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Kasım 2012 - Kongre Özet Kitabı / November 2012 - Congress Abstract Book

8. Uluslararası Katılımlı

Türk Toksikoloji Derneği Kongresi

8th CONGRESS OF THE TURKISH SOCIETY OF TOXICOLOGY

With International Participation

Laboratuardan Kullanıma İlaç: Toksikolojinin Rolü

Drugs From Bench to Market: The Role of Toxicology

15-18 Kasım 2012 / November 15-18, 2012

AKKA ANTEDON HOTEL

BELDİBİ - KEMER / ANTALYA – TURKEY

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“IN LIFE, THE TRUEST GUIDE IS SCIENCE”

Mustafa Kemal Atatürk
(1881-1938)

8. ULUSLARARASI KATILIMLI TÜRK TOKSİKOLOJİ DERNEĞİ KONGRESİ

Laboratuardan Kullanıma İlaç: Toksikolojinin Rolü

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İçindekiler

Contents

BİLİMSEL PROGRAM

SCIENTIFIC PROGRAM

1. GÜN / *DAY 1* **14 KASIM ÇARŞAMBA / *WEDNESDAY, NOVEMBER 14***			
08^{30}-17^{00}	**SÜREKLİ EĞİTİM KURSU 1** / *CONTINUING EDUCATION COURSE 1*		
	Developments in Risk Assessment: Basic Concepts and International Frameworks for Evaluating Toxicity Data for Human Health Risk Assessment Eğitmen / *Course leader:* ***Lynne T. Haber, TERA-USA***		
	08^{30}-12^{00}	**SABAH OTURUMU** / *MORNING SESSION*	
		08^{30}-09^{45}	Hazard characterization and dose-response assessment for **non-cancer** endpoints
		09^{45}-10^{00}	**Kahve Molası** *Coffee Break*
		10^{00}-12^{00}	Hazard characterization and dose-response assessment for **cancer** endpoints
	12^{00}-13^{00}	**Öğle Yemeği** *Lunch*	
	13^{00}-17^{00}	**ÖĞLEDEN SONRA OTURUMU** / *AFTERNOON SESSION*	
		13^{00}-14^{30}	Mode of action with case study
		14^{30}-15^{00}	**Kahve Molası** *Coffee Break*
		15^{00}-17^{00}	Chemical-specific adjustment factors with examples
			Tools and resources
18^{30}-21^{00}	**Akşam Yemeği** *Dinner*		

2. GÜN / *DAY 2* 15 KASIM PERŞEMBE / *THURSDAY, NOVEMBER 15*				
08^{00}-24^{00}	**KAYIT** / REGISTRATION			
08^{30}-12^{30}	**SÜREKLİ EĞİTİM KURSU 2** *CONTINUING EDUCATION COURSE 2*		**SÜREKLİ EĞİTİM KURSU 3** *CONTINUING EDUCATION COURSE 3*	
	Genotoxicity and Methods of Analysis Eğitmenler / *Course leaders:* ***Bensu Karahalil, Yalçın Duydu***		**Data Requirement for REACH Registration** Eğitmen / *Course Leader:* ***Karl-Heinz Cohr***	
12^{30}-13^{50}	**Öğle Yemeği** *Lunch*			
13^{50}-14^{15}	**AÇILIŞ SEREMONİSİ** / *OPENING CEREMONY* **Asuman Karakaya,** *Kongre Başkanı / Congress Chair* **Hilmi Orhan,** *Türk Toksikoloji Derneği Başkanı / Head of Turkish Society of Toxicology*			
14^{15}-15^{00}	**AÇILIŞ KONFERANSI** / *OPENING CONFERENCE* **Thomas Baillie** *(USA)* *Reactive Drug Metabolites Versus Targeted Covalent Drugs. Considerations for Toxicological Risk Assessment* Sunan / Presented by: **Hilmi Orhan**			
15^{00}-15^{30}	**Kahve Molası** *Coffee Break*			
15^{15}-17^{15}	**1. OTURUM** / *1. SESSION* **Toxicological Risk Assessment: Novel Approaches** Oturum başkanları / Chairs: **Sema Burgaz, Jan Commandeur**		**SÖZLÜ SUNUMLAR 1** *ORAL PRESENTATIONS 1* Oturum başkanları / Chairs: **Ayşe Başak Engin, Pınar Erkekoğlu**	
	15^{15}-15^{45}	**Lynee T. Haber** (USA) *21st century Toxicology in Risk Assessment: Use of Biomarker Data and Systems Biology*	15^{15}-15^{30}	**Dilek Battal** *Why We Need Validation of Bioanalytical Methods in Forensic and Clinical Toxicology?*
			15^{30}-15^{45}	**Ayfer Tozan-Beceren** *Investigation of DNA Damage and DNA Repair Capacity in Patients with Colorectal Cancer and Their First Degree Relatives*
	15^{45}-16^{15}	**Günter Speit** (Germany) *Thresholds in Risk Assessment of Genotoxic Carcinogens*	15^{45}-16^{00}	**Aydan Çağlayan** *Assessment of Oxidative Stress and Impaired Antioxidant Defence System in Patients With Epithelial Ovarian Cancer*
			16^{00}-16^{15}	**Özge Ülker** *Investigation of Contact Sensitization Potency of Fragrance Mix and Fragrance Mix Ingredients by Using Ex Vivo Nonradioctive Local Lymph Node Assay*
	16^{15}-16^{45}	**Yalçın Duydu** (Turkey) *Reproductive Toxicity of Borates and Risk Assessment for Humans*	16^{15}-16^{30}	**Semih Kunak** *New Area for Carbonmonoxide İntoxication: Hydro-electric Central Construction*
			16^{30}-16^{45}	**Ali Aşcı** *Evaluation of Oxidant/Antioxidant Status In Neonatal Sepsis*
	16^{45}-17^{15}	**Sait C. Sofuoğlu** (Turkey) *Cumulative Carcinogenic Risk Levels for Disinfection By-Products in İzmir Drinking Water*	16^{45}-17^{00}	**Erdem Coşkun** *Male Infertility And Genetic Factors*
			17^{00}-17^{15}	**Devrim Demir Dora** *Cytotoxicity study on Cationic Solid Lipid Nanoparticles as DNA Delivery System*
17^{30}-18^{45}	**AÇILIŞ KOKTEYLİ** / *WELCOME RECEPTION*			
18^{45}-21^{00}	**Akşam Yemeği** *Dinner*			

3. GÜN / *DAY 3*
16 KASIM CUMA / *FRIDAY, NOVEMBER 16*

08^{30}-09^{15}	**KONFERANS 2** / *CONFERENCE 2* **Ali Esat Karakaya** (Turkey) *Toxicology in Turkey* Sunan / Presented by: **Sinan Süzen**			
09^{15}-09^{30}	**Kahve Molası** *Coffee Break*			
09^{30}-11^{30}	**2. OTURUM** / *2. SESSION* **Toxicology in Preclinical Drug Development** Oturum başkanları / Chairs: **Ali Esat Karakaya, Thomas Baillie**		**3. OTURUM** / *3. SESSION* **İlaç Güvenliliği** Oturum başkanları / Chairs: **Asuman Karakaya, Benay Can Eke**	
	09^{30}-10^{00}	**Ruth Roberts** (Great Britain) *Drug Discovery Safety Science: Objectives, Impact and Future Perspectives*	09^{30}-10^{00}	**Semra Şardaş** (Turkey) *İyi Farmakovijilans Uygulamaları ve 2005'den Günümüze TÜFAM*
	10^{00}-10^{30}	**Hilmi Orhan** (Turkey) *Target Organs and Cellular Reactivity of Metabolites*	10^{00}-10^{30}	**Yelda Kasap** (Turkey) *İlaçta Risk Nasıl Yönetilmelidir /TÜFAM'ın REMS (Risk Degerlendirme ve Azaltma Stratejisi) Çalışmalarından Örnekler*
	10^{30}-11^{00}	**Amit Kalgutkar** (USA) *Mitigating Idiosyncratic Toxicity Risks with Enzyme Covalent Modifiers*	10^{30}-11^{00}	**Hilal İlbars** (Turkey) *Klinik İlaç Araştırmalarında Güvenlilik / Yeni Klinik İlaç Araştırma Yönetmeliği "Veri Güvenliği İzleme Komitesi Tanıtımı"*
	11^{00}-11^{30}	**Jan Commandeur** (The Netherlands) *Role of Polymorphic Enzymes in the Inactivation of Reactive Metabolites*	11^{00}-11^{30}	**Banu Ünal** (Turkey) *Farmakovijilans Risk İletişimi*
11^{30}-12^{30}	**POSTER SUNUMLARI** *POSTER SESSION*		11^{40}-12^{20}	**FİRMA Sunumu / *Industry Activity:* XENOMETRICS** *Ames MPF, umuC ve YES YAS Testleri Tanıtım Sunumu –*
12^{30}-13^{30}	**Öğle Yemeği** *Lunch*			
13^{30}-15^{00}	**4. OTURUM** / *4. SESSION* **Current Topics in Environmental Toxicology & Ecotoxicology** Oturum başkanları / Chairs: **Cafer Turgut, Perihan Kurt Karakuş**		**5. OTURUM** / *5. SESSION* **Türkiye' de Adli Toksikoloji** Oturum başkanları / Chairs: **Tülin Söylemezoğlu, Sinan Süzen**	
	13^{30}-14^{00}	**Filiz Küçüksezgin** (Turkey) *Persistent Organic Pollutants and Metals in Biotic and Abiotic Media from Eastern Aegean Sea*	13^{30}-14^{00}	**Tülin Söylemezoğlu** (Turkey) *Dünyada ve Ülkemizde Adli Toksikolojinin Gelişimi ve Uygulamalar*
	14^{00}-14^{30}	**Pim Leonards** (The Netherlands) *Environment-Friendly Alternatives for Brominated Flame Retardants - Outcome of the European ENFIRO Project*	14^{00}-14^{30}	**Rezzan Gülhan** (Turkey) *Adli Tıp Kurumunda Toksikoloji ve Farmakoloji Uygulamaları*
	14^{30}-15^{00}	**Marc Suter** (Switzerland) *Proteomics in Ecotoxicology*	14^{30}-15^{00}	**Nebile Dağlıoğlu** (Turkey) *Kronik Pestisit Maruziyetinin Farklı Biyolojik Örneklerde Belirlenmesi ve Adli Boyutu*
15^{00}-15^{15}	**Kahve Molası** *Coffee Break*			
15^{15}-17^{15}	**6. OTURUM** / *6. SESSION* **Chemical Carcinogens in Occupational Settings** Oturum başkanları / Chairs: **Bensu Karahalil, Neslihan A. Kocabaş**		**SÖZLÜ SUNUMLAR 2** *ORAL PRESENTATIONS 2* Oturum başkanları / Chairs: **Cemal Akay, Yüksel Çetin**	
			15^{15}-15^{30}	**Cafer Turgut** *The Possibility to Use Persistent Organic Contaminants (POPs) Environmental Data to Predict Contamination in Human*

	15^{15}-15^{45}	**Hermann Bolt** (Germany) *Occupational Cancer of the Urinary Bladder*	15^{30}-15^{45}	**Perihan Binnur-Kurt Karakuş** *Indoor Dust as a Source of Human Exposure to Heavy Metals in Istanbul*
			15^{45}-16^{00}	**N. Ülkü Karabay Yavaşoğlu** *Induction of Oxidative Stress and Histological Changes in Liver by Subacute Doses of Butyl Cyclohexyl Phthalate*
	15^{45}-16^{15}	**Nurşen Başaran** (Turkey) *Use of Comet Assay as a Biomarker for Chemical Exposure in Human*	16^{00}-16^{15}	**Pınar Erkekoğlu** *The Protective Effect of Ascorbic Acid and Selenocompounds Against the Cytotoxicity and Genotoxicity of 3,5 Dimethylaminophenol*
			16^{15}-16^{30}	**Aylin Üstündağ** *Effect of Boron Compounds on Lead and Cadmium Induced Genotoxicity in Cell Cultures*
	16^{15}-16^{45}	**Gert van der Laan** (The Netherlands) *Work Related Lung Cancer*	16^{30}-16^{45}	**Yüksel Çetin** *Evaluation of Cell Death Mechanisms of Palladium(II) Complex as an Anticancer Agent in Human Cancer Cell Lines*
			16^{45}-17^{00}	**Rasih Kocagöz** *Persistent Organic Pollutants and Toxicological Responses in Gray Mullet and Seabass from Büyük Menderes River Estuary and Vicinity*
			17^{00}-17^{15}	**Seher Karslıoğlu-Ceppioğlu** *Matrix Gla Protein, Klotho Gene Polymorphisms and DNA Damage in Chronic Kidney and Coronary Artery Diseases*
17^{15}-17^{30}	**Kahve Molası** *Coffee Break*			
17^{30}-18^{30}	**ÇALIŞMA GRUPLARI TOPLANTISI** *SUBGROUPS' MEETINGS* • Kimyasal Mutajenezis Çalışma Grubu / *Chemical Mutagenesis Working Group* • Klinik Toksikoloji Çalışma Grubu / *Clinical Toxicology Working Group* • Çevresel Toksikoloji&Ekotoksikoloji Çalışma Grubu / *Environmental Toxicology&Ecotoxicology Working Group* • Farmakovijilans ve İlaç Güvenliliği Çalışma Grubu / *Pharmacovigilance and Drug Safety Working Group* • Toksikolojik Risk Değerlendirmesi Çalışma Grubu / *Toxicologic Risk Assessment Working Group*		**POSTER SUNUMLARI** *POSTER SESSION*	
18^{30}-19^{00}	**ENFIRO Projesi sonuçları DVD gösterimi** / *Outcomes of ENFIRO Project: DVD Projection* **Pim Leonards**			
18^{30}-21^{00}	**Akşam Yemeği** *Dinner*			

4. GÜN / *DAY 4* **17 KASIM CUMARTESİ / *SATURDAY, NOVEMBER 17***				
08^{30}-10^{00}	**7. OTURUM** / 7. *SESSION* **Endocrine Disruption by Current Agents** Oturum başkanları / Chairs: **Hilmi Orhan, Murat Özmen**		**8. OTURUM** / 8. *SESSION* **Clinical Toxicology: Therapeutic Drug Monitoring** Oturum başkanları / Chairs: **Çetin Kaymak, Christoph Hiemke**	
	08^{30}-09^{00}	**Hande Gürer-Orhan** (Turkey) *In vitro and In vivo Evaluation of Potential Endocrine Disrupting Effects of Herbal Dietary Supplements*	08^{30}-09^{00}	**Fredrik Kugelberg** (Sweden) *Clinical and Forensic Toxicology - The Swedish Experience*
			09^{00}-09^{30}	**Christoph Hiemke** (Germany) *Therapeutic Drug Monitoring to Guide Psychopharmacotherapy*
	09^{00}-09^{30}	**Belma Koçer Giray** (Turkey) *Toxicological Evaluation of Endocrine Disrupting Chemicals: Phthalates and Bisphenol A*	09^{30}-10^{00}	**Sinan Süzen** (Turkey) *Plasma Concentrations-Genotype Relation and Adverse Effects of Citalopram in Depressed Patients*
10^{00}-10^{20}	**Kahve Molası** *Coffee Break*			
10^{20}-11^{05}	**KONFERANS 3** /CONFERENCE 3 **Thomas Hartung** (USA) *Toward a pathway-based regulatory toxicology* Sunan / Presented by: **Asuman Karakaya**			
11^{05}-11^{20}	**Kahve Molası** *Coffee Break*			
11^{20}-12^{50}	**SÖZLÜ SUNUMLAR 3** / *ORAL PRESENTATIONS 3* Oturum başkanları / Chairs: **Bülent Ergun-Belma Koçer Giray**			
	11^{20}-11^{35}	**Tülin Söylemezoğlu** *Effect of Metallothionein 2a Polymorphism on Toxic Metal Levels in Human Biological Samples*		
	11^{35}-11^{50}	**Turgay Çelik** *Results of Abused Drug analyses with CEDIA and (GC-MS): A Five Years Retrospective Evaluation*		
	11^{50}-12^{05}	**Türkan Yurdun** *The role of the Analytical Toxicology in Emergency Medicine*		
	12^{05}-12^{20}	**Ahmet Sayal** *Volatile Anesthetics and Their Association With Oxidative Stress*		
	12^{20}-12^{35}	**Oğuzhan Yıldız** *Drug-Induced Cardiotoxicity: Experimental Methods*		
	12^{35}-12^{50}	**A. Başak Engin** *Increased Oxidative Stress But Not Tryptophan Degradation in Plasmodium Berghei Infected Mice*		
13^{00}-13^{50}	**Öğle Yemeği** *Lunch*			
14^{00}-18^{00}	**SOSYAL PROGRAM** / SOCIAL PROGRAM • ***Arkeoloji Müzesi*** */ Archeology museum* • ***Antalya Şehir Turu*** */ Antalya City Tour* • ***Kaleiçi*** */ Old Town* • ***Yivli Minare*** */ Yivli Minaret*			
20^{00}-24^{00}	**GALA YEMEĞİ** / GALA DINNER			

5. GÜN / *DAY 5* **18 KASIM PAZAR / *SUNDAY, NOVEMBER 18***				
	9. OTURUM / 9. *SESSION* **Mesleki Toksikolojide Güncel Konular** Oturum başkanları / Chairs: **Ahmet Sayal, Engin Tutkun**		**10. OTURUM** / 10. *SESSION* **Regulatory Toxicology: European Applications** Oturum başkanları / Chairs: **Türkan Yurdun, Nida Besbelli**	
09^{00}-10^{00}	09^{00}-09^{30}	**Ahmet Aydın** (Turkey) *The Effects of Toxicants Occupationally Exposed on Oxidative Stress and Genotoxicity*	09^{00}-09^{30}	**Neslihan Aygün Kocabaş** (Belgium) REACH awareness: Overview of REACH Regulation and Potential Impacts in Toxicology
	09^{30}-10^{00}	**Ömer Hınç Yılmaz** (Turkey) *Amalgam-Cıva: Hasta ve Diş Hekimlerinde Maruziyet*	09^{30}-10^{00}	**Nida Besbelli (**Switzerland) Contribution of Toxicology to the *United Nations Environment Programme* (UNEP)
10^{00}-10^{15}	**Kahve Molası** *Coffee Break*			
10^{15}-11^{15}	**SÖZLÜ SUNUMLAR 4** / *ORAL PRESENTATIONS 4* Oturum başkanları / Chairs: **Hasan Türkez, Turgay Şişman**			
	10^{15}-10^{30}	**Sakine Uğurlu Karaağaç** *Environmental Risk Assessment for Plant Protection Products*		
	10^{30}-10^{45}	**Enes Arıca** *Assessment of Cr and Ni Levels in Placenta by Graphite Furnace Atomic Absorption Spectrometry*		
	10^{45}-11^{00}	**Engin Tutkun** *Tamoksifen Sitrat Solunum Yoluyla Alınan Silikaya Bağlı Gelişen Sistemik Fibroziste Koruyucu Mudur?*		
	11^{00}-11^{15}	**Nazmiye Zengin** *Genotoxic Effects of Monosodium Glutamate on Mammalian Cells in Vitro*		
	11^{15}-11^{30}	**Ayla Çelik** *The Protective Role of Curcumin on Perfluorooctan Sulfonate - Induced Genotoxicity Single Cell Gel Electrophoresis and Micronucleus Test*		
11^{30}-11^{45}	**KAPANIŞ** /CLOSING CEREMONY			

* **Posterlerin** kongre boyunca asılı kalması ve poster sunumları sırasında sunucuların posterleri başında bulunması gerekmektedir.
*** Posters** should be kept hanged during the congress and presenters are requested to stand near their posters during the poster sessions.

KONFERANS ÖZETLERİ

CONFERENCE ABSTRACTS

AÇILIŞ KONFERANSI (OPENING CONFERENCE)

REACTIVE DRUG METABOLITES VERSUS TARGETED COVALENT DRUGS. CONSIDERATIONS FOR TOXICOLOGICAL RISK ASSESSMENT

Thomas Baillie

University of Washington, School of Pharmacy, Box 357631, Seattle, WA 98195-7631, USA

The metabolism of drugs and other foreign compounds to chemically reactive intermediates that covalently modify cellular macromolecules has been implicated as one general mechanism of xenobiotic-induced toxicity, although it is recognized that some reactive electrophiles appear to be benign while others are not. The factors that determine the toxicological potential of a given reactive species are poorly understood, and this limitation in our knowledge has hampered the development of predictive models of toxicity. Based on safety concerns associated with the covalent modification of proteins by reactive drug metabolites, the pharmaceutical industry has been reluctant to develop drugs which interact with their biological target through covalent bond formation, although a number of such agents are known to act *via* this mechanism and have been shown to be safe and effective. In this presentation, the characteristics of targeted covalent inhibitors will be compared and contrasted with those of reactive drug metabolites, and some general principles will be discussed that may guide the rational design of covalent drugs.

KONFERANS 2 (CONFERENCE 2)

TOXICOLOGY IN TURKEY

Ali Esat Karakaya

Gazi University, Faculty of Pharmacy, Department of Toxicology, Ankara, Turkey

There are no well-established criteria to evaluate the level of a specific scientific field in a country. Considering the broad scope of toxicology with its sub-branches and various applications, evaluation of its level would be relatively more difficult compared to other scientific disciplines. In the light of Turkey's science/R&D figures and health indicators, at the least, the following criteria can be used to assess the level of toxicology in Turkey. In this talk the outcomes of these criteria-based evaluations will be discussed.

EDUCATION:
- Undergraduate courses in toxicology
- Graduate Programs (MSc and PhD) in toxicology.

RESEARCH and PUBLICATION
- Number of toxicology articles and their impacts
- Outstanding discoveries in toxicology from Turkey

MANPOWER in TOXICOLOGY:
Existence of;
- Internationally recognized national society of toxicology.
- Internationally recognized toxicologist certification system.

TOXICOLOGY RELATED ESTABLISHMENTS:
Existence of;
- National poison information/control center.
- Independent toxicology research institutes.
- Toxicology oriented contract research organizations (CROs).
- Drug company based safety assessment laboratory facilities.
- National pharmacovigilance system.

KONFERANS 3 (CONFERENCE 3)

TOWARD A PATHWAY-BASED REGULATORY TOXICOLOGY

Thomas Hartung

The Johns Hopkins University, USA

The National Research Council report from 2007 "Toxicity Testing in the 21st Century: A vision and a strategy" has created an atmosphere of departure in the US. It suggests moving away from traditional (animal) testing to modern technologies based on pathways of toxicity. These pathways of toxicity could be modeled in relatively simple cell tests, which can be run by robots. The goal is to develop a public database for such pathways, the Human Toxome, to enable scientific collaboration and exchange. There is a continuously growing awareness about Tox-21c: It was first embraced by scientists and in the US. Most importantly, the US agencies followed fast on the NRC report: the Tox-21 alliance in 2008, EPA made it their chemical testing paradigm in 2009 and FDA followed. Industry got engaged, e.g., with the Human Toxicology Project Consortium. In Europe, all this is rather delayed, with some adaptation of the vocabulary but not necessarily grasping the new approach. This is not alternative methods under a new name. However, interest is lately increasing strongly in Europe. Tox-21c suggests moving to a new resolution, i.e. pathways of toxicity. The problem is that the respective science is only emerging. What will be needed is the Human Toxome as the comprehensive pathway list, an annotation of cell types, species, toxicant classes and hazards to these pathways, an integration of information in systems

toxicology approaches, the in-vitro-in-vivo-extrapolation by reversed dosimetry and finally making sense of the data, most probably in a probabilistic way. The NIH is funding since September 2011 by a transformative research grant The Human Toxome project led by CAAT. The project involves US EPA ToxCast, the Hamner Institute, Agilent and several members of the Tox-21c panel. The new approach is shaped around pro-estrogenic endocrine disruption as a test case. Early on, the need for quality assurance for the new approaches as a sparring partner for their development and implementation has been noted. The Evidence-based Toxicology Collaboration (EBTC) was created in the US and Europe in 2011 and 2012, respectively. This collaboration of representatives from all stakeholder groups aims to develop tools of Evidence-based Medicine for toxicology, with the secretariat run by CAAT. All together, Tox-21c and its implementation activities including the Human Toxome and the EBTC promise a credible approach to revamp regulatory toxicology.

DAVETLİ KONUŞMACI ÖZETLERİ

INVITED SPEAKER ABSTRACTS

1. OTURUM (1. SESSION)

21ST CENTURY TOXICOLOGY IN RISK ASSESSMENT: USE OF BIOMARKER DATA AND SYSTEMS BIOLOGY

Lynne T. Haber[1], John Reichard[2], John Fowler[3]

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Biomarkers, systems biology and related new testing approaches have substantial potential to aid in risk assessment. Biomarkers of effect range from genomics measures to early markers of effect, such a markers of oxidative stress or indicators of cytotoxicity. These biomarkers can be used to enhance the understanding of the biological process of a chemical's toxicity. Some biomarkers can be evaluated in humans using readily sampled material (e.g., blood or urine), allowing for the evaluation of effects at environmentally-relevant exposures. Multiple research initiatives are ongoing to develop and validate high- and medium-throughput tests with the goals of enhancing the predictive accuracy of traditional toxicology testing methods and reducing reliance on animal models. A parallel effort is required in risk assessment to develop methods for the meaningful application of such data. Near-term applications include identification of target biological pathways, improved mode of action determination and target organ identification. Dose-response assessment from new toxicology approaches will also be enhanced by decreasing the need for extrapolation to doses well below the data, and offers the potential for testing in human cells. Exposure assessment can benefit by the increased use of internal dose measures that reflect an individual's overall exposure profile. To use the data from these new technologies in risk assessments, we need new risk assessment tools and improved incorporation of decision analysis methods. A key challenge in such applications is the need to "anchor" the results of *in vitro* testing to classical toxicity tests. Such methods would aid in distinguishing when *in vitro* changes indicate adverse effects from when the observed changes fall within the homeostatic range. Addressing these issues requires a tiered suite of approaches for modeling data (e.g., linked exposure-effect modeling). Furthermore, collaboration among many groups, including industry, government, academics, and non-governmental organizations is important in developing the tools to advance our approach to risk assessment.

THRESHOLDS IN RISK ASSESSMENT OF GENOTOXIC CARCINOGENS

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Despite manifold attempts to reduce exposures towards carcinogens, exposure cannot be completely avoided. Low concentrations of genotoxic carcinogens are present in the environment, at the workplace and in food. Therefore, risk assessment for genotoxic carcinogens is a challenge in toxicology. The critical key events for the induction of cancer by "genotoxic carcinogens" are mutations. The default assumption in risk assessment still is that mutagens have a non-threshold mode of action. Only mutagens with non-DNA targets (e. g. aneugens, inhibitors of DNA synthesis) are accepted examples for threshold effects. However, there is increasing evidence for thresholded dose responses of DNA-reactive mutagens due to the action of physiological protective mechanisms (e.g., metabolic inactivation, DNA repair). New experimental approaches are available to relate exposure-induced DNA damage to endogenous DNA lesions and to characterize the mutagenic potential of induced DNA lesions. Data can be generated which allow to establish health-based exposure limits for selected genotoxic carcinogens. Formaldehyde (FA) is an excellent model substance for which a threshold mode of action can be scientifically justified. Because of its high reactivity and rapid inactivation, FA is a typical site of first contact genotoxin. Animal experiments were performed to detect DNA adducts in the nasal epithelium after inhalation and to determine the mutagenic potential of these lesions. In human volunteers exposed to FA by inhalation under controlled conditions, "no observed effect levels" (NOEL) for irritation and genotoxic effects were estimated. In order to take new scientific insights into consideration, different concepts have been established for risk management such as the ALARA principle (as low as reasonably achievable), the "Margin of Exposure" (MOE), or the "Threshold of Toxicological Concern" (TTC) concept. Actual scientific opinions published by European scientific committees provide advice for the use of the TTC approach for safety assessment of pharmaceuticals, cosmetics and food.

REPRODUCTIVE TOXICITY OF BORATES AND RISK ASSESSMENT FOR HUMANS

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Boric acid and sodium borates have been considered as being

"toxic to reproduction and development", following results of animal studies with high doses. Experimentally, a NOAEL (no observed adverse effect level) of 17.5 mg B/kg-bw/day has been identified for the (male) reproductive effects of boron in a multigenerational study of rats, and a NOAEL for the developmental effects in rats was identified at 9.6 mg B/kg-bw/day. These values are being taken as the basis of current EU safety assessments. In this context boric acid and sodium borates have been classified as toxic to reproduction in accordance with the Regulation (EC) No.: 1272/2008 (CLP). However, such effects have not been proven in humans so far. Recent epidemiological studies conducted in China and Turkey proved the lack of association between boron exposure and reprotoxic effects in male workers even under occupational exposure conditions. Boron mediated adverse effects on the most sensitive reproductive toxicity biomarkers (DNA integrity of sperm cells and sperm quality parameters) have not been identified in both studies. The mean blood boron concentrations of high exposure groups in the studies conducted in China and Turkey are 499.2 and 223.9 ng/g respectively. According to the experiments in rats the blood boron concentrations associated with the NOAELs for developmental and reproductive adverse effects are 1270 ng/g and 2020 ng/g respectively. In this context, there is actually no contradiction between the experimental studies and the human epidemiological study results. The blood boron concentrations determined in workers are far below the critical blood boron concentrations associated with the NOAELs for the developmental and reproductive adverse effects in rats even under worst-case exposure conditions. Consequently, the blood boron concentrations associated with the NOAELs for developmental and reproductive adverse effects in rats are not realistic for humans even under extreme exposure conditions. Therefore, the classification of boric acid and sodium borates as toxic to reproduction and development should be re-evaluated.

CUMULATIVE CARCINOGENIC RISK LEVELS FOR DISINFECTION BY-PRODUCTS IN IZMIR DRINKING WATER

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Environmental risk assessments for trihalomethanes (THMs), the major group among groups of disinfection by-products, have been conducted around the globe and in our country. Cumulative risks have been estimated assuming response addition, that risks associated with the individual THMs (chloroform, bromodichloromethane, dibromochloromethane, and bromoform) are additive. However, response addition should only be applied to components of a mixture, which act via independent modes of action. In addition, risks should be based on a multi-route exposure assessment with its variables preferably measured for the subject population instead of assuming statistics of the American population published by the US Environmental Protection Agency. Taking these concerns into account, we estimated cumulative carcinogenic risks for THMs in Izmir drinking water by reanalyzing our previously (partly) published data (Kavcar et al., *Water Research*, 40, 3219-3230, 2006). Five exposure scenarios (minimum, 5th percentile, median, 95th percentile, and maximum exposure) were constructed. All three exposure routes (ingestion, inhalation, and dermal absorption) were considered. Ingestion of drinking water, inhalation and dermal absorption during showering, bathing, hand washing, and dish washing were the included exposure pathways. THM concentrations in air were estimated by using chemical specific transfer efficiencies. Chemical specific skin permeability coefficients were used to estimate dermal absorption exposures, together with body weight dependent body surface areas. Contributions of exposure routes to the total risk, in the order of low to high, were dermal absorption, ingestion, and inhalation. Cumulative risks were estimated using Cumulative Relative Potency Factors, CRPF, approach proposed by Teuschler et al. (*Journal of Toxicology and Environmental Health, Part A*, 67, 755–777, 2004), and the simple addition method. The cumulative carcinogenic risks estimated by the both methods were acceptable ($<1\times10^{-6}$) in the minimum and 5th-percentile exposure scenarios. They were generally acceptable (1×10^{-6} -1×10^{-4}) in the median exposure scenario but not acceptable ($>1\times10^{-4}$) in the 95th-percentile and maximum exposure scenarios. Simple addition method produced an order of magnitude higher risk levels compared to the CRPF method. Therefore, cumulative carcinogenic risks might have been overestimated in the literature. Nevertheless, risk mitigation measures are needed by Izmir Water Authority.

2. OTURUM (2. SESSION)

DRUG DISCOVERY SAFETY SCIENCE: OBJECTIVES, IMPACT AND FUTURE PERSPECTIVES

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The discovery and development of new drugs is complex, lengthy and expensive; many candidate drugs fall out of development along the way. There are diverse reasons for this attrition, but several analyses highlight safety and toxicity as the primary reason for failure. To address this, we have a multi-faceted approach based on risk prediction/mitigation via early analysis of the potential for unwanted effects related to either target or chemistry. This approach has led to the early closure of several projects saving considerable resources that would otherwise

have been wasted. For example, ALK5 was under consideration as a potential target for oncology therapy but our early analysis of the literature suggested the potential for damage to heart valves. We conducted several studies to test this hypothesis and were able to show that inhibiting ALK5 even in mature adults carried an unacceptable risk for patients. This project was closed early with significant savings of resources. Specifically around chemistry, in one project we noticed high levels of retention of the compound in aorta in pre-clinical rat studies. An analysis of the literature showed that this aortic binding was also seen with VIOXX, which was subsequently withdrawn due to the risk of cardiac damage. To determine if our candidate drug had this unintended toxicity, we analyzed aortic binding and structure by electron microscopy. These studies revealed the potential for interference with the aldehyde chemistry required for elastin biosynthesis with predictable damage to aortic elasticity. These data allowed us to move away from molecules with these unwanted effects. Overall, early assessment of the potential risks in a drug project followed by hypothesis-testing experimental work can underpin early good decisions in drug discovery and development leading to a reduction in expensive late stage attrition.

