11TH CONGRESS OF TOXICOLOGY IN DEVELOPING COUNTRIES

CTDC

13TH - 16TH JUNE 2021
KUALA LUMPUR, MALAYSIA

Multidisciplinary Approaches in Toxicology Towards Supporting Sustainable Development Goals

ABSTRACT BOOK

JOINTLY ORGANISED BY

MySOT Malaysian Society of Toxicology

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FACULTY OF HEALTH SCIENCES, UNIVERSITI KEBANGSAAN MALAYSIA
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AFTER CTDC 11 ENDS, THIS DIGITAL ABSTRACT BOOK IS ACCESSIBLE AT
http://mysot.org.my/ctdc11-abstractbook

SCAN ME

ABSTRACT BOOK FOREWORD:

This abstract book is published for the 11th Congress of Toxicology in Developing Countries (CTDC11), which is jointly organized by the Malaysian Society of Toxicology (MySOT) and the International Union of Toxicology (IUTOX). The CTDC11 will be held online from the 13th to 16th June 2021 due to the COVID-19 pandemic. It will be broadcasted to registered participants worldwide from the Kuala Lumpur Convention Centre, which is located at the foot of the iconic Petronas Twin Towers, displayed on the cover of this book. The CTDC11 programme begins with the pre-congress event of 2 continuing education courses, followed by the 3-day congress of three concurrent sessions on each day. The aims of the CTDC11 are (a) to provide a forum for scientific discussions on the role of toxicology towards supporting and achieving the Sustainable Development Goals, (b) to provide a platform for meeting, discussion, collaboration and networking among the participants of the congress and (c) to promote knowledge-sharing of current scientific findings, best practices and techniques in toxicology.

The CTDC11 has adopted the extended abstract format to widen the benefits of the scientific communication to many interested readers of this abstract book. Abstracts that did not follow the submission guideline or received after the deadline are not included in this book in order to assure harmony and timely publication of the abstract book. The editorial team has reviewed the abstracts submitted by the authors but limited to the suitability of the title and content for the assigned CTDC11 subthemes. The correctness and validity of the information in the abstracts, and compliance to the ethical, and legal consideration remain the authors full responsibilities. Therefore, readers are advised to contact the respective authors of the abstracts for clarification or verification of the abstract's contents.

It is a challenging process to organize the abstracts due the diverse nature of the fields related to toxicology with wide spectrum of the content offered by the authors from the various perspectives of academic, research, professional, regulatory and industrial. Thus, the authors presentation and their abstracts have been systematically arranged to the best fitting subthemes according to the sessions of the 3-day congress programme, namely 2 keynote lectures, 8 symposia, 2 workshops, 1 forum, 7 oral and 5 poster presentations. Readers are advised to use the hyperlinks at the Table of Content and respective pages marked by blue words or blue rectangle of dashed line that allows direct navigation to the sessions of interest within this abstract book. A home button represented by a small image of the Kuala Lumpur Tower surrounded with blue rectangle of dashed line has been made available at pages of the main parts of the book to facilitate readers in returning to the initial page viewed.

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Highest appreciation to the members of the international advisory board in providing valuable guidance on the scientific program and the editorial team for the efforts in the publication of the abstract book.

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CHAIR WELCOME REMARKS

CTDC11
11th CONGRESS OF TOXICOLOGY IN DEVELOPING COUNTRIES

Dear Colleagues,

On behalf of the Malaysian Society of Toxicology (MySOT) and the International Union of Toxicology (IUTOX), we invite you to the virtual 11th Congress of Toxicology in Developing Countries (CTDC11) from 13th - 16th June 2021.

The theme of the Congress is Multidisciplinary Approaches in Toxicology Towards Supporting Sustainable Development Goals and this reflects the commitment of Malaysia and the South East Asia (SEA) region towards achieving the United Nations Sustainable Development Goals for a better and more sustainable future for all. The Congress will provide excellent opportunities for toxicologists especially those from countries often under-represented in global congresses.

We have designed a robust programme for the four-day Congress to include 2 continuing education courses, 2 keynote speakers, 8 symposia and 2 workshop sessions to showcase the latest global updates with emphasis on challenges in developing countries. This will facilitate collaboration and partnerships in education, research and development.

Special thanks to all the speakers, participants, affiliated societies and sponsors for their contributions in making this congress a success. Finally, my special thanks to the organizing committee, IUTOX and MySOT leaders who have worked tirelessly in ensuring the success of CTDC11 despite the various challenges faced due to COVID-19 pandemic.

We look forward to welcoming you to our virtual CTDC11 and we wish you very best wishes for a successful and productive Congress.

Visit us at https://ctdc11.org

SALMAAN HUSSAIN INAYAT-HUSSAIN PhD, DABT, ERT, FASc
Chair of the CTDC11
Kuala Lumpur, MALAYSIA

IUTOX PRESIDENT MESSAGE

Dear Colleagues

It is my pleasure to welcome you all on behalf of the Organising Committee of the 11th Congress of Toxicology in Developing Countries (CTDC11), June 13–16, 2021 co-chaired by Salmaan H Inayat-Hussain & Chan Kok Meng under the auspices of the Malaysian Society of Toxicology (MySOT) and International Union of Toxicology (IUTOX), I congratulate the work of the organising committee. The theme of CTDC11 is *Multidisciplinary Approaches in Toxicology Towards Supporting Sustainable Development Goals* consistent with the United Nations Sustainable Development Goals for a better and more sustainable future for all. Because of COVID19, the congress will be a virtual meeting. Whilst we may miss the onsite interaction with our colleagues and the social enjoyment, we can focus on the science and debate in the Q&A sessions.

Professor Jose Castro is the founder of the first meeting of Toxicology in Developing Countries, TDC (Buenos Aires, Argentina) in 1987. It was followed by three successful yearly meetings before TDC joined under the auspices of IUTOX and was renamed CTDC by 2006.

The CTDC meetings since 1987 have been particularly productive and useful in the exchange of scientific knowledge and meeting the specific needs of developing countries. There has also been generous support from donors and colleagues. The progress has been positive and IUTOX will continue to support the needs of developing countries.

MySOT has provided a solid programme consistent with the environmental and health concerns of our communities that may eventually affect human health and wellbeing.

I wish you all a great meeting and a productive interaction with your colleagues and students after the meeting.

Your Sincerely

Visit us at https://www.iutox.org

DR. PETER N. DI MARCO PhD, FATS
President of the International Union of Toxicology
Western Australia, AUSTRALIA

MYSOT PRESIDENT MESSAGE

Dear colleagues,

On behalf of the Malaysian Society of Toxicology, we warmly welcome you all to the 11th Congress of Toxicology in Developing Countries from the 13th to 16th June 2021.

The toxicological challenges associated with industrialization and globalization remain a major problem faced by many Asian countries including Malaysia. Therefore, the congress' theme 'Multidisplinary Approaches in Toxicology Towards Supporting Sustainable Development Goals', is aptly and reflects the commitment of Malaysia and its counterparts in this region towards making the United Nations' 2030 Agenda for Sustainable Development a reality.

The four-day congress that include 2 continuing education courses, 2 keynote sessions, 8 symposia and 2 workshop sessions will highlight the latest toxicological advancement and challenges in developing countries. Various speakers from across the country and the world will present and discuss some of these important issues at the congress. This will allow participants to extend their collaborative network and explore current and future directions in toxicology.

To organize a congress of this magnitude is not a small task. My special thanks to the dedicated organizing committee led by Dr Salmaan Hussain Inayat-Hussian to make this congress happen despite the various challenges faced amidst the COVID-19 pandemic. Finally, I would also like to dedicate a special thanks to all the sponsors, speakers and participants for their contributions and support in making this congress a success.

Welcome to CTDC11 and I wish you all an enjoyable and productive congress!

Visit us at https://www.mysot.org.my

ASSOC. PROF. DR. CHAN KOK MENG
Co-chair of the CTDC11
President of the Malaysian Society of Toxicology
Kuala Lumpur, MALAYSIA

CTDC11 PROGRAMME:

PRE-CONGRESS CONTINUING EDUCATION COURSES (CEC)

SUNDAY, 13 JUNE 2021

CEC 1: Evolving International Methodologies and Tools for Chemical Risk Assessment

09:00 – 09:10	Welcome Remarks *Chair: Richard Brown, Switzerland; Mary Gulumian, South Africa*
09:10 – 09:50	Introduction to the Course *Mary Gulumian, NIOH, South Africa*
09:50 – 10:30	Overview of IPCS Methodologies and their Interrelationships *Bette Meek, Uni. of Ottawa, Canada*
10:30 – 10:50	Break
10:50 – 11:30	Update on Latest WHO/IPCS Activities on Chemical Risk Assessment Methodologies, Including the Human Health Risk Assessment Toolkit *Richard Brown, WHO, Switzerland*
11:30 – 12:10	Computational Toxicology in Hazard Characterization and Risk Assessment *Bette Meek, Uni. of Ottawa, Canada*
12:10 – 12:50	Information Resources & Applications: Databases for Hazard & Predictive Application of "Omics" Data *Elaine Faustman, Uni. of Washington, USA*
12:50 – 13:10	Question and Answer Session
13:10 – 14:10	Break
14:10 – 17:00	Interactive Exercise

CEC 2: Vaccine Development in the 21st Century

09:00 – 09:10	Welcome Remarks *Chair: Alan Hoberman, Charles River Laboratories, USA*
09:10 – 09:50	Introduction and History of Vaccines *Deborah Novicki, DL Novicki Toxicology Consulting LLC*
09:50 – 10:30	Non-Clinical Regulatory & Testing Considerations for Vaccine Development in 2021 *David Pepperl, Biologics Consulting*
10:30 – 10:50	Break
10:50 – 11:30	Case Studies on Regulatory Toxicology for Prophylactic Vaccines for the Developing and Developed World *Alex Rodriguez, GSK, Belgium*
11:30 – 12:10	Vaccines and Pregnancy: COVID-19 and Special Groups *Alan Hoberman, Charles River Laboratories, USA*
12:10 – 12:30	Question and Answer Session

CTDC11 PROGRAMME:

3 DAYS CONGRESS FROM 14TH TO 16TH JUNE 2021

Kindly refer to the next three pages for the daily programme details

Day-1: Monday, 14th June 2021

09:00 – 09:10	Welcome Speech & announcement of IUTOX Award and Lifetime Achievement Award winners (IUTOX President)		
09:10 – 09:20	Welcome Speech & announcement of MySOT Award winners (MySOT President)		
09:20 – 09:30	Opening Remarks (CTDC 11 Chair)		
Day 1 Subtheme: Challenges and Advances in Chemical Risk Assessment			
09:30 – 09:40	**Symposium 1: New Technologies & Mechanistic Data Supporting the Future of Risk Assessment Under Real-life Risk Simulation Approach** *Chair: Michael Aschner, Albert Einstein Coll. Med., USA*	**Symposium 2: A User-Friendly Tool to Assess Risks from Combined Exposures to Indoor Air Pollutants in Public Spaces of Children** *Chair: Irina Zastenskaya, WHO Europe Regional Office*	**Workshop 1: Challenges and Advances in Pesticides Risk Management (Dietary & Spray Operator Risk Assessments)** *Chairs: Jeong Han Kim, Seoul National Uni; Budiawan, Uni. Indonesia*
09:40 – 10:10	**Experimental Studies on Real-Life Risk Simulation Supporting the Shift to New Risk Assessment Approaches** *Anca Oana Docea, Uni. of Med & Pharm Craiova, Romania*	**Overview of the Approach to Combined Exposures in the WHO Screening Tool** *Bette Meek, Uni. of Ottawa, Canada*	**Update on Pesticides Exposure Risk Assessment for Spray Operators in the Field Condition** *Jeong Han Kim, Seoul National Uni*
10:10 – 10:40	**Complementary and Alternative Models in Risk Assessment: What Can We Learn from Worms?** *Michael Aschner, Albert Einstein Coll. Med., USA*	**The Supporting Database: An Updated Resource of International Guidance Values** *Katleen De Brouwere, VITO, Belgium*	**Value of the Stewardship Practices in Minimizing the Pesticide Exposure to Spray Operators in the Field Condition** *Yoji Hashino, Syngenta Asia Pacific Pte Ltd*
10:40 – 11:00	Break		
11:00 – 11:30	**The Application of Big Data and Machine Learning in Risk Assessment** *Thomas Hartung, CAAT, John Hopkins Sch. Pub. Health, USA*	**Exposure Assessment to Support the Screening Tool** *Irina Zastenskaya, WHO Europe Regional Office*	**Food Safety: Dietary Risk Assessment, An Update on Pesticides Dietary Risk Assessment** *M. Nazrul Fahmi A. Rahim (Malaysia) & Budiawan (Indonesia)*
11:30 – 12:00	**Risk Assessment Evaluations in the 21st Century** *Aristidis Tsatsakis, Uni. of Crete, Greece*	**Application of the Screening Tool** *Tamas Szigeti, National Public Health Centre, Hungary*	**Food safety: Importance of Communication with Key Stakeholders** *Vasant L. Patil, CropLife, Singapore*
12:00 – 12:20	Question and Answer Session		
12:20 – 13:40	Break		
13:40 – 13:50	**Symposium 3 Recent Development in the Public Health Management of Chemical Incidents** *Chair: Richard Brown, WHO, Switzerland*	**Oral Session 1: Ecotoxicology / Environmental Toxicology** *Chair: Mohd Nazil Salleh, PICOM, Malaysia*	**Oral Session 2: Risk Assessment** *Chair: Poh Wen Tsin, NPRA, Malaysia*
13:50 – 14:20	**The 2020 Update of the WHO Guidelines for Poison Control** *Martin Wilks, Swiss CAHT, Switzerland*	**Toxic Effects of Detergent Ariel on Oxidative Damage of Fresh Water Fish, *Channa punctatus*** *Chand Basha Davuljigari, Sri Venkateswara Uni., India*	**Occupational Exposure to Pesticides Among Rice Growers in Malaysia** *Wong Hie Ling, Uni. Malaysia Kelantan, Malaysia*
14:20 – 14:50	**Poisons Centres and Public Health Advice** *Raquel Duarte-Davidson, Public Health England, UK*	**Herbicides and Population Health of Frog, *Fejervarya limnocharis*, in Paddy Fields of Northern Thailand** *Luhur Septiadi, Chulalongkorn Uni., Thailand*	**Cellular Uptake and Biological Impacts of Copper Hydroxide Nanopesticides in *Drosophila melanogaster*** *Eşref Demir, Antalya Bilim Uni., Turkey*
14:50 – 15:20	**Emergency Response Preparedness for Chemical Incidents** *Haidar Rizal Toha, Johor Health Dept., MoH, Malaysia*	**Phthalate and Bisphenol a Mixture-Linked Asthma Development: Positive Probiotic Intervention** *Katarina Baralić, Uni. of Belgrade, Serbia*	**Risk Assessment of Aflatoxin in Herbal Medicines and Plant Food Supplements Marketed in Malaysia** *Siti Soleha Abdullah, Uni. Putra Malaysia*
15:20 – 15:40	Break		
15:40 – 16:10	**International Health Regulations and Core Capacities for Chemical Events** *Richard Brown, WHO, Switzerland*	**Microbial Enzymes from Microcystin-Degrading Bacteria for Bioremediation** *Salfarina Ramli, Uni. Technology MARA, Malaysia*	**Total Diet Study on Exposure to Methylmercury in Malaysia** *Laila Rabaah Ahmad Suhaimi, Min. of Health, Malaysia*
16:10 – 16:40	**Identifying New and Emerging Risks from Chemicals** *Chris Weis, NIEHS, USA*	**Trigonelline Prevents Oxidative Damage in UVB Irradiated Dermal Fibroblasts and Balb/c Mice** *Tanveer Ahmad Malik, Indian Inst. Integrative Medicine, India*	**GIS-Based Interpolation Method to Urinary Metal Concentrations in Malaysia** *Noraishah Mohd Sham, Min. of Health, Malaysia*
16:40 – 17:00	Question and Answer Session		

Day-2: Tuesday, 15th June 2021

09:00 – 09:10	Remarks from ASIATOX President & Introduction to Keynote Speaker		
09:10 – 09:50	**Keynote. The Botanical Safety Consortium: A Public-Private Partnership to Enhance the Botanical Safety Toolkit** *Connie Mitchell, Health & Environmental Sciences Institute, USA*		
Day 2 Subtheme: Emerging Issues in Toxicology			
09:50 – 10:00	**Symposium 4: Emerging Issues of Herbal Medicine Safety** *Chairs: Nurşen Başaran, Hacettepe Uni., Turkey; Nan Mei, FDA, USA*	**Symposium 5: When & How We Can Stop Using Animals in Toxicology** *Chair: Emanuela Corsini, Uni. of Milan, Italy; Thomas Hartung, CAAT, USA*	**Workshop 2: Chemical Stewardship: Global Regulations and Beyond Compliance in Meeting Sustainable Performance of Energy Industry** *Chair: Salmaan Inayat-Hussain, PETRONAS, Malaysia; Hazlina Yon, DOSH, Malaysia*
10:00 – 10:30	**Unpredictable Adverse Effects of Herbal Products** *Nurşen Başaran, Hacettepe Uni., Turkey*	**Applicability Domains and Future of Non-animal Tests** *Nicole Kleinstreuer, NIH, USA*	**Regulatory Expectations for Sustainable Chemicals Management in Developing Countries** *Hazlina Yon, DOSH, Malaysia*
10:30 – 11:00	**Complementary and Alternative Medicines: Malaysia Scenario** *Seetha Ramasamy, NPRA*	**The View of the Chinese Centre for Alternative Research and Evaluation** *Shujun Cheng, Shanghai Jiaotong Uni., China*	**Managing Trade Barrier through Application of Globally Harmonized System (GHS) to Petroleum Substances** *Jessica Ryman-Rasmussen, API*
11:00 – 11:20	Break		
11:20 – 11:50	**Registration of Herbal Drugs in EMA** *Heidi Foth, Martin Luther Uni., Germany*	**The AFSA Collaboration: Implementing Animal-Free Safety Assessment of Cosmetics Globally** *Catherine Willett, Human Soc International Europe*	**UNITAR's Perspective on the Emerging Beyond 2020 Framework and What it Means for the GHS and PRTRS** *Oliver Wootton, UN Inst. Training & Research; Servet Goren, Cefic*
11:50 – 12:20	**Quantitative Analysis of Toxicity Data of Herbal Products** *Nan Mei, FDA, USA*	**The Way Forward: The Experience at CAAT** *Thomas Hartung, CAAT, US*	**Managing Environmental Health Risks in the Oil & Gas Industry** *Nor Rahmah Nor Hashim, PETRONAS*
12:20 – 12:50	**Herbal Products: Regulation and Safety Testing in Thailand.** *Rawiwan Maniratanachote, NSTDA, Thailand*	**Immunotoxicology: A History of a Success** *Emanuela Corsini, Uni. of Milan, Italy*	Question and Answer Session
12:50 – 13:10	Question and Answer Session		
13:10 – 14:10	Break		
14:10 – 14:20	**Oral Session 3: Herbal/Natural Product Toxicology** *Chair: Salfarina Ramli, UiTM*	**Oral Session 4: Genotoxicity** *Chair: Mogana Das Murtey, Uni. Sains Malaysia, Malaysia*	**Oral Session 5: Mechanistic Toxicology** *Chair: A'edah Abu Bakar, PETRONAS, Malaysia*
14:20 – 14:50	**Ochratoxin A and Antioxidant Activities of Roasted Coffee Beans in Phnom Penh, Cambodia** *Oeung Sokunvary, Khon Kean Uni., Thailand*	**Pharmacological Activation of Autophagy Restores Cellular Homeostasis in UVB-Induced Genotoxic Stress Response in Skin** *Sheikh Umar Ahmad, Indian Institute of Integrative Medicine, India*	**Comprehensive Histone, DNA Methylation and mRNA Expression Analysis of Murine Liver Repeatedly Exposed to Chemicals** Jun Kanno, NIEHS, Japan
14:50 – 15:20	**Antioxidant Activities & Anti-inflammation of Coelonin from *Dendrobium scabrilingue*** *Hasseri Halim, Uni. Technology MARA, Malaysia*	**The Presence of Genotoxic and Carcinogenic Phytochemicals in Medicinal Plants Based on the Malaysian Herbal Monograph** *Nur Azra M Pauzi, Uni. Putra Malaysia, Malaysia*	**Fibroblast Growth Factor Receptor 4 as a Potential Druggable Target for Triple Negative Breast Cancer** *Koh Yong Qin, National Uni., Singapore, Singapore*
15:20 – 15:40	*Break*		
15:40 – 16:10	**Fish Acute Toxicity Testing of Litsea Garciae Methanolic Extract in Adult Zebrafish** *Siti Zaleha Raduan, Int. Islamic Uni., Malaysia, Malaysia*	**Role of Nrf2/Nqo1 Pathway in Mediated Arsenite-Induced Malignant Transformation** *Yan An, Soochow Uni., China*	**Cerium Oxide Nanoparticles a Potential Therapy for Hepatic Fibrosis Symptoms** *Adrian Boey, National Uni. of Singapore, Singapore*
16:10 – 16:40	**Toxicity Studies of Supercritical Fluid Extract of Local Ziziphus Mauritiana (Bidara) Fruit** *Arnida Hani The, Uni., Kebangsaan Malaysia, Malaysia*	**Overview of Genotoxicity Field in Malaysian Environment** *Mogana Das Murtey, Uni. Sains Malaysia, Malaysia*	**Reduction of Arsenic Toxicity Through Nrf2 Activation Mediated by (2)-2-Alkenals in Coriandrum Sativum L. Leaf Extract** *Hanako Aoki, Uni. of Tsukuba, Japan*
16:40 – 17:00	Question and Answer Session		

Day-3: Wednesday, 16th June 2021

08:55 – 09:00	Introduction to Keynote Speaker		
09:00 – 09:40	**Keynote: Global Harmonization – Togetherness for the Effective Implementation of the 3Rs of Animal Use within the Toxicity Assessments of Chemicals and Pharmaceuticals** *Fiona Sewell, NC3Rs, UK*		
Day 3 Subtheme: Advances in Toxicity Testing for Product Safety			
09:40 – 09:50	**Symposium 6: Advance Topics in Toxicologic Pathology** *Chair: Maria Lucia Zaidan Dagli, Uni. of Sao Paulo, Brazil*	**Symposium 7: Recent Advances in Liver Disease: from Non-Alcoholic Fatty Liver Disease (NAFLD) to Fibrosis** *Chair: José Manautou, Uni. of Connecticut, USA*	**Symposium 8: 3Rs Alternatives for Regulatory Testing** *Chair: Masao Fukumura, PETRONAS, Malaysia*
09:50 – 10:20	**The Essential Use of Rodent Models for Toxicological Endpoints in Cancer Research** *Maria Lucia Zaidan Dagli, Uni. of Sao Paulo, Brazil*	**Environmental Chemicals as Risk Modifiers for NAFLD** *Juliane Beier, Uni. of Pittsburgh, USA*	**Medical Devices and Non-Animal Methods for Toxicological Risk Assessment** *Christian Pellevoisin, Episkin, France*
10:20 – 10:50	**Bridging the *In Vitro* and *In Vivo* Histopathological Evaluation for the Pharmaco Safety Assessment** *John R Foster, ToxPath Sciences Ltd., UK*	**Impact of Multidrug Resistance Protein 4 (Mrp4) Function on Hepatic Lipid Accumulation** *José Manautou, Uni. of Connecticut, USA*	**Integration of the 3Rs Alternatives in the Safety Testing for Nanotechnologies** *Sasitorn Aueviriyavit, NANOTEC, Thailand*
10:50 – 11:10	Break		
11:10 – 11:40	**Comparative Pathology of the Toxicity of Drugs and Environmental Chemicals for Human Risk Assessment: Are Rodents Relevant?** Jerrold M. Ward, Global VetPathology, USA	**Genetic Susceptibility to Non-Alcoholic Fatty Liver Disease: Asian Genome** Guruprasad Aithal, Queen's Medical Centre, Nottingham, UK	**Applying Zebrafish Embryo Acute Toxicity Test in China: Status and Prospect** *Zhenlie Huang, Southern Medical Uni, China*
11:40 – 12:10	**A Toxicologist's View of Modern Safety Assessment** *Wolfgang Dekant, Uni. of Würzburg, Germany*	**Inorganic Nanoparticles: Impact on Endothelial Biology Liver Fibrosis** *Ho Han Kiat, National Uni. of Singapore, Singapore*	**Current Views on the 3Rs Adaptation for the Skin Sensitization Testing** *Takao Ashikaga, NIEHS, Japan*
12:10 – 12:30	*Question and Answer Session*		
12:30 – 13:30	*Break*		
13:30 – 13:40	**Forum: Women in Toxicology** *Chair: Razinah Sharif, Uni. Kebangsaan Malaysia*	**Oral Session 6: Nanotoxicology** **Chair:** Siew Ee Ling, Uni. Kebangsaan Malaysia, Malaysia	**Oral Session 7: Occupational, Clinical or Regulatory Toxicology** Chair: Ahmad Faizal Abdull Razis, Uni. Putra Malaysia
13:40 – 14:10	**A Portfolio Career in Industry and Academia** *Ruth Roberts, ApconiX*	**Silver Nanoparticles Induced Apoptosis in Hippocampal Neurons through Mitochondrial Dynamics via Elevating Intracellular ROS and Ca^{2+} Level** *Chang Xiaoru, Southeast Uni., China*	**Educational Resources for Training in Non-Animal Regulatory Testing Methods in Developing Countries** *Esther Haugabrooks, PCRM, USA*
14:10 – 14:40	**Exploring *In Silico* Toxicology from a Malaysian's Perspective: The Journey from Europe to Back Home.** *Rozaini Abdullah, Uni. Putra Malaysia*	**Protein Corona Mitigated the Toxicity of Cadmium Telluride Quantum Dots to Macrophages by Targeting Mitochondria** *Na Liu, Southeast Uni., China*	**Challenges of GHS Implementation Worldwide** Goh Choo Ta, Uni. Kebangsaan Malaysia, Malaysia
14:40 – 15:00	*Break*		
15:00 – 15:30	**Traditional Herbal Poisoning in Vietnam** *Uyen Vy Doan, Cho Ray Hospital, Vietnam / National Yang-Ming Uni., Taiwan*	**Toxicity of Curcumin Nanoparticles in Alveolar Macrophage: Effects of Surface Charges** *Lee Wing Hin, Uni. Kuala Lumpur, Malaysia*	**Microplastic Exposure, Possible Health Impact and Policy Measures** *Ahmad Faizal Abdull Razis, Uni. Putra Malaysia, Malaysia*
15:30 – 16:00	**Misuse of Prescription Drugs in Singapore: An Insight from Public Health Specialist** *Chan Wui Ling, Singapore SOT*	**Macrophage Polarization and Inflammation Induced by Silver Nanoparticles via Autophagy in BV2 Cells** *Mengting Shang, Southeast Uni., China*	**Safety Pharmacology Test of Plant-Based COVID-19 Vaccine in Non-Human Primates** *Suchinda Malaivijitnond, Chulalongkorn Uni., Thailand*
16:00 – 16:20	*Question and Answer Session*		
16:20 – 16:30	*Closing Speech & Announcement of the venue of CTDC12 (MySOT President)*		
16:30 – 16:40	*CTDC12 Host Presentation*		

PART II: ABSTRACTS OF THE CONTINUING EDUCATION COURSES (CEC)

CEC 1:
Evolving International Methodologies and Tools for Chemical Risk Assessment

Kindly scroll/flip next few pages
to view the selected abstract

INTRODUCTION TO THE COURSE: EVOLVING INTERNATIONAL METHODOLOGIES AND TOOLS FOR CHEMICAL RISK ASSESSMENT (WHO)

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ABSTRACT

Introduction:
Traditionally, toxicological studies using animal test species are conducted to identify the adverse effects produced by a specific chemical to determine a reference point which is then used to derive either a health-based guidance value or a margin of exposure. In these studies, descriptive and mechanistic toxicology approaches are used.

Objective:
Sheer scale in the numbers of chemicals that need to be studied, breadth of endpoints and pathways to be covered, levels of biological organization that need to be examined, range of exposure conditions that need to be considered, will make the implementation of descriptive and mechanistic toxicology approaches in the hazard assessment of chemicals a difficult task to achieve. Modern methodologies and tools are therefore proposed in the context of prioritisation of chemicals.

Methods:
This course will provide a review of modern methodologies and tools to assess hazardous nature of chemicals including among others the *in silico* tools such as (quantitative) structure activity relationships (Q)SARs) and Physiologically based pharmacokinetic (PBPK) modelling, a computational approach that simulates the absorption, distribution, metabolism and elimination (ADME) of chemical substances in the bodies of organisms.

Results and Discussion:
The use of such modern methodological approach has been recommended by the World Health Organization (WHO) and by different regulatory authorities worldwide such as the United States Environmental Protection Agency (US-EPA) where they have also highlighted the need to develop a guidance to pursue common principles for their application in chemical hazard assessment and risk assessment. Interactive exercises will therefore be provided on these *in silico* approaches that may be implemented in the risk assessment of chemicals.

Keywords: Hazard assessment, Computational toxicology, QSAR, PBPK, Risk assessment

References:

Not applicable

OVERVIEW OF IPCS METHODLOGIES AND THEIR INTERRELATIONSHIPS

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ABSTRACT

Introduction:
Interrelationships of various Guidance documents of the World Health Organization (WHO)/International Programme on Chemical Safety (IPCS) Harmonization Initiative and selected recent Environmental Health Criteria documents (e.g., EHC 240) are "mapped" to provide additional context and guidance.

