for more than 4000 drug users on annual base. On stationary (drop in centers-more services under one roof) and through outreach activities people who inject drugs can use following services: needle and syringe exchange, medical services for long and improper injecting, social services, legal aid support, HIV concealing and testing, education for blood born and sexual infections, motivation for treatment of drug addiction, prevention of opiate overdose etc. One of the biggest challenge is use of Naloxone, opiate antagonist for saving lives. Based on national law civil society organizations are not allowed to buy and distribute. Country don't have comprehensive national data and strategic intervention regarding opiate overdose.

Harm reduction activities was key strategic goals from all HIV and drug strategies in the country from 2003 till today.

In the following years those programs after 20 years of existence and excellent results will face serious challenges regarding financial sustainability.

**Key words: Harm Reduction, HOPS, Needle exchange, saving lives, Naloxone.**

## Acute amlodipine/perindopril intoxication: therapeutic strategy and complications – case report

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In the case report an acute intoxication with combined statin-calcium antagonist – ACE-inhibitor (Lipertrans<sup>®</sup>) drug is presented. The patient was 49-years-old woman admitted to ICU in anuria, hypotension and anemia. The initial physical examination shows heart rate 100 b/min, blood pressure 90/60 mm Hg, without breath obstruction. At the time of admission there was no history of drug use and misuse. The toxicological analyses (GC-MS) show positive benzodiazepine (immunoassay) and presence of amlodipine, perindopril, ephedrine and chlorcyclizine in urine. Amlodipine in blood was 0.06 µg/mL (therapeutic range 0.003 – 0.015 µg/mL) and alprazolam - 0.3 µg/mL (therapeutic range 0.1 – 0.2 µg/mL). The intravenous lipid emulsion (ILE) was applied (Intralipid) and extracorporeal detoxification using carbosorption (Adsorba 300 C). After the initial infusion of ILE the whole amount of amlodipine in blood was measured as lipid-associated. At the end of carbohemoperfusion procedure the blood concentration of amlodipine was 0.16 µg/mL. At 48<sup>th</sup> hour after admission the amlodipine was in therapeutic range and the patient was detoxicated successfully. In conclusion, an ILE is useful tool in clinical toxicology for binding of lipophilic drugs in pharmacologically inactive form. The application of carbosorption is a possible way for elimination of drug and lipid-drug complex from the body.

**Key words: amlodipine overdose; intravenous lipid emulsion**

## HPLC ANALYSIS OF TRAZODONE IN BLOOD: TWO CASES OF TRITTICO INTOXICATION

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### ABSTRACT

A simple and fast, yet effective and precise UHPLC method for qualitative determination of an antidepressant medication trazodone in blood samples has been developed. Excellent linearity ( $r > 0.9999$ ) over sufficiently wide concentration range (from 0.15 up to 15  $\mu\text{g mL}^{-1}$ ) covering therapeutic, toxic, and comatose blood levels has been demonstrated. High precision (RSD < 1.6%), good recovery (85%) and low detection limits (LOQ = 0.15  $\mu\text{g mL}^{-1}$ ) make this relatively rapid method (ca. 30 min for a single run) a suitable asset in identification of acute intoxications, diagnosis refinement and treatment monitoring. The applicability and importance of newly developed method are presented on the basis of two clinical cases of Trittico self-poisoning.

**Keywords:** Trittico, trazodone, overdose, self-poisoning, acute intoxication

### Суицидни опити при деца – медицински, социален и психиатричен проблем

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Самоотравянето е най-честият способ за автоагресия и като такъв се е утвърдил във всички възрасти, поради лесното осъществяване. През последното десетилетие този проблем зачестява и се наблюдава тенденция за спад на възрастта.

По данни на Националния център за обществено здраве и анализи в България, средно по едно дете у нас прави опит за самоубийство, като 5% от тях завършват с трагичен край. Най-честият способ за това е самоотравяне, което ги прави сериозен токсикологичен, психиатричен и социален проблем.

Материал и методи: Направени са две проспективни проучвания на лекуваните в Клиника по токсикология на Университетска болница – Плевен деца със суицидни отравяния и са сравнени два периода – 2001 – 2005г. и 2011 – 2015г. с разлика от 10 години. Това е период през който българското общество е подложено на тежък социален стрес от промените в икономически и политически събития, които променят начина на живот. Това се отразява и на подрастващите поколения.

Резултати и обсъждане: Токсикологичната патология се увеличава в абсолютни стойности.

Мотивацията за самоубийство в тази възраст има сложна генеза и е по-скоро „ зов за помощ“, спрямо семейството и обществото, отколкото реално желание за смърт.