TARGET ORGANS AND CELLULAR REACTIVITY OF METABOLITES

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Most of the drug-induced toxicities are seen in liver, as this organ has anatomical, physiological and biochemical unique features compared to other tissues. It is located alongside the stomach and intestine, which makes liver the central organ for orally taken drugs. It receives 28% of the cardiac output, so significant portions of the drug in systemic circulation passes through the liver and readily accumulates in hepatocytes via the large fenestrae of hepatic endothelium. Lastly, liver has the richest quantity and quality of drug metabolizing phase I and phase II enzymes. Therefore, it is not surprising that the major target for reactive drug metabolites is liver. On the other hand, sufficiently stable metabolites may also pose a risk for extrahepatic tissues; they may circulate in blood until they reach their site of action. Metabolites can be accumulated by specific transport mechanisms or alternatively, reactive metabolites can be formed in respective tissue. In this presentation, examples of hepatic and extrahepatic bioactivations in literature will be highlighted. Special emphasis will be given to preliminary findings of the research in the context of a project on novel reactive metabolites from marketed drugs.

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MITIGATING IDIOSYNCRATIC TOXICITY RISKS WITH ENZYME COVALENT MODIFIERS

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The design of target-specific covalent inhibitors is conceptually attractive because of increased biochemical efficiency through covalency and increased duration of action that outlasts the pharmacokinetics of the agent. Although many covalent inhibitors have been approved or are, in advanced clinical trials to treat indications such as cancer and hepatitis C, there is a general tendency to avoid them as drug candidates because of concerns regarding immune-mediated toxicity that can arise from indiscriminate reactivity with off-target proteins. The lecture will examine potential reasons (e.g., lack of off-target reactivity) for the excellent safety record of marketed covalent agents and advanced clinical candidates for emerging therapeutic targets. While tactics to examine selective covalent modification of the pharmacologic target are broadly applicable in drug discovery, it is unclear whether the output from such studies can prospectively predict idiosyncratic immune-mediated drug toxicity. Opinions regarding an acceptable threshold of protein reactivity/body burden for a toxic electrophile and a non-toxic electrophilic covalent drug have not been defined. Increasing confidence in proteomic and chemical/biochemical reactivity screens will require a retrospective side-by-side profiling of marketed covalent drugs and electrophiles known to cause deleterious toxic effects via non-selective covalent binding.

ROLE OF POLYMORPHIC ENZYMES IN THE INACTIVATION OF REACTIVE INTERMEDIATES

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Adverse drug reactions (ADRs) are still common events that can lead to termination of clinical development programs, labeling of drugs with black box warnings or withdrawal from the marketplace. In particular idiosyncratic ADRs (IDRs), which occur at a very low frequency and which usually are very severe, represent a major challenge because of their unpredictable nature and because basic understanding of their underlying mechanism is still lacking. Chemical modification and/or oxidation of critical target proteins by reactive drug metabolites are considered as potentially important mechanisms, which might initiate the process ultimately leading to tissue damage.

Therefore, genetically determined deficiency of enzymes involved in inactivation of reactive intermediates of drugs, such as glutathione S-transferases (GSTs), and NAD(P)H:quinone oxidoreductase (NQO1), might be predisposing factors for ADRs resulting from bioactivation reactions. A population study has suggested that carriers of a combined null genotype of GSTM1 and GSTT1 are more susceptible for drug-induced liver injury caused by antibiotics and NSAIDs *(Lucena et al., Hepatology 48: 588, 2008)*. However, so far only few non-clinical studies have been performed to experimentally demonstrate the involvement of individual GSTs in inactivation of short-lived reactive drug metabolites. Using a highly active bacterial drug metabolizing P450-BM3 as tool to generate human-relevant reactive drug metabolites and recombinant human GSTs we were able to demonstrate the GST-dependency of inactivation of reactive intermediates of acetaminophen, clozapine and diclofenac. Polymorphic GSTs indeed were shown to contribute to GSH-conjugation. Furthermore, enzyme-catalyzed GSH-conjugation showed remarkable differences in regioselectivity of inactivation when compared to non-enzymatic GSH-conjugation. Excretion of corresponding mercapturic acids and cysteine conjugates, therefore, might not only reflect internal exposure to reactive intermediates, but also involvement of GST in inactivation *in vivo.*

3. OTURUM (3. SESSION)

İYİ FARMAKOVİJİLANS UYGULAMALARI VE 2005'DEN GÜNÜMÜZE TÜFAM

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Pharmacovigilance activities are expanding around the world. This is reflected in the increasing number of national pharmacovigilance centres that have been established in recent years, but on the other hand there are still many countries where no formal systems for pharmacovigilance are in place. In order to ensure that the existing centres are effective, their impact on public health and health costs should be measurable with demonstrable benefits. Pharmacovigilance Center of Turkey (TUFAM) closely follows up drug safety issues and takes required precautions in accordance with the "Regulation Regarding the Monitoring and Assessment of Medicinal Products for Human Use" since 2005. The final goal is to identify the drug risks, to evaluate all the availableinformation regarding these risks by taking intoaccount any uncertainties, and taking appropriatemeasures to minimize their impact on patient's safety to provide the best possible benefit-risk balance. There has been a renewed effort at the Ministry of Health inlate 2012 by the establishment of the Turkish Medicines and Medical Devices Agency. A right step in the right direction was takenimmediately by establishing the Risk Management Department within the Agency. TUFAM andPharmacovigilance Risk Management Unit are withinthis newlyestablished department.

Risk management is a continuing process throughout the lifetime of a medicinal product and a risk management system is a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products. The drugs monitored with a risk management plan will be presented during the course of the session . While a part of precautions taken is similar to those of international health authorities; there are also specific ones in accordance with the conditions of our country.

The Clinical Drug Research Department of the Turkish Pharmaceuticals and MedicalDevices Agency works closely with the National Pharmacovigilancecenter. The benefits for science and the society expected from a trial cannot prevail over the health of the volunteers involved in the trial, or over any potential risks to their health or the other personal rights. It is essential that the study does not have any foreseeable noxious and permanent effects on human health. When a medicinal product is under clinical development, there is limited safety information surrounding its use. It is important to obtain timely and pertinent safety information in order to have a broader picture of the clinical safety surrounding a medicinal product, and if necessary, to take action on important clinical safety information arising during clinical development. Regulation and guidelines set for the rules and principles of GCP will be presented during the course of the session. Viable improvements in regulation; suchas pharmacist in clinical trials and their primary responsibilities will be discussedduring the presentation and the information on Data and Safety Monitoring Board (DSMB); an independent group of experts that advises the study partners will be presented.

On the other hand risk communication is still a challenge and an improving area in drug safety. The process of exchange of risk information among all stakeholders aims to make them aware of the risks identified, and ensurethat the risk assessment results are clearly received and understood. This is the way in which decision-makers communicate with various interested parties. There is need shifting from "information" to "communication" and even to "education". The new approaches and strategies to improve currently used risk communications tools will be discussed during the course of the presentation.

4. OTURUM (4. SESSION)

PERSISTENT ORGANIC POLLUTANTS AND METALS IN BIOTIC AND ABIOTIC MEDIA FROM EASTERN AEGEAN SEA

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This study was performed in the framework of the national monitoring programme of Turkey related to MEDPOL Phase IV and national monitoring project of pollution in Izmir Bay. Aegean Sea is one of the eastern Mediterranean sub basins located between the Greek and Turkish coasts. There is no industry in the area surrounding the northern part of the eastern Aegean coast except Candarli and Izmir Bays. Izmir Bay is one of the great natural bays of the Mediterranean Sea. The city of Izmir is an important industrial and commercial centre and is a cultural focal point for this area. Candarli Bay has been strongly affected by growing population and industrialization. There are only maritime and tourism activities along the southern part of the eastern Aegean coast. Heavy metals and halogenated hydrocarbons in mussel have been monitored in Izmir Bay for trend monitoring of chemical contaminants. Heavy metals have been measured in sediments from the Aegean coast. The highest level of Hg, Cd, Zn were found in sediments from Çandarlı Gulf; Cr,Cu from Datça. The highest concentrations of Hg, Cd, Cu, Zn were found in the Izmir Bay while Cr was measured in Marmaris Gulf. The concentrations of heavy metals in Izmir Bay sediments were generally higher than the background levels from the Mediterranean and Aegean Seas except cadmium. Maximum EFs were calculated in the inner bay and the elevated enrichment levels of Hg, Cr, Zn, Ni, Pb indicate anthropogenic pollution. Outer and Middle Bays show low levels of heavy metal enrichments except the estuary of Gediz River. Fish samples were collected from different parts of Izmir Bay. Heavy metal levels were lower than the results in fish tissues reported from polluted areas of the Mediterranean Sea. The limit value for human consumption of metals, metal concentrations in muscle of *Mullus barbatus* appear to be low. The relatively higher values for chlorinated hydrocarbons found areas from the inner part of Izmir and Candarli Bay sediments. The results indicated that the DDTs were the predominant contaminant in sediments of the Eastern Aegean coast. *p,p'*-DDE was the most often found OCP compound at all stations except Dardanelles Strait Entrance. The total PCB concentrations of the samples collected for this study did not exceed the ERM or PEL values, with the exception of sites Candarli and Izmir Inner Bay, which showed concentrations above the ERL and TEL values. The sediments at Candarli and Izmir Inner Bay could potentially cause acute biological impairment.

ENVIRONMENT-FRIENDLY ALTERNATIVES FOR BROMINATED FLAME RETARDANTS - OUTCOME OF THE EUROPEAN ENFIRO PROJECT

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Several brominated flameretardants (BFRs) have unintended negative effects on the environment and human health. Some of them show a strong bioaccumulation in aquatic and terrestrial food chains, some are very persistent, and some show serious toxicological effects such as endocrine disruption. During the last decade, an increasing number of reports have presented evidence of these negative effects caused by BFRs. A number of BFRs (in particular polybrominated diphenyl ethers (PBDE's), hexabromocyclododecane (HBCD) and tetrabromobisphenol-A (TBBP-A)) can be found in increasing concentrations in the human food chain, human tissues and breast milk. Less toxic alternatives appear to be available already but comprehensive information on their possible toxicological effects are lacking. The European Commission-funded project ENFIRO investigates the substitution options for some BFRs and compares the hazard, exposure, fire performance and application of the alternatives versus the BFRs. In addition, a risk assessment and comparative life cycle assessment are carried out. The current paper shows the main outcomes of ENFIRO. Information on the hazards, exposure, leaching behavior and life cycle assessment of the alternative halogen free flame retardants (HFFRs) compared to the BFRs are discussed.

ENFIRO approach

ENFIRO follows a practical approach in which HFFRs are evaluated and compared to BFRs regarding their flame retardant properties, their influence on the function of products once incorporated, and their environmental and toxicological properties. This is achieved using a tiered approach. In the first phase, a prioritization and selection of the most viable flame retardant/product combinations was conducted. In the second phase, screening and case studies of the selected HFFRs were carried out to gather a comprehensive set of information on toxicological impact and environmental behaviour, as well as the performance of the HFFR in the specific applications.

Hazard assessment

The HFFRs and BFRs were tested with a battery of in vitro studies (cytotoxicity, genotoxicity, estrogenicity, androgenicity, thyroid hormone binding, neuro-toxicity). In addition, the ecotoxicological hazard and persistency tests were carried out. For the comparative hazard assessments, hazard data of the HFFRs and BFRs were converted into hazard profiles using threshold values for PBT (persistence, bioaccumulation, toxicity). The EC50 values of the toxicity data from the literature and ENFIRO were therefore classified according to the DfE

threshold values. From the initial selection of 14 alternative flameretardants six were found to be less toxic and also accumulated less in the food chain than the BFRs. Examples of viable alternatives will be shown.

PROTEOMICS IN ECOTOXICOLOGY

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Classic ecotoxicology has focused upon a bottom-up approach to understand stressor effects in which a few genes, proteins, or biochemical reactions are studied at a time. The invention of new technologies and the unraveling of the genome of key organisms in the last decade has enabled the analysis of the whole transcriptome (gene transcripts), proteome (proteins) and of small cellular molecules (metabolite profiling) resulting in a whole system approaches.
We use such a systems biology approach to understand the biological responses of aquatic model organisms to environmental stressors such as heavy metals, herbicides and physical stressors. Our model organisms are the green alga *Chlamydomonas reinhardtii* and the zebrafish (*Danio rerio*). Using Multidimensional Protein Identification Technology (MudPIT) allows determination of differential expression of proteins, which in addition to providing insights into the modes of toxic action, also allows identifying protein biomarkers. For instance, MudPIT analysis of *C.reinhardtii* exposed to silver allowed discrete identification of roughly 2500 proteins in each sample with a false discovery rate set to 2%, representing major cellular processes. Enrichment analysis showed significant regulation of several biological pathways. Key among them were photosynthesis, ATP synthesis and tetrapyrolle synthesis with all being severely down-regulated. Differently, some pathways that were up-regulated were the lipid synthesis, oxidative stress response, proteolysis and cell wall synthesis. Our results provide the first insights into the mechanisms of toxicity of ionic silver. Silver is taken up into the cells via active metal transporters and inhibits key proteins involved in photosynthesis and ATP synthesis. Silver also induces oxidative stress as deduced from the induction of oxidative stress response proteins such as GPXH. The up-regulation of lipid synthesis also indicates an autophagy response. Importantly, we could link the changes at the proteome to the physiological state of the algae on exposure to silver.

5. OTURUM (5. SESSION)

APPLICATIONS AND DEVELOPMENT OF FORENSIC TOXICOLOGY IN THE WORLD AND TURKEY

Tülin Söylemezoğlu

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Forensic toxicology is the branch of science that studies and practices the application of toxicology for the purposes of law and consists of post-mortem forensic toxicology, human-performance toxicology and forensic urine drug testing as main areas. Nowadays environmental pollution toxicology and aerospace toxicology are recent fields of interest in forensic toxicology also. Forensic toxicology deals with the techniques and methods for determining the identity and amounts of unknown components in the biological specimen. Forensic toxicology laboratory staff must be certified and experienced enough should be working in this field and scientific findings must be objective and precise for public benefit. Pharmacology and physiology knowledge will give idea for effect of drugs and unknown substances in biological systems and examine the adverse effects of these substances on humans. All of this information is necessary in order to evaluate the results in forensic toxicology. Quantitative detection of the suspected toxic agent is the most important data in the evaluation process of forensic toxicology results. Presence of a drug or a xenobiotic in biological samples does not verify the cause of intoxication, and unidentification of a particular toxic substance does not prove the opposite. On the other hand, agents those are not toxic under normal conditions may cause intoxication and death, owing to the comorbidities or genetic susceptibilities of certain people. In this speech, development and application of forensic toxicology at the world and Turkey will be discussed.

PHARMACOLOGY AND TOXICOLOGY PRACTICE IN THE COUNCIL OF FORENSIC MEDICINE

Rezzan Gülhan Aker

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The Council of Forensic Medicine is the official expert witness organization and medico-legal authority functioning under the Ministry of Justice, in Turkey. The main duties and responsibilities of The Council, defined in law (Law No. 2659, art. 2), are to state scientific and technical opinions on matters concerning forensic sciences which are referred by the courts or the offices of judges or public prosecutors; and to provide

forensic medicine specialty training. The Council has branches and units organized under the headquarter which is in Istanbul. The headquarter and the branches have Chemical Analysis Laboratories. Laboratories have toxicology, narcotics, alcohol, instrumental, food and other materials analysis divisions. The main workload of these laboratories consists of the analysis of biological samples for alcohol, substances of abuse and drugs/medicines. The interpretations of their analytical results are done in Expertise Committees by medical experts. The 5th Expertise Committee gives opinions on the effects of alcohol, drugs and toxic substances on human subjects. In this talk, an outline on how the samples are analyzed in the laboratories of Council of Forensic Medicine, analytical procedures and interpretations of the results in expertise committees will be presented. The role of pharmacologists and pharmaceutical toxicologists with a forensic science perspective in this process will be discussed

DETERMINATION OF CHRONIC PESTICIDE EXPOSURE IN DIFFERENT BIOLOGICAL SAMPLES AND THE LEGAL ASPECT

Nebile Dağlıoğlu

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In the last decade, alternative or unconventional matrices have becoming more important in the field of toxicology, owing to the advantages that these specimens are readly available when compared with conventional samples used in routine laboratorial analysis. Conventional biological samples like blood, plasma, serum and urine have already been proven to be the suitable biomarkers of short-term pesticide exposure. Hair, bone, adipose tissue, breast milk, amniotic fluid, cord blood and meconium analysis have been suggested as a tool to monitor long-term pesticide exposure. Organochlorine compounds including organochlorine pesticides (OCPs) such as dichlorodiphenyl trichloroethane (*p,p´*-DDT), hexachlorobenzene (HCB), *ϐ*-Hexachlorocyclohexane (*ϐ*-HCH) and products for industrial use such as polychlorinated biphenyles (PCBs) were widely used in the 20th century. However, the use of OCPs has been banned in many developed countries since 1970s. Similarly, the use of some organochlorine pesticides was restricted in the mid-1980s, in Turkey. After 1985, because of long half- life time and high tendency for bioaccumulation, the use of OCPs has been banned except for endosulfan and toxaphene, by authorities. The decisions with regard to banning PCBs were taken in the USA in early 1970s, yet in our country; however, those decisions have been put into practice after 1996. The Cukurova region is the most important agricultural area. Account for 32% pesticide use in Turkey. In Turkey, there are approximately 11 tons obsolete stocks of DDT and approximately 6.5 tons PCBs. There are also approximately 213 tons of PCBs that are being used by Turkish Electricity Generation and Transmission Corporation. Unfortunately, there is no official data about other stocks of OCPs in Turkey. The characteristic of environmental persistence and liposolubility of organochlorine compounds lead bioaccumulation in biological samples, especially, in adipose tissue, serum, and breast milk. The analyses of the levels of organochlorine compounds in biological samples of human population remain reliable markers in determining the extent of chronic exposure and in the evaluating the hazards.

6. OTURUM (6. SESSION)

CHEMICAL CARCINOGENS IN OCCUPATIONAL SETTINGS: OCCUPATIONAL CANCER OF THE URINARY BLADDER

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North-Rhine-Westphalia is the most populated federal state in Germany, with a long tradition and high impact of both the chemical and the metal industries. Because of the long latency time of relevant occupational tumours, it is important to relate diseases that are now being diagnosed to previous exposures. Examples presented in this lecture are carcinogenic amines inducing occupational cancer of the urinary bladder, and 1,3-propane sultone as an extremely potent carcinogen producing a variety of rare human malignancies. The relevance of occupational carcinogenesis, together with a series of chemical disasters in the last decades of the 20th century, has led to an implementation of preventive legislation on both national and EU levels. As an example for such an implementation, the system of categorisation of carcinogens for the setting of Occupational Exposure Limits (OELs) will be presented, which is used by the EU Scientific Committee for Occupational Exposure Limits (SCOEL). Outstanding examples for the evaluation of carcinogenic compounds and priority settings for newly arising problems will be highlighted.

USE OF COMET ASSAY AS A BIOMARKER FOR CHEMICAL EXPOSURE IN HUMAN MONITORING IN DIFFERENT OCCUPATIONS

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Accidental, occupational and environmental exposure to chemicals used in agriculture and industry is still a continuing problem. People in various occupational settings have the potential to be exposed to hazardous substances, which are known to be genotoxic and can lead to genetic alterations. The exposures to these chemicals have been associated with an increased risk for certain diseases including cancer. Occupational exposure has been estimated to account for nearly 10% of all human cancer. The measurement of molecular or cellular biomarkers as the indicators of exposure or preventive factors has many applications in occupational toxicology. Although a variety of assays have been applied for biomonitoring to estimate the effects of human exposure to genotoxic agents, there is a need for reliable and fast method for screening workers professionally at risk in different occupational settings. The Comet assay, which has been regarded as a simple, inexpensive, reliable, rapid and trusted biomarker assay, has been widely used in human biomonitoring and molecular epidemiology. The Comet assay determines DNA damage and repair in single cells. The evaluation of DNA damage and DNA repair using the Comet assay, is a reliable biomarker of genotoxic exposure and cancer risk. Antineoplastic drugs, ionizing radiation, pesticides, crystalline silica, formaldehyde and metals are some of the toxic chemicals that may pose potential hazards to occupationally exposed workers. In this presentation DNA damage that was assessed by Comet assay in some occupations specially in oncology nurses, radiology technicians, pesticide sprayers, foundry, pottery and plywood workers will be presented.

WORK-RELATED LUNG CANCER

Gert van der Laan

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Lung cancer has been the most common cancer in the world for several decades and by 2008 there were an estimated 1.6 million new cases, representing 12.7% of all new cancers world wide. Turkey with an age adjusted incidence rate of 60.3 ranks among the highest in the world. Although cigarette smoking is the overwhelming determinant of the occurrence of lung cancer, occupational factors play a remarkable role. Also interaction between smoking and exposure to asbestos increases the risk of lung cancer in a more than additive way. In Europe around 10% of all lung cancer deaths were estimated to be caused by exposure to chemicals in the workplace. Composition of an evidence based background document for recognition and prevention of occupational lung cancer with an inventory of occupational exposures at work causing lung cancer. Critical review starting with PubMed search with searchstring ("Work"[MeSH] OR workers OR occupation*[tiab] OR occupational risk*[tiab] OR occupational disease*[tiab] OR "Occupational Diseases"[MeSH] OR "Occupational Exposure"[MeSH] OR occupational exposure*[tiab] OR occupations OR "Occupational Groups"[Mesh] OR "Occupational Health"[Mesh] OR occupational health[tiab] OR "workers' compensation"[MeSH Terms] OR workers compensation[Text Word]) AND (("Lung Neoplasms"[Mesh] OR pulmonary neoplasm*[tiab] OR lung cancer*[tiab] OR (lung[tiab] AND cancer[tiab]) OR pulmonary cancer[tiab]) OR ((lung*[tiab] OR pulmonary [tiab]) AND ("Carcinogens"[Mesh] OR carcinogen*[tiab]))). In addition the ILO and EU lists of Occupational Diseases with their underlying documents, the IARC-monographs and Reports on occupational lung cancer from different national authorities have been reviewed. With the IARC list of occupational agents, mixtures and exposure circumstances that are classified as carcinogenic to humans as a starting point, systematic reviews, meta-analyses and reports from international agencies are summarised and looked for an excess risk in epidemiological studies. Exposure to several occupational carcinogens can contribute to the development of lung cancer: asbestos, beryllium, chromium, diesel exhaust, crystalline silica, coal tar, ionising radiation, nickel, environmental tobacco smoke, PAH's, TCDD, and working as a painter. In cases of lung cancer there is evidence of an occupational disease if there has been long-term high exposure to asbestos (> 20 fibre-years), passive smoking, diesel exhaust. (>15 years in enclosed spaces) and other factors under extreme exposure conditions. From the clinical point of view there is nothing to distinguish work-related lung cancer from lung cancer caused by tobacco smoke found in the general population, although generally patients with work related lung cancer are younger, smoke less and have more small cell lung cancer and adenocarcinoma's. There is, however, evidence of a statistically significant excess risk in certain working populations exposed to substances that are carcinogenic in animal studies. In certain jobs the incidence is more than double that of unexposed groups. The results and consequences for prevention and medical surveillance will be discussed.

7. OTURUM (7. SESSION)

IN VITRO AND IN VIVO EVALUATION OF POTENTIAL ENDOCRINE DISRUPTING EFFECTS OF HERBAL DIETARY SUPPLEMENTS

Hande Gürer Orhan, Yasemin Toker, Duysal Uslu, Özlem Yılmaz Dilsiz, Altuğ Yavaşoğlu, Erdal Bedir

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Phytoestrogens are mostly known for their beneficial health effects however recent studies reported that they can be

hazardous by exhibiting estrogenic activity at susceptible life stages and when administered late in life. Moreover herbal dietary supplements are self-prescribed, get on the market without thorough toxicity testing and are not required to state the purity and amount of their active ingredients. The present study is undertaken to screen the potential endocrine disrupter (ED) effect of widely used herbal dietary supplements in Turkey; Astragalus Root Extract, Black Cohosh Root Extract, Dong Quai, Grape Seed Extract, Gotu Kola, Isoflavones, Saw Palmetto Berries, Spirulina, St. John's Wort, Tribulus Terrestris and Valerian Root Extract. The potential ED effect of selected products is evaluated by a "receptor-binding assay" which is suitable as a high-throughput screening assay for ER ligands. E-Screen assay is used as a second *in vitro* screening assay to evaluate whether the products are estrogenic or antiestrogenic. Among all tested products St. John's Wort was found to have a potential to exhibit estrogenic activity. This possible effect of the product was further analyzed by the golden standard test for endocrine disrupters, uterotrophic assay in rats. Our results indicate that working with individual purified molecules rather than herbal extracts gives more accurate and more interpretable results.

TOXICOLOGICAL EVALUATION OF ENDOCRINE DISRUPTING CHEMICALS: PHTHALATES AND BISPHENOL A

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Endocrine disrupting chemicals (EDCs) are exogenous agents that interfere with the synthesis, secretion, transport, binding, action or elimination of natural hormones. Over 200 environmental chemicals are suspected to cause endocrine disruption. It has been reported that exposure of EDCs may cause several adverse effects on reproduction, and development. Phthalates and bisphenol A (BPA) are abundantly used synthetic plasticizers, mainly targeting fetal and pubertal testis. In our animal studies, anti-androgenic effect of di (2-ethylhexyl) phthalate (DEHP), the most commonly used phthalate derivative, was evidenced by disturbed testicular histology, spermatogenesis, and diminished testosterone levels. Moreover, DEHP was found to induce oxidative stress in rat thyroid, liver and kidney. We also demonstrated that both DEHP, and its main metabolite mono (2-ethylhexyl)phthalate (MEHP) induced oxidative stress in LNCaP and mouse Leydig tumor cells. BPA was shown to adversely affect health in experimental animals, particularly following fetal or early life exposure. However, there are limited human studies concerning their adverse effects. In our studies, plasma DEHP and MEHP levels were found to be increased markedly in pubertal gynecomastia cases, suggesting the possible etiological role of phthalates. Moreover, we also determined high urinary phthalate metabolite and BPA levels in premature thelarce cases and high urinary BPA levels in pubertal precocious patients. These results indicate that exposure of phthalates and BPA may cause abnormal breast development in pre-pubertal boys and girls and may disturb pubertal development. Our results obtained from in vivo and in vitro studies on BPA and phthalates will be discussed comparing with available data.

8. OTURUM (8. SESSION)

CLINICAL AND FORENSIC TOXICOLOGY – THE SWEDISH EXPERIENCE

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Within the justice system in Sweden, the National Board of Forensic Medicine (NBFM) is the central government agency responsible for examinations conducted by a forensic psychiatrist, medico-legal examinations, and forensic toxicological and genetic examinations. The Ministry of Justice is responsible for the laws and ordinances applicable to the NBFM and governs its operations. The work of the NBFM is commissioned by the courts, the police and the public prosecutors. Medical departments within the Swedish healthcare service do not perform this type of work. Forensic toxicology in Sweden is centralized to one laboratory belonging to the NBFM. The working areas of the laboratory are postmortem toxicology, human performance toxicology, forensic drug testing and clinical toxicology. Solid reference data are needed to be able to produce the toxicological reports required in legal cases. Hence, data produced from the measurement of medication concentrations, i.e. therapeutic drug monitoring (TDM), are useful not only for quality improvement of psychopharmacotherapy but also for problem solving of forensic cases. The optimal reference material for a substance should give information on the drug concentration variation in different types of clinical and forensic cases. In Sweden, all forensic toxicology results are collected in a database, leading to several advantages. For example, the blood sampling procedures are standardized and the drug analyses are performed at the same laboratory. By including

both forensic and TDM data a unique reference material of drug concentrations is formed. Compilations have been published for a number of drugs including antidepressants. When it comes to drugs used in the treatment of substance-related disorders a significant overlap exists between therapeutic and toxic concentrations. Hence, high concentrations of drugs like buprenorphine and methadone are not necessarily a proof of intoxication. Other factors to consider in the forensic casework are stereopharmacological aspects, drug stability and pharmacogenetics. Taken together, interpretation of drug concentrations is a complex process. It is important to control the variables we can. Also, we need to be aware of the limitations with reference concentrations of psychoactive drugs.

THERAPEUTIC DRUG MONITORING TO GUIDE PSYCHOPHARMACOTHERAPY

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Therapeutic Drug Monitoring (TDM) aims to maximize the efficacy and tolerability of a drug. It is highly recommended for drugs with a narrow therapeutic index to avoid intoxications. Due to the broad knowledge on drug metabolism, pharmacogenomic and pharmacokinetic properties of drugs, however, TDM is by far more than a tool to avoid intoxications. It is most useful in non-responders to drugs and helpful for individualized pharmacotherapy, since it enables to clarify many specific problems such as uncertain compliance, abnormal pharmacokinetics due to genetic peculiarities or drug-interactions. In psychiatry, TDM was introduced by Swedish investigators for tricyclic antidepressants in 1971, and now it is widely used in many European countries as a standard of care. Nevertheless, many psychiatric patients are treated without TDM, even when it is highly recommended. Non-availability of TDM services is one reason for the limited use in daily clinical practice; another reason is lack of knowledge on the usefulness for psychopharmacotherapy. Analyses of official drug information sources revealed that plasma concentration measurement is often disregarded as an option for treatment optimization. The benefits of TDM can only be obtained if the method is adequately integrated into the clinical treatment process. The TDM group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) therefore issued best practice guidelines for TDM in psychiatry in 2004 (Baumann et al. 2004). These guidelines were recently updated (Hiemke et al. 2011). To optimize TDM the following aspects were addressed: definition of indications to utilize TDM, definition of therapeutic reference ranges and dose related reference ranges for 128 neuropsychiatric drugs to guide psychopharmacotherapy and definition of alert levels for laboratories to warn the treating physician when plasma concentrations are considered to be abnormally high and potentially harmful. For interpretative services, supportive information was given such as cytochrome P450 substrate and inhibitor properties or ratios of concentrations of drug metabolite to parent drug. The aim of this presentation is to give an insight into the actual situation of TDM use in psychiatry in European countries with established services. TDM is on the way to be extended, since the development of new neuropsychiatric decreased markedly during the last years. There is a need to improve therapeutic outcomes with the available drug. TDM is an instrument that can help.

PLASMA CONCENTRATIONS-GENOTYPE RELATION AND ADVERSE EFFECTS OF CITALOPRAM IN DEPRESSED PATIENTS

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Citalopram (CIT), a member of selective serotonin reuptake inhibitors (SSRIs), has been largely prescribed worldwide to treat mainly major depression. Major issues in SSRI treatment are relatively low response rate in monotherapy and discontinuation of therapy due to intolerable advers drug reactions (ADRs). Although SSRIs have superior side effect and safety profiles compared with the trcyclic antidepressants and monoamine oxidase inhibitors, ADRs frequently occur with SSRIs as well. During at therapeutic doses of CIT treatment, the most common side effects reported with this antidepressant are nausea, increased sweating, headache, dry mouth, insomnia, and sedation. There are many factors affect drug response and safety including physiological and environmental factors. Among these genetic differences in drug metabolizing enzymes play a critical role in the variation of interindividual drug response. Within this context, genetic polymorphisms in CIT metabolic (*CYP2C19*2* and **17*) pathway and plasma CIT and its main metabolite, demethylcitalopram (DCIT), were investigated in this study. Genetic polymorphism and plasma concentrations of CIT and DCIT analyses were performed in CIT treated major depression patients. Genotyping assays were carried out using genomic DNA of patients by PCR-RFLP technique. Steady-state concentration of CIT and DCIT were determined using SPE and HPLC. The occurrence of ADRs was assessed using UKU (The Udvalg for Kliniske Undersogelser) side effect rating scale by the psychiatrists during CIT therapy. The most common side effects observed in MD patients were sleepiness/sedation, nausea and vomiting, increased duration of sleep, sexual dysfunction and headache. There was no statistical significant relation between observed ADRs and *CYP2C19*2* and *CYP2C19*17* genotypes in the study group. On the other hand, the metabolic ratio (MR, CIT/DCIT) in patients who had side effects was 20% lower than those who had no side effects. The difference between the

groups was statistically non-significant, however, a borderline alteration was identified (p= 0.067). More specifically, the MR was approximately 35% lower in patients who had sexual dysfunction than those who did not experience this side effect. The difference was statistically significant between the groups (p=0.026). The results suggest that the MR may be of potential use as a biomarker for detecting and preventing ADRs in depressed patients during CIT therapy.
This study is supported by the Scientific and Technical Research Council of Turkey (TUBİTAK) with the project number 109S147.

9. OTURUM (9. SESSION)

THE EFFECTS OF TOXICANTS OCCUPATIONALLY EXPOSED ON OXIDATIVE STRESS AND GENOTOXICITY

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Employees are exposed to physical (noise, cold, heat, radiation etc.) and biological (virus, bacteria, fungi etc.) factors and chemicals (solvents, dust, vapour, fume, pesticide, heavy metal etc.) during their work period. Some kind of health problems are observed such as lung disease, musculoskeletal disease, cancer, cardiovascular disease, reproductive, neurologic and dermatologic disorders due to exposure to these factors. It is important to investigate the molecular mechanisms of these diseases and disorders. For this purpose, oxidative damage and genotoxicity are the most widely used parameters to enlighten the toxicity mechanism in this area. Oxidative stress parameters including superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) enzyme activity and malondialdehyde (MDA) levels and genotoxicity parameters including micronucleus (MN) and sister chromatid exchange (SCE) frequencies were investigated in radiology department staff who were exposed to low dose ionizing radiation and in aircraft maintenance technician who were exposed to jet prepulsion fuel. Antioxidant enzyme activity of radiology staff were higher than control subjects. But MDA levels were significantly lower than control subjects. MN frequency increased and SCE frequency were not changed. Antioxidant enzyme activities and MN frequencies did not changed significantly in technicians exposed to jet prepulsion fuel. MDA levels and SCE frequency were higher than control subjects. As a conclusion occupational chronic exposure to toxicants at low doses affected oxidative stress and genotoxicity parameters. Low dose ionizing radiation activated hormesis and defense mechanisms in biological systems. Jet fuel can be a risk factor for genotoxicity as a result of increased SCE frequencies and MDA levels in aircraft maintenance technicians.