Objective:
The interrelationships of WHO/IPCS documents or products related to methodological approaches to chemical risk assessment are considered as a basis to provide practical advice concerning their implementation in tiered assessment and management strategies. Potential methodological gaps are identified and draft recommendations for follow up included.

Methods:
The level of description has been tailored to increase understanding of the interrelationships of guidance documents on methodology of WHO/IPCS as a basis to facilitate pragmatic application in tiered assessment strategies. Aspects relevant to the selection and application of approaches of varying complexities as a function of important considerations in problem formulation are presented.

Results and Discussion:
While the need for problem formulation to delineate focus to ensure efficiency and effectiveness of risk assessment to meet risk management objectives has been well documented, there is limited existing Guidance on its specific content or form or associated process to ensure adequate transparency and consistency of criteria for selected approaches or considerations for assessment. This is critical as a basis to streamline approaches to risk assessment and management in iterative and tiered fashion to ensure that no more resources are invested than is necessary to set a substance aside as a non-priority for further assessment or to additionally refine assessment as a basis to inform risk management to protect public health.

Keywords: problem formulation, tiered assessment, mode of action, uncertainty analysis

References:

Bhat, V.S., Meek, M.E., Valcke, M., et al. (2017). Evolution of chemical-specific adjustment factors (CSAF) based on recent international experience, increasing utility and facilitating regulatory acceptance. Crit Rev Toxicol, 47 (9), 729-749. DOI:10.1080/10408444.2017.1303818

Boobis, A.R., Cohen, S.M., Dellarco, V., et al. (2006). IPCS framework for analyzing the relevance of a cancer mode of action for humans. Crit Rev Toxicol, 36, 781-792.

Boobis, A.R., Doe, J.E., Heinrich-Hirsch, B., et al. (2008). IPCS framework for analyzing the relevance of a noncancer mode of action for humans. Crit Rev Toxicol, 38, 87-96.

Meek, M.E., Barton, H.G., Bessems, J., et al. (2013). Case study illustrating the WHO/IPCS guidance on characterization and application of physiologically based pharmacokinetic models in risk assessment. Regul Toxicol Pharmacol, 66, 116-129.

Meek, M.E., Boobis, A.R., Crofton, K.R., et al. (2011). Risk assessment of combined exposures to multiple chemicals: a WHO/IPCS framework. Reg Toxicol Pharmacol. 60, S1–S7.

UPDATE ON LATEST WHO/IPCS ACTIVITIES ON CHEMICAL RISK ASSESSMENT METHODOLOGIES, INCLUDING THE UPDATED HUMAN HEALTH RIS ASSESSMENT TOOLKIT

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ABSTRACT

Introduction:
The Guidance documents on chemical risk assessment developed by the World Health Organization (WHO)/International Programme on Chemical Safety (IPCS) are periodically updated to take account of scientific developments and changes in risk assessment practices. Two key guidance documents which have recently been updated will be highlighted in this presentation.

The WHO Human Health Risk Assessment Toolkit: Chemical Hazards provides guidance on how to conduct a chemical risk assessment, including how to obtain information and data published by international organizations. The Toolkit, first published in 2009, has recently been updated to reflect advances in chemical risk assessment methodology, including in dose-response assessment and characterizing uncertainty.

Environmental Health Criteria volume 240 provides guidance on chemical risk assessment methodology, in particular for assessing the health effects of chemicals in food. Key chapters of this publication have recently been updated to reflect the latest scientific advances in the areas of dose-response assessment and derivation of health-based guidance values, assessment of genotoxicity and advances in dietary risk assessment.

These key publications, the recent updates and other WHO/IPCS activities in the area of chemical risk assessment methodology will be presented.

Objective:
Not applicable

Methods:
Not applicable

Results and Discussion:
Not applicable

Keywords: WHO, IPCS, chemical risk assessment methodology, genotoxicity, dietary risk assessment

References:

Not applicable

COMPUTATIONAL TOXICOLOGY IN HAZARD CHARACTERIZATION AND RISK ASSESSMENT

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ABSTRACT

Introduction:
Expansion of regulatory mandates internationally has required more efficient and effective risk assessment and management of much larger numbers of Existing Substances. This requires less reliance on labour intensive animal bioassays with a shift to more predictive inference by computational tools drawing upon a much broader array of data often generated at lower levels of biological organization.

Objective:
To frame the legislative background and integrative mechanistic constructs, such as Adverse Outcome Pathways (AOPs) and Mode of Action (MOA) and their associated quantitation to describe the conceptual basis for computational toxicology. To describe the nature and considerations for evaluation of various computational tools, such as quantitative structure activity (QSAR) analysis and physiologically based pharmacokinetic models (PBPK) in exposure and hazard assessment.

Methods:
A number of computational tools aid consideration of data in hazard and risk assessment. These include tools to facilitate and systematically document the chemical specific evidence for hazard, the quantitation of dose-response relationships in benchmark dose modelling, and the probabilistic characterization of uncertainty in default and chemical specific adjustment factors. In addition, chemically agnostic AOPs (descriptions of key events in the induction of disease) and their application in chemical specific hazard characterization (MOA) provide the conceptual construct for increasing incorporation of mechanistic data in hazard characterization and risk assessment. These mechanistic constructs provide the basis for quantitative characterization of predictive inference based on structural and physico-chemical chemical characteristics in QSAR analysis, toxicokinetics in PBPK modelling and response-response analysis in toxicodynamic modelling.

Results and Discussion:
The basis, nature and interface for computational models and their application in hazard and dose-response assessment are described. Considerations for evaluation of these models in regulatory application are also presented.

Keywords: Benchmark Dose Modelling, Probabilistic Uncertainty Analysis, Adverse Outcome Pathways, Mode of Action, PBPK & QSAR Models

References:

WHO IPCS (2010). Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment. http://www.who.int/ipcs/methods/harmonization/areas/pbpk_models.pdf.

Meek, M.E., Barton, H.A., B., Bessems, J.G, et al. (2013). Case study illustrating the WHO IPCS guidance on characterization and application of physiologically based pharmacokinetic models in risk assessment. Regul Toxciol Pharmacol, 66(1), 116-129. https://doi.org/10.1016/j.yrtph.2013.03.005.

Edwards, S.W., Tan, Y.M., Villeneuve, D.L., et al. (2015). Adverse outcome pathways – Organizing toxicological information to improve decision making. JPET, https://doi.org/10.1124/jpet.115.228239.

What is the QSAR Toolbox? www.qsartoolbox.org

ECHA (2017). Read-Across Assessment Framework. https://echa.europa.eu/documents/10162/13628/raaf_en.pdf

INFORMATION RESOURCES AND APPLICATIONS: DATABASES FOR HAZARD AND PREDICTIVE APPLICATION OF 'OMICS' DATA

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ABSTRACT

Introduction:
Both tremendous opportunities and challenges exist for Risk Assessors. The opportunities in open data sets have allowed many scientists to access vast datasets and track complex experiments conducted on a vast array of chemicals, organisms (C. elegans to human populations) and toxicological endpoints. The challenges to scientists have been to integrate these findings into risk assessment frameworks and models, in order to better inform both qualitative and quantitative risk management decisions.

Objective:
Three case studies will be used to illustrate these opportunities and provide problem-based solutions to these problems.

Methods:
The first case study will focus on the use of ontologies to facilitate cross species extrapolation and interpretation for informing adverse outcome pathways. The second case study will examine the use of systematic review for integrating databases for risk assessment and the third case study will examine the use of various omic platforms to address common risk assessment opportunities with an emphasis on single cell transcriptomics through metagenomics.

Results and Discussion:
These three cases will provide the attendee an introduction with application for the exciting new applications.

Keywords: qualitative risk management, quantative risk management, adverse outcome pathways, transcriptomics, metagenomics

References:

Not applicable

PART II: ABSTRACTS OF THE CONTINUING EDUCATION COURSES (CEC)

CEC 2:
VACCINE DEVELOPMENT IN THE 21ST CENTURY

Kindly scroll/flip next few pages to view the selected abstract

INTRODUCTION AND HISTORY OF VACCINES

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ABSTRACT

Introduction:
'The impact of vaccination on the health…is hard to exaggerate. With the exception of safe water, no other modality has had such a major effect on mortality reduction and population growth' (1). Despite having such high health impact 'comprehensive vaccinology training is not offered to medical/biological sciences students as part of their…courses and consequently there is insufficient knowledge of vaccine topics among health-care providers' (2). We hope this course will pique your interest to learn even more!

Objective:
The aim of this talk is to introduce the audience to vaccines and vaccinology to set the stage for the speakers that follow.

Methods:
The presentation will provide an overview of the following: the history of vaccines and heroes of vaccinology; the innate and adaptive arms of the immune system; types of vaccines and adjuvants and how they interact with the immune system; the concept of 'plug-and-play' vaccines based on platforms; the continuing need for preventive and therapeutic vaccines and vaccines for special populations; and the 'Valleys of Death' and other challenges in vaccine R&D.

Results and Discussion:
Vaccines save millions of lives every year and we have come a long way since the seminal experiments by Edward Jenner with smallpox in the late 1700s. In parallel with an ever-deepening understanding of the innate and adaptive immune systems, the advancements in basic sciences, nonclinical and clinical safety and efficacy testing, manufacturing technologies, regulatory sciences, and the formation of public-private partnerships have set the stage for a promising future. Vaccine and adjuvant platforms, together with experience gained during epidemics and pandemics, offer opportunities for streamlining development of improved existing vaccines and for developing new vaccines for diseases that have been identified as high global health priorities. The speakers that follow will expand upon select concepts introduced in this presentation.

Keywords: Antigen, adjuvant, preventive vaccine, therapeutic vaccine, immune responses

References:

1. Plotkin, SA and Mortimer, EA (1988). Vaccines. Philadelphia PA:Saunders.
2. Lambert, Paul-Henri, and Audino Podda. "Education in Vaccinology: An Important Tool for Strengthening Global Health." *Frontiers in immunology* vol. 9 1134. 24 May. 2018, doi:10.3389/fimmu.2018.01134.

NONCLINICAL REGULATORY AND TESTING CONSIDERATIONS FOR VACCINE DEVELOPMENT IN 2021

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ABSTRACT

Introduction:
The recent Covid-19 pandemic has once again highlighted the important role vaccines play in public health. Prior to approval or even clinical testing, nonclinical evaluation plays a crucial role in ensuring vaccine safety and efficacy. Hence this talk highlights the importantance of understanding and compliance with current worldwide regulatory expectations for nonclinical testing of novel prophylactic vaccines.

Objective:
The aim of this presentation is to discuss important elements of vaccine nonclinical development programs supporting safety, clinical development and licensure.

Methods:
This talk will highlight important nonclinical safety and efficacy considerations and requirements involved in global vaccine development in 2021. The foundations of vaccine safety testing will be presented in light of recent advances in vaccine technology and the evolving regulatory environment during the current Covid-19 pandemic.

Results and Discussion:
Vaccine safety and efficacy testing has traditionally differed significantly from that normally employed for traditional small molecule drug or biologic products. US and worldwide regulators understand this distinction and have defined regulatory expectations commensurate with a vaccine's intended use, biology, and diverse clinical populations. With new classes of both vaccines and adjuvants, and improvements in both immunological and analytical methodologies, the nonclinical regulatory expectations for vaccines have also evolved notably over the past several years. Consequently, this has resulted in a continued evolution in the nonclinical testing paradigms for novel vaccines. Moreover, the recent SARS, MERS and Covid-19 pandemics have also clearly demonstrated the need for both expedited development programs and innovative study designs. This presentation will discuss the unique aspects of vaccines and key nonclinical testing required in light of the rapid evolution of vaccine technologies, worldwide development programs and the changing landscape of recent infectious disease pandemics.

Keywords: Vaccines, Nonclinical, Regulatory, FDA, Safety

References:

None

CASE STUDIES ON REGULATORY TOXICOLOGY FOR PROPHYLACTIC VACCINES FOR THE DEVELOPING AND DEVELOPED WORLD

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ABSTRACT

Introduction:
One third of GSK's vaccines target diseases particularly prevalent in the developing world, including the WHO infectious disease priorities. In addition, the complexity of certain diseases with high medical burden require novel approaches in vaccine development.

Objective:
The aim of this presentation is to discuss important elements of vaccine nonclinical development programs supporting safety, clinical development and/or licensure.

Methods:
We present case studies of different novel vaccines, showcasing specific regulatory toxicology approaches taken to support licensure of these vaccines for use in the developing and developed world.

Results and Discussion:
The session will discuss how regulatory requirements for vaccines have evolved and will present case examples of novel nonclinical regulatory approaches taken to support the development or licensure of Herpes Zoster/Shingles, Malaria and Ebola prophylactic vaccines.

Keywords: vaccines, prophlylactic, zoster, shingles, malaria, ebola

References:

None

VACCINCES AND PREGNANCY – COVID-19 AND SPECIAL GROUPS

ALAN M HOBERMAN

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ABSTRACT

Introduction:
Currently there are a number of COVID -19 vaccines approved for use in humans. The majority of these vaccines have been tested in pregnant animals, but none had completed clinical trials in pregnant women or juvenile populations prior to approval. This talk will review what is known about safety of COVID vaccines in pregnancy and juveniles.

Objective:
The aim of this presentation is to discuss what is known about the safety of these approved vaccine for use in pregnant women and children under the age of sixteen.

Methods:
This talk will present what is known about the results of testing of COVID vaccines in pregnant and juvenile animals and update what has been observed in pregnant women and juveniles. Additionally, trials that are in progress that included pregnant women and/or juveniles will also be reviewed.

Results and Discussion:
Vaccine safety is established in pregnant animals prior to use in women of childbearing potential or pregnant women. Rodent or rabbits models are typical with exposure occurring both prior to pregnancy to assure a response to the vaccine occurring during pregnancy (organogenesis) and with exposure occurring during pregnancy to assure that any direct toxicity of the vaccine can be evaluated. The number of doses administered in these studies is variable but usually follows the N+1 rule, or at least one more vaccination then is to be given in the clinic. Evaluation of the offspring in these studies includes the four endpoints of developmental toxicity (death, malformation, growth and functional development). Interstingly, no specific juvenile studies in animals are required. For juvenile studies in humans, recuirtment of juveniles occurs based on age, with 12 to 16 year olds being administered the vaccine prior to 6 to 11 year olds and then moving to younger children if appropriate. The safety in pregnant women is monitored during clinical use of the vaccine as pregnancies are reported and followed to delivery and for sometime post birth. Formal clinical trials in pregnant women are in progress.

Keywords: Vaccines, Pregnancy, Juveniles, Safety

References:

None

PART III: LIST OF INVITED SPEAKERS ORAL PRESENTATIONS

PART III: ABSTRACTS OF THE INVITED SPEAKERS ORAL PRESENTATIONS

Keynote 1 and Keynote 2

Kindly scroll/flip next few pages
to view the selected abstract

THE BOTANICAL SAFETY CONSORTIUM: A PUBLIC-PRIVATE PARTNERSHIP TO ENHANCE THE BOTANICAL SAFTEY TOOLKIT

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5. AMERICAN HERBAL PRODUCTS ASSOCIATION, SILVER SPRING, MD, USA 6. PROCTER & GAMBLE HEALTH CARE, CINCINNATI, OH USA 6. DIVISION OF THE NATIONAL TOXICOLOGY PROGRAM, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES, RESEARCH TRIANGLE PARK, NC, USA 7. US FOOD AND DRUG ADMINISTRATION, SILVER SPRING, MD, USA

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ABSTRACT

Introduction:

The Botanical Safety Consortium (BSC) is a public-private partnership aimed at enhancing the botanical safety evaluation toolkit. This partnership is the result of a Memorandum of Understanding between the US Food and Drug Administration (FDA), the National Institutes of Health's National Institute of Environmental Health Sciences (NIEHS), and the Health and Environmental Sciences Institute (HESI). The BSC serves as a global forum for scientists from government, academia, consumer health groups, industry, and non-profit organizations to work collaboratively on developing and integrating new methods based on sound science into routine botanical safety risk assessments.

Objective:

The objectives of the BSC are: to engage with a broad group of global stakeholders to leverage the best scientific safety approaches; establish the appropriate levels of chemical characterization for complex botanical substances; identify pragmatic, fit-for-purpose, in vitro and in silico assays to evaluate botanical safety; evaluate the application of these tools via comparison to the currently available safety information; and to integrate these tools and approaches into a framework that can facilitate robust evaluation of botanical substances.

Methods:

Initial endpoints of focus are genotoxicity, hepatotoxicity & ADME, developmental & reproductive toxicity, cardiotoxicity, neurotoxicity, and systemic toxicity. Additional working groups on chemical analysis and data analysis have also been initiated. The consortium also aims to work with global partners to educate and engage scientists about botanical safety. This presentation will provide an overview on the structure, goals, and strategies of this initiative.

Results and Discussion:

This presentation will provide an overview on the structure, goals, and strategies of this initiative, along with the inital data we have generated to date.

Keywords: Herbal, botanicals, in vitro, non-mammalian, supplements

References:

Roe, A. L. *et al.* The Botanical Safety Consortium. *Appl. Vitr. Toxicol.* **5**, 4–9 (2019)

Marsman, D. S., Dever, J. T., Gafner, S. & Rider, C. The Botanical Safety Consortium (BSC): The Development of a 21st Century Framework for Assessing the Safety of Botanical Dietary Supplements. (2019).

Galli, C. L. *et al.* Development of a consensus approach for botanical safety evaluation – A roundtable report. *Toxicol. Lett.* **314**, 10–17 (2019).

GLOBAL HARMONISATION: WORKING TOGETHER TO APPLY AND PROMOTE THE 3RS WITHIN TOXICITY ASSESSMENTS OF CHEMICALS AND PHARMACEUTICALS

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ABSTRACT

Introduction:
Toxicity tests are conducted as part of safety assessment to determine whether chemicals pose a threat to human health or the environment. Though the overall assessment may include a variety of in vitro, ex vivo, and in silico approaches, the current testing paradigm relies heavily on tests in experimental animals. However, animals can be poor predictors of humans and environmental species, with scientists facing growing pressure to reduce the reliance on animal toxicity tests, whilst simultaneously improving the science and predictivity of safety assessment. One of the major hurdles to overcome is lack of global harmonisation, both in terms of current testing requirements and the activities involved in the investigation, validation and ultimate acceptance of techniques or approaches which may replace, reduce or refine (the 3Rs) the use of animals within toxicity studies. The regulatory environment is complex and specific requirements vary greatly depending on product type and use, and geographical region. This can mean that duplicate or very similar tests can be required to market the same product in different regions, and since most companies market their products worldwide, data packages often reflect the needs of the regulatory authority that requires the most data. As geographical regions are at different stages in reviewing requirements for animal testing and the acceptance of non-animal methods, even if only one region maintains a requirement for animal data, this limits any 3Rs benefits and increases effort.

Objective:
The NC3Rs aims to lead the discovery and application of new technologies and approaches that minimize the use of animals in research and improve animal welfare.

Methods:
The NC3Rs works collaboratively with industry and regulators worldwide to collect and share pre-competitive data between companies to build evidence-bases to support recommendations for change in practice or policy.

Results and Discussion:
Projects will be presented that have led to changes in international regulatory guidelines and/or recommendations for best practice study designs to minimise animal use within current regulatory frameworks: 1) the adoption of the one concentration approach for fish bioaccumulation studies within OECD Test Guideline TG305 and OCSPP Test Guideline 850.1730; 2) the adoption of OECD Test Guideline TG433 a new and refined method for acute inhalation studies, which uses fewer animals and avoids lethality as an endpoint; 3) the removal of the requirement for acute oral toxicity studies within ICH guideline M3(R2) for pharmaceuticals; and 4) the use of recovery animals within first-in-human toxicology studies supporting pharmaceutical development.

Keywords: 3Rs, acute toxicity, bioaccumulation, recovery animals, global harmonization

References:
Sewell, F., et al. (2018). An evaluation of the fixed concentration procedure for assessment of acute inhalation toxicity. Regul Toxicol Pharmacol 94: 22-32. doi: 10.1016/j.yrtph.2018.01.001.

Sewell, F., et al. (2014). Recommendations from a global cross-company data sharing initiative on the incorporation of recovery phase animals in safety assessment studies to support first-in-human clinical trials. Regul Toxicol Pharmacol. 70(1):413-29. doi:10.1016/j.yrtph.2014.07.018

Burden N, et al. (2017). Reducing the number of fish in regulatory bioconcentration testing: Identifying and overcoming the barriers to using the 1-concentration approach. Integr Environ Assess Manag 13(1):212-214. doi:10.1002/ieam.1851

Robinson S, et al. (2008). Reducing the number of fish in regulatory bioconcentration testing: Identifying and overcoming the barriers to using the 1-concentration approach. Regul Toxicol Pharmacol. 50(3):345-52.

PART III: ABSTRACTS OF THE INVITED SPEAKERS ORAL PRESENTATIONS

Symposium 1

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to view the selected abstract

EXPERIMENTAL STUDIES ON REAL-LIFE RISK SIMULATION SUPPORTING THE SHIFT TO NEW RISK ASSESSMENT APPROACHES

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ABSTRACT

Introduction:
An individual is always exposed to a multitude of chemicals from different sources at levels around or below the regulatory limits. Contrarily, chronic toxicity studies used to set the safety limits of chemicals are done only for single chemicals each time. Even if these levels obtained based on classic toxicity studies are considered safe, epidemiological studies showed the contrary; the long term-low dose exposure to many chemicals being implicated in the pathogenesis of many diseases.

Objective:
A new methodology with the ambition to investigate in the same animal experiment the long-term effects of low loss of non-commercial mixtures of xenobiotics at several endpoints was proposed.

Methods:
The effects of low, realistic doses of a combination of pesticides, food additives and lifestyle products additives in a long-term regiment for genotoxicity, endocrine disruption, organ toxicity and mechanistic pathways were evaluated. Male and female rats were exposed for 2 years to the test mixture in doses below or around toxicological reference value (TRV). Changes in the blood and urine parameters, and neurobehavior were evaluated every 6 and 3 months, respectively. At the end of the study, the animals were sacrificed and histopathological evaluation was done.

Results and Discussion:
Non-monotonic effects at body weight gain, hepatotoxicity and induction of oxidative stress were observed after 6 and 12 months exposure to mixture of six pesticides and 7 food additives and lifestyle products additives in doses around and below the TRVs. After 18 months of exposure the effects become evident with structural changes at different organs, such as the stomach, liver, testes, kidney, lung and brain in both sexes. Genotoxic effects were observed only in female animals. Oxidative stress induction seems to play an important role in the observed changes. Followed up studies that added vitamin deficiency to long term low dose exposure to non-commercial pesticide mixture showed the association of the two stressors affects long term memory. Studies to provide more information on the long term low dose effects of exposure to chemical mixtures and how the results can be used to develop an integrated approach to testing and assessment in order to integrate in vivo findings using new technologies supporting the 3R concept for the evaluation of chemicals toxicity are under development.

Keywords: risk assessment, chronic exposure, toxicity, pesticides, real-life risk simulations

References:

Tsatsakis AM, et al. (2017). Simulating real-life exposures to uncover possible risks to human health… Hum Exp Toxicol, 36(6), 554-564.

Docea AO, et al. (2018). Six months exposure to a real life mixture of 13 chemicals' below individual NOAELs… Food Chem Toxicol, 115, 470-481.

Tsatsakis AM, et al. (2019). Hormetic neurobehavioral effects of low dose toxic chemical mixtures in real-life risk simulation (RLRS) in rats. Food Chem Toxicol, 125, 141-149.

Docea AO, Goumenou M, Calina D, et al. (2019). Adverse and hormetic effects in rats exposed for 12 months to low dose mixture of 13 chemicals: RLRS part III. Toxicol Lett. 310, 70-91.

Tsatsakis A et al. (2019). The effect of chronic vitamin deficiency and long term very low dose exposure to 6 pesticides mixture on neurological outcomes - A real-life risk simulation approach. Toxicol Lett, 315,96-106.

COMPLEMENTARY AND ALTERNATIVE MODELS IN RISK ASSESSMENT: WHAT CAN WE LEARN FORM WORMS?

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ABSTRACT

Introduction:
Various alternative models have been suggested to diminish animal use in experimentation. These models afford an option for studies on nervous system function, metabolism, oxidative stress, aging, toxicity, including metal toxicity, disease models and drug discovery up to some levels. Each alternative model system has advantages and disadvantages, highlighting the necessity for many models to understand the complexity of each system. Benefits associated with these alternative approaches are time efficiency, reduced manpower, and cost-effectiveness. Besides, the ethical concerns impart limitations on the use of higher vertebrates, and, consequently, the use of alternative organisms has become a relevant alternative to vertebrates.

Objective:
The objective of this presentation is to highlight the utility of *Caenorhabditis elegans* (*C. elegans*) in assessing metal-induced neurotoxicity.

Methods:
C. elegans is a small free-living nematode that inhabits moist soils and uses bacteria as a food source. Under laboratory conditions, *C. elegans* is cultured on bacterial lawns grown on an agar substrate. The development from eggs to adults is in about 2.5 days, with a mean lifespan of around 20 days (20°C) and the adults can reach about 1mm in length. The majority of the animals are hermaphrodites (XX), generally about 300 offspring, but in a thousand individuals about one is male (XO).

Results and Discussion:
Due to many advantages Caenorhabditis elegans (*C. elegans*) has become a preferred model of choice in many fields, including neurodevelopmental toxicity studies. This review discusses the benefits of using C. elegans as an alternative to mammalian systems and gives examples of the uses of the nematode in evaluating the effects of major known neurodevelopmental toxins, including manganese, mercury, lead, fluoride, arsenic and organophosphorus pesticides. Reviewed data indicates numerous similarities with mammals in response to these toxins. Thus, C. elegans studies have the potential to predict possible effects of developmental neurotoxicants in higher animals, and may be used to identify new molecular pathways behind neurodevelopmental disruptions, as well as new toxicants.

Keywords: C. elegans, Manganese, Mercury, Neurodevelopment, Neurotoxicity, Pesticides

References:
Not applicable or not provided by author

THE APPLICATION OF BIG DATA AND MACHINE LEARNING IN RISK ASSESSMENT

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ABSTRACT

Introduction:
A number of high-content and high-throughput technologies as well as the curation of databases of legacy data and scientific publications have made big data in toxicology available in recent years. Machine learning (artificial intelligence, A.I.) allows to mine these data and make "big sense" from these big data providing novel tools to complement risk assessments.

Objective:
Demonstrating the opportunities for A.I. in toxicology with a number of examples.

Methods:
We created a large toxicological databases from the European Chemical Agency (ECHA) extracting using linguistic search engines into a structured, machine readable and searchable database. Adding further public databases, a read-across-based structure activity relationship (RASAR) was developed. Predictions were validated by cross-validation. Other A.I. uses will be discussed.

Results and Discussion:
In collaboration with Underwriters Laboratories (UL), a global safety consulting and certification company, a database with more than 10 million chemical structures (more than 300,000 of which annotated with biological and chemicophysical data and 80,000 with animal data). It took an Amazon cloud server two days to analyze the similarities and differences between the 10 million chemicals to place them on a map, where similar chemicals are put close to each other, dissimilar ones distant. Making use of 74 properties in a data fusion approach, random forrest machine learning was applied in a five-fold cross-validation. Applying this to 190,000 classified chemicals based on animal tests, 87% of the time the computer was correct. Notably, each prediction comes with an expression of certainty based on the constellation of data available. The software was even better for finding toxic than non-toxic substances with 89% success—exceeding the 70 percent probability of animal tests to find a toxic substance again in a repeat animal test, shown in a parallel analysis of the database. The software (the UL Cheminformatics Tool Kit) at this stage predicts nine different hazard classifications, traditional testing for which consumes 57 percent of all animals in safety testing in Europe, or about 600,000 animals per year.

Keywords: 3Rs, alternative methods, machine learning, computational toxicology, artificial intelligence

References:

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PART III: ABSTRACTS OF THE INVITED SPEAKERS ORAL PRESENTATIONS

Symposium 2

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OVERVIEW OF THE APPROACH TO COMBINED EXPOSURES IN THE WHO SCREENING TOOL

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ABSTRACT

Introduction:
The WHO-International Programme on Chemical Safety (IPCS) framework on risk assessment of combined exposure to multiple chemicals serves as the basis for development of a pragmatic screening tool for indoor air in public settings of children by WHO/Euro.

Objective:
To facilitate the consideration of co-exposures in assessing health risks to children in public settings in determining the need to refine evaluation and/or to intoriduce risk reductaion measures.

Methods:
The screening tool comprises a database of supporting toxicological information for selected chemicals and adverse effects (endpoints) and a spreadsheet to calculate risk of combined exposures, based on specified decision rules.

Results and Discussion:
The terminology and approach adopted for the screening tool are consistent with those of the IPCS programme and those of WHO-IPCS framework and its application by WHO. The target audience for the screening tool is public health professionals, risk assessors at national, regional and local levels, and specialists involved in evaluating the quality of indoor air and promoting risk reduction measures in public settings for children. Balance of complexity to reduce uncertainty and ease of application for the target audience has guided the development of the screening tool. The tool addresses early Tiers (0 an 1) of the WHO-IPCS framework to reduce complexity and facilitate communication and application, modified to suit application to indoor air in public settings for children. A number of default adjustments is incorporated to facilitated application. Dose additivity of components of assessment groups is assumed; the current form of the screening tool does not address synergism or antagonism.

Keywords: exposure, chemicals, indoor are, combined risks, children

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Meek, M. E., Boobis, A. R., Crofton, K. R., et al. (2011). Risk assessment of combined expsoures to multiple chemiclas: A WHO/IPCS framework. Reg Toxicol Pharmacol, 60, S1-7.

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THE SUPPORTING DATABASE: AN UPDATED RESOURCE OF INTERNATIONAL GUIDANCE VALUES

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ABSTRACT

Introduction:
A pragmatic screening tool for indoor air in public settings of children has been developed by WHO/Euro. A database of supporting hazarda data is one of the cornerstones of the tool.