Разгледани са подробно психо-социалните фактори:

- ✓ Личността на детето – индивидуални и възрастови особености,
- ✓ особености на семейството и родителите,
- ✓ влияние на социална среда,
- ✓ роля на медиите и интернет пространството – *имитация* на видяно, чуто или прочетено под влияние на средствата за масова информация и интернет пространството.

Заключение: Зад всеки опит за самоубийство и зад всяко дете с проблемно поведение стоят поредица от родителски грешки, неосъзнати неблагоприятия и отсъствие на социални ангажименти.

**Ключови думи:** деца, суицидни опити ,отравяне, самоотравяне, социални фактори

## **Ibogaine in the treatment of drug addiction (critical review)**

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### **Abstract**

Ibogaine is a psychoactive alkaloid derived from *Tabernanthe iboga*, a plant used in initiatory rituals in West Central Africa. Largely because of ibogaine's status as a Schedule I substance in the U.S., the development of ibogaine's use in the treatment of drug addiction took place outside conventional clinical and medical settings. The exact molecular mechanism of the

pharmacological effects of ibogaine is not fully understood yet due to its diverse CNS effects. Ibogaine has shown promising anti-addictive properties in animal studies. Ibogaine is also anti-addictive in humans as the drug alleviates drug craving and impedes relapse of drug use. Although not licensed as therapeutic drug and despite safety concerns, ibogaine is currently used as an anti-addiction medication in alternative medicine in dozens of clinics worldwide. In recent years, alarming reports of adverse reactions and life-threatening complications and sudden death cases, temporally associated with the administration of ibogaine, have been accumulating. However, ibogaine exerts many serious side effects and its effects on drug craving have not been satisfactorily investigated. In the critical survey, all possible aspects regarding the potential alternative use of ibogaine in the treatment of drug addiction as well as serious concerns of the use of it will be discussed

**Keywords: Addiction, addiction treatment, drug abuse, ibogaine, iboga alkaloid, psychedelics, substance-related disorders.**

### ***Vipera ammodytes meridionalis*: The vipoxin neurotoxin**

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Snake bite cases are reported every year in Bulgaria. A bite from a venomous snake is rarely deadly, but it should always be treated as a medical emergency. The variety of clinical symptoms, envenomation diagnostic and therapeutic strategy is individual and depends on different factors. Even a bite from innocuous snake can be serious, leading to an allergic reaction or an infection.

The eastern nose-horned viper *Vipera ammodytes meridionalis* populating partially on Bulgarian area. Its venom neurotoxin, called vipoxin is a heterodimer consisting of phospholipase A<sub>2</sub>, responsible for the neurotoxic effects after envenomation as well as for the various hemotoxic effects (hemolysis, coagulation disorders).

An important aspect of snake envenomation therapy is using of specific antivenom treatment. There is a Bulgarian snake venom antiserum (containing horse antibodies) against



long-nosed viper venom. The recent strategies are focused to limit the antivenom use at unidentified snake-bite casualties or in the absence of life-threatening situation. Acute reactions to antivenom cause the greatest problem and clinicians have to deal with them as much as managing envenoming.

In the present report basic information on vipoxin toxin is presented as well as experimental *in vitro* and *in vivo* data about its toxicological properties (hemotoxicity and neurotoxicity). The disorders in blood coagulation are commented as well as the neuromuscular disturbance.

**Key words:** *Vipera ammodytes*, vipoxin, neurotoxin.

## **SYNTHETIC CANNABINOIDS OVERDOSE – FIRST LETHAL CASE IN BULGARIA**

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Synthetic cannabinoids (SCs) are chemical compounds which represented so called legal alternative to (illegal) cannabis. They are psychoactive substances of varying structure, synthesized in laboratories, which mimic the biologic effects of delta-9-tetrahydrocannabinol (THC) - the main psychoactive ingredient in marijuana, when they are consumed. On the drug market SCs appeared like herbal mixture – herbal incense, tea, herb, spice etc., intended for smoking under the common name “legal highs”.

Reported case concerns 18-years old boy found dead in his bed by roommate after a party. They bought 3 ready for smoking cigarettes containing herbal mixture (“joint”). At the evening of the party the boy smoked all three “happy” cigarettes and after that fall asleep.

Herbal mixture and biological samples (blood, urine, vitreous humor and liver) from autopsy were provided for drug analysis.