AMALGAM AND MERCURY: EXPOSURE TO PATIENTS AND DENTISTS

Ömer Hınç Yılmaz

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Although mercury and its compounds have many attractive and useful chemical properties, its toxicity on human health have long presented a dilemma in public and occupational health area. The key role of toxicologist in this controversy is to understand its toxic properties properly and to ensure the prevention of exposure via regulatory activities. The present mercury vapor in the atmosphere and its human health effects due to this exposure is negligible, but occupationally exposed people and individuals with dental amalgams are known to have greater exposure to elemental mercury. The forms of occupational exposure include the manufacture of the thermostats and thermometers, florescent light bulbs, manometers, batteries and latex paints, in the past.
Historically, the German chemist Stock is known to be the scientist who had reported the close relationship between the number of amalgam fillings and elevated urinary mercury levels. Up to now, the dental profession has been the subject to many studies for effects of mercury vapor. As dental amalgam has potential to release mercury vapor in open-air, it may pose a health risk for dentists and dental technicians occupationally. There is a clear evidence in the scientific literature of elevated body burden of mercury in dentists and dentistry personnel.
Traditional preparation of dental amalgam involves the open-air mixing of mercury and alloy powder. Once evaporized, mercury is readily absorbed via lungs, enters the bloodstream and accumulates in the body, especially in brain, to much higher levels than for most non-occupationally exposed people. Some countries, such as Sweden, Norway, Denmark and Germany have banned or restricted the use of mercury fillings. The other side of the problem is environmental and an important concern of public health. Mercury in dental waste represents about 50 tHg/year. Its roughly estimated that dental amalgam contributes % 21-32 to overall EU mercury emissions to air and up to % 9-13 to overall EU mercury emissions to surface water.
In the light of these facts, governmental policies in our country should focus on decreasing, restricting and, in the further step, banning the use and disposal of mercury, immediately. This is not only an obligation for human and public health, but also an enforcement of REACH policies.

10. OTURUM (10. SESSION)

REACH AWARENESS: OVERVIEW OF REACH REGULATION AND POTENTIAL IMPACTS IN TOXICOLOGY

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REACH which deals with the **R**egistration, **E**valuation, **A**uthorisation and Restriction of **Ch**emical substances is the European Community Regulation on chemicals and their safe use (EC 1907/2006). The law entered into force on 1 June 2007, will come gradually into force in the period up to 2018. The aim of REACH is to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances. Under REACH, 30–40,000 new and existing chemicals will have to be (re) classified and registered. According to the European Chemicals Agency (ECHA) data as of 31 August 2012, 4.632 unique (3.924 phase-in, 708 non-phase-in) substances have been registered at the first deadline for REACH registration (30 November 2010). Chemical safety report (CSR) for substance manufactured or imported in a quantity of 10 tonnes or more per year should be submitted with data on mammalian, environmental toxicity and environmental fate, including persistence, bioaccumulation potential, and toxicity ("PBT", "vPvB" substances) properties of chemicals. Requirements for chemical testing including reproductive and developmental toxicity in experimental animals also promote alternative methods with a minimal use of experimental animals. Existing or new 'experimental data', 'read-across', 'weight-of-evidence' approaches in toxicological and ecotoxicological hazard assessment can be used to fulfill REACH information requirements in CSR. There is still a need to fill testing and monitoring data gaps to ensure that industry is able to assess hazards and risks of the substances, and to identify and implement the risk management measures to protect humans and the environment. Therefore, in order to review and evaluate the following data, the experts need to make clear decision and conduct risk assessment and safety classification. i) the relevant human health endpoints (determination of *Derived No-Effect-Levels*; DNEL or other qualitative or semi-quantitative measures of potency of the substance and testing strategies), ii) the environment endpoints (determination of *Predicted No-effect-Effect levels*; PNEC), iii) exposure scenarios and related exposure (occupational, consumer and related to environment and life cycle) estimation stages. The IT tools (*IUCLID 5*, *Chesar*, and *REACH-IT*) are used for REACH registration and submission process to ECHA.

The intention of REACH is to identify hazardous properties in order that a reliable risk assessment can be made and measures taken to deal with chemicals posing a significant risk. An overview of the REACH regulation (the milestones and timelines, legal implications, roles within industry), its practical implications for toxicological safety evaluation of chemicals and its potential impacts of toxicology will be given in this presentation.

CONTRIBUTION OF TOXICOLOGY TO UNITED NATIONS ENVIRONMENT PROGRAMME

Nida Besbelli

International Consultant, Switzerland

Since early 1970s international efforts have been organized to address the safe management of chemicals. Toxicology has played a leading and supportive role in focusing and organizing these efforts. At the international level, the United Nations Environment Programme (UNEP) has been established by governments to provide support for needed actions on all levels to protect human health and the environment from the potential adverse effects of chemicals. UNEP works to fulfill its mission in a range of ways: promoting exchange of information, developing materials and undertaking training to build the technical and management capacities of governments and providing the organizational and administrative structures for legally binding instruments for the control of specific classes of chemicals. Legally binding instruments addressing the safe management of chemicals include the Rotterdam Convention on Prior Informed Consent Procedure for certain hazardous Chemical and Pesticides in international trade which covers the internationally agreed list of chemicals and pesticides, the Stockholm Convention on Persistent Organic Pollutants and the Basel Convention controlling transboundary movement of hazardous waste and their disposal. Currently negotiations are ongoing to develop a global legally binding instrument for the control and management of mercury. For each of these conventions, results of toxicological studies provide the necessary scientific basis for formulating and agreeing on specific controls and actions that will be undertaken by the governments who are parties to the conventions. UNEP coordinates implementation of Strategic Approach to International Chemicals Management (SAICM) and hosts its secretariat. SAICM is a policy framework to promote chemical safety and has as its overall objective the achievement of the sound management of chemicals throughout their lifecycle so that, by 2020, chemicals are produced and used in ways that minimize significant adverse impacts on human health and the environment. Fundamental to SAICM are science-based risk assessment procedures and science-based risk management procedures. Through the preparation of state of the science reviews, UNEP contributes to the required knowledge base for governments and other stakeholders to formulate actions and partnerships to address specific chemical safety issues In supporting countries to build capacities, UNEP in collaboration with universities and other organizations has prepared training materials and informational and awareness raising materials on the sound management of pesticides for workers, health professionals, students and/or the general public. This presentation will highlight the role and importance of the field of toxicology to enable UNEP and others to make significant progress in address the potential hazards of chemicals.

SÖZLÜ SUNUMLAR

ORAL PRESENTATIONS

SÖZLÜ SUNUMLAR 1 (ORAL PRESENTATIONS 1)

WHY WE NEED VALIDATION OF BIOANALYTICAL METHODS IN FORENSIC AND CLINICAL TOXICOLOGY?

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The aim of quantitative bioanalytical method is to provide accurate and reliable determination of the amount of a target analyte, usually a drug, a metabolite or a biomarker, in complex biological samples (fluids or tissues). The reliability of analytical data is very important to forensic and clinical toxicologists for the correct interpretation of toxicological findings. This makes bioanalytical method validation an integral part of quality management and accreditation in analytical toxicology. Selective and sensitive analytical methods for the quantitative evaluation of drugs and their metabolites are also critical for the successful conduct of preclinical and/or biopharmaceutics and clinical pharmacology studies. The main objective of method validation is to demonstrate the reliability of a particular method for the determination of an analyte concentration in a specific biological matrix. The main characteristics of a bioanalytical method that are essential to ensure the acceptability of the performance and the reliability of analytical results are: selectivity, lower limit of quantification, the response function and calibration range, accuracy, precision, matrix effects, stability of the analyte(s) in the biological matrix and stability of the analyte(s) and of the internal standard in the stock and working solutions and in extracts under the entire period of storage and processing conditions. Consequently, method developing and validation are essentiality for forensic and clinical toxicology studies and each of method developing and validation steps has its own constraints and challenges should be promoted by regulatory agencies.

INVESTIGATION OF DNA DAMAGE AND DNA REPAIR CAPACITY IN PATIENTS WITH COLORECTAL CANCER AND THEIR FIRST DEGREE RELATIVES

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Studies have reported that genetic susceptibility and environmental factors play an important role in the formation of colorectal cancer (CRC). Individuals with incidence of colorectal cancer in the first-degree relatives are about twice as likely to develop CRC as those without any family history. Biomarkers are often utilized for the determination of increased risk of cancer. The aim of our study was to investigate the potential DNA damage using by comet assay and chromosomal aberrations (CAs), measurement of DNA repair capacity by using challenge assay as biomarkers of susceptibility in peripheral lymphocytes of CRC patients and their first degree relatives. Peripheral blood samples were taken from untreated patients diagnosed with CRC (n=56), their first degree relatives (n=50) and healthy controls (n=25) were analyzed by comet assay, challenge assay and CAs. Chromosomal aberration frequency by chromosomal aberration technique in peripheral blood lymphocytes in CRC patients and their first-degree relatives were not statistically different as compared with the controls ($p>0.05$). However, a statistically significant increase in DNA damage was observed by comet assay ($p<0.001$). Challenge assay demonstrated statistically significant reduction in DNA repair capacity in CRC patients ($p<0.001$) and in their first-degree relatives ($p=0.001$) as compared with the controls. The results support the sensitivity of comet assay and challenge assay, which can be utilized clinically for the identification of DNA damage and repair in patients and their relatives as demonstrated with CRC.

ASSESSMENT OF OXIDATIVE STRESS AND IMPAIRED ANTIOXIDANT DEFENCE SYSTEM IN PATIENTS WITH EPITHELIAL OVARIAN CANCER

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Ovarian cancer is a heterogeneous disease with respect to histopathology, molecular biology, and clinical outcome, and is the leading cause of death from gynecological cancers. Hormonal, environmental, dietary and hereditary risk factors trigger the development of ovarian cancer. This study was aimed to determine alterations in oxidant/antioxidant status [lipid peroxidation (tissue MDA, urinary F_2-isoprostan), tissue antioxidant enzyme activities (total SOD, MnSOD, CuZnSOD, CAT, GPx1) and MnSOD protein expression] in the patients undergone surgical operation with confirmed primary malignant epithelial ovarian tumor pathology. The overall data were compared to a control group composed of healthy ovarian tissues of ovariectomized individuals without any benign or malign pathology. In malign group, decreases in the activities of

total SOD, MnSOD, CuZnSOD, and increases in the activities of CAT and GPx1 were obtained significantly along with the marked enhancements in ovarian MDA levels and urinary F_2-isoprostane concentrations as compared to control group. Moreover, ovarian MnSOD protein expression also increased significantly compared to control (1,5 fold) and this enhancement was found to be more significant in high grade tumors. Overall results indicate an oxidant/antioxidant imbalance and the presence of oxidative stress in the primary epithelial serous malign ovarian tumors and suggest the importance of oxidant/antioxidant status in the pathogenesis of the disease. The 3-fold increase in the urine F_2-isoprostan levels of the patients compared to healthy individuals, and more marked enhancements related to tumor grade and stage of the disease suggested that this parameter may be used as a non-invasive primary marker in patients with suspected ovarian cancer.

INVESTIGATION OF CONTACT SENSITIZATION POTENCY OF FRAGRANCE MIX AND FRAGRANCE MIX INGREDIENTS BY USING EX VIVO NONRADIOCTIVE LOCAL LYMPH NODE ASSAY

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Fragrance ingredients are also one of the most frequent causes of contact allergic reactions. The diagnosis is made by patch testing with a mixture of fragrance ingredients, the fragrance mix. Contact sensitivity to fragrance mix (FM) in the standard series is the 2nd most common cause of contact dermatitis after nickel allergy in Denmark, the 3rd most common cause in Israel and the 5th most common cause in Turkey. In our study we aimed to investigate the contact sensitization potency of fragrance mix and the eight components of fragrance mix (oak moss absolute, isoeugenol, eugenol, cinnamic aldehyde, hydroxicitronellal, geraniol, cinnamic alcohol, alpha amyl cinnamic aldehyde) by using ex vivo nonradioactive local lymph node assay. Fragrance mix and each fragrance material were tested at five concentrations. The stimulation index values were calculated for each dose level, an SI ≥3 was considered a positive response. The estimated concentration (EC3) values were calculated. The EC3 values and potency classification for fragrance mix, oak moss absolute, isoeugenol, eugenol, cinnamic aldehyde, hydroxicitronellal, geraniol, cinnamic alcohol, alpha amyl cinnamic aldehyde were calculated to be 4.4% (moderate), 3.4% (moderate), 0.88% (extreme), 16.6% (weak), 1.91% (strong), 9.77% (moderate), 13.1% (weak), 17.93 % (weak), 7.74% (moderate) respectively. The potency of fragrance mix differed from some of its individual components. According to our results it can be suggested that it is necessary to estimate the relative contact sensitization potency of mixtures and the individuals separately.

GENOTOXIC EFFECTS OF MONOSODIUM GLUTAMATE ON MAMMALIAN CELLS IN VITRO

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Glutamate is one of the most common amino acids found in nature. It is produced in the body and plays an essential role in human metabolism. Monosodium glutamate (MSG) is the sodium salt of glutamate and is made by mixing glutamate with salt and water. It is a flavor enhancer commonly used to meats, poultry, seafood, snacks, soups and stews. The aim of the present study was to investigate the ability of MSG to induce chromosomal aberrations in human lymphocytes. For this purposes venous blood from two healthy females, non-smoking volunteers was used. The human peripheral lymphocytes were treated with six concentrations of MSG (250, 500, 1000, 2000, 4000 and 8000 µg/ml) for 48 hour. A negative and a positive control (mitomycin-C) were also applied for each experiment. All of the MSG concentrations significantly increased the chromosomal aberrations frequency compared with negative control in human lymphocytes. Our data demonstrated that MSG showed genotoxic effects in mammalian cells *in vitro*. In addition, further detailed studies on the genotoxic properties of MSG, with help of other tests for genotoxicity, should be conducted.

EVALUATION OF OXIDANT/ANTIOXIDANT STATUS IN NEONATAL SEPSIS

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Sepsis is a serious medical condition that is characterized by a whole-body inflammatory state in the presence of a known or suspected infection. It continues to be the one of the main causes of morbidity and mortality in the intensive care units. The molecular events underlying sepsis are frequently associated with the generation of reactive oxygen species and low antioxidant capacity. Newborns and particularly the preterm infants are more prone to oxidative stress as they have reduced antioxidant defense. Concerning all the available data, this study

was designed to investigate the oxidant/antioxidant status in hospitalized newborns with sepsis in neonatology intensive care unit. The study group was composed of 25 proven sepsis patients, 27 clinical sepsis patients and 35 healthy controls. Erythrocyte antioxidant enzyme activities (glutathione peroxidase 1[GPx1], tihoredoxin reductase [TrxR], catalase [CAT], total superoxide dismutase [SOD]) erythrocyte glutathione (GSH) content and plasma lipid peroxidation levels were determined in all groups. In clinic sepsis patients, GPx1 (43%), CAT (24%), and SOD (25%) activities and lipid peroxidation levels (25%) increased markedly compared to healthy subjects. In proven sepsis patients, CAT (23%) and SOD (40%) activities and lipid peroxidation levels (30%) increased significantly vs. control. Moreover, in proven sepsis TrxR activity (28%) and total GSH levels (35%) decreased markedly in comparison to healthy controls. The results suggest the presence of an oxidative activity and oxidant/antioxidant imbalance in both clinical and proven neonatal septic patients and indicate that the alterations in oxidant/antioxidant status were more pronounced in the proven sepsis group.

MALE INFERTILITY AND GENETIC FACTORS

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Today, it is clearly known that almost half of the infertility cases are contributed by the male factor. Regardless from type of disorder, male factor infertility is strongly related with genetics. Almost in every case diagnosed as primary infertility, there is an underlying genetic reason, which reflects to the phenotype as a disorder. For the treatment, and ultimately for providing fertility, it is crucial to clarify the genetic causes of male infertility. Although numerous gene polymorphisms are related with male infertility, many of them are not yet proven as clinically powerful. The most important confounding factor for this lack is thought to be the effect of environment, especially xenobiotics targeting directly sperm chromatin. Therefore, similar to other population studies, polymorphism studies of male infertility should also be carried out with the chromatin damage assessment of the sperm cells as a biomarker of effect of the exposure. In our study, we have assessed (1) sperm parameters, (2) sperm chromatin integrity by Comet assay and (3) CAG trinucleotide repeats in the exon 1 sequence of androgen receptor gene in 82 infertile patients and 63 healthy controls. Those parameters were evaluated for any possible link with the sperm counts, motilities and morphologies, as well as examining for any correlation between the AR Exon-1 (CAG)n repeat polymorphism and sperm DNA integrity. The ultimate goal of this study is to contribute finding novel biomarkers for individualized treatments of the male infertility. This project was financed by the Research Council of Gazi University, Project No: 02/2009-27.

CYTOTOXICITY STUDY ON CATIONIC SOLID LIPID NANOPARTICLES AS DNA DELIVERY SYSTEM

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Cationic solid lipid nanoparticles (SLNs) have recently been developed as potential DNA delivery systems. As these particles can bind DNA directly via electrostatic interactions, they have some advantages such as production in large scale, easy sterilization and low cytotoxicity. In this study, cationic solid lipid nanoparticles were developed by modified microemulsion dilution method using either precirol or compritol as matrix lipid, Tween 80 and lecithin as surfactants, ethanol as co-surfactant, and Esterquat 1 (EQ1) (N,N-di-(β-stearoylethyl)-N,N-dimethyl-ammonium chloride) or DDAB (Dimethyldidodecyl-ammonium bromide) as charge carriers. SLNs were complexed with green fluorescent protein encoding plasmid DNA (pDNA). After characterization studies, optimum formulations were chosen for cytotoxicity tests. A tetrazolium compound, XTT, was used for cytotoxicity assay. The cytotoxic effects of the free SLNs and SLN-pDNA complexes on Calu-1 and COS-7 cells were determined. To determine the effect of complexation on cytotoxicity, preliminary studies were done by Calu-1 cells incubating with either non complexed SLN formulations cationized by EQ1 or SLN:pDNA complexes; and cell viability was calculated. The cytotoxic effects of the chosen optimum formulations including EQ1 and DDAB were assessed by measuring the viability of COS-7 cells after incubation with different amounts of SLN-plasmid DNA complexes. As a result, complexation with pDNA and lower amounts of SLNs in the delivery system decreased the cytotoxicity. In this study non-cytotoxic cationic solid lipid nanoparticles were developed for efficient DNA delivery.
This study has been financially supported by the TUBITAK (Grant No: 110S020).

SÖZLÜ SUNUMLAR 2 (ORAL PRESENTATIONS 2)

THE POSSIBILITY TO USE PERSISTENT ORGANIC CONTAMINANTS (POPS) ENVIRONMENTAL DATA TO PREDICT CONTAMINATION IN HUMAN

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Persistent organic pollutants (POPs) remain in the environment for long periods and have potential adverse effects. In this study, concentrations of certain POPs such as polychlorinated dibenzo-p-dioxins (PCDDs), -dibenzofurans (PCDFs), co-planar biphenyls (PCBs), hexachlorocyclohexanes (HCH), dichlorodiphenyl-trichloroethanes (DDT), and organochlorine pesticides (OCPs) were investigated in soil samples collected from Taurus mountains. The aim of the study was to investigate the occurence of POPs residues in soils and also to assess the the possible grasshopper effect along an altitudinal transect. In addition, it was aimed to compare the results of the study to data reported in similar studies in other regions.Selected latitudes chosen for sampling were at 121, 408, 981, 1,225, 1,373, 1,639, and 1,881 m above sea level. The samples were analyzed by high-resolution gas chromatography–high-resolution mass spectrometry. The levels of the PCDD in forest soil from Taurus Mountains varied from 4 to 12 pg g^{-1} dry weight (dw) whereas PCDF concentrations ranged from 2 to 7 pg g^{-1} dw. Considerably high levels of DDTs detected in five stations is thought to be as a result of atmospheric long range transport or a possible extensive local application. PCBs level was between 80 and 288 pg g^{-1} dw and HCH concentrations ranged from 141 to 1,513 pg g^{-1} dw. The other OCPs concentration was between 102 and 731 pg g^{-1}. Soil is a good matrix to follow POPs in the environment and may also used to predict human body burden contamination in the food chain.

INDOOR DUST AS A SOURCE OF HUMAN EXPOSURE TO HEAVY METALS IN ISTANBUL

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Indoor dust can be an important pathway in exposure of people to various environmental contaminants including heavy metals, persistent organic contaminants etc. Once the contaminants enter indoors, they become incorporated into house dusts. People spend a considerable amount of time indoors such as homes, offices and schools. Over the past decades, there has been increasing concern about exposure of people, especially of vulnerable groups such as children, to indoor contaminants in order to assess the health impacts. In this study, levels of eight potentially toxic heavy metals in indoor dust from homes in Istanbul were investigated. The concentrations of heavy metals in indoor dust from homes ranged from 60-1800 μg g^{-1} for Cu, 3-300 μg g^{-1} for Pb, 0.4-20 μg g^{-1} for Cd, 210-2800 μg g^{-1} for Zn, 2.8-460 μg g^{-1} for Cr, 8-1300 μg g^{-1} for Mn, 2.4-25 μg g^{-1} for Co, 120-2600 μg g^{-1} for Ni. Considering only ingestion+inhalation, the carcinogenic risk level of Cr for adults and children in Istanbul was in the range of EPA's safe limits ($1x10^{-6}$ and $1x10^{-4}$). According to calculated Hazard Quotient (HQ), for non-cancer effects, the ingestion of indoor dust appears to be the major route of exposure to the indoor dust. Results of the current study highlight the importance of exposure through indoor dust and the good hygiene standards to limit intake of indoor dust. In conclusion, contaminants from the ingestion/inhalation/dermal contact might pose potential risk to the children and adults in Istanbul.

INDUCTION OF OXIDATIVE STRESS AND HISTOLOGICAL CHANGES IN LIVER BY SUBACUTE DOSES OF BUTYL CYCLOHEXYL PHTHALATE

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The present study was performed to evaluate the histopathological effects and to determine oxidative stress inducing potential in liver by subacute exposure of Butyl cyclohexyl phthalate (BCP). The protocol was approved by the Animal Ethical Committee of Ege University (date 23.11.2009, number 2009-165). The animals of the treatment groups were

orally administered 100, 200 and 400 mg/kg/day BCP for five consecutive days per week during 28 days. As a result, no significant changes were observed in body weight gains, and absolute and relative liver weights of liver of BCP treated mice, when compared with control group. Although the degree of lipid peroxidation in the liver tissue of all BCP exposure groups were significantly higher than those of the control ($p<0.01$), SOD and CAT activities in liver tissue of mice of 200 and 400 mg/kg exposure groups were significantly lower than those of the controls ($p<0.01$). Moreover, BCP caused dose-dependent histological changes in the liver of mice such as congestions in vena centralis, an enlargement of the sinusoids, degeneration in hepatocytes, vacuole formations and presence of lipid droplets in hepatocytes, eosinophilic cytoplasm. While iNOS immunoreactivity was increased in all treatment groups, Type IV collagen and Connexin 43 immunoreactivities were decreased in all treatment groups compared to the control group. Significant decrease was observed in the number of TUNEL-positive liver cells of BCP treated mice. These results suggested that BCP exposure induces oxidative stress in liver and exposure of BCP during long time period could lead to hepatocarcinogenesis.

THE PROTECTIVE EFFECT OF ASCORBIC ACID AND SELENOCOMPOUNDS AGAINST THE CYTOTOXICITY AND GENOTOXICITY OF 3,5-DIMETHYLAMINOPHENOL

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Monocylic aromatic amines are considered factors for the development of bladder cancer. Exposure assessments indicate that most individuals experience lifelong exposure to these compounds from several sources, including occupational exposure and tobacco smoke. 3,5-dimethylaniline (3,5-DMA) is significantly associated with bladder cancer incidence in U.S. This study was designed to investigate the possible protective effect of ascorbic acid and selenocompounds against cytotoxicity and genotoxicity of 3,5-dimethylaminophenol (3,5-DMAP), the metabolite for 3,5-DMA, in Chinese Hamster Ovary (CHO) cells. 3,5-DMAP caused a dose-dependent increase in both cytotoxicity and intracellular reactive oxygen species (ROS) generation and the IC_{50} dose was found as 25 mM. 3,5-DMAP treatment decreased the activities of both cytoplasmic and nuclear antioxidant enzymes [i.e. glutathione peroxidase, thioredoxin reductase, catalase, glutathione reductase] and increased superoxide dismutase activity (100%). Elevations in both cytoplasmic (300%) and in nuclear (450%) oxidized glutathione levels along with significant enhancements in lipid peroxidation levels (200% in cytoplasm and 765% in nucleus) were also observed. Protein oxidation significantly increased in both cytoplasm (70%) and nucleus (55%). Besides, in Comet assay, both tail moment and %tail DNA increased significantly by 3,5-DMAP exposure. Both ascorbic acid (50 mM) and selenocompounds (sodium selenite at 10 nM, selenomethionine at 30 mM) were found be protective against the toxic effects of 3,5-DMAP. The results of this study demonstrated that one of the mechanisms underlying the toxicity of 3,5-DMAP is the change in oxidant/antioxidant balance in different cellular fractions and both ascorbic acid and selenocompounds are protective against its cytoplasmic and nuclear toxicity.

EFFECT OF BORON COMPOUNDS ON LEAD AND CADMIUM INDUCED GENOTOXICITY IN CELL CULTURES

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Cadmium (Cd) and lead (Pb) are the toxic heavy metals and important environmental pollutants which can cause serious damage to human health. As the metal ions (Cd^{2+} and Pb^{2+}) accumulate in the organism, there is special concern regarding chronic toxicity and damage to the genetic material. Metal-induced genotoxicity has been attributed to indirect mechanisms, such as induction of oxidative stress and interference with DNA repair. Boron is a naturally occuring element and considered to be essential micronutrient, although the cellular activities of boron compounds remain largely unexplored. The present study has been conducted to evaluate potential protective effects of boric acid (BA) against genotoxicity induced by cadmium chloride ($CdCl_2$) and lead chloride ($PbCl_2$) in V79 cell cultures. Cytotoxicity assays (neutral red uptake and cell titre blue assay) served to determine suitable concentrations for subsequent genotoxicity assays. Chromosomal damage was studied by the *in vitro* micronucleus (MN) test. Both $PbCl_2$ and $CdCl_2$ (at 3, 5 and 10 µM) were shown to induce concentration-dependent increases in micronucleus frequencies in V79 cells. BA did not show cytotoxicity (up to 300 µM) and no genotoxic effects (at 2.5 and 10 µM). Upon pretreatment of cells with low, physiological levels of BA, it was found that the boron compound strongly reduced the genotoxic effects of the the tested metals. Based on the results of this study, it can be suggested that boric acid provides an efficient protection against the induction of micronuclei by lead and cadmium.

EVALUATION OF CELL DEATH MECHANISMS OF PALLADIUM(II) COMPLEX AS AN ANTICANCER AGENT IN HUMAN CANCER CELL LINES

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Cancer is a lethal disease with high mortality rates after cardiovascular diseases. Unfortunately, treatment of cancer is still far from satisfaction bringing the need for new strategies and novel therapeutic molecules. For this reason, metal based agents including palladium compounds have been tested as candidate anticancer drugs. In this study, a newly synthesized palladium compound ([PdCl(terpy)](sac)·$2H_2O$) was analyzed for its use in treatment against cancer. The cytotoxic effects were tested on six different cancer cell lines using various concentrations of the palladium complex in the range of 0 to 50 µM and different incubation times (24-72h). Two cell lines, MDA-435 and HeLa, were chosen for further analysis to understand the means of cell death in response to drug treatment. The results demonstrated that the cells treated with Palladium II complex showed increased caspase 3 activity, and exhibited fragmented nuclei as shown by DNA laddering. Morphological features such as cellular shrinkage and blebbing were also observed indicating that apoptosis was the main mechanism of cell death. In order to investigate which molecules play a role in the apoptosis of these cells, candidate genes such as p53 and caspase 3 were silenced using siRNA technology. Our current results suggest that either apoptosis takes place independent of these proteins or that other pathways are activated in the absence of these molecules as similar levels of cell death were observed after siRNA knockdown.

PERSISTENT ORGANIC POLLUTANTS AND TOXICOLOGICAL RESPONSES IN GRAY MULLET AND SEABASS FROM BÜYÜK MENDERES RIVER ESTUARY AND VICINITY

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In order to determine dimensions of POP pollution, the estuary of Büyük Menderes River, Taşburun Harbour (at 6.5 km distance on the left) and the Batıköy fishpond (at 5 km distance on the right), were selected as sampling stations. Organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs) and polybrominated diphenylethers (PBDEs) were measured in liver and muscle tissues of gray mullet (Mugil cephalus) and seabass (Dicentrarchus labrax L.) by gas chromatography-electron capture detection (GC-ECD). As toxicological responses in liver, protein carbonyl levels and antioxidant enzyme activities were measured by spectrophotometer. OCP levels seemed higher in liver of mullets caught from estuary, except HCHs, however, only DRINs were significantly higher in estuary samples. OCPs were generally comparable in muscle tissue of the mullets, except significantly higher values for DRINs in fishpond samples. Total PCB and PBDE levels were comparable in mullet between stations. As expected, liver pollutant levels were higher than the muscle levels. Similar higher levels in liver compared to muscle were also observed in seabass samples. Although OCP levels seemed higher in 3 of the 5 groups of OCPs in estuary seabass samples, only the statistical difference was observed in total DDTs levels in liver. Total PBDEs and PCBs were much higher in seabass liver samples compared to muscle samples, suggested a recent exposure to these pollutants in the estuary. There was not a significant difference in the levels among the stations. PCO levels were higher in estuary mullets compared to the fishpond, while there was no difference in seabass samples.
This study is supported by the Scientific and Technical Research Council of Turkey (TUBITAK) by the project number 108Y049.

MATRIX GLA PROTEIN, KLOTHO GENE POLYMORPHISMS AND DNA DAMAGE IN CHRONIC KIDNEY AND CORONARY ARTERY DISEASES

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Vascular calcification is an important pathology that is clearly associated with an increased risk of cardiovascular morbidity and mortality. At the pathogenesis of cardiovascular events of chronic kidney disease (CKD), increased vascular calcification has a major role. Matrix GLA protein (MGP) and klotho have

drawn special attention as promoters and inhibitors of the calcification process. In our study, we investigated MGP (T-138C, Glu60X, Thr83Ala) and klotho (Cys370Ser) gene polymorphisms, serum MGP levels, oxidative stress status of 84 CKD patients, 37 healthy controls and 54 patients who underwent coronary angiograms. We also evaluated genotoxicity with alkaline comet assay and urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG). The Glu60X, Thr83Ala polymorphisms were significantly associated with CKD (p<0.05). The correlation between T-138C, Cys370Ser polymorphisms and CKD were not significant (p>0.05). At the haplotype analysis, subjects with the X allele of Glu60X, the Thr allele of Thr83Ala showed a significantly increased risk of CKD (p<0.05). X allele, Thr allele, C allele of T-13C were associated with *Diabetes mellitus* and CKD phenotypes occurring concurrently (p<0.01). There were no differences in the prevalence of chronic artery disease between the different genotypes of MGP, klotho gene polymorphisms (p>0.05). The DNA damage observed in ESRD patients and urinary 8-OHdG levels of CKD patients were significantly higher than controls (p<0.05). According to this study, analyzing the distribution of MGP gene and DNA damage status would be very informative in order to detect their role at CKD.

SÖZLÜ SUNUMLAR 3 (ORAL PRESENTATIONS 3)

EFFECT OF METALLOTHIONEIN 2A POLYMORPHISM ON TOXIC METAL LEVELS IN HUMAN BIOLOGICAL SAMPLES

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Heavy metals are well-known environmental pollutants and genetic factors may modify their toxicokinetics. Metallothioneins (MTs), are low molecular weight, cysteine-rich, metal-binding proteins. The aim of this speech was to discuss association between the metallothionein2A (MT2A) core promoter region −5 A/G single nucleotide polymorphism (SNP) and two toxic metals, Cd and Pb, levels in human biological samples. The core promoter region −5 A/G polymorphism was chosen for the investigation due to almost complete loss of functionality in metal toxicokinetics and thus might exert a stronger biological effect. According to our results, Cd levels were significantly higher in MT2A atypical homozygous and heterozygous individuals in autopsy tissue samples and control blood (p<0.05). Maternal blood Cd levels were statistically higher for mothers with heterozygote genotype compared with homozygote genotype (p<0.05). In contrast, placental Cd levels were significantly higher in mothers with homozygote rather than heterozygote genotype (p<0.05). These results show that the core promoter region polymorphism of metallothionein2A with atypical allele increases the accumulation of Cd in human tissues. Maternal blood, placenta and cord blood Pb levels of heterozygote mothers were significantly higher than typical homozygote mothers (p<0.05). Blood Pb levels of individuals with MT2A homozygote mutant and heterozygote were significantly higher than typical homozygote individuals (p<0.05). In contrast Pb levels were not statistically significant difference with MT2A polymorphism in autopsy tissues (p>0.05). In conclusion, authors suggest that having atypical genotype individuals may be more sensitive for metal toxicity and they should be more careful about protecting themselves against heavy metals.