Objective:
To develop a supporting database with toxicologically relevant information to support flexible application in the different tiers of the screening tool.

Methods:
The toxicological database was constructed using hierarchical searches on health based reference values and acceptable concentrations, and points of departure for inhalation for 5 health endpoints considered most relevant in WHO consultations supporting the development of the screening tool (effects on the respiratory system, effects on the nervous system, effects on the cardiovascular system, eye and respiratory irritation and carcinogenicity).

Results and Discussion:
The selection procedure resulted in a database containing health based references values and points of departure (LOAEL, NOAEL, BMD, TC) for inhalation for the 5 considered health endpoints of the chemicals prioritised in the WHO consultations for the tool development, including substances in the chemical families of aldehydes, aromatic hydrocarbons, terpenes, chlorinated hydrocarbons, esters, PAHs, and nitrogen dioxide. To facilitate assessment of combined exposure in Tier 1, chemicals were group based on evidence of similar endpoints/effects. Chemicals without BMD, LOAEL, NOAEL or TC, or only with NOAEL(s) for the highest test dose were excluded. The health based references and points of departure for the 5 health endpoints can be flexibly applied in the different tiers of tool to calculate risk indices, and to support the grouping of chemicals a in the Tier 1 calculations.

Keywords: health based reference value, point of departure, chemicals, indoor air, grouping

References:

Meek, M. E., Boobis, A. R., Crofton, K. R., et al. (2011). Risk assessment of combined exposures to multiple chemicals: A WHO/IPCS framework. Reg Toxicol Pharmacol, 60, pS1-7. Doi:10.1016/j.yrtph.2011.03.010

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EXPOSURE ASSESSMENT TO SUPPORT THE SCREENING TOOL

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ABSTRACT

Introduction:
The exposure rate is calculated as the concentration of a chemical in an exposure medium multiplied by the rate at which a person inhales or ingests that medium, divided by their representative body weight. Exposure through inhalation is the concentration of a chemical inhaled during a specified exposure period which can be directly measured or modelled.

Objective:
To develop an approach to evaluation of exposure to chemicals in indoor air in public settings for children for calculating health risks using the screening tool.

Methods:
The approaches to sampling and estimation of combined exposures of children to chemicals in public spaces such as schools in the screening tool were recommended by international experts at consultations organized by WHO ECEH. Relevant considerations were quantitative characterization, reliability, relevance to long-term exposure and feasibility of sampling,

Results and Discussion:
Steps addressed relevant to assessment of exposure included selection of sampling sites of concern, appropriate sampling strategy and estimation of exposure. Long-term average exposures are considered most relevant for the characterization of risk in the screening tool. Continuous passive sampling, except of for benzo(a)pyrene, is recommended, relevant for long-term health hazards identified as priorities for inclusion in the screening tool and ease of implementation in public settings such as schools, kindergartens and day-care centres (24 hours per day, five days per week). There are no adjustments for intermittent to continuous exposure, due to the similarity of exposure patterns for many of the supporting toxicological data. Additional factors to address duration (variation in the design of exposure assessment in animal studies versus continuous passive monitoring in schools, potencial greater susceptibility of children) are not incorporated to maximize simplicity in the application of the screening tool.

Keywords: exposure, chemicals, indoor air, combined risks, children

References:

Summary of principles for evaluating health risks in children associated with exposure to chemicals. Geneva: WHO; 2011

Towards a tool for assessment of cumulative risks from indoor air pollutants in public settings for children: the second expert consultation. Meeting report. Copenhagen: WHO Regional Office for Europe; 2020

Methods for sampling and analysis of chemical pollutants in indoor air. Supplementary publication to the screening tool for assessment of health risks from combined exposure to multiple chemicals in indoor air. Copenhagen: WHO Regional Office for Europe; 2020

APPLICATION OF THE SCREENING TOOL

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ABSTRACT

Introduction:
Children, one of the most vulnerable groups, spend considerable time in public settings. There is still an increasing concern on indoor air quality as, among others, occupants still complain about indoor air quality and report health symptoms. Guidelines have already been set in several countries for individual indoor air pollutants; however, the investigation of the combined effects is scarce due to its complexity.

Objective:
To calculate the health risk associated with the exposure to multiple air pollutants in primary school buildings using the screening tool developed by the World Health Organization.

Methods:
The results of the indoor air quality monitoring campaign carried out in primary school buildings across five Central European countries in the framework of the InAirQ project (Transnational Adaption Actions for Integrated Indoor Air Quality Management) were used for the pilot testing. Besides the default values, other compounds investigated in the project and new reference values were also added and used for the calculations.

Results and Discussion:
Considerable differences in the hazard index values (Tier 0) were apparent among the school buildings selected for the calculations. The highest hazard quotient values were obtained for nitrogen dioxide in all cases, except for one location where the concentration of nitrogen dioxide was not monitored. The results also revealed that the non-carcinogenic risk is not negligible for the respiratory system among the five selected priority health effects in many cases (Tier 1, level 1). Furthermore, the screening tool was used to calculate the adjusted point of departure index for the selected effects of interest (Tier 1, level 2). Health concern was indicated for different end-points (respiratory and neurological). Besides nitrogen dioxide, the highest concern was on benzene and formaldehyde in the classrooms based on the outcomes of the assessment. The outcomes of the calculations provide support to the public health experts, the decision makers and other stakeholders to identify the problems and to ensure a healthy school environment for children.

Keywords: children, environmental health, indoor air, monitoring campaign, risk assessment

References:

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PART III: ABSTRACTS OF THE INVITED SPEAKERS ORAL PRESENTATIONS

Symposium 3

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THE 2020 UPDATE OF THE WHO GUIDELINES FOR POISON CONTROL

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ABSTRACT

Introduction:
Poison centres (PCs) are important sources of specialized, multi-disciplinary expertise to enable the best care for patients experiencing health effects as a consequence of exposure to potentially toxic substances such as pharmaceuticals, substances of abuse, natural toxins, pesticides, household products and industrial chemicals. In order to support countries in establishing and strengthening PCs, the WHO produced guidelines in 1997 to provide policy and technical advice for setting up PCs and related facilities and recommend approaches for harmonized data recording.

Since the guidelines were first published, the roles and functions of PCs have evolved and information technology and means of communication have been transformed. The primary activity of a PC remains the provision of advice to health care professionals and members of the general public. This is usually done by telephone but, increasingly, web-based technologies are being used and some PCs have developed online resources for health care professionals in cases of common poisonings. The collection and analysis of incident-related data (toxicovigilance) is a further essential activity as it allows identification of the circumstances of poisonings, the populations at risk and the toxic agents most likely to be involved. Importantly, it may also allow detection of previously unidentified hazards. An increased emphasis on the role of PCs in surveillance, detection and response to public health events caused by chemicals is the focus of separate presentations in this symposium.

These developments, as well as the fact that many countries still lack access to PC services, have prompted a revision and update of the WHO guidance with the publication of the "Guidelines for Establishing a Poison Centre" in 2020. While retaining the general format of the earlier version, the Guidelines are much expanded and include new chapters on training, quality assurance and potential funding sources. The changed title suggests a particular emphasis on supporting countries and regions where PCs are yet to be established. However, the Guidelines also provide a state-of-the-art reference for PCs and clinical toxicology services worldwide.

Objective:
Not applicable or not provided by author

Methods:
Not applicable or not provided by author

Results and Discussion:
Not applicable or not provided by author

Keywords: WHO, Poison Centre, Guidelines

References:

Guidelines for establishing a poison centre. Geneva: World Health Organization; 2020. https://www.who.int/publications/i/item/9789240009523

RECENT DEVELOPMENTS IN THE PUBLIC HEALTH MANAGEMENT OF CHEMICAL INCIDENT: THE IMPORTANCE OF POISONS CENTRES IN ASSESSING RISKS TO PUBLIC HEALTH

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ABSTRACT

Introduction:
The recent publication of the WHO Guidelines for poison control, entitled Guidelines for Establishing a Poison Centre, provides and update of the 1997 version and reflects the development of the role of poison centres in public health and the sound management of chemicals.

Objective:
This presentation will provide and overview of the role that poisons centres provide in managing chemical incident response and supporting public health, including the role that they paly in supporting alerting and toxicovigilance.

Methods:
Not applicable or not provided by author.

Results and Discussion:
Assessments carried out under the IHR show continuing gaps in capacity for managing chemicals. The guidelines describe the role of poison centres in toxicovigilance and the prevention of poisoning and their role in preparedness and response to chemical incidents. The presentataion also provides examples that highlight how poisons centres and public health authorities work together to improve public health response to chemical incidents.

Keywords: Poison Centre, WHO Guidelines for poison control, public health, toxicovigilance, chemical incident management

References:
Not applicable or not provided by author.

EMERGENCY RESPONSE PREPAREDNESS FOR CHEMICAL INCIDENTS

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ABSTRACT

Introduction:
Hazardous industrial chemicals whether in the raw or waste form can lead to environmental pollution if improperly handled. Among the most heinous wrongdoing is deliberate discarding of toxic waste as it can unnecessarily cause ill health effects to the humans in the vicinity of the dumping site thus requiring a rapid medical response. Such an incident had occurred in the State of Johor, Malaysia in the year 2019 where approximately 2.34 tons of toxic chemicals had been dumped into Kim Kim river in Pasir Gudang, Johor that caused a state of emergency requiring extensive resource mobilization.

This talk would highlight the existing disaster response mechanism from the facet of public health and its application during the crisis. Important events that happened during the response phase of the disaster include the offending chemicals identification, medical response mobilization, health protection response and pollution control measures will be elaborated. Post-crisis activities in the recovery and mitigation phase of the chemical incident include steps towards local policy change, further research and public empowerment for future event actions.

Objective:
Not applicable or not provided by author

Methods:
Not applicable or not provided by author

Results and Discussion:
Not applicable or not provided by author

Keywords: Pasir Gudang, Kim Kim river, emergency response preparedness

References:
Not applicable or not provided by author

INTERNATIONAL HEALTH REGULATIONS AND CORE CAPACITIES FOR CHEMICAL EVENTS

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ABSTRACT

Introduction:
Since 2005 the International Health Regulations (IHR), agreed by countries and published by the World Health Organization (WHO), have covered all diseases and events of international public health concern, including those linked to biological, chemical and radiation hazards. This presentation will describe the core capacities required for responding to chemical incidents according to the IHR (2005) and will present some examples of incidents of international public health concern.

The presentation will also describe how the core capacities for responding to chemical incidents are evaluated and the WHO guidance which is available for this, along with more general guidance on the public health management of chemical incidents. Chemical incidents in this context includes industrial and transport accidents, which may in some circumstances constitute a public health emergency of international concern, and also natural-hazard-triggered technological events ('Natech' events). WHO publications which describe these different types of events and their management will be presented.

Objective:
Not applicable or not provided by author

Methods:
Not applicable or not provided by author

Results and Discussion:
Not applicable or not provided by author

Keywords: WHO, Natech, International Health Regulations

References:
International Health Regulations (2005) – 3rd edition. Geneva: World Health Organization (2016).
https://www.who.int/publications/i/item/9789241580496

PART III: ABSTRACTS OF THE INVITED SPEAKERS ORAL PRESENTATIONS

Symposium 4

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UNPREDICTABLE ADVERSE EFFECTS OF HERBAL PRODUCTS

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ABSTRACT

Introduction:
Herbal products are being increasingly used all over the world for preventive and therapeutics purposes because of the belief of their safety being natural. However, as herbal products contain many bioactive components, the lack of sufficient study on their efficacy and toxicity, inadequate controls of their availability reduce their safety.

Objective:
To discuss in detail the unpredictable adverse effects of herbal products due to possible inetractions with drugs and due to the adulteration and contamination of herbal products with prohibited chemicals.

Methods:
Not applicable or not provided by author

Results and Discussion:
Unlike conventional drugs, herbal products are not regulated for purity and potency. Herbal products contain substances which can induce or inhibit enzymes that can take part in drug metabolism. Therefore the concurrent use of drugs with some medicinal plants can cause serious adverse effects and also decrease the efficacy of the therapy . Particularly, drugs with narrow therapeutic index (warfarin, digoxin, etc.), and many plants which affect drug metabolizing enzymes (*Hypericum perforatum, Panax ginseng, Ginkgo biloba*, Ephedra etc.) when used together, may lead to unpredictable adverse reactions. Patients with chronic diseases who also use herbal medicines must consider the adverse effects and interactions between these substances. Some of the adverse effects reported for herbal products could be caused by impurities. On the other hand, herbal adulteration, which is described as intentional substition with another plant or a drug to increase the potency of the product, is one of the common malpractises in herbal raw-material trade. In order to prevent undesirable effects and drug-herbal drug interactions, it is important to have more information and patients using herbal products must consult with their physicians and pharmacists.

Keywords: herbal products, adverse reactions, interactions , adulteration

References:

Rocha,T., Amaral, J.S., and Oliveira, M.B.P.PA. (2016). Adulteration of Dietary Supplements by the Illegal Addition of Synthetic Drugs: A Review. Compr Rev Food Sci F,15,43-66. doi: 10.1111/1541

Boufridi, A., and Quinn. R.J. (2018). Harnessing the Properties of Natural Products Annu Rev Pharmacol Toxicol, 58, 451-71.

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Calahan, J., Howard. D., Almalki. A.J., et al. (2016), Chemical Adulterants in Herbal Medicinal Products : A Review. Planta Medica Georg Thieme Verlag KG Stuttgart · New York .ISSN 0032-0943 doi:10.1055/s-0042-103495.

COMPLEMENTARY AND ALTERNATIVE MEDICINES – MALAYSIA SCENARIO

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ABSTRACT

Introduction:
Control of drugs and cosmetic regulation was promulgated in 1984 where all products must be registered before it is placed on the Malaysian market. Hence pre-market approval was implemented in phases beginning with registration of prescription drugs in 1985, followed by OTC, Health Supplements and traditional medicine. National Pharmaceutical Regulatory Agency (NPRA) as the secretariat to the Drug Control Authority (DCA) was given the task of ensuring the quality, safety and efficacy of these products through the registration, inspection and licensing scheme. The requirement for registration were updated regularly following local and international standards.

Objective:
To share on the current regulatory control of Complementary and Alternative Medicine in Malaysia

Methods:
Not applicable or not provided by author

Results and Discussion:
Not applicable or not provided by author

Keywords: complementary medicine, regulatory control

References:

National Pharmaceutical Regulatory Agency, Ministry of Health, Malaysia. Drug Registration Guidance Document (DRGD). Third Edition–January 2021. Available at https://www.npra.gov.my/index.php/en/component/sppagebuilder/925-drug-registration-guidance-document-drgd.html

QUANTITATIVE ANALYSIS OF GENOTOXICITY DATA ON HERBAL PRODUCTS

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ABSTRACT

Introduction:
Applied genotoxicity methods are changing from qualitative hazard identification to quantitative risk assessment. Quantitative analysis with point of departure (PoD) metrics and benchmark dose (BMD) modeling have been applied to in vivo or in vitro genotoxicity data. Two studies as examples of quantitative analysis of genotoxicity data obtained from herbal products are discussed.

Objective:
To quantitatively evaluate genotoxicity of direct mutagens, herbal dietary supplements, industrial compounds, cosmetic and retail products ingredients, and tobacco products by BMD modeling.

Methods:
Aristolochic acids (AA) are a group of structurally-related nitrophenanthrene carboxylic acids found in many plants, widely used by many cultures as traditional herbal medicines. AA is the causative agent for Chinese herbs nephropathy, also known as aristolochic acid nephropathy (AAN). AA is nephrotoxic, genotoxic, and carcinogenic in humans. A series of genotoxicity and toxicogenomic studies in rats exposed to AA for 12 weeks were conducted.

Results and Discussion:
AA treatments induced DNA adducts and mutations in the kidney, liver, and spleen of rats, and significant alteration of gene expression in both its target and non-target tissues. BMD modeling on the 3-month AA-induced genotoxicity data showed $BMDL_{10}$ for AA-induced mutations in the kidney of rats was about 7 μg/kg body weight per day. Pyrrolizidine alkaloids (PAs) and their corresponding PA *N*-oxides are a class of phytochemicals found in over 6,000 plant species. Humans may be exposed through the consumption of herbal products containing PAs. Recently, we identified specific CYPs responsible for bioactivating three PAs – lasiocarpine, riddelliine, and senkirkine; and demonstrated that PAs induced concentration-dependent increases in micronuclei in three CYP3A variant-expressing TK6 cell lines. BMD modeling demonstrated that lasiocarpine, of the three PAs, was the most potent inducer of micronuclei, with a BMD_{100} of 0.036 μM. Thus, BMD modeling is useful for quantitative evaluation of in vivo and in vitro genotoxicity data.

Keywords: genotoxicity, benchmark dose, aristolochic acids, pyrrolizidine alkaloids

References:

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Li, X., Guo, X., Wang, H.R., et al. (2020b). Aristolochic acid-induced genotoxicity and toxicogenomic changes in rodents. World J Tradit Chin Med 6, 12-25.

Li, X., Chen, S., Guo, X., et al. (2020a). Development and application of TK6-derived cells expressing human cytochrome P450s for genotoxicity testing. Toxicol Sci 175, 251–265.

Li, X., He, X., Chen, S., et al. (2020c). Evaluation of pyrrolizidine alkaloid-induced genotoxicity using metabolically competent TK6 cell lines. Food Chem Toxicol 145, 111662.

HERBAL PRODUCTS: REGULATION AND SAFETY TESTING IN THAILAND

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ABSTRACT

Introduction:
Thailand has a wide variety of natural resources, herbs and plants that are used as raw materials for many products. As the trend of health care and disease prevention through natural ways continue to increase, herbal products attract much attention. The products from herbs can be produced in the form of herbal medicines, dietary supplements and health care products, using technology and innovation to increase efficacy and safety.

Objective:
Not applicable or not provided by author

Methods:
Not applicable or not provided by author

Results and Discussion:
This presentation will share the latest information on the regulation of herbal products in Thailand. According to a gap in the product value chain, it is imperative to assist and promote the manufacturers of herbal products in various aspects, including research and development, testing of efficacy and safety, with cooperation from multiple departments to ensure that the products are qualified for registration and release to the market. The talk will also address testing capabilities, covering experimental design of efficacy testing related to the product health claims, and in vitro pre-clinical safety testing based on the OECD test guidelines that meet the requirement of international standards.

Keywords: herbal products, regulation, safety testing, efficady testing, OECD test guidelines

References:
Not applicable or not provided by author

PART III: ABSTRACTS OF THE INVITED SPEAKERS ORAL PRESENTATIONS

Symposium 5

Kindly scroll/flip next few pages
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APPLICABILITY DOMAINS AND FUTURE OF NON-ANIMAL TESTS

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ABSTRACT

Introduction:
The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is made up of representatives from US federal agencies that require or consider chemical safety testing data, and are interested in more rapid, human-relevant approaches to supplement or replace existing regulatory standard in vivo guideline tests. The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) provides scientific and administrative support to ICCVAM through a variety of efforts including methods development and validation, construction of computational tools, communication and outreach, and stakeholder engagement, all driven by federal agency priorities and decision contexts. This talk will provide an overview of ICCVAM and NICEATM's progress in developing, evaluating, and implementing alternatives to animal testing. Emphasis will be on implementation of the ICCVAM strategic roadmap, ongoing efforts to replace the "six-pack" of acute toxicity tests, and development of computational resources such as in vitro to in vivo extrapolation workflows, toxicity and property prediction models, and chemical characterization tools.

Objective:
This talk will provide an overview of ICCVAM and NICEATM's progress in developing, evaluating, and implementing alternatives to animal testing.

Methods:
Emphasis will be on implementation of the ICCVAM strategic roadmap, ongoing efforts to replace the "six-pack" of acute toxicity tests, and development of computational resources such as in vitro to in vivo extrapolation workflows, toxicity and property prediction models, and chemical characterization tools.

Results and Discussion:
Not applicable or not provided by author

Keywords: ICCVAM, six pack acute toxicity tests, NICEATM, non-animal tests

References:
Not applicable or not provided by author

THE AFSA COLLABORATION: IMPLEMENTING ANIMAL-FREE SAFETY ASSESSMENT OF COSMETICS GLOBALLY

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ABSTRACT

Introduction:
To achieve animal-free safety assessment of cosmetics globally, it is important to harmonize legislation and regulations to allow flexibility in safety assessment approaches. In addition, it is important to enable local capacity in safety assessment using data generated from non-animal approaches, including in silico, in vitro, and human-based data.

Objective:
Provide an overview of an international collaboration to achieve safety assessment of cosmetics without the need ro animal testing globally in the near future.

Methods:
A large collaboration was formed between Humane Society International, global industrial partiers, non-governmental groups and other key stakeholders to facilitate regulatory change in 40 key markets and to build an education and training program allowing all relevant stakeholders to assess the safety of cosmetics without the need for new animal testing. Partner subject matter experts collaborated on development of detailed educational content covering the entire risk assessment process, delivered in 8 overlapping modules, organized around learning objectives and outcomes.

Results and Discussion:
The program covers the risk assessment process as follows: beginning with problem forumulation, including gathering and evaluating all existing data and initial hypothesis generation. Maximizing the use of existing data includes applying History of Safe Use Principles. Safety assessment of cosmetics is necessaarly exposure-led, so a first step is estimating consumer exposure, followed by analysing the potential for expsore-based waiving of toxicological tests. In silico tools are used as a first pass to characterize physical, chemical and biological properties of the ingredients, and explore possilbities for read-across to similar, well-characterized substances. If necessary, information from various in vitro tests can be combined to provde information on and in some cases, points of departure for, local or systemic toxicity. Also if necessary, in vitor and in silico information can be used to estimate interal exposre, and to relate in vitro and in vivo concentrations. Finally, all of this information is compbined in a risk assessment of the particular product for the particular use scenario with a level of certainty necessary for a final risk decision.

Keywords: animal-free, risk assessment, cosmetics, in silico, in vitro, margin-of-exposure

References:

Amaral, R., Ansell, J., Boisleve, F., et al. (2018). Report for International Collaboration on Cosmetics Regulation, Regulators & Industry Joint Working Group (JWG): Integrated Strategies for Safety Assessment of Cosmetic Ingredients: Part 2. PDF: https://www.iccr-cosmetics.org/files/8315/4322/3079/ICCR_Integrated_Strategies_for_Safety_Assessment_of_Cosmetic_Ingredients_Part_2.pdf

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Dent, M., Amaral, R.T., Da Silva, P.A., et al. (2018). Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients. Comput. Toxicol. 7, 20–26. DOI: 10.1016/j.comtox.2018.06.001.

THE WAY FORWARD: THE EXPERIENCE AT CAAT

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ABSTRACT

Introduction:
Increasingly, the limitations of animal-based toxicology, as well as the shortcomings of traditional cell culture to predict human health threats are recognized. The increasing pace of technological developments of modern cell culture, computational methods and their integration leads to "disruptive technologies", which benefits the development of alternatives for safety assessment.

Objective:
Describing the opportunities for a scientific revolution in toxicology and the relevant CAAT programs to promote this.

Methods:
The creation of large toxicological databases ("big data") and data-mining technologies ("artificial intelligence") allow predictive computational approaches on a new scale. The combination of cell culture with bioengineering has led to a number of technologies for more organo-typic cell culture, such as 3D culture, human stem cell-derived systems, perfusion, co-cultures, combinations with scaffolds and sensors, leading to "organ-on-chip" or even multi-organ "human-on-chip" solutions.

Results and Discussion:
By recreating organ architecture, homeostasis of the cell environment and organ functionality, these models mirror more closely the physiological situation. The example of our human iPSC-derived mini-brain is used to illustrate this. The commercial availability of organoids also improves standardization and reproducibility. Computational methods based on A.I. match or outperform already a number of animal tests. Such technological advances promise to be real "game-changers". Combined with an increased mechanistic base of reasoning (e.g. Adverse Outcome Pathway concepts), Integrated Testing Strategies and evidence-based methods of data evaluation and integration, a revolutionary change for how we assess the biological effects of substances has been set into motion. A number of CAAT programs support these developments and their implementation.

Keywords: 3Rs, alternative methods, microphysiological systems, computational toxicology, evidence integration

References:

Anderson, W.A., et al. (2021). Advances in 3D neuronal microphysiological systems: towards a functional nervous system on a chip. In Vitro Cell Dev Biol Animal. Doi: 10.1007/s11626-020-00532-8

Marx, U., et al. (2020). Biology-inspired microphysiological systems to advance medicines for patient benefit and animal welfare. ALTEX, 37, 364-394. doi: 10.14573/altex.2001241

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Rovida, C., et al. (2020). Internationalisation of read-across as a validated new approach 2 method (NAM) for regulatory toxicology. ALTEX 37, 579-606. doi: 10.14573/altex.1912181.

Luechtefeld, T., et al. (2018). Machine learning of toxicological big data enables read-across structure activity relationships (RASAR) outperforming animal test reproducibility. Toxicol Sci, 165, 198-212. doi: 10.1093/toxsci/kfy152.

IMMUNOTOXICOLOGY: A HISTORY OF A SUCCESS

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ABSTRACT

Introduction:
A well-functioning immune system is essential for maintaining the integrity of an organism. Due to its late developing in life, continuous renewal, and delicate control of the balance between activation, silencing and regulation of immune reactivity after each pathogen attack, as well as during immunosurveillance, the immune system is highly vulnerable to chemical or physical insults. Exposure to immunotoxic compounds can have serious adverse health consequences affecting responses to both communicable and non-communicable diseases. It is therefore important to understand the immunotoxic potential of xenobiotics and the risk they pose to humans. Several in vitro methods have been validated and adopted worldwide for the identification of contact allergy, methods addressing chemical-induced immunosupression will be available soon.

Current in vivo models do not always provide a mechanistic understanding of the data, whereas molecular mechanisms may be easier to evaluate using in vitro methods. It is likely that several in vitro assays will be required to define immunotoxicants because of the different components of the immune system and its influences on other systems. Thus, a tiered approach is the most appropriate means to assess immunotoxicity even in vitro. While it is clear that more studies are needed to define the possibility of identifying immunotoxic substances without the use of animals, the road has been paved for the use of testing strategies which together will be able to adequately predict the immunotoxic action of chemicals in vitro. This presentation aims to present and discuss the application and interpretation of in vitro immunotoxicity assays, mainly covering immunosuppression, and to define a tiered approach to testing and assessment.

Objective:
Not applicable or not provided by author

Methods:
Not applicable or not provided by author

Results and Discussion:
Not applicable or not provided by author

Keywords: Not applicable or not provided by author

References:
Not applicable or not provided by author

PART III: ABSTRACTS OF THE INVITED SPEAKERS ORAL PRESENTATIONS

Symposium 6

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THE ESSENTIAL USE OF RODENT MODELS FOR TOXICOLOGICAL ENDPOINTS IN CANCER RESEARCH

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ABSTRACT

Introduction:
Rodent models have been used for cancer research since the end of 19th century and beginning of the 20th century. The most used conventional models are the transplantable tumors, like the Ehrlich ascitic tumor and B16 melanoma; chemical carcinogenesis models, like the DMBA model in the skin of mice; hepatocarcinogenesis models in rats and mice, lung, mammary, intestinal and others. These models have been used for many years as tools to answer relevant questions in cancer research and for the testing of new product safety and efficacy. A new era of cancer research using rodent models started from 1970's onwards. The possibility of manipulating the mouse genome creating the genetically modified models, replacing gene sequences by non functional ones, or inserting new sequences or multiple copies of genes, knockout models and transgenic models, were launched, and since then allow the understanding of the role of genes in vivo. For cancer research, many animal models have been used. Immunodeficient mice, like SCID, NOD-SCID and others have been used to create the "Avatar Mice", which are xenotransplanted with human tumors. These are important to test personalized new therapies. Humanized mouse models have been widely used in studies of human gene function, immuno-oncoloy therapeutics, infectious disease pathology and also preclinical drug evaluation. Many genetically modified (GEM) or genetically edited (CRISPR) mouse models are available and they can be used to understand the pathogenesis of selected cancers and the potential therapeutic approaches.

Objective:
The aim of this talk is to present the essential use of rodent models for toxicological endpoints in cancer research.

Methods:
Examples of the use of rodent models for the study of new antineoplastic or chemopreventive products in vivo, as well as the use of animal models for toxicological endpoints will be presented, with a brief description of the experimental procedures. Ethical aspects will be shown

Results and Discussion:
Although alternative models are being produced, rodent models are still necessary for some toxicological endpoints in cancer research.

Keywords: rodent, cancer, model, CRISPR, toxicologic pathology

References:

Russell, W.M.A., and Burch, R.L. (1959). Principles of Humane Experimental Technique, Springfield, IL, Charles C. Thomas.

Ward, J.M., Mahler, J.F., Maronpot, R.R., Sundberg, J.P (eds). (2000). Pathology of Genetically Engineered Mice. Iowa State University Press, EUA.

BRIDGING THE IN VITRO AND IN VIVO HISTOPATHOLOGICAL EVALUATION FOR THE PHARMACO SAFETY ASSESSMENT

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ABSTRACT

Introduction:
The concepts introduced through the TOX21 and RISK21 initiatives the US National Academy of Sciences has been a spur to the increased investigation of alternative, non-animal, approaches to the safety assessment of novel drugs and chemicals.

Objective:
The presentation reviews the contribution that "non-whole animal" approaches can make to the safety assessment of novel drugs and if, and how they might complement, or even replace, more conventional toxicity studies using animals, to enable safe human clinical trials.