Toxicological experiments performed on herbal mixture determine the presence of two SCs - 5F-ADB (5F-MDMB-PINACA; CAS # 1715016-75-3, Fig. 1) and FUB-AMB (AMB-FUBINACA; CAS # 1715016-76-4, Fig. 1). Blood and urine samples drug analysis also confirmed that these SCs were consumed by the deceased. All other toxicological analyzes were negative.

The results carried out, the data of the deceased's roommate as well as the autopsy findings confirmed that the death was caused by intoxication with synthetic cannabinoids.

**Key words: cannabinoid, overdose, lethal case**

**DRIVERS SUSPECTED OF DRIVING AFTER DRUG ABUSE –  
CONFIRMATORY DRUG ANALYSIS IN DRIVERS BLOOD SAMPLES  
IN NORTHEASTERN BULGARIA, 2017**

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**ABSTRACT**

In 2017 there were 98 blood samples taken by Traffic control Agency and presented at Analytical toxicology Lab, Naval Hospital – Varna, for drug confirmatory analysis. All of the samples were taken from drivers within North-Eastern Bulgaria, suspected of driving after drug abuse. More than 75% of the presented samples are confirmed drug positive by means of gas chromatography methods (GC-MS). It was demonstrated that the most often detected drugs were cannabis (more than 43% of positive samples) and amphetamines (39%), followed by opioids (9%) and cocaine (6%). There were a few confirmed cases of methadone and ecstasy abuse. Age distribution was analyzed, indicating a definite maximum at age 21-25. Attention was drawn on the substantial prevalence of polyvalent intoxications: 31% of positive samples contained two, three, or even four individual drugs in combination.

**Keywords: drugs of abuse, traffic police, drivers**

## THE CLINICAL TOXICOLOGY TODAY - THE BULGARIAN VIEW

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The acute intoxications are chronic psychosocial disorders and are among the three most frequent causes of lethality in Europe and the United States. Their frequency is about 400 to 600 poisonings per 100,000 per year.

The prevalence of those intoxications and the high pre-hospital mortality (80%) significantly outweigh the lethality caused by infectious or others diseases. Yet the hospital mortality, caused by acute intoxications, does not exceed 2-3%.

**Purpose:** The purpose of the report is to present our experience in organizing and providing emergency toxicological assistance.

**Materials and Methods:** Review of the available literature and protocols referring to acute exogenous intoxications and toxo-allergic reactions. The contingent of the Emergency Toxicology Clinic of MMA Sofia was analyzed in 2017.

**Results:** In 2017, 2176 persons sought assistance in the clinic, 1316 were hospitalized, the average hospital stay was 2.34 beds. Outside this contingent, we conducted 1720 immune-tests to detect psychoactive substance used among soldiers (during missions abroad) and military service candidates, 368 Protocols for Exploration of Drug Use of Civilians and 500 examinations and consultations (pre-operative, reporting of hypersensitivity samples) of patients hospitalized in other units of MMA-Sofia.

**Conclusions:** As a result of the acquired practical experience and the evaluation of the data, we can draw the following conclusions:

1. The varied and unpredictable toxicology pathology poses a challenge for society. Continuous improvement of awareness is necessary to achieve good toxicological behavior.
2. The acute toxicology pathology and its specific details pose a challenge for the medical community as a whole.
3. Key to maintaining a high level of preparedness for clinical toxicologists and other medical staff, for emergency adequacy, acute intoxication and toxo-allergic reactions is the improvement of their qualification.

Modern clinical toxicology is becoming more and more relevant. Analyzing the data related to the trends in toxicological morbidity is essential for: the maintenance of the high professional training of the professional toxicologists, the improvement of the qualification of the GPs, the medics from the Center and the emergency departments of the hospitals, as well as for informing population about the various dangers.

**Key words:** clinical toxicology, contemporary view of clinical toxicology, toxicological standard

## СТРАНИЧНИ ЕФЕКТИ ПРИ УПОТРЕБА НА ПО-ВИСОКИ ДОЗИ КОМБУСНА

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Kombucha е ферментирала чаена напитка, която представлява жива симбиозна колония от дрожди и полезни бактерии, обикновено със съкращение "SCOBY". Въпреки че точният ѝ произход все още остава неизвестен, някои твърдят, че Kombucha произхожда от Китай, а името ѝ идва от корейски лекар "Kombu", който използва чай ("ча") за лечебни цели. Има данни за употреба на Kombucha още през 1900 г. в Русия и Германия, а след това набира популярност и в цяла Европа.