RESULTS OF ABUSED DRUG ANALYSES WITH CEDIA AND (GC-MS): A FIVE YEARS RETROSPECTIVE EVALUATION

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CEDIA (cloned enzyme donor immune assay) is a fast and quantitative method which is used for screening of abused drugs but it can give false positive results because of the cross-reactions. These analyses could be verified with semi-quantative GC-MS methods. In this study, we evaluate retrospectively the results of abused drug analyses with CEDIA and afterwards verifying with GC-MS in our toxicology laboratory. In GC-MS analyses, liquid/liquid extraction method (toxitube A & B) was used. In CEDIA analyses no extraction method was required. When CEDIA and GC-MS results were compared quantitatively, CEDIA results were found to be false positive 76,9 % (10/13) for Amphetamine, 73,9 % (34/46) for Opioids, 55,1 % (16/39) for THC, 100 % (0/3) for Cocaine and % 59,0 (26/44) for Benzodiazepine. Additionally, the results from CEDIA analyses were verified with GC-MS method with these rates; % 60 (3/5) for Amphetamine, % 44,4 (12/27) for Opioids, % 32,5 (13/40) for THC, % 0 (0/1) for Cocaine and % 46,1 (18/39) for benzodiazepine. Our findings points that; although the results of CEDIA analyses are quantitative but all of them must be verified with further GC-MS analyses.

THE ROLE OF THE ANALYTICAL TOXICOLOGY IN EMERGENCY MEDICINE

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The field of emergency toxicology is very broad and particularly, to provide clinically useful toxicology test results to support the needs of poisoned patients in the emergency department. Emergency physicians should be expertise to identify and treat acute and chronic poisoning, adverse drug reactions, envenomations, plant toxins, workplace or environmental chemical exposures, criminal poisoning. Acute poisoning requires urgent and adequate medical intervention. Many acutely poisoned patients are treated with no or the limited laboratory helps other than general clinical chemistry and haematology. Metformin, an antihyperglycemic prescribed to control type 2 diabetes, has been associated with significant lactic acidosis. In this study, we present a case of respiratory alkalosis associated with metformin use. This case report describes acute poisoning of a 29-years-old woman who attempted suicide by ingesting 70 tablets of 1000 mg metformin (70 g glucophage). Metformin was analyzed by high-performance liquid chromatography with diode-array detection and as expected, a very high metformin concentration (169.35 µg/mL) was measured in the serum sample. Continuous venovenous hemofiltration was started in emergency department and she was discharged on ninth day. As a result, emergency toxicological analyses were have to be provided at hospitals and emergency departments.

VOLATILE ANESTHETICS AND THEIR ASSOCIATION WITH OXIDATIVE STRESS

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General anaesthetics are frequently used in patients under oxidative stress by the reason of not only a serious illness but also surgical trauma. Some of anaesthetics may worsen oxidative stress on the other hand some of them may act as antioxidants. Sevoflurane and desflurane volatile anesthetics are used commonly for induction and maintance of general anesthesia in anesthetic practice. In our first study, we aimed to observe tissue response of rat that was exposed to sevoflurane and desflurane by analyzing the oxidative stress in liver, brain, kidney and lung tissues, All tissues were analyzed using parameters of oxidative stress, malondialdehyde (MDA) with TBARS test, superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and levels of Cu and Zn. In the first study, animals divided into three groups as control group, sevoflurane group and desflurane group. This study showed that exposure to sevoflurane and desflurane caused oxidative stress which was shown by increased concentration of MDA in lung tissue much more affected from ROS than other tissues due to first tissue exposed to anesthetic gases. While the levels of MDA were statistically significantly decreased in liver in desflurane group but increased in sevoflurane group. It suggested that desflurane were more protective effect than sevoflurane due to decreased MDA levels in liver and there is a statistical significant relationship between sevoflurane group and desflurane group compared to control group in terms of oxidative status. In our second study, we purposed to compare the markers of oxidative status of human erythrocyte in both sevoflurane and desflurane. In order to this, venous blood samples of patients who scheduled for abdominal surgery were collected the following time intervals; initial time and first hour, first day and third days after anesthesia (sevoflurane and desflurane). In addition, the levels of MDA, GSH-Px, SOD, Mg and Zn were determined. No significant diffirences were observed in these measurements at 1st hour, 1st and 3st days compared to initial time in desflurane group ($p>0.05$). But in the sevoflurane group, statistically significant differences were found. In a conclusion of our studies, we investigated tissue oxidative stress and enzymatic antioxidant activity of desflurane and sevoflurane anesthetic agents ($p<0.05$). The authors suggest that further studies with other nonenzymatic indices of oxidative stress such as tocopherols, ascorbate, and 8OHdG can help enlighting this anesthetic agent selection.

DRUG-INDUCED CARDIOTOXICITY: EXPERIMENTAL METHODS

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Cardiovascular toxicity is a potential short- or long-term complication of drug therapy. Some substances cause acute cardiac depression as they lower heart rate, contractility and conduction and in certain causes even cardiac arrest. These

substances include barbiturates or halogenated hydrocarbons. However, many drugs are administered chronically and are cardiotoxic and may trigger the development of cardiac injury even when used appropriately. These substances include primarily chemotherapy medications including anthracyclines and trastuzumab. Cardiac toxicity associated with these drugs can range from asymptomatic subclinical abnormalities, including electrocardiographic changes and temporary left ventricular ejection fraction decline, to life-threatening events such as congestive heart failure or acute coronary syndromes. Assessment of the prevalence, type, and severity of cardiac toxicity caused by various drugs is a critical topic for patient management and specifically for new drug development. There are several approaches of assessing myocardial function and cardiotoxicity in experimental animals for mechanistic insight. As the diastolic function can be estimated non-invasively by Doppler echocardiography, its serial evaluation is well feasible. Parameters such as ejection fraction and fractional shortening may be used to evaluate myocardial function. In addition, morphological studies and measuring myocardial biomarkers, i.e. troponins and CK-MB, may provide information. In my laboratory, current research is focused on evaluating effects of trastuzumab (T) and high dose radiotherapy (RT) on cardiotoxicity in rats. In brief, the results have indicated that T and high dose RT may lead to cardiotoxicity that seems at least additive. My experiences show that echoardiography is a powerful technique for non-invasive and serial determination of cardiac structure and function in cardiotoxicity studies. Morphological studies and biomarkers are also feasible. Cardiotoxicity remains a major problem of hundreds of pharmaceutical agents, industrial chemicals and naturally occuring products and is often a limitating factor in treatment of certain diseases. The unclear incidence of drug-induced cardiovascular events together with uncertainty on their reversibility and long-term safety call for a multidisciplinary effort embracing cardio-oncological expertise supported by primary care physicians, pharmacologists and toxicologists.

INCREASED OXIDATIVE STRESS BUT NOT TRYPTOPHAN DEGRADATION IN PLASMODIUM BERGHEI INFECTED MICE

Funda Doğruman Al[1], **Ayşe Başak Engin**[2], Neslihan Bukan[3], Seda Evirgen Bostancı[4], Kemal Ceber[5], Semra Kuştimur[1]

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To investigate the involvement of systemic oxidative stress in the pathogenesis of murine cerebral malaria (CM), mice were infected with *Plasmodium berghei* ANKA 6653 strain. Although the dysregulated inflammatory response might be attributed to the excess nitric oxide (NO) and reactive oxygen species production, the main mechanism of oxidative stress remains unresolved. During the intraerythrocytic stages of rodent malaria parasite, toxic products of tryptophan (Trp) degradation occur. In order to assess the oxidative status and Trp degradation pattern during *Plasmodium berghei* infection, serum Trp, Kynurenine (Kyn) and urinary biopterin, liver, brain and serum superoxide dismutase (SOD), glutathione peroxidase (GPx), malondialdehyde (MDA) and NO levels were measured. Decreased SOD activities and increased MDA levels could be responsible for increased peroxynitrite production and lipid peroxidation, as well as oxidative stress. Increased biopterin levels which is supported by elevated NO, may cause the inhibition of Trp degradation. In conclusion, *Plasmodium berghei* infection may have led to the upregulation of inducible NO synthase and excessive NO synthesis. Thus, large quantities of toxic redox active radicals attack cell membranes and induce lipid peroxidation. *Plasmodium berghei* infected mice could not demonstrate systemic Trp degradation and related indoleamine-2,3-dioxygenase activity.

SÖZLÜ SUNUMLAR 4 (ORAL PRESENTATIONS 4)

ENVIRONMENTAL RISK ASSESSMENT FOR PLANT PROTECTION PRODUCTS

Sakine Uğurlu Karaağaç

Plant Protection Central Research Institute, Ankara, Turkey

Active substances used in plant protection products can be authorised only if they have no harmful effects on human and animal health and do not cause unacceptable effects on the environment, considering in particular the contamination of water and the impact on non-target organisms. The environmental risk assessment of plant protection products assesses the impact that the use of these has on non-target living organisms and on soil, water, and air. Assessment of the potential risks of environmental damage that might be caused by the use of plant protection products is an important part of registration procedures in many countries. Many countries have their own well-developed national guidelines. Turkey also has national registration directive for plant protection products. There are several general international guidelines produced by different organizations. The criteria used to decide on the acceptability of environmental risks, and the ways in which the risks are estimated vary widely. The environmental risk assessment is divided into two main areas: 1) fate and

behaviour in the environment, 2) effects on non-target organisms. The first area includes the distribution of the plant protection products in the air, in the soil and in the surface and ground waters. Second part includes the effect on birds, fish, earthworms,honeybees, and aquatic organisms. In order to reach reliable conclusions, it is important to ensure that all information used in the risk assessment must be high quality and that the relevant investigations have been carried out according to the principles of Good Laboratory Practice.

ASSESSMENT OF Cr AND Ni LEVELS IN PLACENTA BY GRAPHITE FURNACE ATOMIC ABSORPTION SPECTROMETRY

Enes Arıca, Zeynep Seda Eren, Yasemin Kartal, Vugar Ali Türksoy, Tülin Söylemezoğlu

Ankara University, Institute of Forensic Science, Ankara, Turkey

This study describes the optimization and validation of a quick and simple method for chrome (Cr) and nickel (Ni) levels in placenta samples by graphite furnace atomic absorption spectrometry (GF-AAS), which has been proved to be useful for toxicological research. Ni is generally considered as a hazardous material, but at the same time, it is nowadays recognized as an essential element. Furthermore, it holds a special place among the heavy metals. Cr(III) is a trace element species essential for the proper functioning of living organisms but Cr(VI) has toxic effects on biological systems and classified as a Group 1 human carcinogen. The determination of Cr and Ni levels in biological samples by GF-AAS is the most widely employed techniques, because of its relatively low cost, sufficiently sensitive and high detection limits. A microwave-assisted wet acid digestion procedure was developed as a sample pretreatment. This method was validated with Certified Reference Materials (NC SZC 73016-Chicken) for the evaluation of analytical results. High accuracy was obtained for Cr and Ni in the matrix of total digestion, where losses of the analyte could be attributed to sample treatment with HNO_3. The Mean levels of placenta-Cr and Ni were found as 220,66 ppb (ranging from 31.96 ppb to 913.51 ppb) and 124,24 ppb (ranging from 24.41 ppb to 683.22 ppb), respectively. These results will be discussed according to age, gestational age, smoking habits, and consuming seafood of participants.

TAMOKSİFEN SİTRAT SOLUNUM YOLUYLA ALINAN SİLİKAYA BAĞLI GELİŞEN SİSTEMİK FİBROZİSTE KORUYUCU MUDUR?

Turgut Karaca[1], Ömer Yoldaş[2], Bülent Çağlar Bilgin[3], Ömer Hınç Yılmaz[4], Nihal Karaca[5], Gülçin Şimşek[6], İbrahim Onur Alıcı[7], Andaç Uzdoğan[8], Tezcan Akın[9], **Engin Tutkun**[4], Mustafa Anıl Cömert[7], Ayla Tezer[6], Filiz Akbıyık[8], Kemal Kısmet[10]

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Amacımız tamoksifen sitratın, karaciğer ve akciğer dokusundaki fibrozise ve serum TGFβ-1 düzeylerine etkisini göstermektir. Kristalin silika üç boyutlu kristal kafeslerin düzenlenmesiyle oluşan silikon dioksit (SiO_2) türevidir. Silika nanopartikülleri kimyasal ve mekanik parlatıcılarda, ilaç, kozmetik, vernik ve gıda sanayinde kullanılmaktadır. Kristalin silika inhalasyonu sonucu oluşan silikozis, akciğerde skar ve fibrozise yol açan pulmoner hasarın sonucunda ortaya çıkar. Silikaya maruziyet sistemik sklerozis, romatoid artrit, lupus ve kronik böbrek hastalığı gibi otoimmun hastalıklarla da ilişkilendirilir. Silikanın subkutan veya intraperitoneal enjeksiyonuyla hepatik fibrozis ve siroz geliştiğini gösterilmiştir. Tamoksifen sitrat sentetik bir non-steroid antiöstrojendir ve meme kanseri tedavisinde kullanılır. Tamoksifen sitratın keloidde doz bağımlı şekilde hücre kültüründe fibroblast proliferasyonunu inhibe ettiği ve kollajen üretimini ve total TGFβ miktarını azalttığı gösterilmiştir. Deneysel çalışmamızda 110 dişi yetişkin Wistar Albino rat (200-250 g) kullanıldı. 25 rat silika inhale etti, 25 rat silika inhale etti ve 1mg/kg tamoksifen aldı, 25 rat silika inhale etti ve 10mg/kg tamoksifen aldı, 25 rat yalnız 10 mg/kg tamoksifen aldı ve 10 rat da kontrol grubunu oluşturdu. Ratlar 12 hafta 15mg/m^3, 6s/gün, 5 gün/hafta silika inhale ettiler. Çalışmanın 1-42-84. günlerinde ortamda non-spesifik toz konsantrasyonu ve solunabilir kristal silika konsantrasyonları ölçüldü. 84. günden sonra ratlar sakrifiye edildi. Akciğer ve karaciğer homojenatlarında malondialdehit düzeyi; akciğer ve karaciğer dokusunda fibrozis, serumda ise TGFβ 1, AST, ALT, albumin, T.bilirubin düzeyleri ölçüldü. Çalışmamızda oral tamoksifenin doz bağımlı olarak serum TGFβ-1 düzeyini azalttığını; serum TGFβ-1 düzeyi azalan gruplarda (4-5. gruplarda) silikaya bağlı akciğer fibrozisinin azaldığını tespit ettik. Bu çalışmada oral tamoksifen kullanımının silikaya bağlı gelişen fibroziste koruyucu olabileceğini tespit ettik.

A NEW AREA FOR CARBONMONOXIDE INTOXICATION: HYDRO-ELECTRIC CENTRAL CONSTRUCTION

Semih Kunak

Giresun University Medical Faculty Pharmacology Department, Turkey

In Blacksea region there are many hydro-electric central constructions which are under debate. Here it is evaluate as an occupational respiratory intoxication risk in hydro-electric central construction. In this study 3 posioned workers who are exposed to accumulated exhaust gas from construction vehicles and as a result of explosions of dynamite in hydro-electric central construction at Yağlıdere district of Giresun, Turkey, are evaluated. The incident has occured while caving the main water depot part of the hydro-electric central construction. CO poisoning is the leading cause of death among unintentional poisoning in United States. CO toxicity is the result of a combination of tissue hypoxia-ischemia secondary to carboxyhemoglobin formation and direct CO-mediated damage at cellular level. Presenting symptoms are mostly nonspecific and depend on the duration of exposure and levels of CO. Diagnosis is made by prompt measurement of carboxyhemoglobin levels. Treatment consists of the patient's removal from the source of exposure and the immediate administration of 100% supplemental oxygen in addition to aggressive supportive measures. The use of hyperbaric oxygen is controversial. In closed environments, the concentration of carbon monoxide (CO) can easily rise to health-threatening levels. CO-related incidents are often caused by poor condition or inappropriate use of indoor combustion devices as well as structure fires but are also due to suicides.

SÜREKLİ EĞİTİM KURSLARI

CONTINUING EDUCATION COURSES

DEVELOPMENTS IN RISK ASSESSMENT: BASIC CONCEPTS AND INTERNATIONAL FRAMEWORKS FOR EVALUATING TOXICITY DATA FOR HUMAN HEALTH RISK ASSESSMENT

Lynne T. Haber

TERA-USA

This full-day workshop will provide an overview and update on current methods for human health risk assessment. The morning will focus on more basic concepts, with advanced approaches addressed in the afternoon. The morning will address international risk assessment methods, including methods under REACH, for hazard characterization and dose-response, with an emphasis on how recent developments affect the approaches used. Methods for critically evaluating and integrating data will be discussed.

The afternoon will focus on more advanced topics, including (**1**) WHO/IPCS methods for considering weight of evidence for evaluating mode of action, (**2**) chemical specific adjustment factors, a data-based refinement for uncertainty factors, and (**3**) other resources. The course will be interactive and provide opportunities for participants to ask questions.

GENOTOXICITY AND METHODS OF ANALYSIS

Bensu Karahalil[1], Yalçın Duydu[2]

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In living organisms, various chemicals which alter genetic information cause mutations. These result different types of toxic effects from apoptosis to the development of malign tumor. Genotoxicity assays perform the describing of chemical substances which induce genetic damage, predicting of genotoxic agents when no data on carcinogenicity, clarifying and contributing of the mechanisms of chemical carcinogens. In the context of this course, defining of genotoxicity assays, the usage of biological materials, types of damages, the application areas of genotoxicity assays and advantages and disadvantages of these tests with examples will be discussed.
Course titles 1.Molecular Epidemiology and biomarkers 2. The types of damages 3.Genotoxicity assays a.Ames test b. Sister Chromatid Exchange Assay c. Chromosomal Aberration Assay d. Micronucleus and Cytokinesis Blocked Micronucleus Assay e. Comet (Single Cell Gel Electrophoresis) Assay 4.Advantages and disadvantages of genotoxicity assays

DATA REQUIREMENT FOR REACH REGISTRATION

Karl-Heinz Cohr

DHI, Denmark

REACH is the EU Regulation on chemicals management and is the legal framework for regulation of chemicals in general, existing and new chemicals. REACH is an acronym, which stands for Registration, Evaluation, Authorisation and Restriction of Chemicals. It is a comprehensive legislation that substitutes more 40 single pieces of formerly existing legislation. Some chemical product categories are exempted from REACH, because they are regulated by specific legislation, e.g. biocides and pesticides, cosmetics, food and feed, and pharmaceuticals. REACH describes the data needed for registration of chemicals and how to evaluate the data as to effects of the chemicals on human health and environment. REACH also sets the rules for restriction of use of substances of very high concern (SVHC), and for authorisation of such substances for specific use. Classification, Labelling and Packaging (CLP) of chemicals is closely related to REACH, but is regulated by the CLP Regulation. The CLP Regulation is the EU implementation of GHS, the Global Harmonisation System. CLP/GHS introduces a new system for classification, labelling and packaging.

This CEC will present the content of REACH and CLP, and the data requirement for registration of substances according to REACH and for notification substances according to the CLP Regulation. An on-going project to assist implementation of REACH in Turkey, co-financed by EU and the Republic of Turkey, will be briefly touched upon.

POSTER SUNUMLARI

POSTER PRESENTATIONS

BIOMARKERS

P1

INVESTIGATION OF DNA DAMAGE AND DNA REPAIR CAPACITY IN PATIENTS WITH COLORECTAL CANCER AND THEIR FIRST DEGREE RELATIVES

Ayfer Tozan Beceren[1], Gülden Z. Omurtag[1], Cumhur Yeğen[2], Öznur Şenkesen[3], Semra Şardaş[1],

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 1" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 1" section.

P2

TOPICAL CANNABINOID ADMINISTRATION: A SAFE TREATMENT ROUTE OPTION OF CANNABINOIDS FOR LOCALISED PAIN

Ahmet Doğrul[1], Hüsamettin Gül[1], Zeynep Seda Eren[2], Enes Arıca[2], Ahmet Sayal[1]

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The therapeutic use of cannabinoid ligands is severely limited because of the central CB_1-mediated cognitive, motor and psychotropic side effects. Topical route of analgesic drug administration is a strategy to reduce centrally related side effect. In the present study, we examined systemic and topical analgesic effect of cannabinoids in comparison to the central nervous system depressant activities in mice. Adult Male Bulb-C mice (25–30 g) were used. Analgesia was assessed by tail-flick test. Locomotor activity was used to evaluate the central nervous system side effect. CP 55, 942, a mixed CB1 and CB2 receptor agonist was used as a representative of cannabinoid drugs. CP 55,940 was given by intraperitoneal route or topically immersion of distal part of tail of mice for 3 min. Systemic (0,2, 0,5 and 1 mg/kg, i.p.) and topical administration of CP 55, 940 (1, 2 and 4 mg/ml) produced dose dependent analgesia in distal part of the tail of the mice. While systemic administration of CP, 55, 940 elicited dose dependent significant locomotor depression ($p<0.05$), topical administration of CP 55, 940 did not alter locomotion. These results suggest that topical administration of cannabinoids which target peripheral sites seems a safe option for the treatment of localised pain such as postherpetic neuralgia.

P3

THE RELATIONSHIP BETWEEN THE PLASMA BIOMARKERS AND THE VASCULAR ENDOTHELIAL FUNCTIONS IN DOCA SALT-INDUCED HYPERTENTSION

Suzan Emel Usanmaz[1], Sevtap Han[2], Orhan Uludağ[2], Emine Demirel Yılmaz[3]

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Hypertension is characterized by elevated systemic blood pressure that causes endothelial dysfunction in the vascular bed. The correlation of endothelial functions with possible blood biomarkers were not described well after DOCA salt application. In the current study, to further elucidate the endothelium-dependent relaxation of isolated thoracic aorta and the systemic blood biomarkers related to endothelial functions [nitric oxide (NO), asymmetric dimethylarginine (ADMA), total antioxidant capacity (TAC) and hydrogen sulfide (H_2S)] were investigated in the rat model of the DOCA salt-induced hypertension. In hypertension groups, animals were anesthetized and unilateral nephrectomy was performed. After the one week recovery period, DOCA was administered subcutaneously (30 mg/kg/week) and 1% NaCl and 0.2% KCl were added to their drinking water. After the 4-week experimental period, the rats were anesthetized and the segments of thoracic aorta and the blood samples were collected. Plasma NO, TAC and H_2S levels of rats were measured spectrophotometrically, ADMA levels were measured by using ELISA. Statistical analysis were performed using Student's t-test. In DOCA salt groups, systemic blood pressure was significantly increased at the end of 4^{th} week. Acetylcholine-induced endothelium-dependent relaxations were attenuated significantly in the aorta. Plasma ADMA and H_2S levels were decreased significantly, NO and TAC levels were not changed by DOCA salt-induced hypertension. In DOCA salt-induced hypertension model, decreased ADMA and H_2S levels may be good indicator to monitor the endothelial dysfunction in the vascular bed.

BIOMONITORING

P4

RESULTS OF ABUSED DRUG ANALYSES WITH CEDIA AND (GC-MS): A FIVE YEARS RETROSPECTIVE EVALUATION

Turgay Çelik[1], Hüsamettin Gül[1], Kemal Gökhan Ulusoy[2], Hakan Kayır[2], Enis Macit[2]

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 3" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 3" section.

P5

DETERMINATION OF NICOTINE AND COTININE IN HUMAN PLASMA, URINE AND SALIVA BY GAS CHROMATOGRAPHY–MASS SPECTROMETRY

Emrah Dural[1], **Tülin Söylemezoğlu**[1], Hatice Taslak[2], Gülseren Karabıyıkoğlu[2]

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Nicotine is a major component of tobacco and highly addictive substance. On the other hand, cotinine is the major oxidized primary metabolite of nicotine and their structures are very similar. Cotinine is used as a reliable biomarker to determine active, passive and environmental exposures. The aim of this study was to compare nicotine and cotinine levels in different biological fluids. Plasma, urine and saliva samples, which were taken from 36 non-smoking and 55 smoking volunteers, were collected from Ankara University Faculty of Medicine, Department of Chest Diseases in Ankara. A simple, rapid and sensitive gas chromatography-mass spectrometry (GC-MS) method for determination of low concentrations of nicotine and cotinine in plasma, urine and saliva samples were developed and validated. The calibration curves were linear ($r \geq 0.998$) over concentration range tested (1-5000 ng/ml), with quantification limits of 0.9 ng/ml and 0.7 ng/ml for nicotine and cotinine, respectively. The intraday precision of nicotine and cotinine in all samples was <5% relative standard deviation (RSD). Extraction efficiency was ≥78 for all analytes. There was a clear differentiation between smokers and non-smokers ($p<0.001$) for plasma, urine and saliva samples in terms of nicotine and cotinine levels. Strong, positive and linear correlations were found between plasma and saliva's nicotine and cotinine value (r=+0.78, +72.1, respectively). Also we found that the concentration of cotinine in plasma was successfully predicted from the salivary cotinine concentration by the equation $y=1.306x+97.818$ (x=concentration of cotinine in saliva, y=concentration of cotinine in plasma).

P6

EVALUATION OF DNA DAMAGE USING COMET ASSAY ON IRIDIUM-192 ACUTE EXPOSURE

Zeliha Kayaaltı[1], Esma Söylemez[1], **Dilek Kaya**[1], Engin Tutkun[2], Tulin Söylemezoğlu[1]

[1]Ankara University, Forensic Sciences Institute, Ankara, Turkey, [2]Ankara Occupational Diseases Hospital, Ankara, Turkey

Iridium-192 is a man-made isotope of iridium that provides a source of gamma rays and has been generally used for industrial radiography. It is well documented that ionizing radiation can cause damage to DNA indirectly or directly as a result of free radical formation. Comet assay, one of a well-established genotoxicity test, is used to detect DNA damages including strand breaks, open repair sites, cross-links, and labile sites caused by environmental exposure because of its simplicity, sensitivity and rapidity. In January 2008, two subjects (labelled P1 and P2), working on nondestructive testing, were accidentally overexposed to gamma rays from iridium-192 after breakage of industrial radiography device. One week after exposure, the patients were hospitalized with symptoms of acute diarrhea and pancytopenia and they were discharged from the hospital after a month because the symptoms were normalized. However, one of these patients(P1) attended several clinics reporting gingival bleeding, loss of teeth, excess fatigue, tiredness, and severe muscle and joint pain especially in the lower extremities. In addition to monitoring health effects, lymphocyte DNA damage was evaluated according to the tail moment(TM), tail intensity(TI), and olive tail moment(OTM) comet parameters. DNA damages of P1 and P2 were found higher than those of healthy unexposed to any toxicants. On the other hand, DNA damage level of P1(TM:5.01, TI:54177.75, OTM:1270.83) was detected higher than those of P2(TM:4.81, TI:49519.51, OTM:970.31). In conclusion, these results demonstrate that comet assay is suitable technique for in vivo human biomonitoring, especially in cases of incidental exposure to ionizing radiation.

CARCINOGENESIS

P7

ASSESSMENT OF OXIDATIVE STRESS AND IMPAIRED ANTIOXIDANT DEFENCE SYSTEM IN PATIENTS WITH

EPITHELIAL OVARIAN CANCER

Aydan Çağlayan[1], Berkan Sayal[2], Z. Selçuk Tuncer[2], Kunter Yüce[2], Filiz Hıncal[1], Belma Koçer Giray[1]

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 1" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 1" section.

P8

EVALUATION OF CELL DEATH MECHANISMS OF PALLADIUM(II) COMPLEX AS AN ANTICANCER AGENT IN HUMAN CANCER CELL LINES

Ömer Kaçar[1], **Yüksel Çetin**[1], Zelal Adıgüzel[1], Engin Ulukaya[2], Veysel Yilmaz[3],Ceyda Açılan[1]

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 2" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 2" section.

CLINICAL TOXICOLOGY

P9

TYPES AND FREQUENCY OF THERAPEUTIC DRUGS DETECTED IN TOXICOLOGICAL ANALYSIS FOR 465 PATIENTS

Enis Macit[1], Mehmet Toygar[2], Kemal Gökhan Ulusoy[3], Hakan Kayır[3], Hüsamettin Gül[1], Turgay Çelik[1]

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To diagnose or identify the acute or chronic poisoning in clinical toxicology is very important. In this study the results of toxic drug screening requested from clinics in doubt of poisoning with either therapeutic or other use of drugs were evaluated for five years. The analyses were made using CEDIA and GC/MS methods. General toxic drug screening of total number of 762 samples (465 bloods and 276 urine) from 465 patients/cases which were requested from both clinics of our and other than our hospital were evaluated. The number of requests according to the clinics for GTDS were as follows; Emergency Medicine Clinic 183, Forensic Medicine 36, Intensive Care Unit 17, Pediatrics 25, other clinics 20 and other than hospital 90. In blood samples of GTDS 3 samples found to be positive for narcotic drugs and 19 for therapeutic drugs; in urine samples 11 samples found positive for narcotic drugs and 59 for therapeutic drugs. The frequency and types of drugs detected in blood samples were; narcotics 3, antidepressant drugs 9, NSAI drugs 3 and others 7. In urine samples the frequency and types of drugs were as follows; narcotics 11, antidepressant drugs 21, antipsychotics 6, NSAI drugs 9 and others 23. The reason that the frequency of positive urine samples is higher than blood samples for drugs might be due to delay of request from clinicians or patients demand for therapy. These requests for analyses reveal the awareness and validity of toxicological screening in diagnosis and therapy of poisoning cases.

P10

EVALUATING APPROPRIATENESS OF DIGOXIN, CARBAMAZEPINE, VALPROIC ACID AND PHENYTOIN USAGE BY THERAPEUTIC DRUG MONITORING

Selvinaz Dalaklıoğlu Taşatargil

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Therapeutic drug monitoring (TDM) is a useful tool for the optimization of drug therapy. The aim of this retrospective study was to evaluate the appropriateness of carbamazepine, phenytoin, valproic acid or digoxin treatment by using TDM data. We evaluated the appropriateness of drug usage in 325 patients who received carbamazepine, valproic acid, phenytoin or digoxin in a large teaching hospital during the period from March 2010 to January 2011. The serum drug levels were measured by cloned enzyme donor immunoassay (CEDIA). Total of 325 TDM tests were performed in this period. Among the obtained samples, valproic acid was the most evaluated test in our TDM unit. In valproic acid-treated patients, serum levels in 58 patients (58%) were in therapeutic range. While 11 patients (11%) had serum levels in over the therapeutic range, 31 patients (31%) had sub-therapeutic levels of valproic acid. The results of TDM were mostly found in therapeutic range for carbamazepine. A total of 91 request forms were collected. The overall data show that 64 patients (70.3%) had therapeutic concentrations. In the phenytoin assays, the mean plasma concentrations generally not reached the therapeutic ranges. Among the total of 49 blood samples, the highest number of sub-therapeutic concentrations (65.3%) were detected for phenytoin. Similarly, inappropriate levels of digoxin were established in about half of all cases. Our results suggest that there is a need for interventions to improve the appropriate use of digoxin and phenytoin in patients treated with these drugs.

P11

THE LACK OF RELATIONSHIP BETWEEN ADVERSE EFFECTS AND SERUM CONCENTRATIONS OF CITALOPRAM/N-DESMETHYL CITALOPRAM

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Citalopram is an antidepressant drug which is widely used in patients with major depression. The aim of this study was to investigate the existence of relationship between the adverse effects and serum citalopram/n-desmethylcitalopram concentrations. Major depression patients treated with citalopram (20-30 mg/day, n=46) were studied. Blood samples for monitoring were taken on the 4th week, between at 8^{00}-9^{00} hours. Serum concentrations of citalopram/n-desmethylcitalopram were measured by high-performance liquid chromatography in patients with major depression according to Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria. Adverse effects (gastrointestinal, heart, skin, nervous system, eyes/ears, genital/urinary, sleep, sexual functioning) were determined at 1st, 2nd, 6th weeks. Ethical approval was obtained from Human Ethics Committee of the Gazi University Medical Faculty local ethic committee. Patients provided a complete written informed consent before inclusion in the study. Our results showed that there is no correlation between serum citalopram/n-desmethylcitalopram concentrations and adverse effects. Although some studies have shown correlations between the serum levels and therapeutic effects of citalopram, our results indicated that there is no correlation between the serum levels and adverse effects.

P12

AN EVALUATION OF POISONING CALLS BETWEEN 2001-2011 RECEIVED BY HACETTEPE DRUG AND POISON INFORMATION UNIT

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In this report poisoning calls received by Hacettepe Drug and Poison Information Unit were epidemiologically evaluated. While pharmaceutical drugs were found as the main cause of poisonings with 57,2 %, household products (11,3 %) and pesticides (8.9 %) followed them. Among the drug groups, antidepressants were the primary offenders with 12,9 %, and non-steroidal antiinflamatory drugs ranked second with 10,8 %. The ratio of female to male was 1.2:1.0. Major mode of poisoning was accidental (69,3 %), and most of the victims were younger than 5 years of age (48,1 %). Suicidal attempts were encountered mostly in 17 to 40 years of age (18,2 %). While females were dominant in suicidal attempts, accidental exposures affected both sexes equally. The main offending drug group in females was antidepressants, and analgesics in males. Majority of callers were physicians (68,6 %) and the most of sites of enquirers were State Hospitals (27,8 %). Whereas almost 40.0 % of calls were received from Ankara, Istanbul was the second city with a higly lower percentage (16,9 %).

P13

QUANTITATIVE EVALUATION OF TOXICOLOGICAL ANALYZE DATA FOR LAST 5 YEARS

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Retrospective evaluation of toxicological analyze results is important for prediction of both forensic and clinical aspects and to prevent them as well. The aim of this study is to evaluate the toxicological analyze requests from both clinics and other than the clinics quantitatively for last 5 years. In this time span, 1183 toxicological samples from 726 different patients were analyzed in different extraction and analyze methods such as CEDIA (cloned enzyme donor immune assay), GC-FID (gas chromatography-flame ionization detector) and GC/MS (gas chromatography-mass spectrometry). The samples and number of them were as follows; urine 646, blood 398, stomach ingredients 12, feces 25, water 14 and plants 4, respectively. After analyzing these samples, 31 bloods, 57 urine and 3 other samples found to be positive for narcotic drugs. Toxic drug screening test using the same samples resulted 50 bloods, 159 urine and 1 other samples found to be positive for drugs. These findings reveal that urine samples are found to be much positive for toxicological screening for drugs and narcotics than other samples. And according to the results, toxicology laboratory is helping the clinics for diagnosis and treatment with toxic drug monitoring more than narcotic drug analysis.