Methods:
Not applicable or not provided by author

Results and Discussion:
Before any drug is administered to human beings, both the efficacy and safety has first to be proven through the conduct of animal, and non-animal, approaches including in vitro, in silico, and in vivo approaches. Efficacy studies have traditionally involved a multidisciplinary mix of these approaches and considerable variability in approach occurs between different companies and laboratories. In contrast, establishing the safety of a novel product, and defining its toxicity, has followed a much more prescribed pathway set down by internationally accepted guidelines such as those of the OECD. Goals, set out by the US National Research Council's TOX21 initiative, were to better utilise the newly developed technologies, and move away from the current reliance on animal toxicity testing, in ensuring human safety. While the new technologies have, for many years, been wholeheartedly embraced in establishing efficacy of a novel product, their impact in establishing safety has been minimal. This is understandable because of the conservative nature of the industry, and global drug regulatory agencies continue to request animal studies to support "first in man" and subsequent clinical phase studies.

Keywords: RISK21, TOX21, histopathology, safety, species extrapolation, risk

References:

Thomas, R.S., Paules, R.S., Simeonov, A., et al. (2018). The US Federal Tox21 Program: A Strategic and Operational Plan for Continued Leadership. ALTEC, 35(2), 163-168. doi:10.14573/altex.1803011.

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COMPARATIVE PATHOLOGY OF THE TOXICITY OF DRUGS AND ENVIRONMENTAL CHEMICALS FOR HUMAN RISK ASSESSMENT: ARE RODENST RELEVANT?

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ABSTRACT

Introduction:
Rodents are used in basic and translational research to assist in commercial product development and national government regulation, including for drugs, foods, agricultural and other chemicals, and in assaying health effects of the environment. Pathology is an important endpoint in this research. Some rodent toxicology and carcinogenesis research studies have been criticized for lack of relevance to humans, especially for human risk assessment.

Objective:
This presentation will review similarities and differences of toxicological and other responses of humans and rodents to these substances.

Methods:
Not applicable or not provided by author

Results and Discussion:
Human and rodents share many similarities in their anatomy and histology of organs and other tissues. The general structure, function and physiology of most tissues are often identical if not similar. Responses to exposure to infectious agents, chemicals, natural products, including foods are often similar but can be modified by genetic and environmental factors, even in the same species. The genetic research on mice has shown many genes that effect responses to chemicals with relevance to humans. This presentation will review the similarities and differences in the pathological responses of human and rodent tissues to chemicals. When differences are found, they must be taken into consideration for human risk assessment, used for regulation of chemicals which are drugs, other commercial products and environmental chemicals. Potential differences in the carcinogenic responses may be considered by analysis of the mode of action for chemicals causing the tumors in rodents. Although many of the human carcinogens also cause tumors in rodents, there are many more rodent carcinogens than those in humans, especially of the nongenotoxic type. Weight of the evidence must be used for assessing human risk to rodent carcinogens.

Keywords: pathology, chemicals, humans, rodents, mode of action

References:

EPA Cancer Guidelines. https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment.

Greaves, P., Williams, A., Eve, M. (2004). First dose of potential new medicines to humans: how animals help. Nature Rev Drug Disc, 3, 116. Doi: 10.1038/nrd1329.

Klein, D.E. (2017). The histopathological evaluation of drug-induced liver injury. Histopathology, 7(1), 81-93. doi: 10.1111/his.13082.

Heusinkveld, H., et al. (2020). Towards a mechanism-based approach for the prediction of nongenotoxic carcinogenic potential of agrochemicals. Crit Rev Toxicol, 50(9), 725-739. doi: 10.1080/10408444.2020.1841732.

A TOXICOLOGIST VIEW OF MODERN SAFETY ASSESSMENT

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ABSTRACT

Introduction:
Safety assessment of chemicals has gained a large importance and is required for all uses of chemicals.

Objective:
The presentation will cover the basic principles of safety assessment and the issues arising for their applications.

Methods:
Not applicable or not provided by author

Results and Discussion:
Modern safety or risk assessment relies on two basic pillars, assessment of exposures and assessment of the hazard or intrinsic toxicity of a chemical. While detailed procedures for hazard assessment have been developed and are covered by specific guidance in many legislations, exposure assessment in many cases is based on conservative assumptions of human behavior. More detailed exposure assessments based on use or consumption behavior of items releasing such chemicals are usually only available for large production chemcials. Therefore, improved information on actual exposures is considered a crucial point for further development.

Keywords: hazard assessment, exposure assessment, risk assessment, chemical toxicity

References:
Not applicable or not provided by author

PART III: ABSTRACTS OF THE INVITED SPEAKERS ORAL PRESENTATIONS

Symposium 7

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ENVIRONMENTAL CHEMICALS AS RISK MODIFIERS FOR NON-ALCOHOLIC FATTY LIVER DISEASE

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ABSTRACT

Introduction:
Vinyl chloride (VC), a common environmental pollutant, directly causes liver injury at high exposure levels. Lower concentrations, which do not overtly damage the liver, enhance injury caused by high fat diet (HFD), at least in part, via mitochondrial dysfunction and endoplasmic reticulum (ER) stress. Mitochondria and the ER interact with each other, and are sensitive to (patho)physiological conditions and maladaptive changes.

Objective:
The purpose of the current study was to investigate the mechanistic impact of VC on ER-mitochondria interactions.

Methods:
C57Bl/6J mice were exposed to VC below the current OSHA standard (<1 ppm), or room air for 6 hrs/d, 5 d/wk for up to 12 wks. Mice were fed HFD, or low-fat control diet (LFD). Plasma and liver samples were collected for determination of injury and mitochondria were isolated for analysis of mitochondrial (dys)function.

Results and Discussion:
VC exposure exacerbated liver injury caused by HFD and ER stress. VC exposure also dysregulated energy homeostasis and impaired mitochondrial function – even in the absence of HFD. Evidence for impaired mitochondrial function included dramatic structural changes to the mitochondria, impaired hepatic mitochondrial electron transport chain function and a decrease in maximum mitochondrial respiratory capacity, while fatty acid oxidation and mitochondrial DNA content were unaffected. VC also changed hepatic protein levels of several mitochondrial-associated ER membrane proteins, which are involved in mitochondrial function, and quality control of ER-mitochondrial crosstalk. Taken together, VC dysregulates mitochondrial and ER function, dynamics and interaction. These stress responses therefore play a causative role in VC-mediated liver toxicity and sensitization to other stressors. Importantly, these data raise concerns about potential overlap between diet and VC and emphasize that current safety restrictions may be insufficient to account for other factors that can influence hepatotoxicity in humans.

Keywords: organochlorines, TASH, liver disease, hepatotoxicity, mitochondrial maladaptation

References:
Not applicable or not provided by author.

IMPACT OF MULTIDRUG RESISTANCE PROTEIN 4 (MRP4) FUNCTION ON HEPATIC LIPID ACCUMULATION

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ABSTRACT

Introduction:
Hepatic transporters are important determinants of drug pharmacokinetics and drug-induced liver toxicity (DILI). The expression of drug transporters, such as the multidrug resistance-associated protein 4 (Mrp4), is known to be altered in reponse to DILI. Induction of Mrp4 is observed in hepatocytes undergoing proliferation.

Objective:
Given these findings, we hypothesized that Mrp4 function is important for hepatocyte proliferation and that lack of Mrp4 prevents liver regeneration following partial hepatectomy (PH) in mice.

Methods:
In this study, we performed PH surgery on male wildtype and Mrp4 knockout mice. Plasma and liver tissues were collected at various time points after surgery and evaluated for liver injury and liver regeneration endpoints, and for PH-induced hepatic lipid accumulation.

Results and Discussion:
Our results show that lack of Mrp4 did not alter hepatocyte proliferation and liver injury following PH. However, an unexpectedly, Mrp4 knockout mice exhibited significant increases in hepatic di- and triglyceride content. Gene expression analysis showed that lack of Mrp4 is associated with altered expression of various genes involved in lipid synthesis and metabolism. Further studies showed that the lack on Mrp4 promotes adipogenesis and adipogenic gene expression, both in vitro and in vivo. Indirect calorimetric analysis and measurement of various metabolic endpoints indicate that Mrp4 knockout mice exhibit a metabolic syndrome phenotype. Overall, our observations indicate that lack of Mrp4 leads to pronounced PH-induced hepatic steatosis in mice and also suggest that Mrp4 is be a novel genetic factor in the development of hepatic steatosis and metabolic syndrome.

Keywords: partial hepatectomy, drug transporters, Mrp4, steatosis

References:

Donepudi, A.C., Lee, Y., Lee, J.Y, Schuetz, J.D., and **Manautou, J.E.** (2021). Multidrug resistance-associated protein 4 (Mrp4) is a novel genetic factor in the pathogenesis of obesity and diabetes. *FASEB J.*, Feb;35(2):e21304. doi: 10.1096/fj.202001299RR.

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INORGANIC NANOPARTICLES: IMPACT ON ENDOTHELIAL BIOLOGY AND LIVER FIBROSIS

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ABSTRACT

Introduction:
Nanoparticles exhibit a natural tendency for liver accumulation. While this may impose toxicological concerns, the phenomenon presents opportunity for liver targeting, as an exploit to address chronic liver diseases.

Objective:
To advance our understanding in the area of non-alcoholic fatty liver disease, especially on the impact of inorganic nanoparticles on endothelial biology and liver fibrosis.

Methods:
Pharmacological effects of nanoparticles, such as titanium oxide were investigated in hepatic stellate cells, as well as in liver sinusoid endothelial cells.

Results and Discussion:
With the use of inorganic nanoparticles like titanium dioxide, we have observed an unexpected pharmacological effect in reversing fibrosis, using hepatic stellate cells as a model system. It suppresses the signature of fibrogenesis in terms of α-SMA expression and the deposition of collagen. It also modulates fibrolytic action of matrix metalloproteases. Separately, the same nanoparticles are able to alter endothelial biology leading to enhanced cell leakiness. This effect can help to restore sinusoidal permeability in cases of occlusion due to extensive fibrosis. Taken together, inorganic nanoparticles can exhibit distinct pharmacological activity on different liver cell types, thereby advancing its application in nanomedicine beyond their known capacities as drug carriers.

Keywords: non-alcoholic fatty liver disease, nanoparticles, stellate cells, fibrosis, nanomedicine

References:

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Tee, J.K., Ng, L.Y., Koh, H.Y., Leong, D.T., Ho, H.K. (2018). Titanium dioxide nanoparticles enhance leakiness and drug permeability in primary human hepatic sinusoidal endothelial cells. Int J Mol Sci, 20(1) pii E35

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PART III: ABSTRACTS OF THE INVITED SPEAKERS ORAL PRESENTATIONS

Symposium 8

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MEDICAL DEVICES AND NON-ANIMAL METHODS FOR TOXICOLOGICAL RISK ASSESSMENT

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ABSTRACT

Introduction:
The safety of any medical device is strictly evaluated before being marketed. The ISO 10993-1:2018 standard provides a framework for conducting this evaluation and performing the necessary tests as part of a risk management process. In addition to the chemical analysis, 3 endpoints must always be considered: cytotoxicity, irritation and sensitization.

While ISO 10993-5 has recommended in vitro tests for cytotoxicity since its inception in 1992, irritation has been assessed by in vivo tests until very recently. This is no longer the case with the recent publication of ISO 10993-23:2021, which requires the evaluation of this endpoint by in vitro methods on reconstructed human skin (RhE). Regarding sensitization assessment, the publication this year of part 10993-10 will include an informative annex with the state of the art of non-animal approaches for the evaluation of chemicals and their potential application to the particular case of medical devices. The qualification of some of these methods for medical devices sensitization assessment is in the roadmap of the working group 8 for irritation and sensitization of the ISO technical committee 194.

This presentation will review the latest normative developments in this area, upcoming projects and challenges for regulatory acceptance in the medical device field.

Objective:
Not applicable or not provided by author

Methods:
Not applicable or not provided by author

Results and Discussion:
Not applicable or not provided by author

Keywords: In vitro, medical devices, ISO 10933, irritation, sensitization, reconstructed human epidermis

References:
Not applicable or not provided by author

INTEGRATION OF THE 3RS ALTERNATIVES IN THE SAFETY TESTING FOR NANOTECHNOLOGIES

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ABSTRACT

Introduction:
With the European Directive 2010/63/EU on the protection of animals used for scientific purposes, the internationally recognised 3R Principle was legally recognised. In Thailand, Nanotechnologies have demonstrated significant contribution in various industries especially cosmetics, food and food packaging, and feed and feed additives. Therefore, to safely and effectively utilize of nanomaterials, the toxicological data from reliable predictive models are crucial.

Objective:
Nano Environmental and Health Safety Research Team (NANOTEC) aimed to develop and set up the reliable predictive models as the 3R alternatives in the nanosafety testing. We focus to apply both in vitro model and in vivo zebrafish model to reduce both animal and human ethic problem.

Methods:
We implemented 2D cell model and 3D-tissue model following OECD test guideline and ISO test method for nanosafety testing. Furthermore, we developed 3D-intestinal model derived from human and porcine intestinal organoid as the in vitro tools to evaluate intestinal toxicities. Regarding in vivo model, we use Zebrafish embryo model to evaluate aquatic toxicities.

Results and Discussion:
This presentation will highlight our capabilities on 3R alternatives in the safety testing for nanotechnologies. Following OECD test guidelines and ISO test methods, several guidelines such as OECD TG 439, OECD TG 432, OECD TG 487, ISO 19007 were applied to investigate the hazardous effects of nanomaterials to human. Regarding environmental toxicity, Fish Embryo Acute Toxicity (FET) Test using zebrafish embryo following OECD TG 236 was applied for research and testing of nanomaterial toxicities such as metal nanoparticles and nanoplastics. We also developed the 3D-intestinal model derived from human and porcine intestinal organoid to evaluate intestinal toxicities. The results demonstrated that the developed 3D-intestinal model shows the structure and functionality of intestinal epithelium suggesting the potential tool for 3R alternatives. Furthermore, to increase the predictivity of the in vitro model, microfluidic technology was incorporated with cell culture technology to develop organ-on-a-chip for nanosafety testing.

Keywords: 3R alternatives, 3D-tissue model, nanosafety, zebrafish embryo

References:

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APPLYING ZEBRAFISH EMBRYO ACUTE TOXICITY TEST IN CHINA: STATUS AND PROSPECT

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ABSTRACT

Introduction:
With the global consensus to strengthen the application of three R principle on animal testing, the Chinese Society of Toxicology (CSOT) has established Alternative and Translational Toxicology Expert Committee in 2014. We have devoted much efforts to develop toxicology alternative methods, which includes zebrafish embryo related testing methods.

Zebrafish related studies in China initiated in early 1990s, and developed rapidly in the past decade. According to the reports on 14th International Zebrafish Conference held in 2019, zebrafish research force in China ranked 2nd, right after the United States. Currently, there are increasing zebrafish laboratories being established in universities and academic institutes throughout China. All these have established a strong science and technology backstone to support zebrafish embryo's application in China.

China first established zebrafish embryo acute toxicity test standard is the "Water Quality – Determination of the Acute Toxicity – Zebrafish (*Danio rerio*) Eggs Method (HJ 1069-2019)", which derived from ISO 15088. Recently, we have established "Zebrafish Embryo Acute Toxicity Test Method A and Method B (T/GDST 1-2021)" standard. We used zebrafish embryo for acute toxicity testing of chemicals and consumables (including health food and cosmetics etc.), and published part of the validation data in Journal of Toxicology. The results showed significantly consistent toxicity between zebrafish embryo acute toxicity test results and mouse oral acute toxicity test (GB15193.3-2014) results. Additionally, there are increasing number of Chinese companies adopting zebrafish embryo acute toxicity test as internal quality control to ensure products' safety.

Chinese government has strengthened regulation for consumables, and published the Standard for Publicity and Evaluation of Cosmetics Efficacy regulation on April 9, 2021. This requires scientific evidence for product's efficacy statement. Zebrafish embryo, as a non-animal, high transparency, high reproducibility, high throughput and good predictability model, is increasingly being applied for efficacy testing. There are several standards being established and much more being developed and validated.

In conclusion, zebrafish embryo as alternative testing model is being developed well in China, and its application in acute toxicity testing is attracting much attention.

Objective:
Not applicable or not provided by author

Methods:
Not applicable or not provided by author

Results and Discussion:
Not applicable or not provided by author

Keywords: Zebrafish embryo, ISO 15088, 3Rs, Acute toxicity test, China

References:
Not applicable or not provided by author

CURRENT VIEWS ON THE 3RS ADAPTATION FOR THE SKIN SENSITIZATION TESTING

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ABSTRACT

Introduction:
Recently, multiple in vitro skin sensitization tests have been listed in the Organisation for Economic Co-operation and Development (OECD) guidelines. Not only latest innovation but also regulatory approval status on skin sensitization evaluation will be reported. Considering the current circumstances, such as stricter safety assurance on chemicals make new alternative methods for skin sensitization evaluation seem attractive, especially for chemical industry.

Objective:
We developed a potency prediction model using in vitro and in silico data rather than the conventionally used in vivo data, and established a TTC concept for skin sensitization.

Methods:
The EC3 value, the endpoint of the local lymph node assay (LLNA), was used as the objective variable. In vitro tests data and physico-chemical properties were used as explanatory variables. A quantitative prediction model for EC3 was developed using support vector regression (SVR), a machine learning approach. Predicted EC3 values were used to establish the acceptable exposure level (AEL) for each chemical. Then, the 95 and 99 percentile probability of AELs were calculated as the Dermal Sensitization Threshold (DST) values.

Results and Discussion:
This prediction model was validated by a three-fold cross-validation, and the accuracy of potency class prediction in five categories was 45.8%. Assuming 20% of all chemicals are skin sensitizers, the DST (ug/cm2) for women's face cream was 0.129 (99 percentile) and 3.99 (95 percentile). Furthermore, the threshold concentration of this type of products was 0.008% (for DST 99 percentile) and 0.26% (for DST 95 percentile). This TTC concept for skin sensitization can be applied as a non-animal approach in evaluating the safety profile of new ingredients, for example. In this study, we developed a potency prediction model using SVR, a machine learning algorithm. In future, it is expected that such machine learning-based models for predicting skin sensitization potency will be placed into practical use for predicting acceptable concentrations of ingredients in products

Keywords: Non-animal, TTC, skin sensitization, in vitro, in silico

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PART III: ABSTRACTS OF THE INVITED SPEAKERS ORAL PRESENTATIONS

Forum

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A PORTFOLIO CAREER IN INDUSTRY AND ACADEMIA

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ABSTRACT

Introduction:
Careers rarely take the straight path we envisage. How do we make the best of the opportunities offered to us in a changing employment world? In this talk I will share my journey from academia to large pharma, to smaller biotech and back to academia together with my mistakes, my successes and some of the lessons learned along the way.

Objective:
The objective of this presentation is to stimulate reflection and discussion on the career paths open to us so we can maximise individual and team potential.

Methods:
I have woven together key career phases of my career together with lessons learned and key scientific impact including publications from that role. Phases were roughly divided into PhD, postdoc, industry, biotech and academia (the latter two combined).

Results and Discussion:
A flexible approach to career and to mentoring, networking and teaching drives life-long learning, fulfilment and growth.

Keywords: Career, mentoring, influencing, training

References:

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EXPLORING IN SILICO TOXICOLOGY FROM A MALAYSIAN'S PERSPECTIVE: THE JOURNEY FROM EUROPE TO BACK HOME

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ABSTRACT

Introduction:
Toxicity testing is essential for human risk assessment. Most of toxicity data derived from the in vivo models and these data nonetheless always show a large inter-study variation. These models are commonly used because they represent the entire organism biology that is not replicated by in vitro models, however the extrapolation of toxicity data from in vivo models to humans is imperfect due to differences in anatomy and physiology.

Objective:
The main aim this presentation is to explain the works that has been done in in vitro and in silico studies to predict the in vivo and human situation. In addition, the journey to become a registered toxicologist will be shared during the presentation.

Methods:
To bridge-the-gap between in vitro and in vivo models, a novel method has been developed based on the extrapolation of in vitro concentration-response curves obtained with cell line models to in vivo dose-response curves using physiologically based kinetic (PBK) modeling-based reverse dosimetry. This model simulates the relationship between the external exposure levels and the internal concentrations of a chemical over time.

Results and Discussion:
The in vivo dose effect levels and the points of departure (PODs) for risk assessment including benchmark dose (BMD) or lower confidence limit of the BMD (BMDL) can be defined based on the in vitro effect levels that are assumed to represent the tissue or blood concentration in which may cause toxicity. All of these were obtained from the integrated in vitro-PBK modeling approach. Conclusion: the combined in vitro-PBK modeling approach provides PODs for risk assessment with a similar level of uncertainty as observed in the experimental animal studies, therefore the application of this method could be applied in future human risk assessment studies.

Keywords: risk assessment, in silico, PBK modeling, toxicity testing, toxicologist

References:

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Abdullah, R., Wesseling, S., Spenkelink, B., Louisse, J., Punt, A., and Rietjens, I.M.C.M. (2020). Defining in vivo dose-response curves for kidney DNA adduct formation of aristolochic acid I in rat, mouse, and human by an in vitro and physiologically based kinetic modeling approach. Journal of Applied Toxicology 40(12): 1647-1660.

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TRADITIONAL HERBAL POISONING IN VIETNAM

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ABSTRACT

Introduction:
Traditional herbal medicine is used popularly in Asian countries. In Western countries, it has different names such as homeopathy, complementary and alternative medicine. In Vietnam, Traditional Vietnamese herbal medicine is affected by Traditional Chinese herbal medicine. The source of herbs is from flora, invertebrates, vertebrates and minerals. People who like to use traditional herbal medicine for treatment think that it will be safe, natural and they should use those for long time then it will be effective. Every substance has not only good effects but also side effects or toxic effects. Therefore, when patients have used these for a long time, they could have chronic poisoning. In clinical manifestation of these chronic poisoning, signs and symptoms will be presented similar to those of internal diseases and could be misdiagnosed with any chronic diseases, or physicians cannot find the right diagnosis for those symptoms. The diagnosis in these cases is a challenge to the emergency physicians or general physicians or other specialists. However, the role of medical toxicologist can help to recognize these chronic herbal poisoning. The method of diagnosis and the recognition of these chronic poisoning related to herbal medicine are LEWT method, and the investigation of toxic agent screening (ITAS) have been applied to these cases. Those issues help the medical toxicologists to find the culprit toxins or toxic substances for treatment. Another challenge for us is the lack of chelators for heavy metal poisoning in traditional herbal using. If the cooperation between poison centers in many countries can be developed, the antidotes can be transferred, and it help patients to have better life.

Objective:
Not applicable or not provided by author

Methods:
Not applicable or not provided by author

Results and Discussion:
Not applicable or not provided by author

Keywords: herbal medicine poisoning, Vietnam, LEWT, ITAS

References:
Not applicable or not provided by author

MISUSE OF PRESCRIPTION DRUG IN SINGAPORE: AN INSIGHT FROM PUBLIC HEALTH

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ABSTRACT

Introduction:
Misuse of prescription drugs such as opioids, sedatives and stimulants are common in countries such as the United State of America, Canada and Australia. The evolving epidemic of prescription opioids misuse has placed a tremendous stress on the health care system in these countries with an increase in the attendances at the Emergency Departments and hospitalization rates. Data from the United Nations Office on Drugs and Crime showed that prescription medicine misuse is gaining popularity in South Asia as they are easily available and are perceived to be safer alternatives. Supply of prescription opioids is also increasing in this region. Review of limited peer-reviewed publications showed that prescription medicines misuse (opioids, benzodiazepines, tranquilizers, stimulants) is a problem in several Asian countries

Objective:
To examine the prevalence of prescription medicine misuse in Singapore with a focus on two studies conducted in Singapore.

Methods:
The first study looks at the prevalence of prescription medicine misuse at a population level, conducted through an internet consumer panel, and the second study evaluates the awareness and perceptions of the doctors on prescription medicine misuse in Singapore.

Results and Discussion:
The results of these studies showed that prescription medicine misuse is not only a problem of the Western countries but is also affecting the populations in this region. These data can help inform determine whether changes to prescribing practices are required and inform prevention and education activities in this region.

Keywords: prescription medicine misuse, Singapore, public health, opioids, tranquilizers

References:
Not applicable or not provided by author

PART III: ABSTRACTS OF THE INVITED SPEAKERS ORAL PRESENTATIONS

Workshop 1

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PESTICIDES: RISK ASSESSMENT, MANAGEMENT AND COMMUNICATION APPROACHES TO PROTECT HUMAN HEALTH

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ABSTRACT

Introduction:
Pesticides contribute increase of productivity of agricultural production, but may pose certain risk to human and environmental healths through exposure when pesticides are used. Among human health concerns, ASEAN countries increase concerns on exposure of consumers to pesticides through residues on agricultural commodity and direct exposure of farmers when they apply pesticides.

Objective:
Pesticides should be evaluated through their risk rather than their hazard, as risk can be characterized by examining the toxicity and exposure, which makes it possible to define when a pesticide must be considered risky under specific use condition.

Methods:
Risk assessment principle can be applied in both dietary risk assessment (DRA) and spray operator exposure risk assessment (Opex RA).

Results and Discussion:
DRA: Maximum residue levels (MRLs) are not safety standards for pesticides but indicators for compliance of good agricultural practices (GAP) or registered use pattern. Risk assessment shall be the basis of food safety assessment. Internationally accepted references, such as Codex Guidance Document, FAO Training Manual, WHO GEMS/Food Cluster Diets, including published residue definitions should be used as reference for pesticide residue evaluation and DRA methodology. Due to similar weather patterns, crops and cropping systems in ASEAN countries, data pooling and sharing, as well as accepting/mutual recognition is recommended as part of harmonization effort for local registrations and import tolerance application for key export commodities. **Opex RA:** Risk assessment that consists of hazard evaluation and exposure assessment with subsequent comparison of both should be conducted to evaluate the safety of operators when using pesticides. For exposure assessment, data from databases of the US and EU authorities can be used and their strength is on relevant application scenarios prevailing in these regions. In Asia Pacific region, various authorities in Japan, Korea and China have started certain activities, which can serve as a basis for a comprehensive approach covering a broader region of Asia Pacific. Currently, the calculator (CropLife International's OPEX tool) could serve as a basic model for exposure and risk assessments in ASEAN countries. For appropriate use, it is essential to choose model scenarios that closely reflect application scenarios. In cases where scenarios could result in highly varying exposures, additional personal protective equipment has to be recommended. In addition to appropriate mitigation measures recommendation, the corresponding correct use and maintenance of spray equipment is of great importance. Stewardship activities, as a joint effort by authorities and industry, are essential for the implementation of sustainable and responsible use of pesticides to ensure the health and safety of farmers/spray operators.

Keywords: pesticides, exposure, hazard, risk assessment, risk management/mitigation

References:

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PART III: ABSTRACTS OF THE INVITED SPEAKERS ORAL PRESENTATIONS

Workshop 2

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REGULATORY EXPECTATIONS FOR SUSTAINABLE CHEMICALS MANAGEMENT IN DEVELOPING COUNTRIES

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ABSTRACT

Introduction:
Chemicals are used worldwidely, including Malaysia, as they provide us with much benefits. However, some chemicals pose certain threats to the safety and health of human, as well as the environment. Sound management of chemical at workplace plays an important role in avoiding and minimising risks posed by these harmful chemicals. Protecting employees from the adverse effects of chemicals is one of the primary duties of an employer under the Occupational Safety and Health Act 1994. In Malaysia, chemical management is governed by many agencies through their respective acts causing duplication of effort and some grey areas under chemical management not regulated.

Objective:
To share the current approach of the Department of Occupational Safety and Health (DOSH) in ensuring sustainable chemicals management in Malaysia.

Methods:
A 10-year data from the DOSH online system (Mykpp and yearly performance indicator by 15 state offices in Malaysia) on chemical management enforcement activities was analysed. Compliance to the Use and Standard of Expsoure Chemical Hazardous to Health (USECHH) 2000 Regulation was graded as A (100 – 80%), B (79 – 65%), C (64 – 50%), D (49 – 26%), and E (25 – 0%). Compliance is deemed satisfactory when the score is C and above.

Results and Discussion:
From 2010 to 2020, 9712 workplaces were inspected during routine inspection and 54% were graded A to C, whilst 46% were graded D to E. From 2016 to 2020, 2530 workplaces were recorded for special enforcement and 70% were graded A to C, whilst 30% were garded D to E. Both enforcement approaches showed high percentage of compliance. Significant improvement in compliance with the legislation was observed since USECHH introduction in 2000. USECHH enforcement data analysis specifies lack of compliance in the medical surveillance upon recommendations by chemical risk assessor. Analysis of enforcement on chemical suppliers shows lowest compliance in classification of hazardous chemicals. Noncompliance is common among the small and medium enterprises. Progressive modifications to the organizational structure of each custodian agency fo chemical management and beyond those offered by the existing legislations is recommended to ensure sustainable chemicals management. The way forward is to establish a National Chemical Council or Board.

Keywords: chemical management, compliance, sustainable , chemical legislations, gap

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MANAGING TRADE BARRIERS THROUGH APPLICATION OF GLOBALLY HARMONIZED SYSTEM (GHS) TO PETROLEUM SUBSTANCES

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ABSTRACT

Introduction:
The United Nations Globally Harmonized System (UN GHS) provides a standardized and internationally comprehensible system for hazard identification and labelling of products. Its implementation in national or regional regulatory frameworks facilitates global trade. Crude oil, its refining streams, and petroleum products are traded globally. Petroleum substances are comprised of chemicals that can number in the hundreds and vary in composition due to variability in natural sources and refining conditions. This poses a challenge for data development, hazard identification, and classification.

Objective:
The Objective is data development and hazard identification and classification for petroleum substances, which are Chemial Substances of Unknown or Variable Composition, Complex Reaction Products and Biological Materials (UVCBs).