В началото на ХХ-и век се провеждат множество изследвания в Русия, които показват, че Kombucha подобрява съпротивата срещу рака, може да предотврати сърдечно-съдови заболявания, стимулира храносмилателната система, стимулира имунната система, повлиява възпалителните процеси, СПИН, косопад, сексуални дисфункции, предменструален синдром, предполага се, че може да има и много други лечебни ефекти.

Важно е да се разбере, че страничните ефекти на Kombucha са предмет на вариация въз основа на конкретния човек, който консумира Kombucha, както и начина на приготвяне и консумираната дневна доза. Много хора пият Kombucha редовно и докладват полза без странични ефекти, други съобщават за сериозни странични ефекти. Поради това е важно в клиничната си практика да бъдем запознати със страничните ефекти на тази напитка.

Най-честите нежелани реакции при консумация на Kombucha, са свързани с гастроинтестиналния тракт и включват: запек, диария, лошо храносмилане, гадене и стомашни болки. Другите нежелани реакции са ацидоза, акне, алергични реакции, тревожност, подуване на корема, промени в кръвната захар, объркване, студени тръпки, замаяност, сухота в устата, главоболие, жълтеница, оловно отравяне, промени в настроението, мускулни болки, кожни обриви. В литературата са описани и три смъртни случая на хора, консумирали Kombucha в по-високи дози.

Много хора смятат, че Kombucha е безвредна напитка и търсейки ползите за здравето си, надвишават допустимата доза от 125 ml на ден, но това може да доведе до сериозни нежелани реакции.

## ТРЕТМАН НА ПОСТКОРОЗИВНА ЕЗОФАГИЈАЛНА СТЕНОЗА СО БУЖИРАЊЕ

### ПРИКАЗ НА ДВА СЛУЧАЈА

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**ВОВЕД:** Стенозата е абнормално стеснување на луменот на било каков премин во телото. Стенозата на хранопроводот најчесто предизвикува симптоми на прогресивна тешкотија при голтање (disfagija), регургитација и повраќање. Како резултат на опструктивниот процес може да се појави малнутриција и губење на тежина. Кај пациенти со овие симптоми потребно е да се направи ургентна Ендоскопија и/или РТГ на горен дел на ГИТ со контраст.

Причини кои моѓе да доведат до стенози се: шакациев прстен, ахалазија, корозивна ингестија, тумори, надворешно зрачење, езофагијална склеродермија индуцирана со лекови, постендоскопски третман (radiofrekventna ablacija) и ректи дерматолошки заболувања.

Бужирањето (Bougienage) како метода во медицината за прв пат се среќава во раните 1800 год. и одтогаш опремата што се користи за лекување на езофагијалните стенози значително се развила за да денес бидат вклучени флексибилни жичани водени дилататори-катетери (Eder-Puestow или Savary-Gillard)

Прикажани се два случаја на бужирање на пациенти со корозивна труење. Кај првиот пациент труењето е пред 12 год, додека кај вториот пациент е еден месец пред да се направи бужирање.

Компликации: Главни компликации на езофагијалната дилатација се: крварење, перфорација и пулмонална аспирација.

Студија спроведена за да се анализира кај пациенти кои се рефракторни на ендоскопска дилатација, дали буги дилатација, заедно со интралезиска инјекција на триамцинолон може да го намали бројот и фреквенцијата на ендоскопските дилатации.

Споредбена студија за анализа на успешност на буги дилатација во однос на балон дилатација.

**ЗАКЛУЧОК:** Езофагијална дилатација е иницирана во третманот на езофагијална стриктура. Постојат голем број на опции за успешна дилатација на повеќето стенози, но внимателен избор и пристап е неопходен за да се минимизираат компликациите и да се зголеми терапевтската корист. Езофагеална стриктура е дефинирана како анатомско фиброзно езофагеално ограничување со неможност да се постигне дилатација од  $\geq 14$  mm или да се одржи дилатација 4 недели откако ќе се постигне дијаметар  $\geq 14$  mm. Пациентите со бужи дилатација потребно е да бидат следени проспективно до 1 година.

Нашата анализа покажа дека кај пациенти со формирано сврзно ткиво (12 год) потребни се 7-8 третмани на бужија во однос на бужирање на пациент на 30 дена од ингестијата на

корозивно средство каде беа потребни три (3) третмани. Важно е дека ендоскопијата има голема улога за темелно разбирање на основната етиологија и анатомија на стенозата за развивање на стратечки пристап за дилатацијата која треба да се изведува во терциерните центри со големо искуство.

## ПОКРОВИТЕЛ НА 11-ТА КОНФЕРЕНЦИЈА НА ЗТМ

А.Д. АЛКАЛОИД СКОПЈЕ