P14

EVALUATION OF ADDICTIVE DRUG ANALYSIS RESULTS; A RETROSPECTIVE VIEW

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In this study, the results of addictive drug analyses of 486 samples from 261 patients which were requested from clinics both in our or other than our hospital were evaluated. According to the CEDIA (cloned enzyme donor immune assay) and GC/MS (gas chromatography-mass spectrometry) analyses results, 35 blood and 56 urine samples found to be positive for addictive drugs. In blood samples the number of drug types were as follows; opiate and metabolites 15, cannabinoid and metabolites 19, amphetamine and metabolites 1, benzodiazepines and metabolites 7 and barbiturates 2. The drug frequency in urine samples were as follows; opiate and metabolites 22, cannabinoid and metabolites 24, amphetamine and metabolites 9,cocaine and metabolites 1, benzodiazepines and metabolites 22 respectively. 8 blood and 9 urine samples were found to be positive for both addictive drugs and other drugs. And during the analyses, 55 blood and 127 urine samples of these patients found to be positive for other therapeutic drugs. The reason that the frequency of positive urine samples is higher than blood samples might be due to delay of request from clinicians or patients demand for therapy. The types of addictive drugs detected from analyses are in concordance with previous results in literature and amphetamine like drugs found to be increased.

P15

RADIO-PROTECTIVE EFFECTS OF MELATONIN ON THE SKIN HISTOLOGY IN THE RAT

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In this study, the protective effect of melatonin on the radiation-damaged skin was investigated and effectiveness of the protective effect of melatonin was compared with amifostine. For this purpose, 40 female Sparague Dawley rats were used. Animals were divided into 5 groups. Control group (C), radiation group (R) and 2 experimental groups (radiation + melatonin 25 mg/kg (R+M) and radiation + amifostin 200 mg/kg (R+WR). A single dose of 20 gy gamma radiation was exposed to the left legs of the rat groups of R, R+M, and R+WR. At the end of a four-week of experiment period, the skin on the left femur of each rat was dissected and routine histological procedures were applied. Nikon Eclipse 400 research microscopy was used for histological observations. All histological structures of the skin were found to be normal in the control group. However, we observed that reduction in thickness of the epidermis and the dermal papillae have disappeared, sweat glands, sebaceous glands and hair follicles atrophy was observed in radiation groups. Our findings showed that R+M group, the thickness of the epidermis, collagen synthesis, R and R+WR group was better with histological structure. As a result, the histological abnormalities of radiation is shaped to protect in the skin, it has been found that melatonin has a significant effect compared to Amifostine (WR2721).

P16

ANTI-PSYCHOTIC POISONINGS REPORTED TO THE DRUG AND POISON INFORMATION CENTER OF DOKUZ EYLUL UNIVERSITY

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The aim of this study was to determine the spectrum and severity of poisonings involving antipsychotics, reported to Drug and Poisoning Information Center (DPIC) of Dokuz Eylul University, Izmir, between 1993 and 2011. For this aim, a descriptive, cross-sectional study was carried out using standart questionnaire. The data extracted from records included the age and sex of patients, antipsychotic drug type, exposure reason, exposure site, clinical effects, recommended treatment attemps and outcomes. The severity of clinical manifestations were graded and assessed according to the EAPCCT/IPCS Poisoning Severity Score. The DPIC recorded 78.252 cases between 1993 and 2011. 2.6 % of all drug-induced poisonings was related to antipsychotics. Female/male ratio was 1.7. The ratio of intentional cases was 75.6 %. It has been observed that suicidal poisonings were most common in women. Thioridazine (18.6%) was the most exposed antipsychotic drug.The poisoning symptoms were not related to type of the antipsychotics (typical or atypical); However, the severity of symptoms were mostly mild or moderate in poisonings with typical antipsychotics.

CONSUMER'S PROTECTION

P17

DETECTION OF SILDENAFIL RESIDUES IN DIFFERENT TYPES OF GINGSENG PRODUCTS WITH GC/MS

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Sildenafil was used in the past to treat patients with pulmonary artery hypertension. Then was approved for the treatment of erectile dysfunction (ED) in man by FDA. As this drug in over-dose might cause a series of side-effects, it should be administrated under doctors caution. These dietary supplements could improve male sexual potency without causing any danger unless they do not have any synthetic chemical ingredient. The aim of this study is to detect whether any chemicals like sildenafil, vardenafil or tadalafil exist as an impurity of the ingredients of dietary supplements those are easily found in the market. For the extraction, 10 different types of Panax Gingseng dietary supplements obtained in gelatin capsules from the local market in Ankara, Turkey. All of these products examined are natural dietary supplements for male sexual health. GC-grade acetonitrile and n-hexan were from Sigma-Aldrich, USA. Other reagents were of analytical grade. 3 for each capsules opened carefully and extracted with both n-hexan and acetonitrile over night. After liquid-liquid extraction (LLE), supernatant was dried under a constant flow of N2 gas, 100 µl BSTFA derivatization performed prior to 1µl GC MS injection. Sildenafil was found qualitatively with panaxynol, panaxydiol and some of the ginsenosides (Rg1, Rd, Re) in 3 of the dietary supplements full scan mode. There for while using a dietary supplement or a herbal product, people should be more careful and the administrative authorities should apply more strict rules and regulatory to those kind of products for human health.

P18

DETERMINATION OF THIOGLYCOLIC ACID (TGA) IN COSMETIC PRODUCT USING HPLC - UV DETECTION

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Thioglycolic acid (TGA), used in cosmetic hair-care for "permed hair" as it and its derivatives weaken the keratin structure by breaking the cystine disulfide linkages. TGA is also used as depilating agents to remove unwanted body hair. The break-down of disulfide bonds in the cortex by thioglycolates either rearranges (perms) or entirely destroys (depilates) hair structure. When used as an antioxidant application in cosmetics, thioglycolates protects the product but not the skin against oxidation. TGA, found in cosmetics, is a chemical with values stated in the cosmetic regulatory affair, number 25823 dated 23.5.2005. Cosmetic formulations require selective and sensitive analytical methods for TGA determination. In this study a convenient and reliable method based on high-performance liquid chromatography (HPLC) - UV detection has been developed. The method involves convertion of thiodiglycolic acid into thioglycolic acid by the addition of hydrochloric acid. Thioglycolic acid is evaluated by reverse phase liquid chromatography and detected at 210 nm. Cosmetic Laboratories, along with the European Commission Countries Laboratories from 19 countries, attended the test organized by EDQM-OCCL for TGA quantification PTS (Proficiency Testing Scheme)in hair products and depilatuaries and certified the achieved succesfull Z scores. In conclusion; TGA is proved to be highly toxic which can be absorbed by intact skin causing damage to organs or systems. To prevent the misuse of this product due to unawareness of its toxicity, the cometics sector should be regularly supervised, products tested and prevent the use of products which do not abide the the values.

P19

PARABENLERİN TOKSİKOLOJİK AÇIDAN DEĞERLENDİRİLMESİ

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Farmasötik formülasyonlarda %0.1 - 0.3, kozmetik preparatlarda ve yiyeceklerde %0.01 – 0.1 konsansantrasyonlarında koruyucu amaçlı kullanılan maddelerin genel adıdır. 1984'te parabenlerin 13200 farklı kozmetik formülasyonda kullanıldığı saptanırken 1995'te durulanmayan ürünlerin %99'unda ve durulanan ürünlerin %77'sinde parabenler saptanmıştır. Sonraki çalışmalarda da deodorantlar, kremler ve losyonlar gibi analiz edilen vücut bakım ürünlerinin çoğunda parabenlerin, özellikle

de metilparaben ve propilparabenin (ayrıca ftalatlarla kombine şekilde) bulunduğu gösterilmiştir. Kemirgenlerde ve insanlarda yapılan toksikoloji çalışmalarında parabenlerin non-toksik, genel olarak non-irritan ve non-sensitizan olduğu gösterilmiştir. Parabenler FDA (Food and Drug Administration) tarafından topikal ürünlerde katkı maddesi olarak kullanım için onay almıştır. Bugüne dek, parabenin antimikrobiyal gücü, stabilitesi ve tüm dünya çapında kabul edilir halde olması, parabenleri topikal kozmetik ve farmasötik preparatlarda prezervatif olarak kullanımlarını popülerleştirmiştir. Ancak birçok üretici firma parabenlerin östrojenik olduklarına dair gitgide artan kanıtlar nedeniyle parabenlerin kullanımını azaltmaktadır. Meme kanseri dokusunda parabenlerin bulunduğuna dair bildirimlerin sonrasında topikal formülasyon endüstrisi parabenlerin kullanımı açısından daha da isteksiz hale gelmiştir.

DRUG ORIENTED TOXICOLOGICAL RESEARCH

P20

ERADICATION OF TOXIC MATERIAL BY ASSESSED GREEN ORGANIC CHEMISTRY AS ANTICANCER AGENTS

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Cancer, a disease of the cell cycle, being one of the major health problems, has received enormous biomedical attention over the past two decades. The effectiveness of many existing anti cancer drugs is limited by their toxicity to normal rapidly growing cells. Organic synthesis by non-conventional/modern methods is rapidly gaining importance in view of the fact that the use of many toxic and volatile organic solvents contributes to pollution. Consequently, it is highly desirable to develop environmentally benign processes that can be conducted in aqueous media/solvent-free/solid-supported and to minimize global warming and improve good health. In view of these points, it was thought worthwhile to study new benzimidazoles clubbed with fused heterocyclic ring systems; triazolo-thiadiazoles and triazolo-thiadiazines moieties, as rationally designed with bendamustine, solvent free under scientific microwave synthesizer and *In vitro* anticancer screening at the Development Therapeutic Program (DTP), National Cancer Institute (NCI), Chemotherapeutic Research Division, USA, against full NCI 60 cell line panel. Compound 5h (NCS: 760452) exhibited remarkable activity with Mean GI_{50} =1.04μM, TGI > 100 and LC_{50}> 100 in compare to standard drug (Bendamustine, NSC: 138783, Mean $GI_{50,}$ 60 μM, TGI>100 and LC_{50}> 100). It is may possibly be used as lead compound for developing new anticancer agents.

P21

A COMPARATIVE STUDY ON THE EFFECTS OF GINKGO BILOBA EXTRACT ON CEREBRAL ARTERIES OF OLD AND YOUNG RATS

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The present study aims to evaluate the effects of Ginkgo biloba used since childhood on brain vessels and neurons by comparing its effects on the elderly group. The study included 4 groups of 40 male rats (n = 10): 1. elderly-control group (2 doses of saline for 2 months). 2. elderly-Ginkgo group (2 doses of G*b*E, 100mg/kg/day, 2 months). 3. 30-day old young-control group (2 doses of saline for 2 months). 4. 30-day old young Ginkgo group (2 doses of G*b*E, 100mg/kg/day, 2 months). Cortex and hippocampus regions of the brain tissues removed, dissected and were examined with the light microscopy. Sections were immunohistochemically stained for iNOS and eNOS. İn the elderly-control group, age-related strong positive iNOS and moderate eNOS immunoreactions were observed in some of the neurons and vessel walls in the cerebral cortex. In the elderly-Ginkgo group, it was observed that iNOS and eNOS reactions decreased in the neurons in the cerebral cortex and hippocampus region. INOS and eNOS reactions in the vessel walls in the cortex were negative. In the young-Ginkgo group, neurons in the cortex showed a strong expression of iNOS and eNOS, which was considered quite remarkable. In our study, normal levels of iNOS and eNOS secretion in the young- control group increased in the vessel walls and surrounding neurons after chronic administration of ginkgo, which suggests that this drug may not have a positive effect in young rats at the cellular and molecular level.

P22

CARDIOTOXICITY OF CONCOMITANT VERSUS SEQUENTIAL TRASTUZUMAB WITH THORACIC RADIOTHERAPY: AN ECHOCARDIOGRAPHIC STUDY IN RATS

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The purpose of this experimental study is to compare the effect of Trastuzumab (T) on radiation induced cardiovascular toxicity when used either sequentially or comcomitantly. 108 female Wistar albino rats were divided into 6 groups (G) composed of 18 animals. Rats were sham-irradiated in G1 G2 and G3 were defined as control, T and radiotherapy (RT) groups, respectively. G4 and G6 were the sequential RT - T groups in which T was administered either one week before and after RT, respectively. G5 was concomitant RT-T group in which T was administered 6 h before RT. T was applied intraperitoneally with a dose of 6 mg/kg. 15 Gy RT was in the form of single anterior field with 6 MV photon beams and the dose was prescribed to 2 cm depth. Echocardiographic studies were performed 21 and 70 days after RT. Left parasternal and left apical echocardiographic images of anaesthetised rats lying in the dorsal recummbency position were obtained using using Vivid S (5 MHz frequency transducer, 10x13 mm footprint, General Electric). RT induced significant decreases in ejection fraction, left ventricular mass and fractional shortening ($p<0.05$). T showed additional decrease in ecocardiographic parameters when added to RT either concomitantly or sequentially ($p<0.05$). T and high dose RT may lead to cardiotoxicity that seems at least additive. Echoardiography is a powerful technique for non-invasive and serial determination of cardiac structure and function in cardiotoxicity studies.

P23

ANTIPSYCHOTIC INDUCED HEPATOTOXICITY - CASE REPORTS, LITERATURE REVIEW

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In 1994, 2.216 million people in the United States admitted to a hospital due to the advers drug reactions (ADRs) and it was reported that of these 106.000 had fatal ADRs. Xenobiotics are usually metabolized in the liver in the drug-metabolizing enzyme system. Most adverse drug reactions affect the liver. So far, there are more than 1000 drugs which are responsible for hepatic adverse reactions and %16 of these drugs is neuropsychiatric. Recent studies showed that liver enzyme abnormalities were not only seen with typical antipsychotics drugs but also with atypical antipsychotics. When we review the literature, it has been determined that many case reports were available and these reports were about only one active agent. Olanzapine, Clozapine and Risperidone are atypical antipsychotics which have been commonly used. Asymptomatic elevation of liver enzymes has been observed in approximately 50% of patients treated with atypical antipsychotics. The clozapine related hepatotoxicity has been well documented. Serious hepatotoxicity induced by olanzapine has also been published in the current literature. Several cases of risperidone induced hepatotoxicity; cholestatic hepatitis and immunoallergic hepatitis have been reported. Olanzapine and risperidone also commonly cause asymptomatic increase in liver enzyme levels. In this review, we conducted a PubMed search of published articles using the keywords *"Antipsychotics, hepatotoxicity or "olanzapine hepatotoxicity" or "risperidone hepatotoxicity" or "clozapine hepatotoxicity"* in years between 1998 and 2012. Seventy nine articles which were identified from the literature, medication, dosage, duration of use were evaluated in terms of developing hepatotoxicity.

P24

MULTIORGAN RESPONSE OF CYPS AND ANTIOXIDANT ENZYMES IN RATS UPON INDUCTION BY AROCLOR AND PHENOBARBITAL

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In vitro drug metabolism studies are usually done by incubating the parent compound with rodent microsomes. However, the quantity of metabolites is usually too low in order to allow identification of the chemical structure, and to conduct further toxicodynamic/mechanistic studies. CYPs are the key enzymes in the formation of drug metabolites. In order to increase the amount of metabolites in vitro, various strategies have been implemented such as chemically inducing enzyme expression in rodents, using human CYPs-transfected or random-mutated bacteria, or electrochemically generating metabolites from parent drug. In the present study, we compared two conventional CYP inducing agents, aroclor and phenobarbital (PB), on different organs in rat. Two groups of animals were dosed either with one compound, as well as a control group was included. Liver, kidney, heart, brain and lung tissues were dissected and

microsomal and cytosolic fractions were prepared. Activities of CYP1A1 and CYP2B1/2 in microsomes, and total GST, SOD, CAT and GPx in respective cytosols were determined in different organs. PB caused about 4 fold, while aroclor caused 80 fold increases in CYP 1A1 activity compared to controls in liver. In all other organs, aroclor caused more pronounced effect on CYP1A1 activity compared to PB. On the other hand, CYP2B1/2 activity was induced more with PB compared to aroclor in liver. Induction was also higher in lung with PB, while activities of the other organs were comparable. GST and antioxidant enzymes responded differently in various organs.

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P25

EFFECTS OF POLYCYCLIC AROMATIC HYDROCARBONS ON DRUG METABOLISMS

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Humans are exposed daily to a wide variety of chemicals and foreign substances absorbed across the lungs or skin or via ingestion. Polycyclic aromatic hydrocarbons (PAH) are common environmental contaminants and generally considered potent inducers of some of cytochrome P450 (CYP-450) isoenzymes. PAHs have been shown to induce 3 hepatic CYP-450 isoenzymes, primarily CYP1A1, 1A2 and 2E1. PAHs can influence to drug metabolism by inducing the bioactivating CYP450s. Thus, metabolic clearance and activity of CYP1A-metabolized drugs can alter. In addition to this mechanism, there are some minor mechanisms such as changing expression of certain phase II enzymes, some transport proteins and levels of some plasma proteins. There are many scientific studies on this topic. Some specific examples of studies on the effects of PAHs on some clinical drug's activities have been mentioned in this poster presentation.

P26

ANTIOXIDANT AND CYTOTOXIC ACTIVITY OF NEWLY SYNTHESIZED MELATONIN ANALOGUES

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Melatonin is a hormone synthesized mainly by the pineal gland to help regulate circadian rhythms. Melatonin shows antioxidant activity *in vitro* but at concentrations several orders of magnitude higher than those present *in vivo*. Protective effects of melatonin is indicated in many diseases and conditions such as aging, organ transplantation, Alzheimer's disease, Parkinson's disease, inflammation and hyperglycemia where free radicals are believed to be involved. The present study is undertaken to investigate potential antioxidant activity of newly synthesized indole- based melatonin analogues hydrazide/hydrazone derivatives. Antioxidant activity of the compounds was explored by evaluating their reducing effect against oxidation of a redox sensitive fluorescent probe, 2', 7'-dichlorofluorescin in human erythrocytes *in vitro*. Cytotoxicity of all compounds was also investigated by lactate dehydrogenase leakage assay in CHO-K1 cells. Only a hydrazide derivative melatonin analogue tested was found to have no antioxidant effect. All other hydrazone derivatives were found to have antioxidant activity to some extent. Among the synthesized analogues having o-halogenated aromatic side chain exhibits effective antioxidant properties without having any membrane damaging effect.

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ECOTOXICOLOGY

P27

EVALUATION OF POLLUTION DUE TO MARINAS AND SHIPYARD ACTIVITIES USING MYTILUS GALLOPROVINCIALIS IN TURKEY

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This study presents the effects of pollution activities of two marinas and a shipyard on selected biochemical and physiological markers of Mediterranean mussel, *Mytilus galloprovincialis*, in Turkey. For this aim, Tuzla Shipyard (Istanbul), Kalamış Marina (Istanbul) and Bodrum Turgutreis Marina (Muğla) were selected. Mussel samples were installed for 30 days during March and April 2012 into 11 different stations (4 stations in Tuzla, 4 stations in Kalamış, 3 stations in Bodrum excluding control areas). Digestive glands of collected mussels were removed in the field conditions after sampling and selected enzyme activities (7-ethoxyresorufin-O-deethylase

[EROD], pentoxyresorufin-*O*-deethylase [PROD], glutathione S-transferase[GST], carboxylesterase [CE], glutathione reductase [GR] and acetylcholine esterase [AChE]) were assayed in the laboratory. The physiological responses of the mussels were assesed by application of filtration rate biomarker in laboratory conditions. All selected enzyme activities represented statistical differences comparing with the control mussels and the mussels installed to Istanbul and/or Bodrum stations. GST is significantly inhibited in all samples collected from the marinas and shipyard stations and EROD and/or PROD were activated. The mussel samples from the shipyard area showed the minumum filtration rate values. Results showed that GST, EROD and PROD are the most important enzymatic biomarkers and the filtration rate values are consistent to evaluate the effects of activities for the selected shipyards and marinas.

P28

IN VITRO GENOTOXICITY OF FIPRONIL SISTER CHROMATID EXCHANGE, CYTOKINESIS BLOCK MICRONUCLEUS TEST AND COMET ASSAY

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Fipronil is a phenylpyrazole pesticide developed by the transnational company Rhône-Poulenc Agro in 1987. Data on the genotoxicity and toxicity of Fipronil are rather inadequate. In this study, we aimed to evaluate the potential genotoxic activity of fipronil using the single-cell microgel-electrophoresis or 'comet' assay, sister-chromatid exchanges (SCE) and micronuclei (MN) in human peripheral blood lymphocytes. In addition to Cytokinesis Block Proliferation Index and Proliferation Index was measured for cytotoxicity. In this study, different three doses of fipronil were used (0,7µg/ml/0,3 µg/ml /0.1 µg/ml). Mitomycin C (2 µg/ml) was used as positive control for sister chormatid exchange and micronucleus test systems. Hydrogene peroxide was used as positive control for comet assay. Fipronil induced a statistically significant increase the MN and SCE frequency and DNA damage in dose- dependent manner in human peripheral blood lymphocytes ($p<0.01$, $p<0.05$, for 0,7and 0,3 µg/ml respectively) compared with negative control. There is no significant different between 0,1 µg/ml and negative control for MN. We found that there is significant difference between all the dose of fipronil and negative control for SCE frequency, CPBI and PRI ($p<0.01$). Using the alkaline comet assay, we showed that the all doses of the Fipronil induced DNA damage in human peripheral blood lymphocytes ($p<0.05$).

P29

THE EFFECT OF ATRAZINE ANTIOXIDANT ENZYMES OF GAMMARUS KISCHINEFFENSIS (SCHELLENBERG, 1937)

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Atrazine (2-chloro-4-ethylamino-6-isopropylamino-s-triazine) is one of the most commonly used herbicides found in the rural environments. The aim of this study is to determine toxic effects of atrazine standard exposed during 24, 48, 72, 96-hours, 7th and 14th days on *Gammarus kischineffensis.* Antioxidant protection system consists of enzymes of the living organisms such as catalase (CAT), glutathione S-transferase (GST), glutathione reductase (GR). This system has function for protection from xenobiotic and toxic materials as well. These enzymes are the strong biomarkers of oxidative stress formed in the cell. The 96 hrs LC_{50} value was determined as 18,96 mg/l for atrazine. In this work, the effect of different concentrations (1/10 LC_{50} =1,896 mg/l and 1/100 LC_{50} =0,1896 mg/l) of atrazine at 24, 48, 72, 96-hours, 7th and 14th days on *Gammarus kischineffensis* (Schellenberg,1937) on antioxidant system has been tested, and changes in CAT, GR, GST and AChE (acetylcolinesterase) enzyme activities have been investigated. Our findings were evaluated using a program of SPSS 10.0 Windows Inc., USA. The significance of difference between groups was determined with Kruskal Wallis test at $p<0.05$ significance level. When the differences between groups were found to be significant, then differences between the groups were tested using Conover method. The results showed that atrazine has significant effects on CAT, GR and AChE enzyme activities depending on doses and times tested.

P30

ACUTE TOXICITY OF MANEB AND METHOXYCHLOR ON BUFO BUFO (LINNAEUS, 1758) AND BUFO VIRIDIS LAURENTI, 1768 (SALIENTIA: BUFONIDAE) LARVAE

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Significant declines in amphibian populations have been observed in recent years. Pesticides are thought to be one of the most important causes of this situation. Maneb and Metoxiclor are widely used in our country. At this study, were investigated acute toxic effects of maneb and methoxychlor pesticides on *Bufo bufo* and *Bufo viridis* larvae which lives in our country. Acute toxicity experiments, 10-5000 µg/l maneb and 1-100 µg/l doses range methoxychlor, 21st stage larvae were appilied for 120 hours. As a result of acute experiments, it was found that maneb and methoxychlor pesticides caused morphological changes at larvae. Curvature of the vertebrae, visceral edema and tail deformations are observed as morphological findings. Taken together the findings of acute and chronic toxicity experiments, it was found that maneb and methoxychlor pesticides have negative effects on the development of ***Bufo bufo*** and ***Bufo viridis*** larvae.

P31

MONITORING OF POPs IN BUYUK MENDERES RIVER AND WATER BIRDS BY NON-INVASIVE VERSUS INVASIVE SAMPLING

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Three main groups of persistent organic pollutants (POPs); namely organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs) were quantified in various invasive and non-invasive samples from water birds in the Büyük Menderes River in Turkey. The potential usefulness of those specimens for reflecting the tissue content of pollutants was evaluated. Blood, muscle and liver tissue as invasive, preen gland oil and unfertilized eggs as relatively non-invasive samples were collected from yellow-legged gull (Larus cachinnans michahellis), and euroasian coot (Fulica atra) from two stations on the river; the origin (Işıklı Lake) and the estuary (Söke). Pollutants were measured by gas chromatography-electron capture detection (GC-ECD). The aim was to explore whether non-invasive sampling accurately reflect body burden. As expected, total HCHs and DDTs were the highest in preen gland oil, while CHLs found to be highest in liver, and DRINs were found to highest in muscle tissue of yellow legged gull. In Euroasian coot, all OCP levels were highest in liver, which suggested a recent exposure. Egg pollutant levels were similar to muscle tissue levels in these water birds. Total PBDE levels in preen gland oil and liver were comparable both in gull and coot, suggested a continuous exposure to those pollutants. However, total PCB levels were apparently higher in preen gland oil samples of both species. Present findings suggested that preen gland oil can be used to monitor the internal dose of the pollutants.

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P32

PERSISTENT ORGANIC POLLUTANTS AND TOXICOLOGICAL RESPONSES IN GRAY MULLET AND SEABASS FROM BÜYÜK MENDERES RIVER ESTUARY AND VICINITY

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- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 2" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 2" section.

ENDOCRINE DISRUPTORS

P33

MELATONIN ADMINISTRATION AMELIORATE TESTICULAR MITOCHONDRIAL OXIDATIVE DAMAGE CAUSED BY BISPHENOL A IN ADULT MICE

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Bisphenol A (BPA) is a monomer of polycarbonate plastic used to manufacture plastic baby bottles and lining of food cans. BPA is also used in dental fillings and sealants. It has endocrine-disrupting potential and exerts both toxic and estrogenic effects on mammalian cells. The aim of this study was to investigate if BPA induced oxidative stress and toxicity in the testicular mitochondria of adult male mice, is ameliorated by co-administration of melatonin. Mice exposed to standardized dose of BPA (10 mg/kg body weight), orally for 14 days caused lipid peroxidation (LPO) and decrease in reduced glutathione (GSH) content of testicular mitochondria. BPA also caused decrease in activities of marker mitochondrial enzymes such as succinate dehydrogenase, malate dehydrogenase, isocitrate dehydrogenase. Besides, it also affected activities of antioxidant enzymes such as superoxide dismutase, glutathione reductase and glutathione peroxidase. Concomitant melatonin administration (10 mg/kg body weight; intraperitoneally for 14 days) lowered mitochondrial lipid peroxidation. It also restored the activity of mitochondrial marker enzymes and ameliorated decreased enzymatic and non-enzymatic antioxidants of

mitochondria. Melatonin acts as an antioxidant. These results demonstrate the prowess of melatonin in ameliorating BPA-induced mitochondrial toxicity and the protection is due to its antioxidant property or by the direct free radical scavenging activity.

ENVIRONMENTAL TOXICOLOGY

P34

CHARACTERIZATION OF HAZARDOUS SOLID WASTES LEACHATES BY PHYSICOCHEMICAL AND TOXICOLOGICAL APPROACHES

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Municipal solid waste landfills may contain a huge diversity of contaminants; these wastes should be considered as potentially hazardous complex mixtures, representing a potential environmental, human and animal health hazards due to accumulation of long term exposure. The main aim of this study was to evaluate the physicochemical and toxicological characterization which may lead the integrated solid waste management (ISWM) plan. The characterization of 250 solid waste leachates from mainly industrial use were evaluated by using infrared spectra, fluorescence spectrophotometer, GS-MS, and acute oral toxicity with mouse. The samples showed diverse pH, organic and inorganic composition. The acute oral toxicity results of samples were categorized according to the Globally Harmonized Classification System (GHS) and 4 % of the leachetes found at category 4 (LD50 > 300 mg/kg body weight) whereas 96 % of them found at category 5 (LD50 > 2000 mg/kg body weight). Even though lethality was low, most of the samples were resulted in highly deletorous gross pathology observations. Finally, 50% of the samples were classified as hazardous waste as a result of physicochemical and toxicological analysis. The results showed that the measured physicochemical parameters should be used for an initial categorization of the potential toxicity of solid wastes and the determination of the type of toxicity assay which has to be applied for ISWM system based on 3R (reduce, reuse and recycle) principle.

P35

THE EFFECT OF IMIDACLOPRID ON BLOOD ELECTROLYTES OF RAINBOW TROUT (Oncorhynchus mykiss)

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Imidacloprid [(1-(6-cloro-3-pyridylmethyl)-2-nitroimino-imidazolidine] is one of the neonicotinoid insecticide and also it used for nicotinic acetylcholine agonist.This chemical, one of the most widely used insecticide in agriculture, but information about toxicity on fish is limited. In this study it was aimed to determine the effects of exposure to different doses of imidacloprid on blood biochemistry of rainbow trout (Oncorhynchus mykiss). For control and treatment groups Ca (Calcium), P (Phosphorus), Mg (Magnesium), Fe (Iron), Na (Sodium), K (Potassium), and Cl (Chlorine) parameter were measured in blood samples. Statistical analyses showed that the differences in all values depend on the dose but the Cl was important ($P<0.05$).

P36

INDUCTION OF OXIDATIVE STRESS AND HISTOLOGICAL CHANGES IN LIVER BY SUBACUTE DOSES OF BUTYL CYCLOHEXYL PHTHALATE

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- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 2" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 2" section.

P37

THE POSSIBILITY TO USE PERSISTENT ORGANIC CONTAMINANTS (POPS) ENVIRONMENTAL DATA TO PREDICT CONTAMINATION IN HUMAN

Cafer Turgut[1], Birgül Mazmancı[2], Mehmet Ali Mazmancı[3], Levent Atatanır[4], Perihan Binnur Kurt-Karakuş[5], Bernhard Henkelmann[6], Karl Werner Schramm[7], Serhan Mermer[1], Melis Usluy[8]

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 4" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 4" section.

P38

INVESTIGATION OF DDT AND ITS DEGRADATION BYPRODUCTS IN SOILS FROM SÖKE, TURKEY

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Söke is one of the largest cotton production areas of Turkey. The soils in this area still has significant levels of DDT (1,1,1,-trichloro-2,2-bis(4-chlorophenyl)-ethane) although DDT usage was banned over 30 years ago. In addition to the historical DDT contamination, the widespread usage of dicofol(2,2,2-trichloro-1,1-bis(4-chlorophenyl)ethanol) has lead to new sources of DDT contamination. The aim of this study to investigate the source of DDT contamination in Söke soils: historic, direct application of DDT or as in impurity in dicofol. Soil samples were collected from 0-30, 30-60, 60-90 cm depths respectively for the historic usage. Samples were analyzed by GC/MS/MS. *op*2-DDT, *p,p'*-DDE, were found between 0-30 cm depths; *p,p'*-DDE, *p,p'*-DDT were detected in 30-60 cm depths of soils. DDT was predominantly loctated between the 60-90 depths because of the widespread usage in the past. The accumulation of *p,p'* DDE, *o,p'*-DDE and *p,p'* DDT in the topsoil was the result of the recent dicofol applications.

P39

INDOOR DUST AS A SOURCE OF HUMAN EXPOSURE TO HEAVY METALS IN ISTANBUL

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- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 2" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 2" section.

P40

HEAVY AND ESSENTIAL METAL LEVELS OF TAP WATER

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Heavy metals are a major category of globally-distributed pollutants. Heavy metal toxicity is a serious health problem due to the accumulation and their toxicity depends on a lot of factors such as the dose, route of exposure, and chemical species, as well as the age, gender, genetics, and nutritional status of exposed individuals. Heavy metals may be inhaled as dust or fume, can be vaporized and inhaled or they may enter body via food, drinking water and air. They can enter a water supply by industrial and consumer waste, or even from acidic rain breaking down soils and releasing heavy metals into lakes, rivers, and groundwaters. Water is the source and basis of life and there are serious health risks from drinking water with heavy metals such as cadmium (Cd) damaging a specific structure of the functional unit of the kidney; aluminium (Al) contributing to the brain dysfunction; lead (Pb) causing a wide spectrum of health problems; copper (Cu) causing acute gastrointestinal disorders. In the present study, Cd, Al, Pb, Cu and Zn levels were measured by atomic absorption spectrometry in 100 tap water samples obtained 10 different districts from Ankara in Turkey. As the results, means of Cd, Pb, Al, Cu and Zn levels were determined as 0.06±0.05µg/L, 3.74±4.27µg/L, 49.1±13.08µg/L, 16.80±36.68µg/L and 5.90±1.10mg/L, respectively. These measured metal levels in 100 tap water samples from Ankara were at levels lower than the maximum acceptable concentrations (MACs) prescribed by World Health Organization (WHO) and Turkish Standards Institution (TSE).