Methods:
A Categories (or Groups) approach to petroleum and its refining streams, along with the use of data for substances representative of each Category has been key to addressing this challenge. Physicochemical characterization and hazard data from representative substances from each Category (or Group) has been developed by the American Petroleum Institute (API). Guidance from IPIECA for applying GHS criteria to petroleum substances is then used.

Results and Discussion:
Together, the Categories (or Groups) approach and the application of IPIECA Guidance to GHS ensure international consistency in hazard identification. This reduces trade barriers for petroleum substances. The use of existing data for read-across within a Category reduces the time and cost required for data development while reducing animal testing.

Keywords: Petroleum, UVCBs, IPIECA, American Petroleum Institute (API), Globally Harmonized System (GHS)

References:

API HPV Challenge Program (https://petroleumhpv.org)
API APITOX database (https://apitox.api.org/index.cfm)
CONCAWE (https://www.concawe.eu/reach/petroleum-substances-and-reach/)
IPIECA (2010). Guidance on the application of Globally Harmonized System (GHS) criteria to petroleum substances. (https://www.ipieca.org/resources/good-practice/guidance-on-the-application-of-globally-harmonized-system-ghs-criteria-to-petroleum-substances/#:~:text=Guidance on the application of Globally Harmonized System,petroleum substances produced from oil and gas)
GHS, Rev 8, 2019 (https://unece.org/ghs-rev8-2019)

UNITAR'S PERSPECTIVE ON THE EMERGING BEYOND 2020 FRAMEWORK AND WHAT IT MEANS FOR THE GHS AND PRTRS

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ABSTRACT

Introduction:
UNITAR is a dedicated training arm of the United Nations (UN), with activities related to capacity building and implementing the goals and objectives of global agreements, frameworks and policies. Through its Chemicals and Waste Management Programme (CWM), UNITAR supports countries and stakeholders in their efforts, across a range of relevant topics. Notably, these include the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) and Pollutant Release and Transfer Registers (PRTRs), among others. UNITAR is also a Participating Organization of the Inter-Organization Programme for the Sound Management of Chemicals (IOMC), made up of nine intergovernmental organizations.

Objective:
To present UNITAR's perspective on sound management of chemicals and waste beyond 2020 in relations to GHS and PRTRs.

Methods:
By engaging in policy discussions and plans for the implementation of agreements, UNITAR is well-placed to support countries and stakeholders, with a a core team and an extensive network of experts on specific topics.

Results and Discussion:
Key topics for UNITAR are the GHS and PRTRs. These are well established tools for the sound management of chemicals; the GHS is specifically mentioned in SAICM's Basic Elements of the Overall Orientation and Guidance, and PRTRs directly relate to the Core Activity Area "to promote information access". Nonetheless, as the second Global Chemicals Outlook notes: "Progress has been made in many areas. For example, the number of countries having established PRTRs and implementing the GHS has increased since 2010. However, progress remains insufficient, pointing to an urgent need to take concerted action to develop basic chemicals management systems in all countries". UNITAR hopes that the Beyond 2020 instrument can renew the focus on these two key activity areas, alongside others, with key commitments, goals and targets that can spur the development of these systems in countries and effective implementation by stakeholders. UNITAR supports the prominent inclusion of these topics and is available to support stakeholders in their implementation. PRTRs and the GHS are also IOMC indicators of progress, offering clear and concise activities for implementation that can be measured and reported on.

Keywords: Beyond 2020, GHS, PRTR, sound management of chemicals and waste

References:

Global Chemicals Outlook II: From Legacies to Innovative Solutions: Implementing the 2030 Agenda for Sustainable Development – Synthesis Report, United Nations Environment Programme, 2019

Strategic Approach to International Chemicals Management (SAICM); Overall Orientation and Guidance http://www.saicm.org/Implementation/Towards2020/tabid/5499/language/en-US/Default.aspx

MANAGING ENVIRONMENTAL HEALTH IN THE OIL & GAS INDUSTRY

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ABSTRACT

Introduction:
Environmental health is the interaction between the environment and human health and vice versa whereby exposure to environmental stressors, such as chemicals and noise, influences the health outcomes. The goals in environmental health is to prevent injury and illness and promote the well being of people. There is growing pressure on the the oil and gas industry to balance socio-economic contribution with environmental and health impacts of sustainability. The COVID19 pandemic is accelerating global sustainability movement and seen as supporting the promotion of environmental health in the industry.

Objective:
To share aspects of and challenges in managing environmental health in the oil & gas industry

Methods:
This paper is based on industry experience.

Results and Discussion:

This paper discusses the environmental health issues in the oil and gas industry ranging from ambient air quality, water quality, homes and communities, and climate change. The wide scope of environmental health sees implementation of initiatives related to environmental health across a wide spectrum of practice. Focusing on impacts of chemicals, this paper continues the discussion on managing environmental health by highlighting examples of internal and external factors that drive corporations to take active roles in addressing environmental health issues. As an emerging area of focus, the challenges to operationalize environmental health range from regulatory framework to human capital and technology. The interdisciplinary nature of environmental health also presents a unique challenge calling for collaboration among practitioners, including toxicologists. Despite the challenges, environmental health is a strategic investment in sustainability for the industry aiming to protect business, the environment, and community from chemical impacts.

Keywords: environmental health, human health risk assessment

References:
Not applicable or not provided by author

PART IV: LIST OF ORAL SESSIONS

PART IV: ABSTRACTS OF THE ORAL SESSION'S PRESENTATION

Oral Session 1:
Ecotoxicology / Environmental Toxicology

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TOXICITY EFFECT OF DETERGENT ARIEL ON OXIDATIVE DAMAGE OF FRESHWATER FISH, CHANNA PUNCTATUS

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ABSTRACT

Introduction:
Detergents are extensively used chemicals at home, as well as in industry and some of their ingredients are highly toxic to aquatic organisms.

Objective:
The aim of this study is to investigate the toxicity of commercial detergent, Ariel on liver and gill tissues of fresh water fish, *channa punctatus*.

Methods:
The probit method was used to determine the median lethal concentration (LC_{50}) of Ariel detergent. The LC50 value of Ariel detergent for 96 hours was 32 ppm. To evaluate the detergent-induced toxicity, the fish *channa punctatus* were exposed to $1/5^{th}$ of 96h LC_{50} concentration (6.4 ppm) for a period of 7 and 14 days.

Results and Discussion:
Detergent caused a decrease in the activities of superoxide dismutase, catalase, glutathione-S-transferase, glutathione reductase, and glutathione levels, whereas the activity of xanthine oxidase and MDA levels increased in both liver and gill tissues after 7 and 14 days exposure. Morphological impairments of liver tissues, characterized by loose arrangement, irregular distribution and degeneration of the hepatocytes with increased sinusoidal space and vacuolization was observed. Gill tissue showed hyperemia in the afferent and efferent branchial arteries and congestion in the secondary lamellae after 7 and 14 days detergent exposure. In conclusion, the data indicate that exposure to detergent profoundly induces the oxidative stress in selected tissues, which leads to histopathological impairments suggesting the deleterious effect caused by the detergent was probably due to the combined effects of the ingredients of detergent, further these impairments were found to be time-dependent.

Keywords: Ariel, Detergent, oxidative stress, histopathology, fresh water fish

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HERBICIDES AND POPULATION HEALTH OF FROG, FEJERVARYA LIMNOCHARIS, IN PADDY FIELDS AT NORTHERN THAILAND

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ABSTRACT

Introduction:
Herbicides has been intensively used in Thailand's agriculture, leading to a potential environmental risk to human and non-target organisms (Laohaudomchok et al., 2020). Prior studies using sentinel species (Roy, 2002), showed that frogs living in field with herbicide use in northern Thailand had higher residues and changes in morphological and physiological status (Thammachoti et al., 2012; Jantawongsri et al., 2015).

Objective:
We aimed to examine the potential influence of herbicides on the rice frog Fejervarya limnocharis populations based on morphometric/gravimetric parameters and size-frequency distribution.

Methods:
Samplings of waters and frogs (IACUC of CU-ACUP Review No.2123002) were conducted from two paddy fields with different degree of herbicide utilization at Nan province, northern Thailand, during wet season (July) to dry season (February). Herbicide residues were screened by ELISA. Frogs from these sites were compared for condition factor, hepatosomatic index (HSI), gonadosomatic index (GSI) by two-way ANOVA and Tukey's HSD test; and size-frequency distribution by two-sample Kolmogorov-Smirnov test.

Results and Discussion:
Atrazine was detected in the waters from the contaminated site (Maneein et al., 2011), while atrazine and paraquat tissue residues were markedly different between sites (Jantawongsri et al., 2015). At individual level, condition factor showed significant site-related differences in wet season, indicating potential influence on the overall health. Gravimetric analyses showed significant site-related differences in HSI of both males and females in wet season, indicating a higher exposure to xenobiotics. Although no significant site-related difference was found in GSI of both males and females, it was noteworthy that females from the contaminated site tended to have higher GSI, indicating potential effect of xenoestrogens. At population level, growth patterns were markedly different between sites. Size-frequency distribution showed significant site-related differences and disproportionate distribution of frogs in the contaminated site. Overall results suggest that herbicides could influence non-target organisms at individual and population levels, leading to subtle and perpetual changes towards biodiversity loss in agroecosystem.

Keywords: agrochemicals, gravimetric analysis, morphometric analysis, population, sentinel species

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PHTHALATE AND BISPHENOL A MIXTURE-LINKED ASTHMA DEVELOPMENT: POSITIVE PROBIOTIC INTERVENTION

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ABSTRACT

Introduction:
The linkage between environmentally relevant chemicals, phthalates and bisphenol A (BPA), and various allergic symptoms, including asthma, has become a topic of great importance. Epidemiologic studies have demonstrated the simultaneous nature of human exposure to these substances due to their ubiquitous use in a variety of consumer products.

Objective:
To explore the mechanisms of bis(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP) and BPA mixture-induced asthma development and test multi-strained probiotic as potential positive intervention.

Methods:
Comparative Toxicogenomics Database (CTD), Cytoscape software and ToppGene Suite were used for in silico analysis. In vivo subacute experiment (ethical approval 323-07-11822/2018-05) was conducted on rats divided into seven groups (n=6): (1) Control: corn oil, (2) P: probiotic ($8.78 * 10^8$ CFU/kg/day); (3) DEHP: 50 mg/kg b.w./day, (4) DBP: 50 mg/kg b.w./day, (5) BPA: 25 mg/kg b.w./day, (6) MIX: DEHP + DBP + BPA; (7) MIX + P. Lungs and thymus were extracted and prepared for redox status analysis.

Results and Discussion:
There were 24 DEHP, DBP and BPA asthma-related genes, while apoptosis, inflammation and oxidative stress were highlighted as the most probable mechanisms. The ability of the mixture to induce oxidative stress in lung and thymus tissues was confirmed by subacute in vivo experiment. In thymus, total oxidative status (TOS) and superoxide anion (O2·-) elevation, as well as total thiol groups (-SH) reduction, were observed only in the MIX group. The decrease in total antioxidative status (TAS) was the most prominent in MIX, but was also noted in DBP and BPA groups. Although change in superoxide dismutase activity (SOD) was not statistically significant, this parameter was the lowest in MIX group. By contrast, in lungs, a significant decrease in SOD was observed in DEHP and MIX groups, but was more pronounced in MIX. The same pattern could be observed for advanced oxidation protein products (AOPP). Probiotic annulled mixture-induced changes in TOS, TAS and -SH in thymus, as well as AOPP in lungs, where it also alleviated the change in SOD.

Keywords: endocrine disruptors, oxidative stress, toxicogenomic data mining, multi-strain probiotic

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MICROBIAL ENZYMES FROM MICROCYSTIN-DEGRADING BACTERIA FOR BIOREMEDIATION

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ABSTRACT

Introduction:
Bioremediation using bacteria has been proposed as eco-friendly and results in cost-effective outcome. Microcystins (MC) are the most widely distributed and abundant toxins associated with freshwater harmful algal blooms (HABs). The degradation activity of MC-degrading bacteria in the aquatic environment, MIr enzymes, and the phylogenetics of these bacteria have been widely reported. Furthermore, a complete genome of MC-degrading bacteria allows the preparation of recombinant MIr enzymes, which opens to enzyme based-bioremediation potentials.

Objective:
To review studies that investigate the activity of MIr enzymes obtained from MC-degrading bacteria on the mechanism of degradation of mirocystin and other harmful pollutants found in aquatic environment. The review also emphasizes on studies that apply MC-degrading bacteria and MIr enzymes for enzyme-based bioremediation purpose.

Methods:
In this systematic review, the questions and inclusion criteria were first determined. Inclusion criteria include MC-degrading bacteria, their degradation mechanism on aquatic pollutants, recombinant MIr enzymes, bioaugmentation and bioremediation studies. The title and abstract screening was carried out in more than one databases. RevMan software was used to manage and find overlapped studies.

Results and Discussion:
This review provides the current state of understanding on the MIr enzymes. Our findings highlight critical knowledge gaps, such as field applications, and the incorporation of molecular approaches. Our results show the effect of MIr enzymes on pollutants fate and the variables that need to be considered for the optimization of approach for the enzyme-based bioremediation in aquatic system.

Keywords: Bioremediation, aquatic pollutant, MC-degrading bacteria, MIr enzyme, recombinant enzyme

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TRIGONELLINE PREVENTS OXIDATIVE DNA DAMAGE IN UV-B IRRADIATED DERMAL FIBROBLASTS AND BALB/C MICE VIA ACTIVATION OF PI3K-AKT-NRF2 AXIS

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ABSTRACT

Introduction:
Excessive exposure to Ultarviolet (UV) radiation negatively affects the human skin, characterized by photodamage, which includes premature aging and carcinogenesis. UV-B radiation causes about 90% of non-melanoma skin cancers by directly or indirectly damaging the DNA.

Objective:
The effects and mechanisms of Trigonelline (TG) against UV-B induced photodamage were explore using i*n-vitro* and i*n-vivo* models of skin photodamage

Methods:
Primary human dermal fibroblasts (HDFs) were cultured in the presence or absence of TG for 24 hours. Effects of UV-B and TG were assessed by examining cell viability, oxidative stress & DNA damage through biochemical assays, florescent microscopy and protein expression studies. In *in-vivo* study, TG pre-treated Balb/C mice were irradiated with 180mj/cm^2 of UV-B dose thrice a week on alternative days for four months (Ethics committee approval number 1080/2/17).

Results and Discussion:
TG significantly alleviates UVB–induced cell death effects in HDFs. TG protects HDFs and Balb/C mice from UV-B-induced DNA damage by regulating the expression profile of DNA damage marker proteins P53, ATM, ATR, ϒH$_2$AX, Chk1 and Chk2. TG offers geno-protection to UVB–irradiated HDFs and Balb/C Mice by alleviating CPD induction, reducing the number of tunnel positive cells and by decreasing the expression levels of DNA damage marker protein ϒH$_2$AX in immunocytochemistry. Furthermore, TG prevents the UVB-induced oxidative stress by activating the various downstream proteins of PI3K-AKT-Nrf2 signalling pathway. PI3K inhibitor (LY294002) significantly increased the expression of ϒH$_2$AX and p-P53, indicating TG mediates its photo-protection via PI3K-AKT-Nrf2 signalling pathway.

Keywords: Ultraviolet-B, Photo-damage, Oxidative stress, DNA damage, Trigonelline

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PART IV: ABSTRACTS OF THE ORAL SESSION'S PRESENTATION

Oral Session 2:
Risk Assessment

Kindly scroll/ flip next few pages to view the selected abstract

OCCUPATIONAL EXPOSURE TO PESTICIDES APPLIED AMONG RICE GROWERS IN MALAYSIA

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ABSTRACT

Introduction:
Rice is a staple crop mainly grown in developing countries, which often rely on pesticides to ensure high grain yields. The common use of knapsack sprayers in rice may cause higher exposure than mechanical application methods (Phung et al. 2012), particulary walking in submerged rice systems. To date, there is no established model/algorithms available to assess pesticide risk in rice systems (Wong and Brown 2021).

Objective:
This study investigates potential rice growers' exposure to pesticides under major pesticide use scenarios and associated factors of exposure and risk in submerged rice systems.

Methods:
To estimate rice growers' exposure to active substances, contextual information was collected from 37 rice growers using personal interview and questionnaire surveys (approved by Faculty of Earth Science, UMK) across a cropping season in 2019 in Kelantan, Malaysia together with label collection. Pesticide application rate was the key parameter of four selected exposure models for four potential scenarios, where exposure estimates larger than the agricultural operator exposure level (AOEL) indicates potential health risk.

Results and Discussion:
Overall, 15 of 37 rice growers submitted the questionnaire surveys comprising a range of total spraying days (3 – 35 days) and total grown areas (1.6 – 20.3 ha). A total of 34 pesticide products were applied (20 insecticides, 11 herbicides and 3 fungicides), including 11 products that were not registered for use on rice in Malaysia. On single spraying days, the four selected models predicted total exposures of 0.20 – 969 µg kg bw^{-1} day^{-1} to single active substances, comprising the largest dermal contact from residues on treated foliage (EFSA 2014; 8.74 – 969), followed by dermal exposures while handling knapsack sprayers (AOEM; Groβkof et al. 2013) and that for application, washing and maintenance (WHO 2018; 0.40 – 404), and the least for legs contact from contaminated rice paddies (0.20 – 153). Each model had estimated exposures larger than the AOELs (52 – 151 of 288 applications). The analysis indicated higher exposure associated with wettable powder formulations and a requirement to generate local information to replace the use of default model parameters. Study findings can be used to mitigate pesticide risk in rice more effectively.

Keywords: paddy, growers, knapsack/backpack sprayers, models/algorithms, regulatory

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A SYSTEMATIC *IN VIVO* STUDY OF COPPER HYDROXIDE NANOPESTICIDES USING *DROSOPHILA MELANOGASTER*: CELLULAR UPTAKE AND BIOLOGICAL IMPACTS

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ABSTRACT

Introduction:
One of the fastest-moving fields in today's world of applied science, nanotechnology allows the control and design of matter on an extremely small scale. Understanding the interactions between nanopesticides and edible plants, as well as non-target animals, is crucial in assessing the potential impact of nanotechnology products on the environment, agriculture and human health.

Objective:
We need better insight into cellular uptake and biological effects to derive conclusive evidence on the safety or toxicity/genotoxicity of nanopesticides using *Drosophila melanogaster*.

Methods:
Third instar larvae were fed with copper (II) hydroxide ($Cu(OH)_2$) nanopesticides (Kocide® 3000) and its microparticulated (or bulk) form, as copper (II) sulfate pentahydrate ($CuSO_4.5H_2O$) at concentrations ranging from 0.01 to 5 mM. Viability, morphological deformations, locomotor activity, phenotypic variations, internalization, lipid peroxidation product formation, oxidative stress, intracellular reactive oxygen species production, and genotoxicity were the end-points evaluated in *D. melanogaster* larvae.

Results and Discussion:
The obtained results show that $Cu(OH)_2$ nanopesticides have the ability to be distributed inside midgut cells and translocate to the general body compartment (internal hemolymph) interacting with hemocytes. $Cu(OH)_2$ nanopesticides had non-genotoxic potential, in agreement with their inability to increase ROS, malondialdehyde and GSH production. On the other hand, the fact that $CuSO_4.5H_2O$ exposure produced more harmful effects than $Cu(OH)_2$ nanopesticides. This is the first study to report findings of nanogenotoxicity, phenotypic variations and locomotor behaviour in *D. melanogaster*. Our results once again validated *D. melanogaster* as a dynamic *in vivo* model to explore possible risks and effects of this nanopesticide.

Keywords: nanopesticides, nano-copper hydroxide, *Drosophila melanogaster*, genotoxicity, health

References:

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RISK ASSESSMENT OF AFLATOXIN IN HERBAL MEDICINES AND PLANT FOOD SUPPLEMENTS MARKETED IN MALAYSIA

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ABSTRACT

Introduction:
Aflatoxin B1 (AFB1) is a mycotoxin produced by *Aspergillus* species of fungi which may lead to aflatoxicosis. AFB1 contamination in herbs has become a great concern since there is an increasing demand for herbs as an alternative treatment to treat diseases as well as to maintain health.

Objective:
The objective of this study is to determine the risk assessment of AFB1 in herbal medicines and plant food supplements (PFS) using Margin of Exposure (MOE) approach.

Methods:
29 herbal medicine and PFS samples were purchased over the counter and from online shop using targeted sampling. AFB1 was extracted with 70% methanol, filtered using immunoaffinity column and quantified using ELISA assay. Next, the MOE values were calculated based on the Benchmark Dose Level$_{10}$ ($BMDL_{10}$) derived from the animal data and estimated dietary intake (EDI) in adults as described in EFSA scientific opinion for risk assessment of aflatoxins in food (EFSA, 2020).

Results and Discussion:
AFB1 was detected in 20 out of 29 herbal medicine and PFS samples, ranged from 2808 ng/kg to 895560 ng/kg. The estimated EDI of AFB1 in positive samples ranging from 0.1053 to 671.67 ng/kg per body weight/day. Next, the calculated $BMDL_{10}$ values for AFB1 were ranged from 63.46 to 5069.24 ng/kg per body weight/day. The MOE values of less than 10,000 for all positive samples indicated a high priority for risk management actions. This study provide data that can create awareness to the public and emphasize the need for stringent standards towards production and quality assessment of herbal products to reduce the risk of AFB1 exposure through herbs and PFS in Malaysia.

Keywords: Risk assessment, Aflatoxin B1, Herbal Medicine, Benchmark Dose, Margin of Exposure (MOE)

References:

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TOTAL DIET STUDY ON METHYL MERCURY IN MALAYSIA

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ABSTRACT

Introduction:
Malaysia Total Diet Study 2017/2018 on methyl mercury was conducted by the Food Safety and Quality Division in collaboration with all State Health Departments and selected Food Safety and Quality Laboratories and National Public Health Laboratories.

Objective:
This study aimed to estimate dietary exposure of methylmercury in the adult Malaysian population through consumption of fish.

Methods:
A total of 35 food composite samples from group fish were prepared as "ready for consumption" and tested for methyl mercury. Sampling was taken at identified sampling point in Peninsular Malaysia, Sabah and Sarawak. Dietary exposure was calculated by multiplying the consumption data with concentration of methyl mercury in the respective food item, and divided by body weight.

Results and Discussion:
Results showed that 86% of the composite samples were not detected with methylmercury. Methylmercury was detected in sea fish only and the highest methylmercury level was 0.18 mg/kg. From this study dietary exposure for methylmercury among adult Malaysian population was 0.13 µg/kg.bw/week which is below the PTWI of 1.6 ug/kg.bw/week by the Joint FAO/WHO Expert Committee on Food Additives and Contaminant (JECFA). This finding indicates that exposure from methylmercury is unlikely to cause undesirable health effects to the general adult Malaysian population.

Keywords: Total Diet Study, dietary exposure, methyl mercury

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GEOGRAPHIC INFORMATION SYSTEM-BASED INTERPOLATION METHOD TO URINARY METAL CONCENTRATIONS IN MALAYSIA

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ABSTRACT

Introduction:
In recent years, there has been an increasing ecological and global public health concern associated with environmental contamination by arsenic (As), cadmium (Cd), nickel (Ni) and lead (Pb).

Objective:
This study aims to visualize distribution of these heavy metals concentration in urine samples of respondents from all states in Malaysia.

Methods:
This cross-sectional study compiled urine samples from 817 Malaysian adults from all states in Malaysia between October 2017 and March 2018 (Ethics Approval NMRR-18-204-39712 (IIR)). Spatial inverse distance weighted (IDW) interpolation method was used to derive a map, which illustrate the distribution of As, Cd, Ni and Pb from urine samples. IDW interpolation showed the spatial prediction in raster format. Moran's *I* Index was also used to assess the spatial autocorrelation in the study area for all the metals.

Results and Discussion:
The mean concentration for Ni and Cd was highest in Perak, whilst As and Pb were predominantly in Terengganu and Kelantan. Moran's *I* index showed significant spatial autocorrelation in the study area for all metals except for Pb (p-value<0.05). From the IDW, individuals living in North East and Western region had the highest concentrations for As and Cd. However, those in the Central region were less exposed (Ni, Cd and As). In comparison to individuals living in other parts of the region, the North and North West region were less exposed to Pb. In conclusion, this study provides a quantitative information based on the interpolation method and spatial autocorrelation for heavy metals in urine samples. With these geographic information system (GIS) techniques, health authorities can better predict in assessing exposure to heavy metals in population of an area to prioritize control and preventive measures.

Keywords: heavy metal, GIS, interpolation, urine, Malaysia

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PART IV: ABSTRACTS OF THE ORAL SESSION'S PRESENTATION

Oral Session 3:
Herbal/Natural Product Toxicology

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OCHRATOXIN A AND ANTIOXIDANT ACTIVITIES OF ROASTED COFFEE BEANS IN PHNOM PENH, CAMBODIA

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ABSTRACT

Introduction:
Coffee is one of the major commoditites being traded all over the world. The major mycotoxin contaminated in coffee is ochratoxin A (OTA), a toxin that relates to nephrotoxic, teratogenic, carcinogenic and immunotoxic effects. Coffee is also known as a potential source of antioxidants. So far, there is no study of OTA contamination and antioxidant activities in coffee in Cambodia.

Objective:
The aims of this study were to determine the contamination of OTA, potential antioxidant activities and correlation between OTA levels and antioxidant activities of roasted coffee beans in Cambodia.

Methods:
Fourty samples of roasted coffee beans, imported from different countries and locally grown, were collected from four local markets in Phnom Penh. Coffee samples were extracted and OTA levels were determined by HPLC with a fluorescence detector. The method validation was performed. Total polyphenolic contents (TPC) and potential antioxidant activities were also determined in coffee. Antioxidant activities were measured by diphenyl-1-picrylhydrazyl (DPPH) and ferric reducing antioxidant power assays (FRAP).

Results and Discussion:
The validation parameters showed that the analysis was acceptable. OTA levels in 9 samples (22.5%) were detectable, while 3 samples (7.5%) contained OTA above the LOQ (0.62-1.12 ng/g). Approximately, 50% of samples from Brazil and Cambodia were contaminated with OTA. None of the coffee samples contained OTA higher than the limits regulated by the European Union. OTA levels were higher in Robusta than in Arabica coffee. Total polyphenolic contents ranged from 17.83-33.03 mg GAE/g, while antioxidant activity determined by DPPH and FRAP assays ranged from 71.01%-81.95% and 36.48-115.78 mg Trolox/g, respectively. Antioxidant activities in Robusta were significantly higher than in Arabica coffee. No correlation between OTA and antioxidant activities was found. This report is the first survey of OTA contamination in coffee in Cambodia. The result can be beneficial for risk assessment approach to minimize mycotoxin exposure through coffee consumption in Cambodia.

Keywords: roasted coffee bean, mycotoxins, ochratoxin A, antioxidant, Cambodia

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ANTIOXIDANT ACTIVITIES AND ANTI-INFLAMMATION OF COELONIN FROM DENDROBIUM SCABRILINGUE

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ABSTRACT

Introduction:
Reactive oxygen species (ROS) and inflammation have been associated to the development of a wide range of diseases such as cancer, metabolic disorder, and cardiovascular disease. Plants produce variety of phytochemicals, thus studies of antioxidant and anti-inflammatory activities of phytochemicals are still of interest. Coelonin, is a phenolic compound isolated from species of orchids including *Dendrobium scabrilingue.*

Objective:
This study aimed to investigate the antioxidant activity of coelonin in vitro. The effects of coelonin on H_2O_2-induced oxidative stress and LPS-induced inflammation in RAW264.7 cells were assessed.

Methods:
MTT assay was carried out to determine the non-toxic dose of coelonin. Next, the antioxidant and anti-inflammatory effects of coelonin was evaluated. The oxidative stress and inflammation of RAW 264.7 cells were induced by hydrogen peroxide (H_2O_2) and lipopolysaccharide (LPS) respectively. Intracellular ROS levels were evaluated by using DCFDA assay. The SOD, GPx and CAT activity was measured by using SOD, GPx and CAT cellular Assay kit. Nitrite oxide production level was measured using Griess Reaction assay.

Results and Discussion:
From the cytotoxicity results, the non-toxic concentration of ceolonin was found below 20μM. Pretreatment of the cells with the non-toxic doses of coloenin prior to H_2O_2 exposure significantly decreased production of intracellular ROS in a dose dependent manner. At the concentration of 20μM, coelonin decreased intracellular ROS in RAW264.7 cells by 75%. Pre-incubation of the cells with coelonin prior to H_2O_2 exposure significantly prevented a decrease in SOD, GPx and CAT levels in a dose dependent. The results indicate that the compound enhanced antioxidant enzyme activities in H_2O_2 treated RAW264.7 cells. Pre-treatment of the cells with coelonin prior to LPS exposure significantly decreased NO and TNF-α secretion in a dose dependent manner. The present study shows the antioxidant activity and ability of ceoleonin to prevent LPS-induced inflammation in RAW264.7 cells.

Keywords: coelonin, RAW264.7, ROS, antioxidant, anti-inflammation

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FISH ACUTE TOXICITY TESTING OF LITSEA GARCIAE METHANOLIC EXTRACT IN ADULT ZEBRAFISH

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ABSTRACT

Introduction:
Litsea garciae (LG) bark is currently used in Sarawak by locals to treat various diseases traditionally. However, there is no preliminary study conducted to evaluate the respective plant's acute toxicity up to the present time.

Objective:
The recent study's main objective was to determine the LG bark methanolic extract's acute toxicity in adult zebrafish.

Methods:
The raw LG bark underwent a successive maceration technique and freeze-dried. The methanolic extract was administered in a static system by immersion based on OECD Test Guideline No 203. The acute toxicity test implemented 96 hours of observation for any mortality or visible abnormalities related to the zebrafish's appearance and behaviors (ethical approval IIUM/IACUC-2019(21)).

Results and Discussion:
The test group (limit 100mg/L) and the control group recorded zero mortality and no significant abnormalities. Hence, LC50 was not determined. In agreement, the present findings revealed the significance of relatively safe and less toxic methanolic extract of LG bark for further biomedical applications.

Keywords: *Litsea garciae*, bark, methanolic, acute toxicity, adult zebrafish

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TOXICITY STUDIES OF SUPERCRITICAL FLUID EXTRACT OF LOCAL ZIZIPHUS MAURITIANA (BIDARA) FRUIT

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ABSTRACT

Introduction:
Ziziphus mauritiana (bidara) fruit is considered as an underutilized fruit in Malaysia and did not received much attention on its possible health effects. Literature search have shown that studies on Z. mauritiana fruit, especially locally grown are very limited. Hence, this study was initiated to determine the fundamental information on its safety.

Objective:
To determine the acute toxicity, cytotoxicity, and genotoxicity of supercritical fluid extract (SFE) of local Z. mauritiana fruit extract.

Methods:
Acute toxicity study (FST/2018/ARNIDAHANI/28-NOV./971-DEC.2018-JAN.-2020) was done in Sprague Dawley rats following OECD Test No.420 . A total of 48 rats were divided into 4 groups receiving 0 (control), 1, 2.5 and 5 g extract/kg body weight, accordingly. Cytotoxicity study was done by using the MTT test on V79-4 normal cell lines, with water extract as comparison. Genotoxicity study was done through micronucleus assay with acridine orange staining.

Results and Discussion:
From the acute toxicity results, all rats survived during the course of study period with no evidence of clinical or toxic manifestation. The body weight, food and water consumption, organs' weights and biochemical parameter of treated animals were not significantly different ($p>0.05$) compared with the control group during the period of study. Cytotoxicity results show Z. mauritiana SFE extract demonstrated a cytotoxicity effect (IC50: 0.48 mg/ml) towards the V79-4 cells, whereas the water extract showed otherwise (IC50: 175.67 mg/ml). Lastly, the SFE extract did not show genotoxic effect based on the parameters studied. As a conclusion, this study shows the safety information of Z. mauritiana SFE fruit extract.

Keywords: supercritical fluid extraction, acute toxicity, cytotoxicity, genotoxicity, Ziziphus mauritiana

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PART IV: ABSTRACTS OF THE ORAL SESSION'S PRESENTATION

Oral Session 4:
Genotoxicity

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PHARMACOLOGICAL ACTIVATION OF AUTOPHAGY RESTORES CELLULAR HOMEOSTASIS IN ULTRAVIOLET-(B)-INDUCED GENOTOXIC STRESS RESPONSE IN SKIN

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ABSTRACT

Introduction:
Ultraviolet-B exposure to skin causes photo-damage and acts as the primary etiological agent in photo-carcinogenesis. Recently, autophagy has been found to positively regulate skin homeostasis by enhancing DNA damage recognition. Here, we investigated the geno-protective roles of autophagy in primary Human Dermal Fibroblasts (HDFs) against UV-B –induced genotoxic stress response.

Objective:
The main objective in undertaking this study is to provide experimental evidences into the roles of autophagy in regulating UV-(B) –induced genotoxic stress response in primary human dermal fibroblasts.

Methods:
Molecular biology tools including western blotting, RNA interference and biochemical assays were used. Confocal and florescent microscopy based assays were employed to study protein expression and calcium signalling, and GFP-RFP-LC3B puncta assay for assaying autophagosome formation to follow the experimental findings.

Results and Discussion:
We found that UV-(B) -irradiation to HDFs leads to induction of DNA photo-adducts (CPD & 6-4PP). Further, our results revealed that impaired autophagy is an immediate molecular event induced following exposure of UV-B –irradiation to primary HDFs and pharmacological activation of autophagy regulates DNA Damage Response via regulation of oxidative and endoplasmic reticulum stress responses. Autophagy deprivation to HDFs via P62 silencing augments the UV-B -induced DNA damage response whereas *Atg7* silenced HDFs reveal an unexpected consequence by decreasing the UV-B -induced DNA damage via over activation of AMPKα as an adaptive response to genotoxic stress caused due to autophagy deficiency. Our findings provide critical insights that indicate the regulatory and functional role of autophagy in regulating UV-B induced photo-damage and support the potential role of interventional autophagy as promising therapeutic strategy against skin photodamage disorders.

Keywords: UV-B, Oxidative stress, Endoplasmic Reticulum Stress, Autophagy, DNA Damage Response

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THE PRESENCE OF GENOTOXIC AND CARCINOGENIC PHYTOCHEMICALS IN MEDICINAL PLANTS BASED ON THE MALAYSIAN HERBAL MONOGRAPH

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ABSTRACT

Introduction:
Medicinal plants are essential in Malaysia's long history of traditional and complementary medicine. The scientific data of 76 Malaysian medicinal plants are published in the Malaysian Herbal Monograph (MHM). Although phytochemicals are vital for human health, certain phytochemicals, such as aritolochic acid, safrole and lasicoarpine, can induce toxicity including hepatoxicity, genotoxicity and carcinogenicity.

Objective:
The objective of this study was to screen for the potential presence of genotoxic and carcinogenic phytochemical constituents in the 76 published monographs of Malaysian medicinal plants.

Methods:
Plant species containing genotoxic and carcinogenic agents were identified by screening the phytochemical profiles of the 76 medicinal plants published in the MHM. Next, the number of registered natural products containing those plants were generated using the local official engine database search (QUEST3+ Product Search).

Results and Discussion:
11 out of the 76 medicinal plants, including *Alipinia galanga*, *Cinnamomum verum*, *Myristica fragrans, Ocimum basilicum, Orthosiphon aristatus, Piper betle, Piper sarmentosum, Citrus hystrix, Chromolaena odorata, Gynura procumbens* and *Areca catechu* were found to contain genotoxic carcinogen including alkenylbenzene such as methyleugenol and safrole, and pyrrolizidine alkaloid such as lasiocarpine and retrorsine. Through QUEST3+ search, 412 registered natural products have been found to contain these plants species as ingredients. Additionally, 130 registered products containing other plants species known to be genotoxic and carcinogenic such as *Tussilago farfara, Asarum* spp and *Gynura* spp were also identified. In conclusion, consumption of medicinal plants in natural products may expose Malaysians to genotoxic and carcinogenic phytochemicals. Thus, exposure assessments should be conducted to minimize the potential health risks in Malaysian population.

Keywords: Alkenylbenzene; Carcinogenic; Genotoxic; Medicinal plant; Pyrrolizidine alkaloid

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ROLE OF *NRF2/NQO1* PATHWAY IN MEDIATED ARSENITE-INDUCED MALIGNANT TRANSFORMATION

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ABSTRACT

Introduction:
In arsenic toxicity, activation of the erythroid 2-related factor 2 (NRF2) pathway is regarded as a driver of cancer development and progression; however, the mechanisms by which *NRF2* gene expression regulates cell cycle progression and mediates pathways of cellular proliferation and apoptosis in arsenic-induced lung carcinogenesis are poorly understood.

Objective:
To know the mechanisms underlying NRF2 and its target gene proteins in regulating arsenite-induced dysregulation of cellular proliferation.

Methods:
In this study, we explored the regulatory functions of *NRF2* expression and its target genes in immortalized human bronchial epithelial (HBE) cells continuously exposed to 1.0 μM sodium arsenite over approximately 43 passages (22 weeks).

Results and Discussion:
The experimental treatment induced malignant transformation in HBE cells, characterized by increased cellular proliferation and soft agar clone formation, as well as cell migration, and accelerated cell cycle progression from G0/G1 to S phase with increased levels of cyclin E-CDK2 complex ,decreased cellular apoptosis rate. Moreover, we observed a sustained increase in NRF2 protein levels and those of its target gene products (NQO1, BCL-2) with concurrent decreased expression of apoptosis-related proteins (BAX, Cleaved-caspase-3/Caspase-3 and CHOP) and increased expression of the anti-apoptotic protein MCL-1. Silencing *NRF2* expression with small interfering RNA (siRNA) in arsenite-transformed (T-HBE) cells reversed the malignant phenotype. Further, siRNA silencing of *NQO1* significantly decreased levels of the cyclin E-CDK2 complex, inhibiting G0/G1 to S phase cell cycle progression and transformation to the T-HBE phenotypes. This study demonstrated a novel role for the *NRF2/NQO1* signaling pathway in mediating arsenite-induced cell transformation by increasing the expression of cyclin E-CDK2, and accelerating the cell cycle and cell proliferation. Arsenite promotes activation of the *NRF2/BCL-2* signaling pathway inhibited CHOP increasing cellular resistance to apoptosis and further promoting malignant transformation.

Keywords: Arsenite; Cellular proliferation; Cellular apoptosis; NRF2; NQO1

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OVERVIEW OF GENOTOXICITY FIELD IN MALAYSIA ENVIRONMENT

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ABSTRACT

Introduction:
Environmental pollution presents the most damaging impact on ecosystem change, as well as public health due to increasing morbidity and mortality. Environmental factors are powerful forces in reshaping human genomes where throughout their development, human have been exposed to various environmental genotoxicants. This exposure may increase risks of cancers and other diseases to human health.

Objective:
The aim of the study is to discuss the general overview of the genotoxicity field in Malaysian environment and the genotoxicity of some environmental genotoxicants are discussed.

Methods:
Comprehensive overview of the literature synthesizing the findings of the literature retrieved from searches of computerized databases, hand searches and authoritative texts.

Results and Discussion:
Environmental pollution is a complex issue because it can take different forms and the effects are generally devastating. Environmental exposure to genotoxic compounds to produce adverse change at the cellular and organismal levels as they can lead to deadly diseases including cancer and can also be passed through future generations, affecting population gene pool and structures. Because of the potential health hazard represented by exposure to genotoxic chemicals, it is important that all chemicals for which there is possible human exposure be screened for genotoxic activity. If genotoxic hazard is detected, then the risks of exposure can be assessed, and the use of the chemical controlled and when appropriate eliminated from the market and the environment. This overview will discuss the role of genotoxicity field in Malaysian environment cases encompasses soil, water and air.

Keywords: genotoxicity, environment, soil, water, air

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PART IV: ABSTRACTS OF THE ORAL SESSION'S PRESENTATION

Oral Session 5: Mechanistic Toxicology

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COMPREHENSIVE HISTONE, DNA METHYLATION, AND MRNA EXPRESSION ANALYSIS OF MURINE LIVER REPEATEDLY EXPOSED TO CHEMICALS

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ABSTRACT

Introduction:
The Percellome Project aims at reinforcing and replacing the "safety factor" in toxicology by comprehensively identifying the transcriptomic networks induced by xenobiotics in murine organs.

Objective:
The Project started off by gathering high-quality transcriptomic data of single oral dosing studies, followed by a new repeated dosing protocol to gain chronic toxicity information from a very short small-scale study.

Methods:
"Percellome" normalization method was developed to generate absolute copy numbers of mRNAs in a "per one cell" basis from the Affymetrix GeneChips[(a)]. Data of mouse liver after a single oral gavage (4 time points (2, 4, 8, and 24 hours after dosing) x 4 dose levels (control, low, middle, and high), triplicate, 48 GeneChip data per chemical/organ from 48 mice) on 160 chemicals are compiled. A new repeated dosing study protocol consists of 14-day repeated dosing to all 48 mice followed by dosing on 15 day with the single dose study protocol mentioned above. GeneChip, whole genome bisulfite analysis (WGBA) and ChIP-seq against H3K4me3, H3K27me3, H3K27Ac, and H3K9me3 were obtained from a same sample and analyzed for the effect of repeated dosing on DNA methylation and Histone modification.

Results and Discussion:
mRNA, DNA methylation and histone data for CCl_4, clofibrate, and valproic acid were analyzed. Firstly, the effect of repeated dosing on mRNA expression can be interpreted as a combination of two elements, i.e. baseline response (BR: gradual shift of the basal mRNA expression level by repeated dosing) and transient response (TR: alteration of the magnitude and/or pattern of the quick response in 2 to 24 hours). The BR and TR were generally linked in CCl_4, i.e. lower BR linked to suppressed TR and vice versa. The link were in some part chemical dependent. However, 14-day CCl_4 pre-treatment did not alter DNA methylation, whereas ChIP-seq revealed that BR and TR of mRNA of some characteristic genes was in good correlation with histone modification. Analysis on other chemicals will be presented. (Supported by Health and Labor Sciences Research Grant of MHLW, Japan)

Keywords: Per cell normalization, gene expression network, toxicity prediction, epigenetics, transcriptomics

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FIBROBLAST GROWTH FACTOR RECEPTOR 4 AS A POTENTIAL DRUGGABLE TARGET FOR TRIPLE NEGATIVE BREAST CANCER

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ABSTRACT

Introduction:
Triple negative breast cancer (TNBC) does not respond to hormonal therapy and therefore cytotoxic chemotherapy remains the main systemic treatment for TNBC. Fibroblast growth factor receptor 4 (FGFR4) and its downstream signaling pathway are involved in TNBC cell survival. Targeting FGFR4, which are differentially expressed in cancer cells may present a novel strategy for TNBC treatment.

Objective:
To investigate the effect of reversible and/or irreversible FGFR4 inhibitors on FGF19/FGFR4 signaling pathway involvement in regulating cellular proliferation and survival of MDA-MB453 cells.

Methods:
MDA-MB453 cells were cultured in Dulbecco's Modified Eagle Medium containing 10% fetal bovine serum and were treated with different FGFR4 inhibitors; FGF401, H3B-6257 and BLU9931 at concentration range of 0.02-10μM. Caspase 8 activity and the proliferation of MDA-MB453 cell following FGFR4 inhibitors treatment were assessed using Caspase-Glo® 8 assay and MTS assay, respectively. Key proteins involved in FGF19/FGFR4 signaling pathway was assessed using immunoblot.

Results and Discussion:
FGF401 had the greatest impact on MDA-MB453 cell proliferation with IC50 4.4±0.8 nm, followed by H3B-6257 (106.0±36.5 nm) and BLU9931 (110.6±32.8 nm). The caspase 8 activity of MDA-MB453 cells downregulated by ~12%, ~10%, ~15%, following treatment with FGF401, H3B-6257, and BLU9931, respectively, suggesting that treatment with FGFR4 inhibitors may not affect cell apoptosis through caspase 8. Immunoblot analyses showed upregulated pERK expression in FGFR4 inhibitors treated cells compared to control at 24h and 48h, suggesting that FGFR4 inhibitors might not affect cell viability via ERK pathway. The effect of FGFR4 inhibitors on PI3K/Akt pathway is required. Nevertheless, reversible-covalent inhibitor (FGF401) compared to irreversible inhibitor of FGFR4 (H3B-6257 and BLU9931) showed greater potency on MDA-MB453 cell. FGFR4 inhibitors might provide a druggable alternative over conventional cytotoxic chemotherapy for improved safety and efficacy for TNBC treatment.

Keywords: Cancer, FGFR4 inhibitors, Caspase 8, Cell proliferation, FGFR signaling pathway

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CERIUM OXIDE NANOPARTICLES AS A POTENTIAL THERAPY FOR HEPATIC FIBROSIS SYMPTOMS

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ABSTRACT

Introduction:
Liver fibrosis is a serious hepatic disease condition, and is mediated primiarly by hepatic stellate cells (HSCs). Certain nanoparticles have been found to be able to reduce liver fibrosis in cultured HSCs. Cerium oxide nanoparticles (CeNPs) potentially reduce liver fibrosis symptoms in the hepatic stellate cell line LX2.

Objective:
The study aimed to demonstrate that CeNPs are a potential therapeutic method for relieving liver fibrosis symptoms.

Methods:
The human hepatic stellate cell line LX2 was used to investigate the effects of CeNPs. TGF-β-activated LX2 cells were exposed to CeNPs, and fibrosis marker genes measured using RT-PCR and western blots. We further measured other HSC phenotypes, such as cell mobility, oxidative stress, autophagy and matrix remodelling.

Results and Discussion:
We determined that fibrosis was inhibited in CeNP-treated cells through a reduction in the expression of marker genes, such as collagen-I and smooth muscle actin. When we investigated the mechanisms underlying this reduction, we found that oxidative stress was reduced in treated cells, leading to a reduction in TGF- β signalling, hence HSC activation. This was further confirmed by the observation that treated cells showed reduced cell mobility, altered matrix remodelling, and reduced cell contractability. This suggests that CeNPs represent a potential therapeutic option for liver fibrosis.

Keywords: Liver, fibrosis, nanoparticles

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REDUCTION OF ARSENIC TOXICITY THROUGH NUCLEAR FACTOR E2 RELATED FACTOR 2 ACTIVATION MEDIATED BY THE (*E*)-2-ALKENALS IN *CORIANDRUM SATIVUM* L. LEAF EXTRACT

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ABSTRACT

Introduction:
The *Coriandrum sativum* L. leaf hexane extract (CSLE) contains various aliphatic electrophiles. We have previously found that (*E*)-2-alkenals in the extract are essential for the activation of the Kelch-like-ECH-associated protein 1 (Keap1)/nuclear factor E2 related factor 2 (Nrf2) system associated with cytoprotection. We hypothesized that CSLE also activates Nrf2 *in vivo* and represses xenobiotic toxicity.

Objective:
The aim of this study was to determine whether or not CSLE containing (*E*)-2-alkenals could activate Keap1/Nrf2 system to suppress toxicity of inorganic arsenite (iAsIII) *in vitro* and *in vivo*.

Methods:
We determined the modification site of recombinant murine Keap1 (mKeap1) by (*E*)-2-decenal using ultra-performance liquid chromatography-elevated collision energy mass spectrometry (UPLC-MS^E). Human liver cell line (HepG2) and C57BL/6J mice were pretreated with CSLE or (*E*)-2-alkenals, and then cytotoxicity of iAsIII was assessed by MTT assay. Arsenite level was measured by inductively coupled plasma mass spectrometry (ICP-MS). The University of Tsukuba Animal Care and Use Committee approved protocols for animal experiments.

Results and Discussion:
UPLC-MS^E analysis revealed that (*E*)-2-decenal modified mKeap1 at Cys241, Cys249, Cys257 and His274. Exposure of HepG2 cells to CSLE, (*E*)-2-decenal or (*E*)-2-dodecenal upregulated Nrf2-related downstream genes, such as Heme Oxygenase-1, the GCL modifier subunit, the GCL catalytic subunit and MRP3, which were involved in cytoprotection against iAsIII. Pretreatment with CSLE or (*E*)-2-butenal, a prototype of (*E*)-2-alkenal, prior to exposure to iAsIII reduced iAsIII-induced cytotoxicity in HepG2 cells and the intracellular As level. Oral administration of CSLE to mice upregulated downstream proteins of Nrf2 and suppressed accumulation of As in liver tissue. The present study indicates that CSLE containing (*E*)-2-alkenals diminishes iAsIII-mediated toxicity through activation of the Keap1/Nrf2 system. Because the *C. sativum* leaf contains a mixture of aliphatic electrophiles, the intake of this vegetable could be an effective approach to activate the Keap1/Nrf2 system, leading to excretion of As from the body.

Keywords: *Coriandrum sativum* L., cilantro, Nrf2, arsenite, (*E*)-2-decenal, (*E*)-2-alkenal

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PART IV: ABSTRACTS OF THE ORAL SESSION'S PRESENTATION

Oral Session 6:
Nanotoxicology

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SILVER NANOPARTICLES INDUCED APOPTOSIS IN HIPPOCAMPAL NEURONS VIA MITOCHONDRIAL DYSFUNCTION

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ABSTRACT

Introduction:
Silver nanoparticles (AgNPs) have been reported to accumulate in the central nervous system (CNS) and induce neurotoxicity. Although previous studies have reported toxicity in neuronal cell lines after AgNPs exposure, mechanistic research is largely unknown in biological safety and neurotoxicity, especially in the hippocampus.

Objective:
This study aimed to investigate mechanism of hippocampal neuronal apoptosis and role of reactive oxygen species (ROS) and Ca2+ level in mitochondrial dynamics.

Methods:
The apoptosis ratio, ROS production and Ca2+ level were detected by flow cytometer. Mitochondrial morphology and function were observed by transmission electron microscopy (TEM), and JC-1 and ATP detection assay kit, respectively. Expressions of mRNA and protein related to mitochondria-mediated apoptosis were analyzed by RT-qPCR and western blot, respectively. Animals experiments were approved by the Animal Experimental Ethics Committee of Southeast University (No.20190226007).

Results and Discussion:
As a result, apoptosis was observed in hippocampal neuronal HT22 cell line and hippocampal neurons of mice intravenously injected with AgNPs. Additionally, mitochondria could be severely disturbed by AgNPs in morphology and function, characterized by mitochondrial fission and disappearance of cristae, ROS overproduction and significant reduction in mitochondrial ATP and mitochondrial membrane potential (MMP). Mechanistically, this effect is mediated by phosphorylation and translocation to mitochondria of dynamin-related protein 1 (Drp1) at a serine 616 (S616) by Ca2+/calmodulin-dependent kinase II (CaMKII), which partly dependent on the ROS-mediated Ca2+ overload. Fortunately, additional antioxidants and calcium inhibitors pretreatment could mitigate apoptosis and cytotoxicity through improvement of mitochondrial function. In conclusion, our data basically revealed that AgNPs induced apoptosis by promoting excessive Drp1 phosphorylation and mitochondrial fission. ROS-mediated intercellular Ca2+ level was the key effector mediating AgNPs-induced Drp1 phosphorylation and mitochondrial dysfunction.

Keywords: Silver nanoparticles, Mitochondria, Drp1, Oxidative stress, Ca2+

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Greish, K., Alqahtani, A.A., Alotaibi, A.F. et al., 2019. The effect of silver nanoparticles on learning, memory and social interaction in BALB/C mice. Int J Environ Res Public Health 16.

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PROTEIN CORONA MITIGATED THE TOXICITY OF CADMIUM TELLURIDE QUANTUM DOTS TO MACROPHAGES BY TARGETING MITOCHONDRIA

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ABSTRACT

Introduction:
The immunotoxicity of cadmium telluride quantum dots (CdTe QDs) targeting macrophages has been documented, and the protein corona (PC) adsorbed on particles will affect their toxicity. Here, we further investigated how does PC affect the adverse effect of CdTe QDs on mitochondria about their structure, function, quantity, morphology, and mitochondrial quality control in macrophages.

Objective:
This study aims to provide a view to alleviate the toxicity of CdTe QDs from both the synthesis and mechanism aspects, and to consolidate their safe use.

Methods:
Mouse leukemic monocyte-macrophage cells (RAW264.7) were employed as a model. The PC-CdTe QDs complexes were obtained through incubating QDs with PBS containing 10% FBS. Cells were exposed to 0.1, 0.5, and 1.0 μM CdTe QDs and PC-CdTe QDs complexes for 24 h, and corresponding fluorescent probes and kits were used to detect mitochondrial structural damage and dysfunction. Western blot was used to measure the level of key protein molecules relating to mitochondrial quality control.

Results and Discussion:
The protein corona alleviated the inhibition of CdTe QDs on mitochondrial activity, the damage to mitochondrial membrane, the level of reactive oxygen species, and the reduction of ATP. Also, CdTe QDs increased the number of mitochondria in macrophages, while the PC-CdTe QDs complexes did not. In line with this, the mitochondria of macrophages showed different morphology of mitochondrial network, CdTe QDs transformed the network into fragment, punctate and short rod, while PC-CdTe QDs complexes altered the mitochondrial network to a highly branched state, which was related to the imbalance of mitochondrial dynamic (fission and fusion). Mechanically, CdTe QDs promoted mitochondrial fission and inhibited mitochondrial fusion, while protein corona reversed this trend. Besides, CdTe QDs promoted the expression of signaling molecules related to mitochondrial biogenesis including PGC-1α-NRF1/NRF2-TFAM, while PC-CdTe QDs complexes played opposite role; with regard to mitophagy, these two materials showed the same promoting effect.

Keywords: quantum dots, protein corona, mitochondrial quality control

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TOXICITY OF CURCUMIN NANOPARTICLES IN ALVEOLAR MACROPHAGE: EFFECTS OF SURFACE CHARGES

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ABSTRACT

Introduction:
Curcumin (diferuloylmethane) is a natural dietary polyphenol compound that possesses superior therapeutic potential against various chronic diseases owing to its strong anti-oxidant and anti-inflammatory properties. Although tremendous works have been initiated on the development of this compound, the toxicity of Cur-NPs in healthy cells are overlooked.

Objective:
This study aimed to evaluate the toxic effects of curcumin nanoparticles (Cur-NPs) with alterable surface charges in alveolar macrophages (NR8383).

Methods:
Cur-NPs with different surface charges were prepared with different polymer coatings such as dextran, polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP). The toxicities of fabricated Cur-NPs against NR8383 were evaluated with lactate dehydrogenase assay, intracellular ROS production, reduction of ATP content and membrane depolarization. Apoptosis in NR8383 cells was investigated using flow cytometry analysis with Annexin APC/7AAD staining.

Results & Discussion:
The surface charges of curcumin nanoparticles (~28 nm) coated dextran, PVA and PVP were 0 ± 0.1 mV, - 25.3 ± 1.5 mV and +10.1 ± 0.9 mV, respectively. MTS assay revealed that positively charged Cur-NPs (9.77 µg/ml) exerted the highest cytotoxic effect against NR8383 followed by negatively charged Cur-NPs (13.33 µg/ml) and neutral Cur-NPs (18.68 µg/mL). Surface charge dependent toxicity was also observed for other biological activities in NR8383 such as mitochondrial membrane potential, ATP content and intracellular ROS level which followed the decreasing pattern: positive Cur-NPs > negative Cur-NPs > neutral Cur-NPs. The highest oxidation activity in lysosome and apoptosis (65%) were seen in NR8383 treated with positively charged Cur-NPs.

Keywords: Alveolar macrophage, toxicity, curcumin, nanoparticles, surface charge

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MACROPHAGE POLARIZATION AND INFLAMMATION INDUCED BY SILVER NANOPARTICLES VIA AUTOPHAGY IN BV2 CELLS

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ABSTRACT

Introduction:
As the release of silver nanoparticles (AgNPs) in the environment continues to increase, concerns about their potential toxicity to humans are heightened. AgNPs can enter the brain through multiple pathways, and microglia, as immune cells of the central nervous system, are rapidly activated in brain injury. However, AgNPs induce neuroinflammation and its mechanisms have not been well characterized.

Objective:
In this study, we investigated the possible molecular mechanisms of nanosilver-induced neurotoxicity by exploring changes in microglia polarization, inflammatory response, and autophagy-related proteins.

Methods:
We tested cell viability using the CCK-8 assay. The expressions of inflammation-related genes in microglial cell line (BV2) after exposure to AgNPs were detected by qRT-PCR. Flow cytometry and Western Blot were used to detect the alterations of phenotypic proteins and autophagy-related proteins, respectively. Autophagosomes were observed using transmission electron microscopy. The cells were treated with autophagy inhibitor to explore the molecular mechanism of AgNPs-induced microglia polarization.

Results and Discussion:
We found that exposure of BV2 cells to AgNPs (5 μg/mL) for 12 or 24 h resulted in increased mRNA expression of pro-inflammatory cytokines and decreased mRNA expression of anti-inflammatory cytokines. With 5 μg/mL AgNPs for 2, 6,12,24 h exposure increased M1 markers of iNOS expression and decreased the expression of M2 markers of CD206 in a time-dependent manner in BV2 cells. Meanwhile, the expression of inflammatory proteins IL-1β and NF-κB increased significantly. AgNPs induced increase in intracellular autophagosome and upregulation of LC3II, Beclin1, and p62 expression levels. The autophagy inhibitor 3-Methyladenine caused more AgNPs-treated microglia polarized to M1 pro-inflammatory phenotypes in BV2 cells. Increased expression of inflammation-related mRNA and protein in BV2 cells when autophagy was blocked. This study confirms that AgNPs inhibits the pro-inflammatory phenotypic polarization and inflammatory response of microglia through autophagy activation. It also provides a theoretical basis for understanding the neurotoxicity of AgNPs and guiding their rational use.

Keywords: AgNPs, Microglia, Autophagy, Polarization, Inflammation

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PART IV: ABSTRACTS OF THE ORAL SESSION'S PRESENTATION

Oral Session 7:

Occupational, Clinical or Regulatory Toxicology

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FACILITATING ACCESS TO EDUCATIONAL RESOURCES FOR TRAINING IN NONANIMAL METHODS IN DEVELOPING COUNTRIES

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ABSTRACT

Introduction:
The use of new approach methodologies (NAMs), or nonanimal methods, for chemical safety testing has increased exponentially. Yet with different regional legislation and safety requirements, challenges arise concerning implementing NAMs in a global market, including access to training and educational opportunities for the use of NAMs especially in non-OECD countries.

Objective:
This presentation will highlight open resources and training opportunities related to the use of advanced in vitro and in silico toxicological methods to facilitate improved international implementation.

Methods:
This presentation will highlight open-source materials and resources for the advancement of the OECD test guidelines program and the implementation of regulatory safety testing strategies using nonanimal approaches. In addition, we share approaches and programs that we use to maximize international participation, in part by offering free virtual training and open-access portals containing expert presentations and collated educational resources to improve uptake of NAMs.