FOOD SAFETY

P41

QUINOLONE ANTIBIOTIC RESIDUES IN RAW MILK AND CHICKEN LIVER IN KONYA

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The objective of this study was to evaluate the presence of quinolone antibiotic residues (ciprofloxacin, enrofloxacin, marbofloxacin, danofloxacin, difloxacin, flumequin, sarafloxacin and oxolinic acid) in raw milk and chicken liver samples in Konya. A total of 100 samples, including 50 raw milk and 50 chicken liver samples, were examined for quinolone antibiotics. The samples were analyzed by an enzyme-linked immunosorbent assay (ELISA) screening method. Of the 50 chicken liver samples analyzed for residues of quinolone, 17 (34%) were positive

and in one of them the value (147.88 µg/kg) was above the maximum residue limits (MRLs). The mean contamination level was 47.5 µg/kg. None of the milk samples were found to be positive for quinolone residues. All of the analyzed samples except one showed the presence of quinolone residues below the MRLs established by European Union (EU) and Turkish Legislation. So that obtained results from analysis of milk and chicken liver samples were considered to be a positive sign in terms of food safety. Also these analyses are performed as routine according to the National Residue Monitoring Plan of the Republic of Turkey. Therefore, routine drug residues surveillance and monitoring programs in edible animal products like milk, meat and eggs should be continued to ensure food safety in the country.

P42

AMYGDALIN CONTENTS OF APRICOT SEMEN HARVESTED IN MALATYA REGION

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Apricot and its seeds are consumed as food stuff extensively and play an important role in the economy of Malatya. Apricot seeds draw attention toxicologically due to high amount of amygdalin, cyanogenetic glycoside, which is hydrolyzed to produce cyanide. Important poisoning cases especially in children are seen time by time. In this study the simple modified high pressure liquid chromatography (HPLC) method was performed for determination of amygdalin in the raw seeds of 13 kinds of apricot cultivated in Malatya, in the seeds of two types of sulphurated apricot, and two types of roasted apricot. HPLC assay was performed on a reversed-phase C18 column by using phosphate buffer (pH2.8) and methanol with a ratio of 75:25 (v/v) as a mobile phase at a flow rate of 1ml/min with UV detection at 210nm. A standard curve was linear in the range of 20 to 400ppm (r=0.9982). Limit of detection and quantitation were 1.2 and 4.0 ppm, respectively. The established method showed a good overall intra-day and inter-day variation of 0.8-3.8%. The amygdalin contents of apricot seeds were different for each other (<0.08-44.41 mg/g). The amygdalin contents of bitter cultivars such as Paviot (44.4 mg/g) and Alyanak (31.3 mg/g) were found higher than those of sweet cultivars such as Cologlu and Cataloglu (<0.08 mg/g). As a conclusion, scientific contribution was provided to overcome the poisoning with these seeds thanks to the analysis of amygdalin content. With this knowledge some necessary regulations can be set by related authorities.

P43

GENOTOXIC EFFECTS OF MONOSODIUM GLUTAMATE ON MAMMALIAN CELLS IN VITRO

Nazmiye Zengin, Deniz Yüzbaşıoğlu, Fatma Ünal

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 1" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 1" sec tion.

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FORENSIC TOXICOLOGY

P44

WHY WE NEED VALIDATION OF BIOANALYTICAL METHODS IN FORENSIC AND CLINICAL TOXICOLOGY?

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- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 1" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 1" section.

P45

PRESCRIPTION DRUGS CASES OF FATAL POISONING IN POSTMORTEM EXAMINATIONS THE PERIOD 2007-2011 IN CUKUROVA REGION, TURKEY

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The aim of the present study is to describe the evolution of prescription drugs poisoning during a period between 2007 to 2011 based on data collected from result of toxicological analysis in the Turkish Forensic Medicine Council Adana Group Administration. This study was based on autopsies samples sent to the laboratory of forensic toxicology covering the time period between 2007 to 2011. Cases were analyzed according to the following criteria; age, region, month, gender, presence or not of autopsy report and post mortem blood prescription drugs determination. Prescription drugs (benzodiazepines,

barbiturates, antidepressants vs.) were analyzed by immunoassay (Cloned Enzyme Donor Immunoassay [CEDIA]) or gas chromatography-mass spectrometry (GC/MS). Based on the scene investigation, autopsy examination, and toxicology study, 564 of the 7681 deaths were determined to be caused by poisonings. 564 out of the 143 toxicology analysis performed were recorded as prescription drugs. The age range was from 1 to 80 years (mean+/-S.D.= 29.19±18.56). Males predominated in prescription drugs abuse associated fatalities with 79 cases (55.20%) while females represented 64 cases (44.80%). Identification of substances detected in prescription drug related deaths are important in order to observe in drug usage. Based on our retrospective evaluation and analytical screenings of drug related deaths in Cukurova Region reveal that frequently seen substances are benzodiazepines and antidepressants. This study confirmed type of active ingredients in prescription drugs in Cukurova Region.

P46

LEGAL MARIJUANA: SYNTHETIC CANNABINOIDS

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Abuse of products containing synthetic cannabinoids has become a recent concern. Advertised as “herbal incense”, these products are sold at smoke or head shops and over the internet under a variety of names such as Spice, K2, Super Nova, Yucatan Fire, Diamond and Cloud 9. Synthetic cannabinoids are functionally similar to tetrahydrocannabinol (THC) and mimic the effects of marijuana when smoked. However, many of them are stronger than THC and pose a greater health risk. Short-term loss of consciousness, paranoid hallucinations, pallor, tremors and seizures are common symptoms. At least of synthetic cannabinoids may have carsinogenic potantial. The rapid growth in popularity of synthetic cannabinoid use among teens and adults is of serious in our country as all of the world. Some of these compounds were taken the list of prohibited substances in our country since 2010 according to the Early Warning System (EWS). They are preferred because of having an affordable price and no banning by law-enforcement. Formulation of these compounds are new and rapidly evoling. For this reason, there is no a common mass or ultraviolet library of synthetic cannabinoids. It is difficult to detect and identify because they do not show cross-reactivity in drug test assays. In this study we aimed to present a general approach to synthetic cannabinoids.

GENOTOXICITY

P47

MICRONUCLEUS TEST IN HUMAN LYMPHOCYTES CULTURE FOR MONITORING GENOTOXIC EFFECTS OF APIGENIN

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Herbal agents are widely used products in complementary, traditional, and alternative medicine. Flavonoids are the most common group of biologically active polyphenolic compounds in human diet. Apigenin is a natural flavonoid found in high amounts, in parsley, peppermint, lemon, berries and fruits. It possesses free radical scavenning, anticarcinogenic, tumor inhibition and antigenotoxic properties. The present study was planned to determine the possible genotoxic effect of Apigenin in cultured human peripheral blood lymphocytes using *in vitro* micronucleus (MN) assay. Peripheral blood obtained from two healthy young donors, was treated with four different concentrations of apigenin (1,25; 2,50; 5,00; 10,00 µg/ml) for 24 h. A negative, a positive (methyl methanesulfonate) and a solvent (DMSO) control were also applied for each experiment. Apigenin increased the MN frequency in a dose dependent manner (r=0,95), but this increase was not statistically significant. However, Apigenin did not affect cytokinesis-block proliferation index (CBPI). The results suggest that Apigenin did not affect the micronuclei frequency in human lymphocytes culture. In addition, this conclusion needs to be supported by the different genotoxicity tests.

P48

DRUGS AND XENOBIOTICS INDUCED MITOCHONDRIAL TOXICITY

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Mitochondria are one of the membrane-bound organelles of almost all eukaryotic cells. Their primary function is to generate large quantities of energy in the form of adenosine triphosphate. In addition to producing energy, mitochondria perform many substantial metabolic processes such as pyruvate oxidation, fatty acid beta-oxidation, the tricarboxylic acid cycle, urea generation and controlling cell life and death. Unlike other organelles, mitochondria have their own DNAs (mtDNA), which

is a circular, double-stranded and 16,569-bp DNA molecule. mtDNA is more vulnerable to damages than nuclear DNA for a number of reasons, including lack of protective histones, its proximity to free radical compounds generated during oxidative phosphorylation, a generally lower efficiency in DNA repair mechanisms, and a high rate of mitochondrial replication. Mitochondria as the center of cellular bioenergetics are a perfect target for drugs and xenobiotics used in the treatment of various pathological conditions. Metabolites of drugs can bloke the mitochondrial respiratory complexes of the electron chain and cause reactive oxygen species (ROS). ROS start mechanisms of cell death especially in the brain, muscle, heart, liver, kidney and insulin-producing islets of the pancreas in which used oxidative phosphorylation as the primary source of energy. Furthermore, metabolites of drugs can cause mtDNA mutations and oxidative stress. Xenobiotics also cause mitochondrial dysfunction. Since damages to mitochondria is now understood to play a role in the pathogenesis of a wide range of seemingly unrelated disorders, in this review, how mitochondria function and how drugs and xenobiotics damage mitochondria will be discussed.

P49

THE EFFECTS OF FIVE FOOD DYES ON THE LONGEVITY OF DROSOPHILA MELANOGASTER

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In this study, the effects of sunset yellow, ponceau 4R, allura red, brilliant blue FCF, and brown HT on the longevity of *Drosophila melanogaster* was investigated. The effects of different concentrations of these food dyes (0.5 ppm, 1 ppm, 1.5 ppm, and 2 ppm) were separately administered one by one to female and male populations of *Drosophila melanogaster* for application groups. In all of application groups of each population the longevity decreased, depending on the concentrations of food dyes. It was found that the difference between the groups was significantly important ($p<0.05$). We observed that brilliant blue FCF caused the biggest decreased in life span amoung the other food colouring dyes followed by ponceau 4R, sunset yellow, brown HT and allura red during this study.

P50

SOME TEXTILE DYESTUFFS' EFFECTS OVER DROSOPHILA MELANOGASTER'S LONGEVITY AND PERCENTAGE OF SURVIVAL

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In this study, three reactive dyestuffs (reactive red 120, reactive blue 19, reactive black 5) in different concentrations(10 ppm, 20 ppm, 30 ppm, 40 ppm) where are used in textile industry were investigated over *Drosophila melanogaster*'s longevity and percentage of survival. *Drosophila melanogaster* wild type were used in experiments. whether groups have difference between each other have been calculated with using Anova(Multiple Range Test) statistically. İn female individuals applied Reactive Red 120 logevity and percentage of survival have been decreased during concentrations increased, in male individuals it has been increased. İn females exposed to Reactive Blue 19, percentage of survival have been decreased during concentrations increased, longevity has been increased. İn males longevity and also percentage of survival have been decreased during concentrations increased. İn males and females applied Reactive Black 5 decreasing of percentage of survival's dose of 40 ppm has been identifed in comparison with control groups significantly. For this substance, longevity has been decreased for males otherwise it has been increased for females. One of this three dyestuff substance, Reactive Black 5, has been identified which had more effect than others on percentage of survival over *Drosophila melanogaster.* Reactive dyestuffs contain heavy metals can cause these substances to pass through the human body through sweat. As a result of this, chrome ulcer, acute and chronic poisoning, anemia, lung diseases, allergy cases can be seen. İn this study, substances investigated of their effects have been purposed to obtain their toxic and genotoxic effects on human health.

P51

PROTECTIVE EFFECT OF LYCOPENE AGAINST OCHARATOXIN A INDUCED RENAL OXIDATIVE DNA DAMAGE AND APOPTOSIS IN RATS

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Ochratoxin A (OTA), one of the most abundant mycotoxins in the world, is produced by a number of *Aspergillus* and *Penicillium* fungal species as a secondary metabolite. This study was designed to investigate the possible protective role of lycopene against the histopathological changes, DNA damage and apoptotic cell death induced by OTA in the rat kidney. OTA exposure was introduced as 0.5 mg/kg/day for 14 days and lycopene was

applied as 5 mg/kg/day for 14 days. DNA damage and apoptosis was assessed using Comet and TUNEL assays, respectively. OTA treatment caused several histopathological changes including tubular epithelial cell desquamation and detachment, and tubular hyaline cast formation. Lycopene supplementation was only partially protective against OTA-induced histopathological changes. OTA exposure caused marked increases in tail length (80%), tail moment (188%), and tail intensity (87%) vs. control and lycopene administration along with OTA treatment provided significant decreases ($p<0.05$) in comet parameters vs. OTA group. TUNEL analysis revealed a significant increase in the number of TUNEL-positive cells in kidney cortex (~10-fold) and medulla (~3-fold) in OTA group vs. control ($p<0.05$). Lycopene administration alone did not provide any significant difference in the number of TUNEL-positive cells but the mean number of apoptotic cells was significantly decreased in OTA plus lycopene group when compared to OTA group. These results indicate that OTA may cause DNA damage, histopathological changes, and apoptosis in rat kidney and lycopene might be partially protective against the renal toxicity induced by OTA.

P52

EVALUATION OF DNA DAMAGE INDUCED BY THE VACCINE ADJUVANT SQUALENE WITH COMET ASSAY

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Squalene has been used for various applications, especially in vaccine as adjuvant. An immunological adjuvant is a substance employed to increase or to modulate the immune response against an antigen. The genotoxic effects of the vaccine adjuvant Squalane was assessed by comet test in human lymphocytes *in vitro* and in rat lymphocytes *in vivo.* Five different concentrations of squalane (1250, 2500, 5000, 10000 and 20000 µg/ml for human lymphocytes and 0.07, 0.14, 0.28, 0.56 and 1.12 mg/kg (bw: body weight) for rat lymphocytes) were studied. Squalene did not affect significantly the comet tail length (except 2500 µg/mL) and comet tail intensity at all treatments *in vitro*. The results obtained in the Comet test demonstrate that squalene did not induce DNA damage *in vitro*. According to *in vivo* assay; squalene significantly increased the comet tail length at 0.14, 0.28 and 0.56 mg/kg doses and significantly decreased at the lowest and highest doses in Group 1 (1 day after injection). Also, this chemical significantly decreased the comet tail intensity at the lowest and highest doses in Group 1. In Group 2 (14 days after injection), squalene increased the comet tail length (except 1.12 mg/kg) and comet tail intensity (except 0.07 and 1.12 mg/kg) at all treatments. The discrepancy between *in vivo* and *in vitro* models could be explained by mechanistic and metabolic reasons, including repair capacity of DNA lesions. However, further *in vitro* and *in vivo* studies are required to be sure on the effect.

P53

EVALUATION OF CYTOTOXIC AND GENOTOXIC EFFECTS OF FERULIC ACID

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Ferulic acid (4-hydroxy-3-methoxycinnamic acid), a phenolic compound, found in whole grain foods, citrus fruits, banana, coffee, bamboo shoots, cabbage, spinach, eggplant and broccoli, has been suggested to be an antioxidant. Antioxidants are suggested to play an important role in preventing diseases related to reactive oxygen species (ROS) production such as cancer, neurodegenerative and cardiovascular disorders or aging. Recent studies have suggested the protective role of ferulic acid against cancer, cardiovascular disease, diabetes and Alzheimer's disease. In the present study, cytotoxicity of ferulic acid was determined by neutral red uptake (NRU) assay in Chinese hamster ovary cells (CHO) and genotoxic/antigenotoxic effects of ferulic acid was assessed by micronucleus (MN) assay in human lymphocytes. In MN assay, the cells were treated with 5, 10, 25, 50, 100, 200 and 500 µM concentrations of ferulic acid. Hydrogen peroxide, 50 µM, was used as the positive control. According to the study, MN frequencies of ferulic acid treated lymphocytes were found to be decreased when compared to hydrogen peroxide treated lymphocytes. In NRU assay, ferulic acid didn't show cytotoxic activity in the concentrations of 2, 5, 10, 25, 50, 100, 200, 400 µM.

P54

INVESTIGATION OF GENOTOXICITY RISK AND DNA REPAIR CAPACITY IN PATIENTS UNDER ANASTROZOLE THERAPY

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Breast cancer is the worldwide most common cancer in women with an increase of incidence in postmenopausal women. Anastrozole is considered type II, non-steroidal and third generation aromatase inhibitor (AI) that is used in the first line adjuvant endocrine therapy of postmenopausal breast cancer. However, the knowledge on the genotoxic potential of AI's have not been elucidated sufficiently. Therefore this study aims to investigate the DNA damage risk profile of anastrozole by using formamidopyrimidine DNA glycosylase (Fpg) and endonuclease III (endo III) and to measure the individual DNA repair capacity by challenge assay combined with comet assay in breast cancer patients and their controls. For this purpose, postmenopausal women diagnosed with breast cancer and have not been treated yet were selected prospectively as control group (n=12) and patients who received anastrozole (n=6) at least 6 months have been included retrospectively to our study group. No significant difference were found between the two groups as evaluated for DNA damage and repair parameters; basal damage, oxidative base damage, susceptibility to DNA damage and repair capacity ($p>0.05$). However, DNA damage sensivity were observed to increase by age in all studied groups.

P55

EFFECT OF BORON COMPOUNDS ON LEAD AND CADMIUM INDUCED GENOTOXICITY IN CELL CULTURES

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- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 2" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 2" section.

P56

EVALUATION OF GENOTOXIC EFFECTS OF HERBICIDE PENDIMETHALINE BY COMET ASSAY

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Herbicides are some of the compounds most frequently released into the environment because of their widespread use in agriculture. Despite the beneficial effects associated with the use of herbicides, many of these chemicals may pose potential hazards to humans and to nature. Pendimethaline (N-(1-ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzeneamine) a dinitroaniline herbicide, is an inhibitor of growth and cell division and selectively controls weeds. It is classified as a slightly toxic compound by Environmental Protection Agency (EPA). It is also classified in group C (human possible carcinogen) but there is scanty knowledge about its genotoxic effects. In vitro genotoxic effects of different concentrations of pendimethaline on human lymphocytes were investigated by single cell gel electrophoresis (comet) assay. The cells were incubated with 1, 2.5, 5, 7.5, 10, 25, 50, 75, 100 and 1000 µM concentrations of the pendimethaline for 0.5 h at 37°C and DNA damage was compared with that obtained in lymphocytes from the same donor. Hydrogen peroxide, 50 µM, was used as a positive control. Significantly increased DNA damage were found at 1, 2.5, 5, 7.5, 10, 25, 50, 75, 100 and 1000 µM concentrations of pendimethaline by comet assay in human lymphocytes.

P57

ASSESSMENT OF THE CYTOTOXIC, GENOTOXIC AND ANTIGENOTOXIC POTENTIAL OF ROSMARINIC ACID IN IN VITRO MAMMALIAN CELLS

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Rosmarinic acid (RA), which is found in many *Lamiaceae* plants used commonly as culinary herbs such as lemon balm, rosemary, oregano, sage, thyme and peppermint, is a natural phenolic antioxidant. Chemically, rosmarinic acid is an ester of caffeic acid. A number of bioactivities have been assigned to RA, such as antidepressive, hepatoprotective, anti-inflammatory, antiangiogenic and antitumor. RA is also known to possess marked antioxidant properties. In this study the aim was to investigate the cytotoxic, genotoxic and antigenotoxic potential of RA in *in vitro* mammalian cells. Cytotoxicity of RA was assessed by neutral red (NR) uptake test in Chinese Hamster Ovary (CHO) cells and the in vitro genotoxic and antigenotoxic effects of RA were assessed by cytokinesis-blocked micronucleus and alkaline comet assays in human lymphocytes. Tested concentrations of RA (5-200 µg/ml) decreased the viability of CHO cells during 24h exposure dose dependently and IC_{50} value of RA was found as 175 µg/ml. No genotoxicity was observed at low concentrations

(5-50 µg/ml) of RA both in micronucleus and comet assays, whereas the two highest concentrations (100 and 200 µg/ml) caused genotoxicity. RA caused a reduction in the frequency of micronuclei and the extent of DNA damage induced by H_2O_2 especially at high concentrations when compared to cultures treated with H_2O_2 only. These results suggested the protective effects of RA against H_2O_2 induced chromosome breakage and loss and primary DNA damage in cultured human lymphocytes.

P58

MODULATING EFFECTS OF VANILLIC AND TRANS-CINNAMIC ACIDS ON HYDROGEN PEROXIDE INDUCED GENOTOXICITY IN THE COMET ASSAY

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Vanillic acid (4-hydroxy-3-methoxybenzoic acid) which is found in vanilla and trans-cinnamic acid which is the precursor of flavonoids and especially found in cinnamon oil are both natural plant phenolic acids. Phenolic acids are secondary plant products that are widely found in plant-derived foodstuffs and they are suggested to possess many physiological and pharmacological functions. Many studies have suggested that phenolic acids could inhibit the oxidative stress induced by free radicals. In vitro and in vivo experiments have shown that phenolic acids exhibit powerful effects on biological responses by scavenging free radicals and eliciting antioxidant capacity. In the present study, the *in-vitro* genotoxic and antigenotoxic effects of vanillic acid and trans-cinnamic acid were evaluated by alkaline Comet assay. Briefly, after treating human lymphocytes with the vanillic and trans-cinnamic at concentrations of 5-1000 µM with/ without 50 µM H_2O_2, the basic alkaline single cell gel electrophoresis technique was followed. Vanillic acid and trans-cinnamic acid at tested concentrations have not induced DNA damage alone as compared with the controls. Both vanillic and trans-cinnamic acids seem to decrease the DNA damage, since at all concentrations the DNA damage were found to be significantly less than the damage induced by H_2O_2. In conclusion, our results show that both vanillic acid and trans-cinnamic acid protect the lymphocytes against H_20_2 induced genetic damage.

P59

INVESTIGATION OF MUTAGENIC AND ANTIMUTAGENIC PROPERTIES OF SOME EXTRACTS OF AJUGA VESTİTA BOISS. BY SALMONELLA / MICROSOME MUTAGENICITY TEST

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In this study, the petroleum ether, acetone and methanol extracts of *Ajuga vestita* BOISS. were examined in terms of mutagenic and antimutagenic activities by the *Salmonella* / microsome mutagenicity test. Mutagenic experiments were performed in the presence and absence of S9 on *Salmonella typhimurium* TA 98 and TA 100 strains. The results showed that all extracts which tested did not have any mutagenic effect at all concentrations. Moreover, several concentrations of the extracts showed antimutagenic activity against both NaN_3 and Daunomycine mutagens. The antimutagenic activities ranged from 0.75% (TA100–Acetone extract–1000 µg/plate) to 81.49% (TA98–Petroleum ether Extract–500 µg/plate).

P60

MILNACIPRAN, AN ANTIDEPRESSANT DRUG, INDUCED MICRONUCLEUS IN HUMAN PERIPHERAL LYMPHOCYTES

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Milnacipran is an antidepressant agent that selectively inhibits the reuptake of both serotonin and noradrenaline. Milnacipran is an orally administered drug and indicated for the treatment of major depressive disorder. The antidepressant effects of Milnacipran, a serotonin-noradrenaline reuptake inhibitor (SNRI), are similar to tricyclic antidepressants, but serotonin-noradrenaline reuptake inhibitors are better tolerated. In this study, possible genotoxic effect of Milnacipran was investigated using *in vitro* micronucleus (MN) assay in human peripheral lymphocytes. Peripheral blood obtained from two healthy young donors, a man and a woman, was treated with six different concentrations (2,50; 5,00; 10,00; 20,00; 30,00 and 40,00 µg/ml) of Milnacipran for 48 hours. A negative and a positive (mitomycin-C) control were also applied for each experiment. In addition, cytokinesis-block proliferation index (CBPI) was also calculated. According to the results, compared to negative control Milnacipran significantly increased the

frequency of MN in all concentrations (except to 2,50 µg/ml) in a dose-dependent manner. However, Milnacipran did not affect cytokinesis-block proliferation index (CBPI). These data demonstrated that Milnacipran may have clastogenic effect to human lymphocytes *in vitro*.

P61

GENOTOXICITY TESTING OF THE INSECTICIDE SPIROTETRAMAT USING THE PISCINE MICRONUCLEUS TEST

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There are many chemical in environment and their genotoxic effects aren't known. Insecticides are intensively use for increase yield of harvest per unit area. In the present study, genotoxic effects of a widely used insecticide, spirotetramat, were evaluated on a commercially important fish species, *Oreochromis niloticus*, using the micronucleus test and morphological nuclear abnormalities analyses, under laboratory conditions. Fish were exposed to 100, 200 and 500µg/L doses of spirotetramat for 24, 72 and 96 h under laboratory. Ethyl methane sulphonate at a single dose of 10 mg/L was used as positive control. Our results demonstrated that the micronucleus frequencies in erythrocytes increased following spirotetramat treatment with all doses of spirotetramat at the first day. But this increase is not important in istatistically. Treatment with positive control EMS significantly induced the formation of micronuclei in peripheral erythrocytes. Thus did not demonstrate the genotoxic potential of spirotetramat on fish for this doses.

P62

GENOTOXIC EFFECT OF ARSENIC COMPOUNDS IN HUMAN KERATINOCYTES IN CULTURE

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Background: Arsenic is an environmental chemical of toxicological concern today. Arsenic is widely distributed in nature in the form of either metalloids or chemical compounds. It shown to induce chromosomal aberration, genotoxic effect and enhances the clastogenicity and mutagenicity of DNA damage. Aim: The aim of this study was to determine the DNA damaging potential of sodium arsenate, sodium arsenite and arsenic trioxide in human immortalised keratinocytes (HaCat) cells in culture using comet assay. Studies were carried out in parallel with and without buthionine sulfoximine (BSO intracellular glutathione synthesis inhibitor). Methods: The cells are treated with arsenate, arsenite and arsenic trioxide (10 µM) for 24 hr with and without buthionine sulphoximine (10 µM). Comet assay measures the DNA damage in individual cell with and without BSO (10 µM). Results: The mean DNA damage for HaCat cells dosed with arsenate and arsenite at (10 µM) for 24 hr was significantly increased compared to control cells. However, DNA damage induced by 10 µM arsenic trioxide for 24 hr was not significantly different from control. Similarly DNA damage was increased in HaCat cells treated with 10 µM arsenate and arsenite in presence of (10 µM) BSO respectively but not arsenic trioxide all compared to control. Conclusions: Arsenate and arsenite induced significant DNA damage, but not arsenic trioxide which induces oxidative DNA damage in cancerous cells but not in normal human HaCat cells. Arsenite was more cytotoxic and genotoxic than arsenate, as well as they induced the same profile of genotoxicity.

P63

GENOTOXIC EFFECTS OF SOME ANTITUBERCULOSIS DRUG AND MIXTURES IN RATS

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In this study 1.5 months age 40 male albino Wistar rats were used, five groups were formed for one control and four experimental groups. Rats in the control group were administered isotonic sodium chloride solution via gastric gavage during 90 days. For treatment groups, isoniazid at 31.5 mg/kg, rifampicin at 54 mg/ kg, pyrazinamide at 189 mg/kg and isoniazid+ rifampicin+ pyrazinamide mixture at the same doses were given into the stomach with gavage at 90 days. At the end of the study, blood and tissue samples were taken. Samples were evaluated by comet assay and micronucleus techniques. When experimental

groups compared to control group, head intensity of isoniazid, rifampicin and mixture groups decreased; tail intensity and tail migration increased in all treatment groups in the blood samples. Head intensity of pyrazinamide and mixture groups decreased, tail intensity increased, tail migration of pryzinamide, rifampicin and mixture groups increased in the liver samples. In kidney samples, head intensity levels of isoniazid, rifampicin, and mixture groups decreased, tail intensity and tail migration of mixture group increased ($p < 0.001$). According to control group micronucleus analysis of whole blood, micronucleus rate increased in only rifampicin group ($p < 0.001$). The result of the study, it was decided that antituberculosis drugs and their combinations given 90 days caused to double strande breakes of DNA in blood, kidney and liver cells at different degrees; also rifampicin was caused chromosomal damage.

P64

GENOTOXICITY OF COPPER OXIDE NANOPARTICLES IN HUMAN LYMPHOCYTES BY MICRONUCLEUS ASSAY

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Nanotechnology which deals with materials as small as a 1 billionth of a meter, began to enter into physical sciences and engineering at least 20 years ago. Nanomaterials such as Copper oxide nanoparticles (CuO NPs) are increasingly used in various applications such as catalysts, gas sensors, microelectronic materials and cosmetics. Compared to classical substance (in micro scale), the nanoparticles may interact with biological systems by more efficient approaches, but sometimes causing toxicity. The aim of this study was to analyze the genotoxicity of cupper oxide nanoparticles (CuO NPs) in human peripheral lymhocytes by using micronucleus assay. Lymphocytes were exposed to four different concentrations (25, 50, 75 and 100 µg/ml) of CuO NPs (Aldrich, <50 nm) for 48 h. The results show that CuO NPs increased MN frequency at all concentrations ($r=0,94$) compared the negative and solvent control. However, this increase was statistically significant in only 100 µg/ml. CuO NPs decreased cytokinesis block proliferation index (CBPI) at all concentrations but neither of them were statistically significant. MN formation is associated with early events in carcinogenesis. This is supported not only by theoretical considerations but also by a large range of experimental findings. Because of these findings, CuO NPs may have genotoxic potential especially at higher concentrations. However more studies are required to evaluate genotoxic risk of CuO NPs.

P65 (Selected as oral presentation)

THE PROTECTIVE ROLE OF CURCUMIN ON PERFLUOROOCTAN SULFONATE - INDUCED GENOTOXICITY SINGLE CELL GEL ELECTROPHORESIS AND MICRONUCLEUS TEST

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Perfluorooctane sulfonate (PFOS) is a man-made fluorosurfactant and global pollutant. PFOS a persistent and bioaccumulative compound, is widely distributed in humans and wildlife. Therefore, it was added to Annex B of the Stockholm Convention on Persistent Organic Pollutants in May 2009. Curcumin is a natural polyphenolic compound abundant in the rhizome of the perennial herb turmeric. It is commonly used as a dietary spice and coloring agent in cooking and anecdotally as an herb in traditional Asian medicine. In this study, male rats were treated with three different PFOS doses (0.6, 1.25, 2.5 mg/kg) and one dose of curcumin, from *Curcuma longa* (80 mg/kg) and combined three doses of PFOS with 80 mg/kg dose of curcumin by gavage for 30 day at 48 h intervals. Here, we evaluated the DNA damage via single cell gel electrophoresis or Comet Assay and micronucleus test in bone marrow *in vivo*. PFOS induced micronucleus frequency and decreased the ratio of polychromatic erythrocyte to normochromatic erythrocyte in bone marrow. Using the alkaline comet assay, we showed that the all doses of the PFOS strongly induced DNA damage in rat bone marrow and curcumin prevented the formation of DNA damage induced by PFOS.

P66

MUTAGENIC ACTIVITY OF 3 NEWLY SYNTHESIZED BENZOXAZINE DERIVATIVE

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Benzoxazines are chemical compounds that are being synthesized using fenol, formaldehyde and an amine's condensation. Besides their uses in industrial areas, they are reported to have bacteriostatic, neuroprotective and antioxidative effects. In the present study, Ames plate incorporation test has been employed to test the mutagenic activities of the newly synthesized 3 benzoxazine derivative (BS 12, BS16, BS17). All

three compounds are dissolved in DMSO (dimethylsulphoxide) and the cytotoxic doses of the compounds are detected using *Salmonella typhimurium* TA100 strain. Mutagenic activities of the compounds are detected using the same strain. All the three compound showed mutagenic activity in a dose dependent manner. The test system showed that BS17 is the most effective compound. The results of a former assay (rec assay) we conducted in our laboratory showed that BS12, BS16 and BS17 are all have reverse effect. As a result we conclude that these three compounds that have reverse effect also have mutagenic effect and in the light of these results, these compounds may be considered as potential anticancer agents.

P67

A STUDY ON MUTAGENIC EFFECTS OF NOVEL BENZOXASOLE DERIVATIVE COMPOUNDS BY AMES/SALMONELLA MICROSOMAL TEST SYSTEM

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Despite being among the leading class of drugs with chemotherapeutic effects used with therapeutic purposes nowadays, the development of resistance of organisms towards these drugs or possessing unwanted side effects have limited the fields of their use. Thus, research is directed towards novel drug designs of lowered side effects and increased chemotherapeutic effects of drugs. Benzoaxasole and its ring derivatives structurally resemble adenine and guanine heterocyclic bases present in nucleic acid structure. Therefore, assuming that the chemotherapeutic activities of the benzoxasole derivatives takes place by inhibiting the nucleic acid synthesis research on biological activities of these compounds has increased. The present work reports a study on both cytotoxic and mutagenic activities of 4 synthesized novel benzoaxasole derivative compounds (synthesized at Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry) drug-active compound complexes thought to possess a chemotherapeutic effect employing Ames/ Salmonella Microsomal test system using *Salmonella typhimurium* TA 98 ve TA 100 strains. One of the tested compounds(5-nitro-2-(p-nitrobenzyl) benzoxazole) present in TA 98 strain showed mutagenic activity. The other compounds showed negative results. These results would shed light into chemotherapeutically efficient drug-active compound complex designs as a guide to more effective novel anticancer drug development.

P68

PROTECTIVE EFFECT OF RESVERATROL ON SEPSIS-INDUCED DNA DAMAGE IN THE LIVER AND RENAL TISSUE CELLS OF RATS

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Sepsis is a state of disrupted inflammatory homeostasis. Polymicrobial sepsis induced by cecal ligation and puncture (CLP) is the most frequently used model since it closely resembles the progression and characteristic of human sepsis. There is increasing evidence that oxidative stress has an important role in the development of sepsis-induced multi-organ failure. The use of antioxidants seems to decrease the oxidative damage and improve survival in septic rats. Resveratrol (RV) has been reported to have an antioxidant, antiproliferative, and anti-inflammatory properties in various models. It has also been found to inhibit the proliferation of a variety of human cancer cell lines, including breast, prostate, colon, pancreatic, and thyroid. The aim of our study was to investigate the effect of RV on sepsis-induced DNA damage in the liver and renal tissue cells of Wistar albino rats by the alkaline comet assay. DNA damage was found to be high in the sepsis-induced rats compared to the controls and RV-treated sepsis-induced rats. DNA damage in RV-treated sepsis-induced rats was significantly lower than sepsis-induced rats. In conclusion, this study demonstrates that RV reduces sepsis-induced DNA damage in the liver and renal tissue cells and RV might have the possible beneficial effects against sepsis-related multi-organ failures.