Results and Discussion:
There is a growing body of evidence-based advocates, in which PCRM is a part, that is interested in advancing scientifically robust nonanimal approaches through outreach and educational opportunities. Through the International Council on Animal Protection in OECD Programmes (ICAPO), PCRM encourages broad adoption of nonanimal test guidelines (TG) for safety testing – currently, there are 26. With 36 OECD member countries, only four of which are developing countries, it is pivotal to encourage countries to submit proposals to expand available replacement approaches and to submit case studies detailing regulatory uses of NAMs. PCRM does this through our NAMs Use for Regulatory Application (NURA) program, which trains regulatory scientists and industry personnel on nonanimal approaches. We also focus on collaboration and training for early-career end users. The first North American Summer School (McCarthy et al., 2020) generated participation from over 20 countries, with active participation from many students outside of North America, including India, Brazil, Ukraine, Nigeria, and Uganda.

Keywords: Education, OECD, nonanimal, safety assessment, regulatory acceptance

References:

McCarthy, J., Herrmann, K. B., Sullivan, K., Haugabrooks, E. (2020). Summer school on innovative approaches in science. ALTEX. 38(1), pp. 158-162. doi: 10.14573/altex.2012153.

CHALLENGES OF GHS IMPLEMENTATION WORLDWIDE

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ABSTRACT

Introduction:
The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) was established in 2003 and many countries are implementing GHS in their respective countries. However, there are challenges that impede GHS implementation worldwide.

Objective:
The objective of this presentation is to identify and discuss challenges of GHS implementation that could affect global chemical hazard communication.

Methods:
The method adopted in this study is based on desktop review.

Results and Discussion:
The challenges that impede GHS implementation worldwide include adoption of different versions of the GHS document; adoption of different building blocks, absence of global list of classified chemicals; different chemical mixture classification throughout the supply chain; and absence of the definition for GHS implementation.

Keywords: GHS, chemical safety, hazard communication

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MICROPLASTIC EXPOSURE, POSSIBLE HEALTH IMPACT AND POLICY MEASURES

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ABSTRACT

Introduction:
Plastics production has increased globally due to their versatility and low production cost. Coastal countries generate about 275 million metric tons (MT) of plastics, of which 4.8 to 12.7 million MT enters the ocean. As of 2019, plastic production stands at 368 million MT, the figure is expected to double in 20 years to come. These plastics enter into the ocean as waste discharge or accidental spill. Microplastics (MPs) are plastic of size less than 5µm synthesized primarily in micro size or secondary due to breakage of larger plastics, they are mostly polymers synthesized from polyethylene (PE), polypropylene (PP), polystyrene (PS), polyethylene terephthalate (PET) and polyesters.

Objective:
This paper reviews the burden of MPs pollution and control measures in place by exploring information within the last 22 years from scientific and general databases.

Methods:
Literature reviews

Results and Discussion:
MPs are found in food, water, beverages and salts in the supermarkets readily available for human consumption. Animal studies showed varying effects of MPs, with human health impact unknown, thus making them a threat to humans and natural ecosystem. MPs have been recognised by UN under SDG 14, to be measured by index of floating plastic debris density as an indicator, which until now have no internationally acceptable index. The review finds countries with regulations on MPs, such as the USA and China, are poorly implemented especially in rural settings and products containing micro beads are still in use. Weakened institutions, non-uniform policies, international trade, increased plastic production, poor plastic waste management, resistance from plastic industries, poor consumer education and apparent lack of studies on impacts of MPs on the environment and human have been a major setback for combating MPs pollution. Prompt global awareness and readiness, collaboration between scientists, plastic industries, governments, NGOs and community members, global evidence-based acceptable and measurable policies by all countries, plastic alternatives, studies on human health impact, regulations on plastic containing foods, consumer education, and regulation of plastic at level of production, pollution source, remediation and clean-up are clearly needed for a holistic fight against MPs pollution and intending consequences on humans and the environment.

Keywords: Microplastics, marine pollution, UN SDG, UNEP,

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SAFETY PHARMACOLOGY TEST OF PLANT-BASED COVID-19 VACCINE IN NON-HUMAN PRIMATES

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ABSTRACT

Introduction:
After the COVID-19 was first identified in Wuhan, China in December 2019, Thailand is the first country that made the confirmation of the case outside China. Henceforth, Baiya Phytopharm Co., Ltd, a Thai biotechnology company, has developed a plant-produced subunit COVID-19 vaccine (namely BY301) and mixed with the excipient aiming to stabilize the vaccine at the storage temperature of 2-8 °C.

Objective:
In reference to the ICH S7A Safety Pharmacology Studies for Human Pharmaceuticals, this study identifies potential undesirable pharmacodynamic properties of the excipient and BY301 relevant to human safety.

Methods:
The safety pharmacology on the physiological functions of three vital organ systems, covering Central Nervous System (CNS), Cardiovascular System (CVS) and Respiratory System (RS) was assessed. Ten juvenile/sub-adult female cynomolgus monkeys, aged 3 to 5 years, body weight between 2.4 to 3.1 kg were divided into 2 groups (n = 5 for each group) and intramuscularly injected with excipient alone or 10 µg of BY301 for 2 times on Day-0 and Day-21. The animals were followed up for 35 days after the first injection.

Results and Discussion:
The overall results of the monkey health based on body weight changes, blood biochemistry (ALT, AST, TP, BUN, ALB, ALP, TBIL, CHOL, GLU, TRIG, UA, GLOBU and CREA-P levels), hematology (RBC, WBC, HGB, HCT, PLT, PCT, NRBC, LYMPH, MONO, EO, BASO, NEUT and MPV), and the specific endpoints for the CNS (motor activity, behavioral changes, coordination, sensory/motor reflex responses and body temperature), CVS (blood pressure, heart rate, and electrocardiogram) and RS (respiratory rate, hemoglobin oxygen saturation and lung sound) did not suggest abnormal signs being induced by the excipient and the BY301. The monkey body weight was increased by 1.38% for excipient group and 1.66% for BY301 group, and body core temperature was ranging by 36.2 - 38.9 °C. Overall, it can conclude that two times of intramuscular administration of the excipient and BY301 are unlikely to cause adverse effects to the physiological functions of three vital organ systems, which is reflected with relevance to safety in healthy pubertal humans consistent with the scope of the ICH Topic S7A guidance document.

Keywords: COVID-19, safety pharmacology, Baiya SARS-CoV-2 Vax 1, cynomolgus monkey, ICH S7A

Reference:

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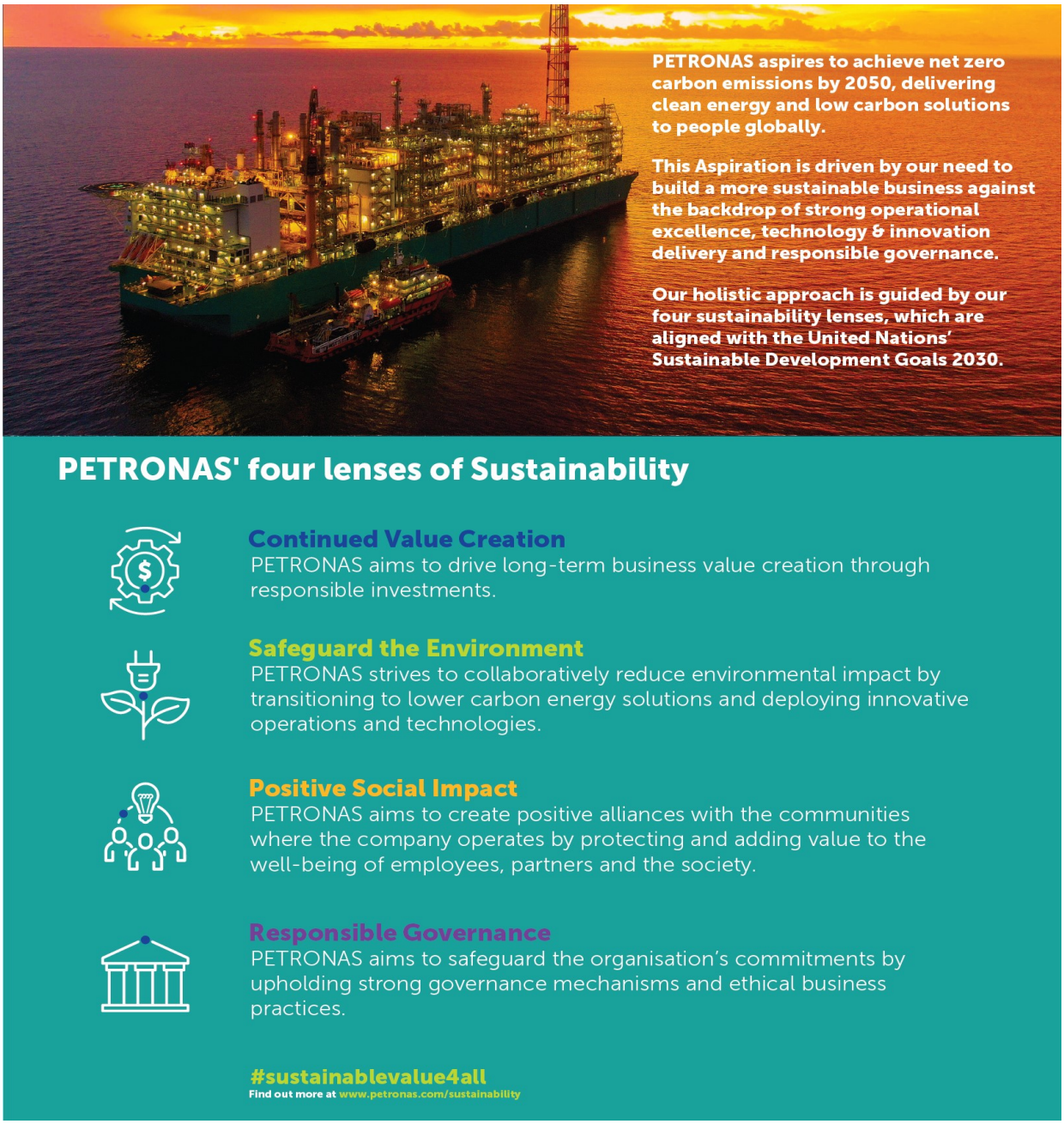

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CROPLIFE ASIA

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CropLife Asia is a non-profit organization dedicated to promoting plant science. Our mission is to empower the region's farmers to produce safe, affordable, and nutritious food while promoting food safety best practices across the food value chain.

A safe and secure food supply chain is crucial in supporting the world's economy and trade as it contributes to food and nutritional security which underpins sustainable development. With the world's population expected to grow to nearly 10 billion in 2050, the increased demand for food will create both opportunities and challenges for food safety. Challenges such as climate change will put greater stress on our farmers, food producers and handlers to ensure food safety from farm-to-fork. Thankfully, the innovative technologies of plant science can help farmers produce safe and nutritious food with overall less impact on the environment.

Biotech crops have been developed with improved traits such as increased yield, better resistance to pests and/or improved nutrition, among others. Crop protection products (or pesticides) allow farmers to grow more food on less land and raise productivity per hectare. Without pesticides, 40% of global rice and maize harvests could be lost every year and losses for fruits and vegetables could be as high as 50-90%. These plant science technologies are crucial tools that help farmers address global challenges such as food insecurity, food safety and climate change.

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CHINESE SOCIETY OF TOXICOLOGY

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Chinese Society of Toxicology
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Founded in 1993, the Chinese Society of Toxicology (CST) is a national professional and scholarly non-profit organization in China. The CST is affiliated to China Association for Science and Technology, and is a member of IUTOX and ASIATOX. CST comprises more than 17,000 individual members & 189 organizational members from universities, academic institutions, government and industries, etc, in China, and counts about 100 individual members from around the world. The CST is governed by a Council with 150 council members led by its Standing Committee. Prof. Ping-Kun Zhou serves as the present President and Dr. Chao Liu serves as Secretary General.

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CST holds ~20 domestic conferences, symposia and meetings, continuing education courses annually, also a series of international conferences & symposia that cover a broad range of topics in toxicology sciences. The CST National Congress is held every two years with 1500 to 1800 participants each time. The CST Youth Forum of Science and Technology gathers young scientists and professionals in toxicology and cross disciplines from all over the country every other year.


The 5 th Science and Technology Forum of Chinese Society of Toxicology
October 25-28, 2016, Shenzhen, 500 participants


The 7th National Toxicological Congress of Chinese Society of Toxicology (NTCSOT-VII)
October 25-28, 2015, Wuhan, 1800 participants

CST has established 4 kinds of science and technology awards, including Outstanding Contribution Awards and Youth Scientist Awards. The CST publishes its official journal *Toxicology Research* in jointly with British Toxicology Society and Oxford University Press (OUP), also the *Chinese Journal of Pharmacology and Toxicology* in collaboration with Chinese Society of Pharmacology.

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The 9th International Congress of Asian Society of Toxicology (ASIATOX-IX), October 20-23, 2021, in Hangzhou, China.
Congress Website: http://www.asiatox2020.com/en
Email: asiatox2020@chntox.org

The XVII International Congress of Toxicology (ICT-2025), October 2025, in Beijing, China

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PART VI: LIST OF POSTER PRESENTATIONS

PART VI: ABSTRACTS OF THE POSTER PRESENTATIONS

(a) Occupational, Clinical or Regulatory Toxicology

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GRIEVOUS COCKTAIL: A CASE OF COMBINED DRUG INTOXICATION

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ABSTRACT

Introduction:
Since the establishment of the Poison Centre in Malaysia, more than 35000 cases have been reported with case fatality rate of 35.88/1000. Albeit poisonings being not uncommon, it could be challenging to manage a case of multiple drug overdose due to the different toxidromes and interactions.

Objective:
We report a case of combined drug intoxication managed using various modalities in a rural setting in Malaysia.

Methods:
We examine the diagnostic challenges (e.g., inability to measure plasma levels of fluoxetine) and the limited treatment options available in our setting to manage a case of combined drug intoxication.

Results and Discussion:
An 18 year old man with autism spectrum disorder was brought in by his father after he was found unconscious with empty packets of 200 tablets of 200 mg sodium valproate, 15 tablets of 20 mg fluoxetine and 16 tablets of 500 mg paracetamol. He then developed multiple episodes of seizures. Examination revealed depressed conscious level, hypopnea, rigidity and hyperreflexia with ECG showing prolonged QT interval; leading to intubation. Blood analysis revealed respiratory acidosis, deranged liver function test and high plasma levels of paracetamol and sodium valproate. After intravenous N-acetylcysteine and hemodialysis, the persistently high plasma levels of sodium valproate and hemodynamic instability necessitated continuous veno-venous hemodiafiltration after the initial dialysis. After a prolonged hospital stay due to ventilator associated infection, patient was discharged well. This case illustrates the challenges in management of multiple drug overdoses with overlapping toxidromes in a rural setting. Prompt recognition and management of this condition is needed to prevent significant morbidity and mortality.

Keywords: paracetamol, sodium valproate, fluoxamine, combined drug intoxication

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ANALYSIS OF CANNABIS AND ITS METABOLITES 11-OH-THC and THC-COOH, IN POST-MORTEM FLUID AND TISSUES BY LC-MS/MS

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ABSTRACT

Introduction:
Cannabis sativa is one of three widely recognized plant species of cannabis. The prevalence of illicit use of cannabis has brought a special interest in analyzing major cannabinoids and their metabolites in biological samples. LC-MS/MS has proven to be a reliable approach for analyzing the presence of tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC) and carboxy-THC (THC-COOH) in post-mortem investigations.

Objective:
Study the concentration and distribution of THC, 11-OH-THC and THC-COOH in various post-mortem fluid and tissue samples using LC-MS/MS.

Methods:
43 post-mortem cases containing different fluid and tissue samples previously screened and found to be positive for cannabinoids were extracted using Solid Phase Extraction (SPE) and analyzed for THC and its metabolites by LC-MS/MS for THC. Samples were pre-treated with alkaline hydrolysis prior to SPE. (JPCC; ethical approval no. H-02-J-002, Ministry of Health, Jeddah Health Affairs).

Results and Discussion:
This study showed that THC or one of its metabolites were detected in different concentrations in various tissues and fluids for all 43 cases. Thus, it's difficult to quantitate or interpret the role of THC in the cause of death because of the variation in concentration in the various specimens. THC-COOH was detected in most types of specimens and, it can be the best indicator to detect cannabinoid in toxicology analysis. No single body fluid or tissue can be considered ideal for the detection of THC or its metabolites during toxicology analysis. Inclusion of several specimens in post-mortem analysis can help enhance the quality of cannabinoids investigation.

Keywords: Cannabis analysis, THC, post-mortem, LC-MS/MS

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MULTI-LEVEL ANALYSIS OF RADIATION EFFECTS ON BONE MICROARCHITECTURE: A SYSTEMIC REVIEW

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ABSTRACT

Introduction:
Modern radiation therapy has become an effective method to treat and monitor tumour growth in cancer patients. It has proved to be a successful way to minimize mortality rates. However, the adverse effects of radiation have been historical evidence in the clinical environment involving diminishing the quality and density of bone and causing fragility fracture to the bone in the long run.

Objective:
To review the existing literatures on the effect of irradiation on morphology, mechanical and tissue properties of murine model bone.

Methods:
Guided by PRISMA Statement (Preffered Reporting Items for Systemic reviews and Meta –Analyses) review method, a systemic review of the Scopus, Web of Science and Science Direct databases identified 1416 related studies. Following the screening, eligibility and quality appraisal process, 6 articles were eligible for review.

Results and Discussion:
This review revealed an association between bone destruction and the magnitude of time and dose post-irradiation. The effect of radiation on the microstructure of the femur, primarily at a later time was noticeable at low (1 Gy) and high radiation dose (30 Gy) in non-osteoporotic mice. The trabecular bone volume fraction trabecular number and trabecular thickness were significantly reduced. The mechanical strength was significantly impacted in both shorter and longer periods. The bone deterioration has been confirmed to manifest at irradiation and contralateral sites, showing that irradiation's local and systemic impact negatively affects the bone. It was also observed changes in osteoclast and osteoblast activities, therefore might increase the severity of inflammatory response. The mechanism may be partly associated with bone toxicity which correspond to an early post-radiation reaction. Bone toxicity is a predictive factor that correlates to bone fractures and subcutaneous tissue alteration.

Keywords: radiation effects, bone morphology, bone mechanical stength, bone tissue properties

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RECEPTOR TYROSINE KINASES: A SUITABLE TARGET IN THE MANAGEMENT OF DRUG-INDUCED AND DIET-INDUCED STEATOSIS

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ABSTRACT

Introduction:
Drug-induced steatosis is one of the major toxicological challenge associated with the usage of various drugs such as valproic acid, amiodarone, methotrexate (Rabinowich & Shibolet, 2015). High fat diet is another cause of steatosis and is also known to exacerbate drug-induced steatosis (Zhang et al., 2014). Thus, it is imperative to identify a suitable target to manage steatosis.

Objective:
In our study we sought to understand the role of receptor tyrosine kinases (RTKs) in the development and pathogenesis of drug-induced and diet-induced steatosis.

Methods:
In-vitro model for drug-induced steatosis was developed using HepG2 cells treated with valproic acid. For diet-induced steatosis model, HepG2 cells were treated with free fatty acids such as palmitic acid and oleic acid. RTK inhibitors for epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR) and fibroblast growth factor receptor (FGFR) were used to study its effect on lipid accumulation in drug-induced and diet-induced steatosis model.

Results and Discussion:
Amongst three RTK inhibitors tested namely, Gefitinib (EGFR inhibitor), Sunitinib (VEGFR inhibitor) and BLU9931 (FGFR4 inhibitor), Gefitinib was found to reduce lipid accumulation by approximately 20% in both drug-induced and diet-induced steatosis without compromising cell viability. The effect of EGFR inhibiton on ipid accumulation was confirmed using another EGFR inhibitor, Erlotinib and EGFR Si RNA in diet-induced steatosis model. EGFR is known to regulate sterol regulatory element binding protein (SREBP) which controls genes involved in *de-novo* lipogenesis (Komposch & Sibilia, 2015; Pang et al., 2020). Thus, inhibiting EGFR may block SREBP and *de-novo* liogenesis and reduce lipid load. Further, EGFR inhibition was also found to induce autophagy in both the models. As autophagy is the mechanism by which excess and unwanted cellular components are removed, we are interested in understanding if autophagy plays any role in lowering lipid accumulation in drug-induced and diet induced steatosis model (Singh & Cuervo, 2012).

Keywords: Steatosis, EGFR, Gefitinib, Autophagy, SREBP

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DISTURBANCE OF ANTIOXIDANT CAPACITY INDUCED BY OCCUPATIONAL EXPOSURE TO HERBICIDES IN THAI FARMERS

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ABSTRACT

Introduction:
Occupational exposure to herbicides has been seriously reported to induce acute and chronic diseases. The adverse health effects after herbicide exposure were based on an induction of free radical. The imbalance between free radical and antioxidant defense system is an important role to induce deleterious health effects.

Objective:
The aim of this study is to determine the urinary oxidative status in Thai farmers using single or mixture of herbicides during agricultural activities.

Methods:
Ethical approval for this study was granted by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University. Subjects were recruited for face-to-face interview. Two spot urines (pre- and post-working) were collected for determination of malondialdehyde (MDA) and total antioxidant capacity (TAC). All data were compared between two groups according to type of herbicide application (single and combined herbicide use).

Results and Discussion:
Most subjects were male farmers (64.18%) with duration of agricultural activities ranging from 20 – 40 years. Fifty-eight percent of the subjects mostly applied the combined herbicides between glyphosate, paraquat, and 2,4-D. The cumulative exposure intensity index (EII) was estimated and showed a greater value in farmers using single herbicide than combined herbicide use. The level of urinary MDA in workers using combined herbicides was slightly increased compared to those of workers using single herbicide. However, it was not found a significant difference in urinary MDA level between single and combined herbicide application. The urinary TAC in workers using single herbicide was significantly increased compared to those of workers using combined herbicides. Our result implied that the exposure to herbicides during agricultural activities posed a potential risk to induce alteration of antioxidant status.

Keywords: herbicide, Thai farmers, malondialdehyde, total antixodiant capacity

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EFFECT OF PERSONAL HYGIENE ON HEALTH STATUS OF GARBAGE SCAVENGERS IN GENUK SEMARANG, INDONESIA

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ABSTRACT

Introduction:
Health status of garbage scavengers or pemulung is often neglected due to the lack of knowledge and awareness on personal hygiene during collecting garbage. Amarin et al. (2020) reported that most of the garbage scavengers failed to maintain clean skin, healthy habits must be considered, such as maintaining clean clothes, bathing regularly, bathing using clean water and soap.

Objective:
This study was conducted to analyze the effect of personal hygiene and the use of personal protective equipment with the occurrence of diseases at garbage scavengers in Genuk, Semarang.

Methods:
A descriptive cross-sectional study was conducted to observe personal hygiene and health status of 36 garbage scavangers in Genuk, Semarang, Indonesia. The respondents were selected by purposive sampling. Personal hygiene data and the use of personal equipment were obtained through direct observation and observation questionnaires. Physical examinations by two general practitioners were done to observe the health status. Human ethics was approved by Bioethic Unit of FK UNISULA.

Results and Discussion:
Personal hygiene among the scavengers was poor. Most of the respondents did not use personal protective equipment, including gloves, mask, boots and hats during garbage collection. Low awareness to wear protective equipment caused 99.4% of the scavengers contact with disease vector and 52.8% respondents exposed to the nasty smell during collecting garbage. Physical examinations revealed 15 common diseases, in which hypertension was the predominant disease in respondents. Chi-square test showed that the disease suffered by scavengers was not associated with personal hygiene. It is concluded that health status of scavangers in Genuk, Semarang should be monitored.

Keywords: Scavenger, protective equipment, working environment, personal hygiene, health status

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PART VI: ABSTRACTS OF THE POSTER PRESENTATIONS

(b) Ecotoxicology or Environmental Toxicology

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SSRI GROUP OF ANTIDEPRESSANTS AND ITS POTENTIAL TOXICITY FOR SOIL ORGANISMS: A BRIEF REVIEW

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ABSTRACT

Introduction:
Pharmaceuticals are not entirely assimilated by the human body, entailing a potential accumulation in sewage sludge (SS). Consequently, the selective serotonin reuptake inhibitors (SSRI) have been reported in measurable concentrations both in SS and the environment, bringing the attention to the effects posed by this group of antidepressants towards non-target soil organisms.

Objective:
The main purpose of this work is to present a review of the range concentrations of most prescribed SSRI found on SS worldwide and describe their effects on soil fauna reported so far.

Methods:
This work's methodology consisted in a critical literature review, focusing on SSRI quantification on SS in different countries, and ecotoxicological tests performed with soil organisms. The most prescribed SSRI considered for this project were Sertraline (SER), Citalopram (CIT) and Fluoxetine (FLX).

Results and Discussion:
Collected data comprised three continents (North and South America, and Europe). The highest concentration found was for SER, in Brazil, with a range of 0.16 to 1.40 mg kg^{-1} DM (dry matter). Second highest was CIT, also in Brazil, ranging from 0.04 to 1.18 mg kg^{-1} DM. FLX followed, with highest concentrations found in the USA, ranging from 0.09 to 1.10 mg kg^{-1} DM. Reported effects on soil organisms include SER and CIT accumulation on leaves and roots of *Spinacea oleracea L* and SER accumulation on leaves and roots of *Lepidium sativum*. For FLX, biochemical changes and enzimatic inhibition were reported for *Folsomia candida* in acute tests, whilst chronicle tests showed that toxicity for reproduction increased as following generations were exposed. CIT was also reported to cause inhibitory effect on soil microbial community. Thus, the increasing accumulation of SSRI in the environment, its potential toxicity for soil organisms, and the data gap on the subject, reveal the importance of projects like this for general awareness.

Keywords: pharmaceuticals in sewage sludge, soil ecotocixity, sertraline, citalopram, fluoxetine

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EGCG AMELIORATES ALUMINUM MALTOLATE INDUCED NMDAR EXPRESSION CHANGES OF SH-SY5Y CELL LINE

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ABSTRACT

Introduction:
Aluminum (Al) is a heavy metal accumulates highly in hippocampus, which is also affected in neurodegenerative disorders like Alzheimer's disease (AD) (1). Al neurotoxicity affects different cellular signaling pathways related to neurodegenerative processes especially N-methyl-D-aspartate receptors (NMDAR) (2,3) and treatment strategies are tried to be developed through this pathway (4).

Objective:
To investigate the effect of aluminum maltolate (Al(Malt)3) on NMDAR 1/2A/2B expressions in vitro SH-SY5Y cell line and the protective role of epigallocatechin gallate (EGCG).

Methods:
SH-SY5Y cells were grown in favorable cell conditions. Cell proliferation was measured with the xCelligence system. Cells were plated for RNA extraction in 6-well plates, 5x10^6 cells per well. Cells were exposed to 10 µM and 25 µM EGCG; and 50 µM Desferoxamine (DES) as a positive control one hour before 200 µM Al(Malt)3. After 24 h mRNA expression levels were assessed with real time PCR.

Results and Discussion:
SH-SY5Y (neuroblastoma) cells treated with Al(Malt)3 for 24 and 48 hours at increasing doses showed a significant decrease in viability at 200 µM and over doses for 24 hours and 100 µM and over doses for 48 hours (both, $p<0.001$). Al(Malt)3 significantly decreased NMDAR1/2B subunits mRNA expression levels. While both doses of EGCG treatment upregulated mRNA expression levels NMDAR 1 and 2B, only the 10 µM EGCG treatment significantly increased NMDAR 2B levels. NMDAR2A mRNA expression levels did not change with the administration of Al(Malt)3 or EGCG. Studies have shown that Al can induce neurotoxicity by inhibiting NMDAR protein expressions (3) and it has been shown that Al can affect the Ca+2 signal system, and neurotoxic effects can be observed on NMDAR (5). In the SH-SY5Y cells that received EGCG, the increase in NMDARs responsible for synaptic pilasticity, suggested that EGCG can be effective in neuron recovery. This work was supported by TUBITAK (project number 115S533).

Keywords: Aluminum, epigallocatechin gallate, neurotoxicity, N-methyl-D-aspartate receptor

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TOXICITY ASSESSMENT OF EMAMECTIN BENZOATE AND ITS FORMULATIONS

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ABSTRACT

Introduction:
The bio-pesticide, Emamectin benzoate (EMB) mainly used in agriculture and veterinary medicine in developing countries is considered safe due to its target specificity (1). Conversely, non-regulated uses and several toxicology studies have raised concerns that EMB can induce cytotoxic and genotoxic effects (2, 3), and is a potential risk to human and environment.

Objective:
The objective of this study was to identify the toxic and genotoxic effects of technical grade EMB (80%) and its commercially used formulations in Pakistan, tycon 1.9% EC and tycon plus 5 % EW.

Methods:
All experiments were approved by the Institutional Animal House Committee #05 and 47. Acute oral and dermal LD_{50}, ocular and dermal irritation in albino rats and rabbit, toxicity (LC_{50}) in freshwater fish (*Labeo rohita*) was determined using OECD Test Guidelines (4). *In vivo* acute oral toxicity was assessed in rats (n=3/sex/group) at doses of 50 and 100 mg/kg body weight (BW). After 48 hours, gross and clinical pathology were investigated. Genotoxicity was assessed by *in vivo* bone marrow micronucleus and Comet assay. Mutagenicity was assesses in *S. typhimurium* strains TA98 and TA100.

Results and Discussion:
EMB formulations (80%, 5%, and 1.9%) were found moderately toxic (2) based on the Oral LD_{50} (122 to 168 mg/kg), severe eye irritant, and highly toxic to fish (LC_{50} ranged 9 to 43 µg/L). Acute oral exposure resulted in significant decrease in red blood cells, hemoglobin, and mean corpuscular volume (MCV). Slight increase in liver enzymes (ALP, ALT), blood urea, glucose, albumin, and total protein levels in rats administered 100 mg/kg. No significant DNA damage was observed in Comet assay and all formulations were found non-mutagenic in TA98 and TA100. Bone marrow toxicity was observed at high dose by reduction in the percentage of polychromatic erythrocytes (PCEs) at both (5% and 80%) concentrations. This study reveals that acute oral exposure to EMB formulations cause hemotoxicity and hepatotoxicity in rats and high toxicity to fish as aquatic organisms. It may contribute to the existing information about the toxicity of EMB for its safer use.