P69

ABSENCE OF MUTAGENIC ACTIVITY OF BULK FILL FLOWABLE COMPOSITE

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Flowables are one type of these restorative materials. The second-generation flowables developed since 2000 promise increased mechanical properties and are proposed for use in bulk restorations. Bulk fill flowables are available that may be applied in thicknesses of 4mm with enhanced curing and controlled shrinkage thus reducing the time of the treatment session but the monomers and co-monomers could be released into the oral cavity and pulp due to the lower inadequate polymerization and lead to mutagenicity. Thus the aim of this study was to assess the potential mutagenic potentials associated to extracts from a self-adhesive bulk fill flowable composite Vertise Flow (Kerr Coo.). Disc shaped specimens were prepared by placing them into teflon molds according to the manufacturers' instructions in sterile conditions. The dimensions of the discs were 5 mm in diameter and 2 mm thick. The specimens were eluted in 10 mL dimethyl sulphoxide (DMSO) and the extracts were tested after an incubation period of 24 h at 37^{0}C and 168 h at 37^{0}C Mutagenic effects of the materials were tested on *Salmonella typhimurium* TA 100 strain using the standard plate incorporation assay in the absence of S9 fraction from rat liver. The dose of the material and incubation period as well as the interactions between these factors exhibited no difference on the *Salmonella thyphimirium* revertant colony number. It can be concluded that the bulk fill composite with enhanced polymerization depth 2mm has no mutagenic potential.

P70

ANTIGENOTOXIC EFFECTS OF ALPHA-TOCOPHEROL AGAINST MMC- INDUCED SCE FORMATION

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Vitamin E has anticancer effects as a lipid antioxidant and free radical scavenger. Due to this properties vitamin E has been suggested to reduce cancer risk. Cancer prevention studies with vitamin E have primarily utilized the variant of α-tocopherol because of its superior activity in the classical fertility-restoration assay and its higher blood levels over other tocopherols. In this study, potential antigenotoxic effects of α-tocopherol was investigated against mitomycin C's (MMC, antitumoral agent) genotoxic effect. MMC is known as an inducer of SCE (sister chromatid exchange) formation. The induction of SCEs by MMC may reflect the action of basic cellular DNA repair processes. Human lymphocytes were treated with MMC for 24 hours and three different treatments were used for investigating antigenotoxic effects of the α-tocopherol: 1) MMC and α-tocopherol was simultaneously added tlymphocytes as co-treatment (24 h); 2) α-tocopherol was added 1h before MMC as pre-treatment (25 h) and 3) α-tocopherol was added 1h after MMC as post-treatment (23 h). 40% ethanol was used as solvent control. No significant difference was observed between negative and solvent control. All concentrations (25, 50, 100 and 200 µg/ml) of α-tocopherol showed statistically significant reduction of SCE formation compared to positive control (MMC) at 23 and 25 hours. At simultaneous treatment (24h), only 200 µg/ml had statistically significant effect. These results indicated that α-tocopherol has a reductional effect against MMC induced SCEs especially at pre-treatment and post-treatment than simultaneous treatment in human lymphocyte culture.

P71

GENOTOXICITY TESTING USING THE MICRONUCLEUS AND COMET ASSAYS IN NORMAL HUMAN CELL BASED 3D EPITHELIAL MODELS

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Safety assessment of new products for human use requires genotoxicity testing to ensure non-carcinogenicity. Current in vitro assays have low specificity resulting in a high rate of false positives. To determine the biological relevance of positive in vitro genotoxicity results, in vivo assays are conducted. However, in vivo genotoxicity testing of cosmetic ingredients was banned in 2009 by the 7th Amendment to the Cosmetics Directive.3D reconstructed human tissue models, which have in vivo-like barrier function and metabolism and which allow for topical exposure, are considered as models with improved biological relevance compared to 2D cultures. Toward this end, the Reconstructed Skin Micronucleus (RSMN) and Comet assays (CA) that utilize MatTek's highly differentiated EpiDerm™ tissue model have been adapted for use with tracheal, vaginal, oral, and corneal tissues. RSMN assay results show statistically significant dose-dependent increases in cells containing micronuclei (MNC) for 9 direct genotoxins and 6 genotoxins that require metabolic activation, and no increases for 4 non-genotoxins. In addition, CA results show statistically significant increases in % tail DNA after treatment with a model genotoxin. Utilizing the RSMN protocol with tracheal, vaginal, oral, and corneal tissue models, statistically significant increases in MNC (0.3 to 1.2%) were observed after treatment with genotoxins. Similarly, CA results with tracheal, vaginal, oral, and corneal tissue models showed statistically significant increases in % tail DNA. Hence, the EpiDerm RSMN and CA assays can be applied to other in vitro human epithelial tissue models to predict genotoxic effects following real life exposure conditions.

P72

GENOTOXIC AND OXIDATIVE DAMAGE POTENTIALS IN HUMAN LYMPHOCYTES AFTER EXPOSURE TO TERPINOLENE IN VITRO

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Terpinolene (TPN) is a monocyclic monoterpene found in the essential oils of various fir and pine species, as well as plants such as *Manilla elemi*, *Nectranda elaiophora*, and *Dacrydium colensoi*. Recent reports indicated that these monoterpenes could exhibit antioxidant effects in several models. However, so far, the nature and/or biological roles of plenty of TPN have not been elucidated exactly. The aim of this study was to investigate the genetic and oxidative effects of TPN in cultured human blood cells (n=3) for the first time. TPN was added into culture tubes at various concentrations (0 to 200 mg/L) for 72h. Sister chromatid exchanges (SCE) and micronucleus (MN) tests were used for genotoxic influences estimation. In addition, biochemical parameters (total antioxidant capacity [TAC] and total oxidative stress [TOS]) were examined to determine oxidative effects. In our in vitro test systems, it was observed that TPN had no mutagenic effects on human lymphocytes. On the other hand, TPN (at 10, 25, 50 and 75 mg/L) treatment caused increases of TAC levels in human lymphocytes without changing TOS levels. In conclusion, TPN can be a new resource of therapeutics as recognized in this study with their non-mutagenic and antioxidant features.

P73

ASSESSMENT OF CYTOGENETIC AND OXIDATIVE EFFECTS OF A-PINENE IN CULTURED WHOLE HUMAN BLOOD CELLS

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Alpha-pinene, a bicyclic monoterpene, is present in the oils of many species of coniferous trees, most notably the pine, and is known for its diverse biological properties such as antimicrobial, anti-inflammatory, antiproliferative and antioxidant. However, there are limited data on the cytogenetic and antioxidant effects of a-pinene. The purpose of this study was to investigate the genetic safety and oxidative effects of a-pinene cultured human blood cells (n=3). Genotoxicity was assessed by using micronucleus (MN) and chromosomal aberration (CA) tests. In addition, we measured total antioxidant capacity (TAC) and total oxidative stress (TOS) levels in plasma samples to determine oxidative stress. Human peripheral lymphocytes were treated in vitro with varying concentrations of a-pinene (0 to 200 mg/L). Our results showed that a-pinene did not cause any statistically important changes in the rates of studied genotoxicity endpoints. But dose-dependent alterations were observed in TAC and TOS levels. a-pinene treatment caused increases of TAC levels (at 25 and 50 mg/L) and treatment decreases of TOS levels (at concentrations of over 150 mg/L) on human lymphocytes. As conclusion, the findings of present study, confirm for the first time that a-pinene could be a significant source of natural antioxidant compounds that may have beneficial health effects.

IMMUNOTOXICOLOGY

P74

INVESTIGATION OF CONTACT SENSITIZATION POTENCY OF FRAGRANCE MIX AND FRAGRANCE MIX INGREDIENTS BY USING EX VIVO NONRADIOCTIVE LOCAL LYMPH NODE ASSAY

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- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 1" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 1" section.

P75

INVESTIGATION OF THE DERMAL SENSITIZATION POTENTIAL OF COSMETIC MATERIALS BY USING THE EX VIVO LOCAL LYMPH NODE ASSAY- BRDU

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Fragrance mix and balsam of peru are commonly used in cosmetic products. In the present study, *ex vivo* LLNA-BrdU method was used to evaluate the contact sensitizing potential of these cosmetic mixtures. Fragrance mix and balsam of peru at the concentrations of 0, 0.5, 5, 25, 50% in acetone:olive oil (4:1 v/v) (AOO) were applied topically on the dorsum of both ears of the 8-12-week-old female Balb/c mice. The stimulation index values and estimated concentration (EC3) values were calculated and potency classification was found for each mixture. According to the results of *ex vivo* LLNA-BrdU assays, EC3 values were found to be 3.09% (moderate) for balsam of peru and 4.44

% (moderate) for fragrance mix. Th1 cytokines (IL-2, IFN-γ) and Th2 cytokines (IL-4, IL-5) releases from lymph node cell culture as non-radioactive endpoints were also investigated. Cytokine analyses results indicate that both Th1 and Th2 cytokines are involved in the regulation of murine contact allergy and can be considered as useful endpoints.

IN VITRO TOXICOLOGY

P76

CARVACROL, A PHENOLIC MONOTERPENE, IS A POTENT ANTICANCER AND CYTOTOXIC AGENT

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Carvacrol (CVC), a phenolic monoterpene, is present in the many essential oils of medicinal and aromatic plants and has attracted attention because of its beneficial biological activities, especially its antioxidant feature. According to our best knowledge, its anti-proliferative, antioxidant and cytotoxic effects on cultured primary rat neuron cells and N2a neuroblastoma cell line has never been explored although various biological activities of CVC have been demonstrated. Therefore, the purpose of this study was to investigate the genetic, oxidative and cytological effects of different concentrations of CVC on cultured primary rat neuron and N2a neuroblastoma cells line via various actual methods. Our results indicated that CVC (at 100, 200 and 400 mg/L) treatment caused decreases of total antioxidant capacity (TAC) levels in N2a neuroblastoma cell line compared to cultured primary rat neuron cells. Also, CVC (at 200 and 400 mg/L) treatment caused increases of total oxidative stress (TOS) levels in N2a neuroblastoma cell line compared to primary rat neuron cells. After 24 h treatment, 3-(4,5 dimetylthiazol -2-yl) - 2,5 diphenlytetrazolium bromide (MTT) assay showed that 200 and 400 mg/L of CVC significantly reduced the proliferation rates in both cultured primary rat neuron and N2a neuroblastoma cells. On the other hand, the mean values of the total scores of cells showing DNA damage (for comet assay) was not found significantly different from the control values in both cells ($p>0.05$). These findings demonstrate the remarkable potentiality of CVC as a valuable source of antioxidants, which possess original anticancer abilities in the treatment of cancer.

P77

CYTOTOXIC AND ANTICANCER EFFECTS OF THYMOL

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Thymol (5-methyl-2-isopropylphenol) (TYM), is a monocyclic monoterpene present in the essential oils of *Thymus* and *Origanum* plants has reported for its antioxidant, antispasmodic, antibacterial, radioprotective and anti-inflammatory effects. The beneficial health properties of TYM have encouraged us to look into its anticancer activity. To our best knowledge, reports are not available on the anticancer activity of TYM in cultured primary rat neuron and N2a neuroblastoma cells. Therefore, the present study is an attempt towards exploring the potential anticancer activity of TYM, if any, on cultured primary rat neuron and N2a neuroblastoma cells. Our results indicated that TYM (at 10, 25 and 50 mg/L) treatment led to increases of total antioxidant capacity (TAC) levels on cultured primary rat neuron cells compared to N2a neuroblastoma cells. Also, TYM (concentrations of over 100 mg/L) treatment led to increases of total oxidative stress (TOS) levels in both cell types. The mean values of the total scores of cells showing DNA damage (for comet assay) was not found significantly different from the control values in both cells ($p>0,05$). On the other hand, after 24 h treatment with TYM, 3-(4,5 dimetylthiazol -2-yl) - 2,5 diphenlytetrazolium bromide (MTT) assay showed that TYM application significantly reduced the cell viability rates in cultured primary rat neurons (only at 400 mg/L) and N2a neuroblastoma cells (at 200 and 400 mg/L). Summarizing, our data suggest that TYM represents a promising anticancer agent to improve brain tumors therapy.

P78

IN VITRO EFFECTS OF PHENOLIC COMPOUNDS PELARGONIDINE AND GALLIC ACID ON ACRYLAMIDE INDUCED GENOTOXICITY

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Acrylamide (AA) is genotoxic and has been classified as a probable human carcinogen. Acrylamide is used in the industry and can be a by-product in high-temperature food processing. It is reported to interact with DNA, but the mechanism of this interaction is not fully understood. Acrylamide is mainly neurotoxic in experimental animals as well as humans and has also been shown to be mutagenic and carcinogenic. The aim of this study was to investigate the influence of Pelargonidin (PG) and Gallic acid (GA) on genotoxic effects of Acrylamide (AA) on human lymphocytes cultured. The sister chromatid exchange (SCE), chromosome aberration (CA) and micronucleus (MN) tests were used for investigating the effects genotoxicity of AA. Replication index (RI) and mitotic index (MI) were also calculated to determine the cytotoxicity of AA. In addition, the anti-genotoxic effects of PG and GA against genotoxicity of AA

were also investigated in the absence and presence AA. These results demonstrate the clastogenic activity of AA in vitro and suggest that its specific effects depend on the dose. AA was observed as a cytotoxic and genotoxic compound. In the, CA, MN, SCE, RI, MI test with (human blood lymphocytes cultured) in vitro a significant decrease of genotoxicity frequency induced by acrylamide was observed in the presence of gallic acid. It is obvious that GA with antioxidative activity may reduce the genotoxicity induced by AA human lymphocytes cultured. GA was not genotoxic and cytotoxic however, it had an antigenotoxic effect via decreasing the effects of AA. PG was not genotoxic and cytotoxic. So, we concluded that GA showed a stronger antimutagenic effect than PG according to the frequency of CA, MN, SCE, MI and RI.

P79

RESVERATROL AMELIORATES METHOTREXATE-INDUCED HEPATOTOXICITY IN RATS VIA INHIBITION OF LIPID PEROXIDATION

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Hepatotoxicity is one of the major complications of methotrexate (MTX) therapy. This study was carried out to evaluate the possible protective effect of resveratrol (trans-3,5,4'-trihydroxystilbene, RVT) against MTX-induced hepatotoxicity. Rats were randomly divided into four groups as control, MTX-treated (7 mg/kg/day, intraperitoneally [i.p.], once daily for 3 consecutive days), MTX + RVT-treated (20 mg/kg/day, i.p), or RVT-treated. First dose of RVT was administrated 3 days before the MTX injection and continued for 3 days. Histopathology of liver was evaluated by light microscopy. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were used as biochemical markers of MTX-induced hepatic injury. The levels of thiobarbituric acid-reactive substances (TBARS, a marker of lipid peroxidation) and activities of hepatic antioxidant enzymes such as catalase (CAT) and glutathione S-transpherase (GST) were used to analyze oxidative stress-mediated lipid peroxidation in liver sections. Our results showed that MTX administration significantly increased ALT, ASP, and ALP levels. TBARS, CAT, and GST levels were also markedly increased in liver after MTX administration. RVT treatment significantly prevented MTX-induced hepatotoxicity, as indicated by AST, ALT and ALP levels, and liver histopathology. Moreover, administration of RVT significantly decreased the elevated levels of TBARS, and CAT and GST activities in the liver compared to MTX-treated group. These results revealed that RVT may have a protective effect against MTX-induced hepatotoxicity by inhibiting oxidative stress-mediated lipid peroxidation. Consequently, RVT treatment might be a promising strategy against MTX-induced hepatotoxicity.

P80

POTENTIAL ROLE OF GLOBULARIFOLIN IN CELL SURVIVAL AND INFLAMMATION

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The nuclear factor-kB (NF-κB) is a key participant in innate and adaptive immune responses, induced by a large number of stimuli including bacterial and viral molecules, inflammatory cytokines, as well as cellular and oxidative stress. Activation of NF-kB accelerates the pro-inflammatory response by activating other pro-inflammatory pathways. NF-kB is considered not only promoting the inflammatory response but also its resolution. Some medicinal plants that find use in folkloric medicine for anti-inflammatory purposes are reported to contain iridoid glycosides. Globularifolin, isolated from *Globularia cordifolia,* is an acylated iridoid glycoside. As no anti-inflammatory activity data are present in the literature, aim of this study was to investigate the cytotoxic effect of globularifolin and the effect on NF-kB activity. Cell viability assay was conducted on THP-1 cells, a myelomonocytic cell line, and measured by the Cell-Titer Blue assay, after 24, 48 and 72h incubations with 7.8-1000µM globularifolin. Influence of 6.25-200µM globularifolin on NF-kB expression in unstimulated and LPS stimulated THP-1Blue cells was quantified using Quanti-Blue assay. Viability assay has proved that globularifolin had no toxic effect in this concentration range. Conversely, proportional to the dose, globularifolin increased cell growth by 5-65% ($p<0.01$). In unstimulated cells, 50-200µM globularifolin induced a significant NF-kB expression. By contrast in LPS-stimulated cells, the higher concentrations suppressed NF-kB expression dose-dependently and a significant decrease was observed in the presence of 200µM globularifolin. These results imply that globularifolin might represent a potential immunomodulatory agent and justify further studies employing more complex *in vitro* models such as peripheral blood mononuclear cells.

P81

ASSESMENT OF CYTOTOXIC EFFECTS OF COBALT CHLORIDE AND ARSENITE TO VERO CELLS AND PROTECTIVE EFFECT OF ZINC CHLORIDE: A PRELIMINARY STUDY

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The objective of the present study was to investigate the possible time- and dose-dependent cytotoxic effects of cobalt chloride and sodium arsenite to Vero cells. The cultured cells were incubated with 10 different concentrations of cobalt chloride (0.5 to 1000 µM) or arsenite (0.05 to 120 µM) for different time periods and cytotoxicity was determined by MTT assay. Possible protective effects of $ZnCl_2$ and vitamin E were also tested. A gradual decrease in cell proliferation was observed at concentrations ~≥200 µM of $CoCl_2$ at incubation periods of 24, 48, 72, and 96 h. Treatment of cells with 500 and 1000 µM cobalt chloride caused a significant decrease in cell survival. Pretreatment of cells with $ZnCl_2$ for 4 or 24 h provided significant protection against $CoCl_2$-induced cytotoxicity. However, vitamin E was not protective. Arsenite also caused a dose- and time-dependent decrease in cell survival following 24 or 48 h incubation. A sharp decline in cell proliferation was noted ≥40 µM concentrations of arsenite following 24 h of incubation. Cytotoxicity was more pronounced at concentrations ≥20 µM of arsenite at 48 h. A slight increase in cell proliferation was noted at 0.05 and 0.1 µM concentrations of this metal for 48 h. However, neither $ZnCl_2$ nor vitamin E pretreatment of cells caused a protection against cytotoxic effect of arsenite. Regarding renal toxicity of these metals, results obtained in this study should be considered in detail in order to define exact mechanisms of toxicity in Vero cells.

P82

ANTIOXIDANT ACTIVITY OF SEVERAL HERBAL DIEATARY SUPPLEMENTS

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The aim of the present study is to investigate potential antioxidant activity of various herbal dietary supplements and herbal molecules *in vitro* in human erythrocytes. Formation of ROS in erythrocytes was detected by a fluorescence probe, DCFH-DA. The cells were incubated with selected dietary supplements namely Astragalus Root Extract, Black Cohosh Root Extract, Dong Quai, Grape Seed Extract, Green Tea Leaf Extract, Gotu Kola, Isoflavones, Saw Palmetto Berries, Spirulina, St. John's Wort, Tribulus Terrestris, Valerian Root Extract. Afterwards their potential prooxidant or antioxidant effect was evaluated by formation of ROS *in vitro*. Spirulina was found to be the only prooxidant herbal supplement where all other products found to have antioxidant properties with varying efficacy. Our results indicate that Green tea and St. John's Wort was the most active antioxidants among tested ones. Several marker compounds were also tested in erythrocytes in the presence or absence of oxidative challenge. Galangin is found to have antioxidant activity whereas apigeninin were found to have prooxidant activity.

P83

EVALUATION OF GENOTOXIC AND CYTOTOXIC ACTIVITIES OF SOME HYDRAZONE DERIVATIVES AS NEW ANTICANDIDAL AND ANTICANCER AGENTS

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In vitro toxicity tests are well-accepted and developing techniques for pharmaceutical industry. Performing *in vitro* models to predict the toxicity of drug candidates on humans is the first priority in the early stages. As with all drug candidates, it is required to evaluate genotoxic and cytotoxic properties of anticandidal drugs by using in vitro models in the early stages of drug research. In this study, it is aimed to investigate the genotoxic and cytotoxic activities of novel and effective hydrazone compounds, which were synthesized in the department of pharmaceutical chemistry and was proved to have antimicrobial activity by microdilution broth test, by using *in vitro* models. The compounds were tested *in vitro* against various *Candida* species and compared with ketoconazole for their antifungal activity. Genotoxicity of the most effective anticandidal compounds was evaluated by umuC assay using umuC easy CS kit and Ames assay using Ames MPF™ 98/100 mutagenicity assay sample kit. Furthermore, all compounds were evaluated for their cytotoxic effects using the In Cytotox-XTT 1 parameter kit against A549 cancer cell lines and NIH3T3 cell lines. Compound 8 was the most effective antifungal derivative against *C. albicans* (ATCC-90028). It did not show any genotoxicity in the presence/absence of S9 enzyme fraction against *Salmonella typhimurium* strains TA 98/100 with Ames MPF test and TA1535/pSK1002 with umu-C easy assay. Compound 5

can be identified as the most promising anticancer agent against A549 cancer cell lines due to its inhibitory effect on A549 cell lines and low toxicity to NIH3T3 cells.

P84

AN INVESTIGATION OF THE EFFECTS OF CINNAMOMUM BARK EXTRACTS ON CYTOTOXICITY, APOPTOSIS AND GENE EXPRESSION IN HUMAN LEUKEMIA CELL LINE

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Cinnamon is a widely used food spice. Recently cinnamon bark and leave extracts have been shown to exhibit diverse biological functions including anti-inflammatory, antioxidant, antimicrobial, antidiabetic and antitumoral effects by several in vitro and in vivo studies. In this study, we investigated the effects of the *Cinnamomum cassia* bark extracts on cytotoxicity, apoptosis and the expression changes of apoptosis pathway and cell cycle genes in a human leukemia (HL-60) cell line. For this aim methanolic extract of *Cinnamomum cassia* was sequentially partitioned into hexane, chloroform, ethyl acetate, and water. WST-1 assay was used for determination of cytotoxicity, and Annexin V and JC-1 assays were undertaken in order to analyse the apoptotic effect, at 24 hours intervals for three days. As we found hexane extract was the most effective extract exhibiting marked cytotoxicity (IC_{50}: 4.48 µg/ml) against HL-60 cell line, this extract was used for apoptosis and gene expression analysis. The hexane extract induced apoptosis and also showed significant cytostatic effect. We found increased expression of genes which are responsible for cell cycle pathways as: CCNG2, CCNG1, CCNH, CCNF, ATR, CDK5R1, CDKN2D, CDK5RAP1, CHEK1, CHEK2, and BAX. Increased expression of genes which induces apoptosis were found as: TNFRSF25, TNFRSF1A, CASP4, CASP1, TRADD, CD27, CD40LG, FAS, TRAF2. Further studies to elucidate the molecular mechanism of these genes' expressions at protein levels would be worthwhile. Our results consider the hexane extract of cinnamon bark as a promising agent in the field of developing cancer chemopreventive agents.

P85

ANALYSIS OF THE VALIDATED EPIDERM SKIN CORROSION TEST (EPIDERM SCT) AND ITS PREDICTION MODEL FOR SUB-CATEGORIZATION ACCORDING TO THE UN GHS AND EU CLP

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Skin corrosion refers to the production of irreversible damage to the skin manifested as visible necrosis through the *epidermis* and into the *dermis*, following the application of a test material. OECD has adopted 2 ECVAM-Validated reconstructed human skin models (EpiDerm and EPISKIN) for testing skin corrosion (OECD TG 431). However, OECD TG 431 currently does not satisfy international labeling guidelines for transport of dangerous goods since none of the methods were adopted with prediction model allowing for sub-categorization. Current poster evaluates data obtained with EpiDerm Skin Corrosion Test (SCT) for ability to discriminate between UN GHS 1A, 1B/1C classes and non-corrosives. Data obtained during the ECVAM validation study (Phase I and Phase III) plus additionally tested chemicals were analyzed based on the MTT viability assay and the 3 minute exposure period. For the dataset containing > 80 chemicals (with known in vivo GHS classifications), the 3 min endpoint produced sensitivity > 90% for predicting sub-category 1A.It has been demonstrated, that the MTT-reducers require special attention and additional testing using freeze-killed tissues at both 3 min and 1h endpoint is necessary. EpiDerm SCT provides an *in vitro* procedure allowing the identification of non-corrosive and corrosive substances and mixtures. As demonstrated by results obtained in this study, it also allows a partial sub-classification of corrosives into sub-bcategory 1A, 1B/1C and no category. Adoption of the 3 min endpoint onto the EpiDerm SCT prediction model to identify severly corrosive substances would lead to significant reduction in animal use for corrosion sub-group package labeling.

P86

DEVELOPMENT OF THE EPIOCULARTM EYE IRRITATION TEST FOR HAZARD IDENTIFICATION AND LABELLING OF EYE IRRITATING CHEMICALS IN RESPONSE TO THE REQUIREMENTS OF THE EU COSMETIC DIRECTIVE AND REACH LEGISLATION

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The recently implemented 7th Amendment to the EU Cosmetics Directive and the EU REACH legislation have heightened the need for in vitro ocular test methods. To address this need, the

EpiOcular™ eye irritation test (EpiOcular-EIT), which utilises EpiOcular tissue model, has been developed. The EpiOcular-EIT is based on an initial training set of 39 liquid and 21 solid test substances and uses a single exposure period and a single cut-off in tissue viability, as determined by the MTT assay. A chemical is classified as an irritant (GHS Category 1 or 2), if the tissue viability is ≤ 60%, and as a non-irritant (GHS unclassified), if the viability is > 60%. EpiOcular-EIT results for the training set, along with results for an additional 52 substances, discriminated between ocular irritants and non-irritants with 98.1% sensitivity, 72.9% specificity, and 84.8% accuracy. To ensure the long-term commercial viability of the assay, EpiOcular tissues produced by using three alternative cell culture inserts were evaluated in EpiOcular-EIT with 94 chemicals. The assay results obtained with the initial insert and the three alternative inserts were very similar, as judged by correlation coefficients (r^2) that ranged from 0.82 to 0.96. EpiOcular-EIT was pre-validated in 2007/2008, and is currently involved in a formal, multi-laboratory validation study sponsored by COLIPA under the auspices of ECVAM. The EpiOcular-EIT, together with EpiOcular's long history of reproducibility and proven utility for ultra-mildness testing, make EpiOcular a useful model for addressing current legislation related to animal use in the testing of potential ocular irritants.

P87

CYTOTOXICITY STUDY ON CATIONIC SOLID LIPID NANOPARTICLES AS DNA DELIVERY SYSTEM

Hasan Akbaba[1], Mustafa Kotmakchiev[2], **Devrim Demir Dora**[3], Ceren Korkmaz[4], Gülten Kantarcı[1]

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 1" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 1" section.

METAL TOXICOLOGY

P88

RESPONSE OF THE ENDOCRINE SYSTEM AND THE OTHER BLOOD PARAMETERS IN THE NILE TILAPIA EXPOSED TO CADMIUM AND LEAD

Ceren Özlem Gürler, Zehra Doğan, Ali Eroğlu, Kadir Kocalar, Emine Baysoy, Sedefgül Yüzbaşıoğlu Arıyürek, Gülüzar Atlı, Mustafa Canlı

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The aim of this study was to determine the alteration in levels of hormone (cortisol, FSH, LH, TSH, T3, T4, prolactin) and blood parameters (glucose, cholesterol, total protein, ALT, AST, AP, LDH, trigliserit, lipase) in Nile tilapia following acute (48 h) exposure to cadmium and lead. One year old *O. niloticus* were obtained from fish culturing pools of Cukurova University. Fish were treated with 20 µM of Cd ($CdCl_2.H_2O$) and Pb ($PbNO_3$) for 48 hours. A total of eight fish were used for each group. At the end of the exposure period, fish blood was obtained from the caudal vessel and was centrifuged at 3000 rpm for 5 min. Then, the blood plasma was transferred to eppendorf tubes. Plasma biochemical parameters and hormone levels were measured by a coulter instrument (Beckman Coulter Unicel DxC 800) using appropriate kits. No fish mortality occurred within 48 h. Acute metal exposures decreased the levels of all the hormones comparing to control levels. However, significant alterations occurred only in glucose and cholesterol levels following acute exposure of fish to cadmium and lead. Cholesterol levels decreased by both metal exposures, though glucose level increased in cadmium exposed fish. Whether significant or not, data showed that acute metal exposures caused alterations in the levels of hormones and the other plasma parameters of fish, suggesting their sensitivity to metal exposures. It seems that cholesterol, glucose and hormone levels of fish blood plasma may represent environmental metal stress and thus may be useful as sensitive indicators in ecotoxicological studies.

P89

EVALUATION OF TRACE ELEMENT STATUS IN PATIENTS WITH PROSTATE CANCER, BENIGN PROSTATIC HYPERPLASIA AND CHRONIC PROSTATITIS

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A growing body of evidence has indicated that many trace elements play an important role in a number of biological processes by activating or inhibiting enzymatic reactions. The aim of this study was to investigate the levels of trace elements in serum of patients with prostate cancer (PCa), benign prostatic hyperplasia (BPH), chronic prostatitis (CP), and control subjects in Turkish men. Serum samples were provided by 42 subjects with PCa, 44 patients with BPH, 25 CP patients, and 40 control individuals. Chromium (Cr), Manganese (Mn), Iron (Fe), Zinc (Zn), Copper (Cu), Magnesium (Mg), Cobalt (Co), Vanadium (V), Molybdenum (Mo), and Selenium (Se) in serum samples were analyzed using atomic absorption spectrometer (AAS). Significantly higher serum concentrations of Mn, Cu, Mo

and lower levels of V, Se were found in PCa patients as compared to control subjects. Moreover, significantly lower serum levels of V, Mg, Se were determined in BPH and CP patients as compared to control individuals. However, significantly an increase of Mo level was found in patients with BPH and CP in comparison to control samples. The levels of Cr and Fe were not significantly different in patients compared to control subjects. The results obtained indicate that the higher concentrations of Mn, Cu, and Mo might be involved in the progress of prostatic diseases. Our findings suggest that the administration of Se, Mg, and V as dietary agents may be beneficial in the prevention and treatment of human prostatic diseases.

P90

ASSESSMENT OF CR AND NI LEVELS IN PLACENTA BY GRAPHITE FURNACE ATOMIC ABSORPTION SPECTROMETRY

Enes Arıca, Zeynep Seda Eren, Yasemin Kartal, Vugar Ali Turksoy, Tulin Söylemezoğlu

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 4" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 4" section.

P91

EFFECTS OF METAL EXPOSURES ON METALLOTHIONEIN LEVEL IN XENOPUS LAEVIS TADPOLES

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The effects of cadmium (Cd), lead (Pb), copper (Cu), and their mixtures on metallothionein (Mt) concentrations in *Xenopus laevis* tadpoles as a test organism has been investigated because of metal contamination of drinking water supplies has been identified as a problem in many European countries. For this aim, acceptable limit values ??for drinking water directives of the European Union (EU) (80/778/EEC; revised 98/83/EC) and the average lethal concentration (LC_{50}) ??values obtained through 96 h tests were selected to exposure. The stage 46 tadpoles were exposed to 0.005 (EU legistation value), 0.52 (LC_{50}/10), 2.59 (LC_{50}/2) and 5.18 ppm (LC_{50}) for Cd; 0.01 (EU legistation value), 12.3 (LC_{50}/10), 61.53 (LC_{50}/2) and 123.05 ppm (LC_{50}) for Pb; 0.01, 0.085 (LC_{50}/10), 0.425 (LC_{50}/2) and 0.85 ppm (LC_{50}) for Cu and the concentration of double (1:1) or triple (1:1:1) mixtures by 96 h static renewal test system. In addition, tadpoles were exposed to metals or their mixtures for 24 h period using LC_{50} and LC_{50}/2 concentrations of 96 h tests. The Mt concentrations were determined spectrophotometrically. As a result of 96 h and 24 h applications, Mt levels were increased in relation to concentration and the results were found statistically significant compared to control animals (p<0.05 and p<0.01). The study results indicated that tested metals have toxic potential on tadpoles and they caused to Mt induction. In particular, mixtures of metals even in low doses are increased toxicity. In addition, results of the study indicated that *X. laevis* tadpoles are appropriate organisms for determining the toxicity of selected metals and use of Mt for this aim is an useful biochemical marker.

P92

EMBRYOTOXIC EFFECTS OF NANO-TiO_2 IN ZEBRA FISH (DANIO RERIO)

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This study evaluates toxic effects of laboratory synthesized and 1% or 3% Mn doped nano titanium dioxide (nano-TiO_2) on embryonic development of zebrafish (Danio rerio). The zebrafish embryos on developmental period of 8 to 120 hpf were exposed to serial concentrations of TiO_2 samples after sonification for 20 minutes. Embryo toxic effects were evaluated on 24 hpf and 120 hpf. Heart rate, developmental malformation and mortality were evaluated in the study. Particle size distributions of the each sample were also analyzed with NanoSight NS500. Particle size distribution results showed that mean nanoparticle size ranged between 42.3 (±2.03) nm to 197.5 (5.5) nm within 1000 ppm stock solution of 1% Mn doped TiO_2 after sonification while nonsonified samples distributed 53.0 (±3.0) mn to 191 (±9.5) nm particle size. Particle size distribution was recorded as 54.7 (±2.0) nm to 194 (±7.6) nm and 44.7 (±3.7) nm to 188 (±10) nm for 1000 ppm stock solution of 3% Mn doped TiO_2 before and after sonification, respectively. The heart rate of fish embryos in 24 hpf significantly inhibited after exposure to tested chemicals for both samples. Also malformation was increased

with the exposure doses on both chemicals and 3% Mn doped and sonified samples were more effective than 1% Mn doped and sonified samples. Results showed that NPs of laboratory synthesized TiO_2 may have toxic potential on fish development in ecosystem. Embryonic developmental malformation assays of zebrafish may suitable for determining nano-TiO_2 toxicity.

P93

EFFECT OF METALLOTHIONEIN 2A POLYMORPHISM ON TOXIC METAL LEVELS IN HUMAN BIOLOGICAL SAMPLES

Tülin Söylemezoğlu, Zeliha Kayaaltı

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 3" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 3" section.

P94

ASSOCIATION BETWEEN AUTISM AND ARSENIC, LEAD, CADMIUM AND MANGANESE LEVELS IN HAIR AND URINE: A CASE REPORT

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Autism is a neurodevelopmental disorder characterized by stereotypic/repetitive behavior and impaired communication, imagination, and social interactions. The etiology of autism is believed to be a complex combination of environmental, neurological, immunological, and genetic factors. In recent years, studies have investigated the possible association between the etiology of autism and potential roles of various environmental agents, especially heavy metals. The aim of the present study was to examine levels of toxic metals in hair and urine samples of an autistic child at the age of 6 years. The levels of toxic metals including lead, cadmium, arsenic and manganese in the hair and urine of this child were determined by atomic absorption spectrometry and compared with those of healthy children which were assessed in previous studies. Results showed that the autistic child had higher hair levels of lead (0.80µg/g vs 0.01µg/g), cadmium (0.083µg/g vs 0.06µg/g) and arsenic (0.09µg/g vs 0.06µg/g) respectively. Urine levels of lead (12.54µg/g vs 3.36µg/g) and cadmium (3.24µg/g vs 0.53µg/g) were higher than those of controls; whereas arsenic levels in urine were lower (6.81µg/g vs 32.06µg/g). Moreover, hair and urine samples of this autistic child contained lower concentrations of manganese (0.12µg/g and 0.028µg/g) as compared to healthy children (0.41µg/g and 4.81µg/g). In conclusion, our study demonstrated elevation in the levels of lead and cadmium in the both hair and urine of a child with autism, suggesting a role of heavy metals in the genesis of the symptoms of autism.

P95

DETECTION OF CADMIUM, LEAD, ALUMINIUM AND ZINC IN GRANULATED SUGAR

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One of the most important environmental problems is heavy metal pollution of soils. Heavy metal accumulation in soils has an important influence both on the fertility of soils, functions of ecosystem and on the health of living organism beings via food chains. As a result of poor agricultural practices, mineral exploitation, industrial waste dumping and indiscriminate disposal of urban wastes emitted from heavy metals adversely affect the health of living organism. Heavy metals which cannot be degraded or destroyed are notable for their wide environmental dispersion, their tendency to accumulate in select tissues of the human body, and their overall potential to be toxic even at relatively minor levels of exposure. Heavy metals are dangerous for life because they tend to bioaccumulate in target organs and affect their functions. Bioaccumulation means an increase in the concentration of heavy metal in a biological organism over time. In the present study, cadmium (Cd), aluminium (Al), lead (Pb) and zinc (Zn) levels were measured by atomic absorption spectrometry in granulated sugar samples from different cities of Turkey. As a result, Cd, Pb, Al and Zn levels were determined as 0.002 ppb, 61.65 ppb, 64.04 ppb and 1.53 ppb, respectively. In the future studies, authors suggest that more granulated sugar samples obtained the other different cities of Turkey may be searched in terms of heavy metal toxicities. In conclusion, in all steps starting from granulated sugar raw material storage, production line, packing stages to transmit all kinds of heavy metal contamination should be avoided.

OCCUPATIONAL TOXICOLOGY

P96

EVALUATION OF BIOCHEMICAL AND HEMATOLOGICAL PARAMETERS AMONG WORKERS OCCUPATIONALLY EXPOSED TO TOLUENE

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Hippuric acid in urine is a worldwide used biomarker for the diagnosis and biomonitorization of occupational exposure to toluene. Especially, in non-hygienic conditions like the lack of workplace air monitoring and preventive measures, it is essential to establish the workers' exposure to industrial solvents. The aim of the study is to investigate the efficiency of biochemical and hematological parameters in biological monitoring of workers in annual periodical examinations. In this study, 380 workers from nine different sectors exposed to industrial toluene were selected as participants and urine hippuric acid levels were analyzed with HPLC. ALT, AST, creatinine and hemogram analyses were made by biochemical autoanalyser with commercial kits. Serum ALT, AST, creatinine, hemoglobin, lymphocyte, neutrophil, platelet levels were compared among groups whose hippuric acid urine levels which are ≤ 1000 µg/L and ≤ 2000 µg/L. An additional comparison were made between different occupations. No statistically significant difference was found between these groups. It is noteworthy to emphasize that, even in toxic blood levels, none of the biochemical and hematological parameters showed statistically significant changes. These results suggest that hematological and biochemical laboratory parameters are not effective prognostic markers in annual periodical examinations of workers and an effective parameter in diagnosis in emergency services. The unique valuable marker is hippuric acid levels in urine.

P97

EVALUATION OF TRACE ELEMENT STATUS IN WORKERS EXPOSED TO JET PROPULSION FUEL

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Jet propulsion fuel (JP-8) is the major military fuel used by North Atlantic Treaty (NATO) member countries, with over 60 billion gallons per/year. Due to the widespread use in the military and commercial airline industry, over 2 million people/year are occupationally exposed to JP-8 and other jet fuels. Previous reports suggest that long term occupational exposure to JP-8 have been reported to have toxic effects on various organs and systems. On the other hand, trace elements are essential micronutrients required in minute amount by a number of metabolic processes. The present study was designed to evaluate the expected toxic effects of long term exposure to JP-8 on the trace elements homeostasis in workers. This study was carried out on 43 adult subjects who work in aircraft fuel system maintenance and are exposed to JP-8 for not less than 2 years. Thirty eight healthy subjects, matched with age with workers, with no access to such type of occupational exposure were included as control. Concentrations of cupper (Cu), zinc (Zn), iron (Fe), selenium (Se), magnesium (Mg), manganese (Mn) and molybdenum (Mo) in the serum samples were analyzed. The results showed that serum Se, Mg and Mn levels of exposed workers were found to be significantly lower than those of control subjects. Long-term exposure to JP-8 resulted in disturbances of Se, Mg and Mn but had no effect on Cu, Zn and Fe content in serum samples of workers.

P98

A NEW AREA FOR CARBONMONOXIDE INTOXICATION: HYDRO-ELECTRIC CENTRAL CONSTRUCTION

Semih Kunak

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 4" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 4" section.

P99

OCCUPATIONAL AND ENVIRONMENTAL EPIDEMIOLOGY FOR OCCUPATIONAL TOXICOLOGY STUDIES

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Human health sources from interaction between the genetic structure and environment of the person. We can avoid from many illnesses if we know toxic factors around us, so we can take preventative action, while we can't control our genetic structure. It is known that people working in toxic substances very much suffer from these repeated exposures. But, to those affected by toxic substances around are not limited within the employees in the work surrounded. Toxic agents can be carried by the water, air, products, workers etc. and create a health risk for the others in the environment too. Occupational health

hazards that impair the health of employees are preventable. As it is known, work environment defines a special world that is an important part of the human life. Occupational toxicology is a discipline that requires synthesis of epidemiology in a real sense. The aim of epidemiology is to investigate the causes and distribution of diseases in the human communities. Occupational epidemiology is a branch of epidemiology primarily concerned with the diseases which occurrence in the workplaces. The epidemiological studies on the groups, who are under occupational risk and exposed to toxicological factors, make it possible to reveal diseases originating from the work environment. The starting point of the occupational epidemiology is to clarify any possible connections between occupational exposure and the formation of the disease. In this presentation will be discussed types of occupational and environmental epidemiological studies, which are used in the toxicological research within a systematic.

OXIDATIVE STRESS

P100

THE PROTECTIVE EFFECT OF ASCORBIC ACID AND SELENOCOMPOUNDS AGAINST THE CYTOTOXICITY AND GENOTOXICITY OF 3,5-DIMETHYLAMINOPHENOL

Pınar Erkekoğlu[1,2], Ming-Wei Chao[1], Wenjie Ye[1], Laura Trudel[1], Jing Ge[1], Bevin P. Engelward[1], Belma Koçer Giray[2], Gerald Wogan[1], Steven R. Tannenbaum[1]

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 2" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 2" section.

P101

MATRIX GLA PROTEIN, KLOTHO GENE POLYMORPHISMS AND DNA DAMAGE IN CHRONIC KIDNEY AND CORONARY ARTERY DISEASES

Seher Karslı Ceppioğlu[1], Selma Yazar[2], Türkan Yurdun[1], Mustafa Canbakan[3], Mehmet Karaca[4], Yaşar Keskin[5], N. Emel Lüleci[5], Denizhan Karaçimen[4]

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 2" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 2" section.

P102

INFLUENCE OF CHRONIC CADMIUM EXPOSURE ON THE TISSUE DISTRIBUTION OF COPPER AND ZINC AND OXIDATIVE STRESS PARAMETERS

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Cadmium (Cd) is one of the major toxic agents associated with environmental and industrial pollution. The aim of this study was to investigate the effect of oral cadmium intoxication on the antioxidant response and its relationship with essential bioelements such as cupper (Cu) and zinc (Zn). In this study, 50 wistar albino male rats were included in Cd-exposed (n=30) and control groups (n=20). Control rats were fed with ordinary food and tap water. Cd-exposed group were administered 15 ppm of Cd in drinking water for 8 weeks. Concentrations of Cu, Zn, and Cd in the tissue samples were analyzed. The activities of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) as well as the concentration of malondialdehyde (MDA), as an indicator of lipid peroxidation, were measured in homogenates of the tissue samples. Cd accumulated mainly in liver, kidney and heart tissue, respectively. Exposure to Cd led to a significant decrease in the activities of SOD and a significant increase in the activity of GPx and MDA concentration in these organs. Also orally administration of Cd caused a significant reduction of Zn and Cu in the tissues. In conclusion, the results allow us to hypothesize that exposure to Cd enhanced risk of liver, kidney and heart damage due to oxidative stress and deterioration of bioelements. Further studies are needed to explain the effect of long-term exposure to Cd on distribution of biolements and its relationship with oxidative stress.

P103

THE EFFECT OF ALUMINUM ON TESTES AND ANTIOXIDANT SYSTEM IN RATS

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Aluminum (Al) is the third most abundant element and the most common metal in the earth's crust. The most common route of exposure to Al is oral intake. Al toxicity is a major area of interest and many studies are carried out to make its effect clear on biological systems. In recent years, it became clear that Al is a potential toxic agent in humans and has been implicated in the pathogenesis of several clinical disorders, such as dementia, respiratory tract disorders and allergic reactions. The aim of this study was to evaluate the effect of Al on oxidative stress status in rat's testese and erythrocyte. For this purpose forty rats (F-344) were divided into two equal groups as experimental and control. The solution of $AlCl_3.6H_2O$ was given orally (75 mg/kg/day) to the experimental group daily with a special canule throughout one month. One month later the rats were sacrified and the testese and erythrocyte were taken out. Al concentrations, cupper, zinc dependent superoxide dismutase (Cu,Zn-SOD), selenium dependent glutathione peroxidase (Se-GPx) activities, and malondialdehyde (MDA) levels were measured. The results indicated that the concentrations of Al on testese and erythrocyte were found higher compared to control ones ($p < 0.05$). While MDA levels higher compared to control group, Cu,Zn-SOD and Se-GPx activities were determined lower compared to control one ($p < 0.05$). In summary, our results showed that Al may have toxic effect on testes and antioxidant system in rats.

P104

EFFECTS OF POMEGRANATE SEED OIL ON PENTACHLOROPHENOL TOXICITY LIPID PEROXIDATION AND SOME BIOCHEMICAL PARAMETERS IN RATS

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In the study Sprague-Dawley male rats were used and five groups were formed. The first group was held as the control group. The second group was given 0,15 ml/kg pomegranate seed oil (PSO), the third group was given 40 mg/kg pentachlorphenol (PCP), the forth group was given 40 mg/kg PCP+0,15 ml/kg PSO during 28 days as specified into stomach by gavage. When PCP group compared to control group, an increase in malondialdehyde, nitric oxide and superoxide dismutase levels and decrease in catalase and glutathione peroxide level were seen. According to PCP group in PCP+PSO group, reduce in malondialdehyde, nitric oxide and superoxide dismutase levels; and increase in catalase and glutathione peroxide levels were explored. BUN, glucose, cholesterol, LDL, creatinin, triglyceride, uric acid levels and AST, ALT, ALP activity were increased in PCP group. Compared to control group HDL, total protein and albumin levels were decreased. PCP group compared to PCP+PSO, BUN, glucose, cholesterol, LDL, creatinin, triglyceride, uric acid levels, AST, ALP, ALT activities were decreased and HDL, total protein and albumin levels were increased. When control group and PCP+PSO were compared, it was seen AST, ALP, ALT activity and glocose, creatinin, LDL levels were increased, but there were no significant change BUN, HDL, chlosterol, trigliceride, uric acid, total protein and albumin. As as result, at 40mg/kg PCP causes liver damage, lipid peroxidation and decrease in anti-oxidant enzyme activity on rat. Overall, it has determined PSO protects against PCP toxicity.

P105

VOLATILE ANESTHETICS AND THEIR ASSOCIATION WITH OXIDATIVE STRESS

Ahmet Sayal[1], Yasemin Kartal[2], Zeliha Kayaaltı[2], Ahmet Aydın[3], Hülya Türkan[4], Bensu Karahalil[5]

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 3" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 3" section.

P106

EVALUATION OF OXIDANT/ANTIOXIDANT STATUS IN NEONATAL SEPSIS

Ali Aşcı[1], Özge Sürmeli Onay[2], Pınar Erkekoğlu[1], Murat Yurdakök[2], Şule Yiğit[2], Belma Giray Koçer[1]

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 1" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 1" section.

P107

INCREASED OXIDATIVE STRESS BUT NOT TRYPTOPHAN DEGRADATION IN PLASMODIUM BERGHEI INFECTED MICE

Funda Doğruman Al[1], **Ayse Başak Engin**[2], Neslihan Bukan[3], Seda Evirgen-Bostancı[4], Kemal Ceber[5], Semra Kuştimur[1]

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 3" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 3" section.

PESTICIDE TOXICOLOGY

P108

HISTOPATHOLOGICAL EXAMINATION OF THE EFFECTS OF ALPHA-CYPERMETHRIN ON THE REPRODUCTIVE SYSTEM IN MALE RATS

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The aim of this study was to investigate histopathologically the effects of subchronic administration of alpha-cypermethrin on prostate and seminal vesicle tissues of male rats. In study, 2 control (normal and oil-control) groups and 3 dose (0,09; 0,18 and 9 mg/kg/day) groups were determined, each group containing 10 male rats. Totally 50 male rats (albino Wistar) were used in the study. Dissolving alpha-cypermethrin in corn oil, the groups were treated with gavage for 13 weeks. At the end of the study, 5 µm sections from prostate and seminal vesicle tissues were stained with Hematoxylin-Eosin and investigated under the light microscope. When it was compared with the control groups, the histopathologic findings noted in prostate tissues of the rats in each three dose (0,09; 0,18 and 9 mg/kg/day) groups are infolding of epithelium, stenosis of lumen, a decrease in secretion, and mononucleer cell infiltration. The histopathologic findings in seminal vesicle tissue are infolding of epithelium, mitosis in epithelial cells and decrease in secretion. The results obtained indicated the active ingredient ADI (0-0,02 mg/kg) value of the near-dose group (0,09 mg/kg/day) or other dose groups are the same histopathologic findings that the higher doses increase in direct proportion to the severity of the findings.

P109

HISTOPATHOLOGICAL EFFECTS OF ALPHA-CYPERMETHRIN ON RAT LUNG

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In this study, the effects of alpha-cypermethrin subchronic application were to investigate histopathologically on lung tissue of male rats. In study, 2 control (normal and oil-control) groups and 3 dose (0,09; 0,18 and 9 mg/kg/day) groups were determined (n=10). Alpha-cypermethrin (purity 97%) was dissolved in corn oil and the rats were treated orally for 13 weeks. The albino Wistar male rats were housed under controlled conditions and were fed with standard pelleted food and tap water *ad libitum*. At the end of 13 weeks, the rats were sacrificed by cervical dislocation. Lung tissue of rats was fixed with Bouin and 5 µm thick sections were stained with H&E. Stained sections were investigated under the light microscope. There was no difference between the control groups in the histopathological. Dose groups compared with the control groups, some histopathological changes on lung tissue of rats were determined. Results of histopathological observation, bronchiole around the mononuclear cell infiltration, septal thickening in interalveolar area, hypertrophy of alveolar and disorder, alveolar rupture and in interalveolar area congestion. Alpha-cypermethrin caused some histopathologic effects on lung tissue of male rats on all the dose group. Between the lowest and highest dose groups showed similar findings histopathologically and the high-dose group were increased severity of symptoms.

P110

THE EFFECTS OF AZADIRACHTIN TO THE ADULT EMERGENCE OF PIMPLA TURIONELLAE L. (HYMENOPTERA: ICHNEUMONİDAE)

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In recent years the most extensively studied plant-based insecticide is *Azadirachta indica*. Azadirachtin, obtained from this plant, shows effects such as repellants, feeding inhibitory, fertility reduction, sterilizing, fatal, anti-egg drop, development and growth inhibitory in insects. These effects have been observed in many species of Orthoptera, Homoptera, Heteroptera, Lepidoptera, Diptera, Coleoptera and Hymenoptera. In the presented study, the effects of different concentrations of *Azadirachta indica* extract (NeemAzal-T/S) on adult emergence of *Pimpla turionellae* L. were investigated. Concentrations of 0.50,1.00 and 2.00 ppm were prepared from 10% azadirachtin dissolved in distilled water. These concentrations were given to the last instar stage of *Galleria mellonella* L. (Lepidoptera: Pyralidae) larvaes into the dorsal thorax by the topical application. Then 10 larvaes were left into the glass jars with onionskin paper. All larvaes kept in the glass jars till they pupaed. On the other hand new four female and two male adults of *Pimpla turionellae* L. (Hymenoptera: Ichneumonidae) were choosen and kept in different beakers feeding with honey-water mixture everyday in the same time. Two *G. mellonella* pupae applied with azadirachtin in the highest productivity egg days of 16^{th}, 19^{th}, 22^{nd}, 25^{th} and 28^{th}, were given to the *P. turionellae* females for parasitism. Then the parasited pupaes were kept in the plastic cups until the emergence of adults in the laboratory conditions (50±5% relative humidity at 24 ± 2 ° C and 12 h fotoperiod). In the study due to increase at the concentrations, a decrease was observed in the adult emergence. The sublethal doses of azadirachtin in insects

significantly affect the lifetime, adult emergence and adult emergence time. These reducing affect shows azadirachtin can be used in the biological control programmes.

P111

ALTERATION OF RAT LIVER FLAVIN-CONTAINING MONOOXYGENASE (FMO) ACTIVITY, PROTEIN AND mRNA EXPRESSION BY ELLAGIC ACID

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Flavin-containing monooxygenases (FMOs) are flavoproteins which contain FAD molecule. They are phase I xenobiotic-metabolizing enzymes bound to smooth endoplasmic reticulum and nuclear envelope. FMOs are responsible for oxidation of wide-range of nucleophilic nitrogen, sulfur, phosphorus, and selenium heteroatom-containing drugs such as tamoxifen, imipramine, methimazole and other chemicals by using NADPH as cofactor. Ellagic acid (EA) is a polyphenolic compound that exists naturally in the plant species, and considered as anti-mutagenic, antioxidant, anti-inflammatory, and potent anti-carcinogenic agent in mammalian cells. The aim of the present study was to determine the *in vivo* effect of EA on FMO activity, protein and mRNA expressions in rat liver. 10 mg of EA in DMSO/kg body weight was injected intraperitoneally to Wistar albino rats for 9 consecutive days. On the other hand, a group of rats was injected only with DMSO solution and used as control. Following the decapitation of the animals, the livers were removed and microsomal fractions were prepared by differential centrifugation. FMO activities by using methimazole as substrate and FMO3 protein expressions by Western blot were determined. The results showed that ellagic acid significantly increased the FMO activity (57%,$p<0.0001$), and FMO3 protein expression (40%,$p<0.0001$) with respect to control group. However, mRNA expression stayed stable ($p=0.8$) In conclusion, FMO dependent metabolism of drugs and other xenobiotics may be altered due to the changes in activity and protein expressions of FMO enzyme by the ellagic acid found in the diet.

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

P112

EMBRYOTOXICITY OF NITROPHENOLS TO THE EARLY LIFE STAGES OF ZEBRAFISH (DANI O RERIO)

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The Nitrophenols are water-soluble compounds. These compounds pose significant health risks since they are priority pollutants. Acute toxicity and teratogenicity of 2-Nitrophenol and 2,4-Dinitrophenol were investigated in a 4-day using zebrafish embryos. Both nitrophenols caused teratogenicity and embryo mortality in the fish embryos. The median lethal concentrations (LC_{50}) and median effective concentrations (EC_{50}) for 2-Nitrophenol are 18.7 mg/L and 7.9 mg/L respectively; the corresponding values for 2,4-Dinitrophenol are 9.65 mg/L and 3.05 mg/L. The main endpoints are coagulated embyos, exogastrulation, tail malformation, vertebra defects and delayed growth in two nitrophenols. 2,4-Dinitrophenol was found more toxic than 2-Nitrophenol in applied doses. This paper is the first to describe the teratogenicity and embryotoxicity of two nitrophenols to the early life stages of zebrafish.

P113

EFFECT OF CYSTEINE, FETUIN, AMINOACID SOLUTION AND ANTIOXIDANT ON POST-THAW BULL SPERMS QUALITY

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The objectives of this study were to assess the effects of different antioxidants on sperm parameters, plasma membrane integrity, DNA damage as well as antioxidant activities after freeze-thawing in bull sperms. The pooled ejaculates were collected from three Holstein bulls twice a week split into five experimental groups and diluted to $15x10^6$/ml with the modified base extender containing antioxidant (0.5 ml), fetuin (2 mg/ml), aminoacid solution (13%), cysteine (5 mM) and control. The extended samples were cooled slowly to 4°C, loaded into straws and frozen using digital freezing and liquid nitrogen. Frozen straws were thawed at 37°C to analyze progressive motility and sperm motion characteristics as well as membrane integrity using hypo-osmotic swelling test. Biochemical assays were

performed using commercial kits. DNA damage was evaluated by Comet Assay. Using antioxidant, fetuin, amino acid solution and cysteine did not give better result on the percentages of post-thaw sperm CASA and progressive motilities. Spermatozoa frozen in which containing cysteine exhibited the greatest value of VAP (100.8±1.19 µm/s), VCL (176.0±1.79 µm/s) and plasma membrane integrity (48.1±0.79%) compared to other groups ($P<0.05$). Total abnormalities had greater in control and fetuin groups (17.5±0.57%; 15.5±1.98%, respectively) than that of the other groups ($P<0.05$). DNA damage was affected by type of antioxidant; fetuin resulted in greater chromatin damage than the other groups ($P<0.05$). As regards to antioxidant activity; although there were no significance differences in the GSH, CAT and total antioxidant activities, GPx activity were affected by type of antioxidant, notably cysteine yielded the lowest activities when compared to the other groups ($P<0.05$).
In conclusion, antioxidant, aminoacid solution and cysteine have reduced abnormal spermatozoa rates and cysteine has exhibited cryoprotective activity on plasma membrane integrity but antioxidants which are used do not provide any further improvement on the antioxidant enzyme activity. On the other hand fetuine, which has been linked to the deleterious effect on sperm values, increases DNA damage.

P114

MALE INFERTILITY AND GENETIC FACTORS

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- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 1" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 1" section.

RISK ASSESSMENT

P115

ENVIRONMENTAL RISK ASSESSMENT FOR PLANT PROTECTION PRODUCTS

Sakine Uğurlu Karaagaç

- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 4" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 4" section.

TARGET ORGAN TOXICITY

P116

THE RELATION BETWEEN GREEN TEA CONSUMPTION DURING PREGNANCY AND APOPTOTIC SIGNALING IN NEWBORN HEART MUSCLE CELLS

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In this study, possible link between apoptotic changes in newborn rat heart tissue and green tea consumption during pregnancy have been examined, using immunohistochemistry. In our study, 12 female Wistar albino rats were used. All female rats were kept overnight with male rats in the same cage. The next day, female rats that have identified with vaginal smears, were divided into groups. Group1: Control, Group2: Green tea (50 mg/kg, green tea extract, 20day gavage). Newborns were removed at the first day of the born, and their hearts were dissected. Subsequently, TUNEL assay and immunohistochemistry using Caspase-3, Caspase-9, and Cytochrome-c antibodies were performed with the obtained newborn cardiac tissues. In the green tea applied group, especially in atrial cardiac muscle cells, an increased number of TUNEL-positive cells were determined compared to the control group. In immunohistochemical evaluations of the control group, weak Caspase-3 and Cytochrome c release, as well as Caspase-9 release ranging weak to moderate, were identified. Immunoreaction for Caspase-3 expression was moderate, while Caspase-9 and Cytochrome c immunoreactions revealed quite high levels in the green tea applied group. Green tea consumption during pregnancy, in comparison to control, causes an increase of apoptosis in cardiac muscle cells, especially in the heart of the newborn. Particularly, increased Cytochrome c level in high-dose green tea applied group indicates a significant role of mitochondria during apoptotic signal. Increased apoptosis in the heart tissue, depending on green tea consumption, suggests a link for the advanced age-related heart diseases.

P117

NEGATIVE EFFECT OF LONG AND SHORT TIME APPLICATION WHEY PROTEIN ON RAT LIVER; AN HISTOLOGIC AND BIOCHEMICAL STUDY

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The aim of the study was to show side-effects of whey protein on liver in terms of inflammation and apoptosis with the help of rats who are fed by whey protein in the long time and short time. 30 male Wistar albino rats are divided into 3 groups. First group of rats are control group, second group is fed by whey (WK) for short time (5 days, 252 gr/kg), third group is fed by whey (WU) for long time (4 weeks, 252 gr/kg). They are measured according to inflammatory cytokine expression IL-1β, IL-6, TNF-α and intermediatefilament CK-18 with ELISA and immunohistochemistry methods. Findings are evaluated by the use of apoptosis TUNEL staining. According to IL-1β serum levels and immunohistochemistry results highest level is found to be the group WU (P<0.01). IL-6 and TNF-α serum levels and immunohistochemistry results are close to each other; whereas, in short run fed group it is a bit lower WK and found to be the highest in the long run fed group (P<0.01). When measured according to CK-18 serum levels, immunohistochemistry and TUNEL method the highest results are found in short run fed group WK and long run fed group are found to be intermediate (P<0.01). To conclude, the usage of whey protein unconsciously and without exercising, it increases the inflammation markers in liver in long time usage and increase the apoptosis signals in the short time usage which is a negative effect of whey protein.

P118

TAMOKSİFEN SİTRAT SOLUNUM YOLUYLA ALINAN SİLİKAYA BAĞLI GELİŞEN SİSTEMİK FİBROZİSTE KORUYUCU MUDUR?

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- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 4" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 4" section.

P119

DRUG-INDUCED CARDIOTOXICITY: EXPERIMENTAL METHODS

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- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 3" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 3" section.

P120

THE EFFECTS OF GENDER DIFFERENCE ON MCT-INDUCED TOXICITY

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In the present study, it was aimed to compare the effect of gender difference on hemodynamic consequences in the development of monocrotaline (MCT)-induced pulmonary hypertension in rats. The effect of antioxidant enzyme systems on the development of pulmonary hypertension mediated by the phytotoxin MCT and the effect of gender on these antioxidant systems were also investigated. For this purpose, the right ventricular pressures and right ventricular / heart weight ratios were compared between groups and the glutathione level, and superoxide dismutase (SOD), catalase (CAT) and glutathione-S-transferase (GST) activities were determined in lung and liver tissue samples of rats. Right ventricular pressure and right ventricular / heart weight ratios were significantly increased in the MCT group compared to control group. In the MCT group, right ventricular pressures were significantly higher in males than females. MCT-induced pulmonary hypertension resulted in decreased glutathione level, decreased GST and SOD activities and increased CAT activity in lung and liver tissues of both male and female rats. In addition, the lung and liver glutathione levels, and GST and SOD levels were higher in female control rats compared to male control rats. The results of the present study, that antioxidant enzyme activities were different between the groups, highlight the possible role of oxidative stress in the pathogenesis of MCT-induced pulmonary hypertension in rats. Moreover, the lower antioxidant defense capacity of male rats than female rats may be considered as a cause of more aggressive course of MCT-induced pulmonary hypertension in males compared to females.

OTHER TOPICS

P121

PEPPER SPRAY: LESS-THAN-LETHAL INFLAMMATORY AGENT

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Riot control agents are highly potent irritants, that are called as "lacrimators" or "tear gases". These chemicals interacts with sensory neurons and present site-spesific and time-dependent toxicity. At the site of exposure area, eyes or skin, it causes pain and irritation. The most commonly available riot control agent is pepper spray that is a chemical incapacitant causing intense irritation of the mucous membranes and skin. These formulations contain different amounts of *Oleoresin capsicum* that is an oily resin derived from *Capsicum annuum* or *Capsicum frutescenes* as major compound. The *Oleoresin capsicum* contains organic compounds that are called capsaicin and capsaicinoids. These extracts have mainly ocular and dermal effects and the other effects are on respiratory system, nervous system, mucous membranes and reproductive system. Pepper spray has been accepted by government and law enforcement as less-than-lethal inflammatory agent. Pepper sprays active ingredients may associated with public health risk. In this review we discussed chemical characteristics, systemic and local effects and the toxic effects on several systems of pepper spray and its main compound, capsaicin.

P122

THE ROLE OF THE ANALYTICAL TOXICOLOGY IN EMERGENCY MEDICINE

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- Sözlü Sunum olarak seçilmiştir. Özet "Sözlü Sunumlar 3" bölümünde bulunmaktadır.
- Selected as oral presentation. Abstract can be found in "Oral Presentations 3" section.

P123

THE INVESTIGATION OF HISTOPATHOLOGICAL EFFECTS OF MACROVIPERA LEBETINA (LINNAEUS, 1758) (REPTILIA: VIPERIDAE) VENOM ON MICE'S HEART AND LUNG TISSUES

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Thirteen venomous snake species one of which is *Macrovipera lebetina* (Levantine viper) belongs to the group of cobra and vipers live in Turkey. Based on body and venom gland size, *Macrovipera lebetina* is one of two most venomous snake species in Turkey. This species bite has been reported lethal to such large animals as horse, cattle and camel. However mechanisms and type of of histological damage in living tissue has not been elucidated yet. Venom colected from *Macrovipera lebetina* has been stored after lyophilization. The dry venom was dissolved in physiological saline at the time of dosing and doses of 0.5, 1 and 1.5 mg/kg was injected via the caudal vein of mice (*Mus musculus*). The animals were dissected two hours post injection and lung and heart tissue were sampled for histological examination by routine preparation procedures and stained with hemotoxylene & eosine. Results of the histological investigations showed alveolar deformation (thick and narrow), congestion and epithelial thickening. Celular degeneration, neutrophil infiltration and hemorrage were detected in the heart. The results showed same histopathological effects in the lowest and highest dose groups and intensity of effects increased in the highest dose proportionally

P124

EFFECTS OF DELTAMETHRIN CONCENTRATIONS ON LIFE TABLE DEMOGRAPHY OF FRESH WATER ROTIFER BRACHIONUS CALYCIFLORUS UNDER DIFFERENT CHLORELLA VULGARIS DENSITY.

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The effects of different concentration (1.5, 2.0, 2.5, 3.0 and 3.5 mg/L) deltamethrin, a synthetic pyrethroid insecticide, on the life table demography of fresh water rotifer Bracionus calyciflorus at the Chlorella vulgaris density being 1.0×106, 3.0×106, and 5.0×106 cells ml-1 was investigated in this study. The results showed that at 25 °C, the 24 h LC50 of deltamethrin to B. calyciflorus was 3.5 mg/L. Compared with the controls at the same food density, when the C. vulgaris density was 1.0×106cells ml-1, 3.5 mg/L of deltamethrin prolonged the generation time of B. calyciflorus significantly, and 2.0 mg/L of deltamethrin increased the percentage of B. calyciflorus mictic offspring. When the C. vulgaris density was 3.0×106cells ml-1, the deltamethrin at all test concentrations except 2.0 mg/L decreased the percentage of mictic offspring; when the C. vulgaris density was 5.0×106cells ml-1, all test concentration deltamethrin had no effects on the life table demography ($P > 0.01$). C. vulgaris density had significant effects on the generation time, life expectancy at birth, net reproduction rate, percentage of mictic offspring of B. calyciflorus ($P<0.01$), deltamethrin concentration had significant effects on the generation time and the percentage of mictic offspring ($P<0.01$), and the interaction of C. vulgaris density and deltamethrin concentration had significant effects on the percentage of mictic offspring ($P<0.01$). As a result of, among all the studied parameters, the generation time and the percentage of mictic offspring were more sensitive to deltamethrin pollution under the algal densities of 1.0×106and 3.0 ×106cells ml-1.

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Yazar Dizini / Author Index

Yazar Dizini / Author Index

Notlar / Notes

Notlar / Notes

Notlar / Notes

Notlar / Notes

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