Keywords: Biopesticide, Emamectin benzoate, Acute toxicity, Genotoxic

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TRIGONELLINE PREVENTED ULTRVIOLET-B RADIATION EXPOSURE CULMINATES IN PHOTODAMAGE IN SKIN VIA MODULATION OF ER-STRESS AUTOPHAGY SIGNALLING AXIS

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ABSTRACT

Introduction:
Ultraviolet (UV) radiation has been reported a human carcinogen that initially leads to photodamage. Endoplasmic reticulum (ER)-stress and autophagy are the intracellular process responsible for the restoration of cellular homeostasis during unfavourable conditions. Natural products are the best treatment regime of the prevention of UV-B mediated photodamage.

Objective:
The aime of the present study was to finde out the role of Trigonelline (TG) on ER-stress autophagy in UV-B radiations-induced skin photodamage that has yet to be elucidated.

Methods:
In vitro cell models were exposed to UV-B at different time interval. *BALB/c* mice were exposed to UV-B for 16 weeks (Ethics Committee approval 1-1080-2-17-2017). TG was topically applied 1 hour pre- and post-exposure to UV-B. ER-stress, autophagy, inflammation, and collagen degradation were analysed by various biochemical and molecular biology techniques.

Results and Discussion:
In Hs68 cells, UV-B exposure induced radical oxygen species (ROS) generation leading to depletion of ER-calcium and increased ER stress protein markers and apoptotic protein expressions dose and time dependently. In fibroblasts, UV-B induced autophagy after 4-8 hours exposure to rescue the cellular homeostasis. After 24 hours exposure, UV-B radiation perverts the autophagy and directs cells toward photodamage. TG treatment successfully reduced oxidative stress, restored Ca2+ homeostasis and re-established the ER function and prevented apoptotic cell death process. TG treatment in UV-B exposed skin cells also abates UV-B-mediated phototoxicity, oxidative stress, inflammation and apoptosis. At molecular level, TG treatment significantly prevents ROS generation and lipid peroxidation, restores collagen synthesis and matrix metalloproteinase levels. Thus, TG is a potential photo-protective agent.

Keywords: Ultraviolet radiations, skin photodamage, autophagy, ER-stress, Trigonelline

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TOXICITY ASSESSMENT IMIDAZOLIUM-BASED IONIC LIQUIDS FAMILY BY USING MICROTOX® M500 ANALYZER

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ABSTRACT

Introduction:
The study focused on toxicity assessment benchmarking of three different ionic liquids from imidazolium family. The experimental result agreed that longer alkyl chain length give lower EC50 values, which signaled that ionic liquids having higher toxicity.

Objective:
Toxicity assessment of three different ionic liquids from 1-Decyl-3-Methylimidazolium chloride (DMIM Cl) , 1-Butyl-3-Methylimidazolium Tetrafluoroborate (BMIM BF4) and 1-Ethyl-3-Methyl Imidazolium Octyl-Sulphate (EMIM OS) using MICROTOX® M500 Analyzer

Methods:
The inhibition test of Vibrio fischeri was done by evaluating the light output of the bacterium when being exposed to a certain substance. The percentage decreased in the light output of the bacteria is linked to inhibition in the respiration activity which serve as indirect toxicity measurement of the test substances. The effective concentration, EC50 measured by the instrument (usually in (mg/L)) are used as indicator of toxicity where low EC50 value represent higher toxicity and vice versa.

Results and Discussion:
The results indicate that the greater the light loss of the Vibrio fischeri suspension, the more toxic the sample is. On other hand, difference in cation type used in this experiment provides a limitation for this study to assess effect of anion moieties toward ionic liquid's toxicity. However, the toxicity contribution of octyl sulfate ion towards imidazolium ionic liquid agreed to be higher than tetrafluoroborate based on the experimental finding, as well as previous literature studies. It is encouraged to have further extensive research on the effect of different anion in imidazolium ionic liquids towards ecotoxicity of ionic liquids, as well as environmental biodegradability of imidazolium ionic liquids.

Keywords: Ionic liquid; Imidazolium; Microtox; Toxicity Assessment; Benchmarking

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THE ROLE OF NRF2 ON THE CELL APOPTOSIS IN ARSENIC-INDUCED MALIGNANT TRANSFORMATION IN HACAT CELLS

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ABSTRACT

Introduction:
Arsenic is confirmed a human carcinogen and chronic exposure to arsenic can reduce cells apoptosis and cause malignant transformation. However, the exact mechanism remains to be elucidated.

Objective:
Explore the dynamic changes of apoptosis and its related proteins expression during sodium arsenite ($NaAsO_2$)-induced malignant transforamtion, and the role of nuclear factor erythroid 2-related factor 2 (Nrf2) in this process.

Methods:
Human epidermal keratinocyte (HaCaT) cells were cultured to 35 generations with 0.0 or 1.0 μM $NaAsO_2$**.** The changes in cell apoptosis rate and related proteins; Cleaved-caspase-3, Cleaved-caspase-8, Cleaved-caspase-12, CHOP, Bcl-2, Bax, Mcl-1 and Nrf2 in cells exposed to 1.0 μM $NaAsO_2$ for 0, 1, 7, 14, 21, 28, and 35 passages were detected by flow cytometry and Western blot. The levels of Nrf2, apoptosis rate and apoptosis related proteins in arsenite-transformed HaCaT cells after Nrf2 siRNA transfection were also detected.

Results and Discussion:
Compared with passage 0 cells and passage-control cells (0.0 μM $NaAsO_2$), the apoptosis rate, the protein expression levels of Caspase-3, Cleaved-caspase-3 protein and Cleaved-caspase-3/Caspase-3 showed downward trend. No obvious change was observed on apoptosis related proteins including the Cleaved-caspase-8, Caspase-8, Cleaved-caspase-12, Caspase-12 protein. Exposure to 1.0 μM $NaAsO_2$ for 21 passages decreased the expression of CHOP and Bax protein, and increased the expression of Bcl-2, Mcl-1 protein after 14 passages. The expression of Nrf2 protein was significantly increased in T-HaCaT cells. After transfection of arsenite-transformed HaCaT cells (T-HaCaT) with Nrf2 siRNA, the cell apoptosis rate significantly increased. the expression of Cleaved-caspase-3, Caspase-3, CHOP, Bax protein, on the contrary, the Bcl-2, Mcl-1 protein levels were decreased. The ability of colony formation and migration of T-HaCaT cells were decreased after Nrf2 siRNA transfection.

Keywords: $NaAsO_2$, Malignant transformation, Apoptosis, Apoptosis related proteins, Nrf2

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ESTRADIOL AND BISPHENOL A ESTROGENIC EFFECTS ON THE ROTIFER BRACHIONUS NEVADA

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ABSTRACT

Introduction:
Rotifers are microscopic aquatic invertebrates used as experimental models due to ease of culture, short life cycle, fast reproduction and small size. They promise to be an effective experimental model for endocrine disruption studies. On the other hand, current bioethical principles call for the replacement of vertebrate animal models, which is an opportunity for the definition of new invertebrate experimental models.

Objective:
To evaluate estrogenic effects of estradiol and bisphenol A on rotifers. To propose a mechanism for estrogenic effects induced in rotifers.

Methods:
Brachionus nevada individuals were cultured at 0.001, 0.01, 0.1, 1, 10, 100 and 1000 µg/L of estradiol and 0.1, 1, 10, 50, 100 mg/L of bisphenol A. The acute toxicity was estimated by lethal concentration 50. Additional cultures in the presence of the chemicals and tamoxifen, a potent estrogen receptor antagonist, were performed as a means to approach a proposal for mechanism of action mediating the toxicity.

Results and Discussion:
Lethal concentration 50 for estradiol was 1,053.04 µg/L and 21,593.10 µg/L for estradiol plus tamoxifen, showing a significant (<0.0001) dose-response curve shift to the right. Lethal concentration 50 for bisphenol A was 2.45 mg/L and 5.93 mg/L, with no significant shifts for the dose-response curve. These observations suggest that the acute toxicity is mediated by the estrogen receptor only for estradiol while bisphenol A acute toxicity is independent of estrogen receptor. The data supports the utility of rotifers as a model for endocrine disruption toxicological studies.

Keywords: estrogenicity, alternative methods, rotifers, bisphenol A

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PART VI: ABSTRACTS OF THE POSTER PRESENTATIONS

(c) Food, Herbal or Natural Product Toxicology

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SINGLE ORAL DOSE TOXICITY STUDY OF *ARECA CATECHU* AND *CYMBOPOGON NARDUS* AQUEOUS EXTRACTS IN RATS

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ABSTRACT

Introduction:
Herbal medicines are generally safe and been used widely for its traditional uses. Nevertheless, inherent toxicity of a herb may pose risk to consumers. Establishing the safety profile of herbs is important to determine limit dose of consumption. Plants named *Areca catechu* (AC) and *Cymbopogon nardus* (CN) are traditionally used orally for medicinal purposes but lacking information on its safety.

Objective:
To investigate acute toxicity effect of AC seed and CN aerial aqueous extracts respectively via oral administration in rats.

Methods:
This experiment was conducted according to Organisation of Economic Co-operation and Development (OECD) Test Guideline 420 with animal ethics approval (ACUC/KKM/02(1/2013)). Freeze-dried aqueous extract of plants were given to female Sprague Dawley rats (n=6/plant) at dose 300 and 2,000 mg/kg body weight. The rats were observed for clinical signs at first 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours and then daily for 14 days. On necropsy day, their liver, kidneys and gastrointestinal tracts were examined.

Results and Discussion:
No mortality or signs of toxicity was observed. Body weight, food and water intake of the rats showed increment throughout 14 days. There were episodes of loose stools occurred within four hours after administration of 2,000 mg/kg body weight (sighting and main dose) of AC seed extract but resolved thereafter. The loose stools could be from toxicity effect of high dose. However, evidences show AC seed as a dose-dependant laxative. Gross examination on the organs showed no abnormalities. The calculated human equivalent dose (HED) for the 2,000 mg/kg body weight is 32.26 mg/kg body weight (equivalent to 2,419.5 mg for a 75 kg human). In summary, single dose of AC seed and CN aerial aqueous extracts at 300 and 2,000 mg/kg body weight did not exhibit acute toxicity effects on Sprague Dawley rats. The No Observed Adverse Effect Level (NOAEL) is more than 2000 mg/kg body weight. Longer duration of repeated dosing is highly recommended to further evaluate the potential toxicity of these two herbs.

Keywords: Herb, safety, acute toxicity, *Areca catechu*, *Cymbopogon nardus*

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HEXANE EXTRACT OF GARLIC SUPPRESSES METHYLMERCURY-MEDIATED TOXICITY

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ABSTRACT

Introduction:
Garlic (*Allium sativum* L.) contains numerous sulfur compounds. We have previously found that reactive sulfur species with higher nucleophilicity such as glutathione persulfide, glutathione polysulfide, protein-bound persulfides, and hydrogen sulfide can covalently bind to methylmercury (MeHg) to give bismethylmercury sulfide [$(MeHg)_2S$], which is less toxic than MeHg with electrophilicity. It was not clear, however, whether such reactive sulfur species are present in garlic.

Objective:
The purpose of the study was to determine whether garlic components containing reactive sulfur species could react with MeHg to yield the sulfur adduct.

Methods:
We extracted garlic with hexane and then performed silica gel column chromatography to separate constituents. To evaluate existence of reactive per/polysulfide species with sulfane sulfur, formation of $(MeHg)_2S$ during reaction of the extract and MeHg was monitored by high-performance liquid chromatography and atomic absorption spectrophotometry. MeHg-mediated toxicity was determined by MTT assay in cells (HepG2 and SH-SY5Y cells) and body weight loss in C57BL/6J mice. The University of Tsukuba Animal Care and Use Committee approved protocols for animal experiments.

Results and Discussion:
We found that numerous garlic constituents could intract to MeHg to form $(MeHg)_2S$. Hexane extract of garlic decreased MeHg-mediated toxicity *in vitro*. The levels of cysteine persulfide, glutathione persulfide, hydrogen persulfide, glutathione, and H_2S in mice plasma were significantly increased after 2 h of administration of the garlic hexane extract (250 mg/kg). Although a single oral dose of 50 mg/kg of MeHg decreased the body weight, and 40% of the mice died within 10 days of exposure, simultaneous administration of the garlic hexane extract and MeHg caused suppression of the MeHg-induced toxic effects. These results suggest that ingesting garlic may decrease MeHg toxicity by formation of $(MeHg)_2S$ that inhibit adverse reactions. Reactive per/polysulfides with nucleophilc sulfur in garlic could react with envrionemental electrophiles yielding electrophile-sulfur addcuts to decrease their health risks.

Keywords: methylmercury, reactive sulfur species, garlic, detoxication, bismethylmercury sulfide

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ACUTE ORAL TOXICITY STUDY OF *ACALYPHA INDICA* AND *EUPHORBIA HIRTA* IN SPRAGUE DAWLEY RATS

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ABSTRACT

Introduction:
Acalypha indica (AI) and *Euphorbia hirta* (EH) are herbal plants that belong to the same family, *Euphorbiaceae* which can be found in the tropical regions with numerous therapeutic benefits due to their anti-oxidant and anti-microbial activities, commonly used for respiratory ailments. Despite numerous pharmacological studies were reported, safety assessment of these medicinal herbs is still limited.

Objective:
The study aims to assess the acute toxicity of *Acalypha indica* and *Euphorbia hirta* aerial extracts given oral administration once to female Sprague Dawley rats and observed for 14 days..

Methods:
Study was conducted according to OECD TG 420 with the approval of Animal Care and Use Committee (ACUC/KKM/02(1/2013). Sighting (300 mg/kg and 2000 mg/kg BW; n=1/dose level) and main studies (2000 mg/kg BW; n=4) were performed to determine the cut-off value of median lethal dose (LD_{50}). Body weight, food and water intake were measured weekly and clinical observation were carried out daily. On day 15, all rats were euthanized and gastrointestinal tract, kidney and liver were harvested.

Results and Discussion:
Body weight, food and water intake of each rat were normal for both treatments with no mortality and clinical signs of toxicity at all dose levels. Macroscopic evaluation of all organs revealed no abnormality except for reddening of ileum with prominent Peyer's in EH-300 mg/kg group. Based on findings in the main studies, this may not be attributed to the test item. In addition, there was no observed effect in AI main group from the extract administration. Traditionally, AI and EH are known for their expectorant benefits apart from AI being consumed for diuretic and laxative use whereas EH is commonly taken for its analgesic effect. Based on this study, LD_{50} is estimated to be greater than 2000 mg/kg of body weight for AI and EH since there were no mortality and acute toxicity observed. However, further investigation should be conducted to identify toxicity effects in longer duration of the herbal plant treatment.

Keywords: *Acalypha indica*, *Euphorbia hirta***,** toxicity, rat, herbal plant

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OXIDATIVE STRESS AND DNA DAMAGE EFFECT OF *DIOSCOREA HISPIDA* DENNST ON PLACENTAL TISSUES OF RATS

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ABSTRACT

Introduction:
In Malaysia, *Dioscorea hispida* Dennst. is known as "ubi gadung". It has been traditionally used as a remedy and source of carbohydrate. Steroidal saponins from the tubers were found to have various pharmacological activities. However, other alkaloid compounds like dioscorine and high concentration of cynogenic glycosides could potentially produce toxicity effects when ingested during pregnancy.

Objective:
To assess the effect of *D. hispida* aqueous extract (DHAE) on the production of reactive oxygen species (ROS) and their effects on DNA damage in placental tissues of Sprague Dawley rat.

Methods:
Pregnant rats were randomly divided into four groups and orally treated with DHAE at 0, 250, 500 or 1000 mg/kg body weight (BW) from gestation day 6 until 20. The rats were sacrificed on day 21 and placental tissues were collected. The level of ROS, superoxide dismutase (SOD) and malondialdehyde (MDA) were measured. The DNA damage was determined using comet assay. The experiment was approved by Animal Care and Use Committee, Ministry of Health Malaysia (ACUC/KKM/02(10/2016).

Results and Discussion:
No significant production of ROS and SOD activities in all groups. Significant changes were observed in the MDA level at 1000 mg/kg BW DHAE. Comet assay revealed a significant increase ($p < 0.05$) of DNA damage on rats treated with 250 and 500 mg/kg BW DHAE but not at the highest concentration. It was postulated that the placental cells could have undergone necrosis which destroyed all components including DNA. This occurrence simultaneously reduces the level of DNA damage which can be represented by low level of tail moments. This finding correlates with our histopathological examination where necrotic cells of spongiotrophoblast was observed in the basal zone of placental tissue. The high amount of hydrogen cyanide and other compounds in 1000 mg/kg BW DHAE could elevate the production of ROS and directly induce cell necrosis which requires further investigation.

Keywords: *Dioscorea hispida*, DNA damage, reactive oxygen species, placenta

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EVALUATION OF *SWIETENIA MACROPHYLLA* TOXICITY USING CELL-BASED ASSAY

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ABSTRACT

Introduction:
Swietenia macrophylla (family Meliaceae) is a timber species with medicinal value. It is commonly known as big-leaf mahogany or tunjuk langit. The seed is used traditionally and has been proven to exhibit anti-diabetic, anti-hypertensive, anti-diarrhoeal and analgesic activities. However in 2018, there were several cases of liver injury suspected to be associated with *S. macrophylla* seed consumption.

Objective:
The aim of this study is to assess the toxicity of *S. macrophylla* seed extracts (50:50 aqueous ethanolic, 100% ethanolic, and 100% methanolic) using cell-based assay.

Methods:
HepG2 cell line was used as an *in vitro* liver model. The cells were treated with various concentrations of the extracts for 24, 48 and 72 hours. For the 24-hour exposure, cells were treated with the extract in serum-free medium but for the 48- and 72-hour exposure, 2% foetal bovine serum was added to the treatment medium because of longer incubation time. Cytotoxicity was assessed by 3, (4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide (MTT) assay.

Results and Discussion:
The aqueous ethanolic, ethanolic and methanolic extracts only decreased approximately 45%, 47% and 61% of HepG2 viability at the highest concentration tested (1,000 µg/ml) after 24 hours exposure, respectively. The median inhibitory concentration (IC_{50}) was considered > 1,000 µg/ml for both the aqueous ethanolic and ethanolic extracts while for the methanolic extract, the IC_{50} was calculated to be 483.60 ± 90.95 µg/ml based on non-linear regression. When the experiment was repeated with 48- and 72-hour exposure, none of the extracts decreased cell viability more than 50%. The IC_{50} values for all three extracts with 48- and 72-hour exposure were therefore considered > 1000 µg/ml. These observations showed that *S. macrophylla* seed extracts do not appear to be tremendously cytotoxic based on MTT assay. There are three plausible explanations, (1) the extract is by nature not cytotoxic; (2) MTT assay is not sensitive enough to detect subtle toxicity; and (3) the toxic constituent(s) is not soluble in water, ethanol, and methanol, thus not extracted and not tested in the cytotoxicity evaluation.

Keywords: *Swietenia macrophylla*, cell-based assay, MTT assay, toxicity, cytotoxicity

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NEUROTOXIC EFFECT OF MALAYSIAN COBRA VENOMS AND NEUTRALIZATION BY THAI`S ANTIVENOMS

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ABSTRACT

Introduction:
N. sumatrana and *N. kaouthia* are two medically important species of cobra in Southeast Asia. They are known to cause neurotoxicity symptoms. In Malaysia, systemic envenoming caused by cobra is treated using antivenoms imported from Thailand. Variations in venom in a locality could cause antivenom produced in another locality to be ineffective and increase treatment cost.

Objective:
Objectives of this study are to assess neurotoxic effect of Malaysian *N.sumatrana* and *N.kaouthia* and effectiveness of Thai antivenom for reversing neurotoxicity using *in-vitro* preparation.

Methods:
In-vitro neurotoxic effects of *N. sumatrana* and *N. kaouthia* crude venom were assessed by indirect stimulated chick biventer cervicis preparation. The neurotoxicity activity was determined using time for 90% reduction in twitch response (t_{90}) and response to exogenous ACh, CCh and KCl. Neutralization was assessed using cobra antivenom and kingcobra antivenom by pre-incubation of antivenom and addition of antivenom at t_{90}. Animal ethic approval ID:IIUM/IACUC-2019(13).

Results and Discussion:
Both venoms were found to elicit concentration-dependent effect and reduced response to exogenous agonists in the chick biventer cervicis preparation. *N. kaouthia* venom was found to be more potent than *N. sumatrana* venom based on t_{90} value. Both venoms contain postsynaptic neurotoxin and myotoxin based on ACh, CCh and KCl responses.In the pre-incubation study, all antivenoms significantly attenuated reduction of twitch compared to venom alone but when added at t_{90}, did not restore twitch height for Cobra Antivenom and King Cobra Antivenom. Our finding showed that neurotoxicity caused by Malaysian *N.sumatrana* and *N.kaouthia* could be differentiated using *in vitro* preparation and the effect can be prevented by pre-incubation using Thai's Cobra Antivenom and King Cobra Antivenom.

Keywords: venom, neurotoxicity, antivenom, *Naja sumatrana* , *Naja kaouthia*

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HISTOLOGICAL EFFECT OF ORAL GENTAMICIN-NIGELLA SATIVA EMULSION TREATMENT IN RABBIT OSTEOMYELITIS MODEL

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ABSTRACT

Introduction:
A stable emulsion which contains gentamicin and *Nigella sativa* oil (NSO) has been formulated as a potential antimicrobial therapy to treat osteomyelitis caused by *Staphylococcus aureus*. Previously, gentamicin and *N. sativa* emulsion (GNE) was reported to be particularly effective against *S. aureus* and produced better inhibition and capable to impede the ability of bacteria to form biofilm.

Objective:
To asses the safety and the possibility of current formulation to act as enabler for gentamicin absorption into the blood, thus allowing gentamicin to be delivered orally to treat osteomyelitis in rabbits.

Methods:
In this study, 12 rabbits were divided into four equal groups, two of which orally treated with GNE at doses of 50 $mg_{gentamicin}$/kg (Group III) and 100 $mg_{gentamicin}$/kg (Group IV).The doses were given daily for one week. Ostoemyelitis was established using *S. aureus* in rabbits in Group II, III and IV prior to the treatment period,while Group I served as the sham control. After the rabbits were sacrificed, the kidneys and livers were removed for histological examination. The procedure of animal care and handling was approved by the Institutional Animal Care and Use Committee of International Islamic University Malaysia (No of IACUC Approval: IIUM/IACUC Approval/2016/ (9) (48)).

Results and Discussion:
Toxicity in kidney and liver tissues were observed in Group IV (100 $mg_{gentamicin}$/kg) as exemplified by the structural damage, inflammation and vacuolation. No histopathological lessions were observed in either liver or kidney tissue in Group III (50 $mg_{gentamicin}$/kg). This show that the current formulation of GNE could be a safe therapeutic option for patients with osteomyelitis condition. However, there is a need to refine the dosing regimen in order to further minimize toxicity but at the same time can provide an effective dose for bacterial eradication.

Keywords: Osteomyelitis, GNE Staphylococcus aureus, antibiotics.

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TOXICITY PROFILE OF THE AERIAL METHANOL EXTRACT OF *ALYSICARPUS GLUMACEUS* VAHL DC (LEGUMINOSAE) IN *DROSOPHILA MELANOGASTER*

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ABSTRACT

Introduction:
Alysicarpus glumaceus Vahl DC (*Leguminosae)* is used to treat asthma, cough, wound, thrush, sores, mental and stomach disorders. It is widely distributed across Africa, Asia and Australia. It is also used as fodder and for grazing. Recent report on its use in combination with other plants in Nigeria suggests it has central stimulantory effects.

Objective:
This study was done to determine the safety profile of the aerial methanol extract of *Alysicarpus glumaceus* in *Drosophila melanogaster.*

Methods:
Toxicity study were done in two phases for 7 days. The first phase (minimum concentration), *D. melanogaster* were treated with 10 mg, 20 mg, 30 mg, 40 mg and 50 mg of the extract /10 g diet; and in the second phase (maximum concentration), with 100 mg, 250 mg, 500 mg, 750 mg and 1000 mg of the extract /10 g of diet and mortality was observed daily. The data obtained from the experiment was analyzed by probit analysis using Graphpad prism 5.

Results and Discussion:
The median lethal concentration (LC_{50}) in *Drosophilia. melanogaster* was estimated to be greater than 1000 mg/10 g of diet from the daily mortality reading recorded for 7 days for both phases of the study. From the results obtained in this study, it can be concluded that the aerial methanol extract of *Alysicarpus glumaceus* is relatively non-toxic.

Keywords: Toxicity, *Alysicarpus glumaceus*, *Drosophila melanogaster,*

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ASSESSMENT OF CURCUMIN PIPERIDONE DERIVATIVES-INDUCED ANTI-PROLIFERATION ON HUMAN GLIOBLASTOMA LN-18 CELLS

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ABSTRACT

Introduction:
Curcumin has been found to possess anti-cancer effects on many cancer cell lines. However, the drawbacks of curcumin having a poor bioavailability and rapid metabolism have prompted researchers to look for alternatives, such as designing new synthetic curcumin derivatives. Our group have synthesized new curcumin piperidone derivatives in order to overcome the drawbacks of curcumin.

Objective:
To study the anti-proliferative effect of the piperidinone derivatives FLDP-5 and FLDP-8 curcuminoid analogues on human glioblastoma LN-18 cells

Methods:
The cytotoxicity of FLDP-5 and FLDP-8 were assessed using MTT assay (0.625 – 20 µM). Then, we further proceeded to flow cytometric assessment of the mode of cell death induced by these compounds using Annexin V-FITC/PI staining. The role of reactive oxygen species (ROS) and mitochoria in the cell death process were investigated using HE and TMRE staining respectively in conjunction with flow cytometry.

Results and Discussion:
The results from MTT assay and apoptosis assessment showed that the curcuminoid derivatives, FLDP-5 and FLDP-8 induced cytotoxicity through apoptosis in human glioblastoma LN-18 cells in a concentration-dependent manner after 24 hour treatment. The IC50 values for the FLDP-5 and FLDP-8 derivatives were 2.5 µM and 4 µM respectively, which were more potent compared to curcumin (IC50 of 45 µM). A significant increase ($p<0.05$) in the superoxide anion level upon 1 hour treatment confirmed the oxidative stress involvement in the cell death process induced by these derivatives. Interestingly, the loss of mitochondrial membrane potential ($\Delta\Psi m$) was seen as early as 30 minutes treatment with the derivatives ($p<0.05$), which indicated an early mitrochondrial damage. These findings elucidate the potential of FLDP-5 and FLDP-8 curcuminoid derivatives in human glioblastoma LN-18 cells and further investigation into the underlying mechanism could greatly enhanced the understanding of the anti-cancer role of these compounds.

Keywords: Curcumin, Curcuminoid derivatives, Anti-proliferation, Apoptosis

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UNDERSTANDING THE REPRODUCTIVE TOXICITY OF PHYTOESTROGENS: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction:
Phytoestrogens are naturally occurring compounds present in various food sources. Phytoestrogens are mimicking estrogen structurally and may also exert estrogenic effects on their own. Many studies have reported the health benefits of phytoestrogens; however, knowledge of these compounds' toxicity to female reproduction is crucial to define appropriate conditions for use and safe product development.

Objective:
This study aims to provide an overview and critical evaluation of evidence from the scientific literature on reproductive toxicity of phytoestrogens in in vitro and in vivo experimental studies.

Methods:
A literature search was performed on full-text electronic databases such as Scopus, Science Direct, PubMed, and Google Scholar that looked into adverse effects of phytoestrogens in vitro and in vivo studies. The search was limited to articles published in the English language since the past decade (1 January 2011 to 31 December 2020). Titles and abstracts of articles found were assessed to remove duplicate data. All potentially relevant full texts were screened to verify the study's eligibility.

Results and Discussion:
A total number of 1409 studies were identified through the literature. Of these, 444 studies were duplicated studies. After further screening through titles, abstracts, and full texts, 418 studies were excluded due to fail to meet inclusion criteria, while 26 studies were selected for this study. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 guidelines and checklists were used to develop the study criteria to eliminate attrition biases, raised from incomplete reporting data for each outcome and reporting biases. The selected studies in this systematic review showed that exposure to phytoestrogens might decrease fertility, inhibit endogenous estrogen production in the ovary, cause disturbances to immune system regulation, and lead to defects in follicle development. The adverse effects reported raise awareness of the toxicity of phytoestrogens, particularly to female reproduction that can potentially impair the function of a woman's reproductive organs.

Keywords: phytoestrogen, flavonoid, reproductive toxicity

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PART VI: ABSTRACTS OF THE POSTER PRESENTATIONS

(d) Computational Toxicology

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COMPUTATIONAL PREDICTION OF PULMONARY PERMEABILITY OF CHEMICALS

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ABSTRACT

Introduction:
Pulmonary permeability values obtained from in vitro experiments, known as apparent permeability (Papp), is critical for drug transportation and development. However, in vitro experiments are time-consuming and labor-intensive, and there are currently no computational models for assessing human lung permeability. Computational prediction models for in vitro airway epithelial barrier permeability are therefore desirable.

Objective:
The aim of this study is to develop a model to predict the pulmonary permeability of various chemicals.

Methods:
A total of 59 chemicals with Papp values representing the permeability characteristics of Calu-3 (human lung cancer cell line) were divided into training and test datasets. An ensemble regression model was developed by integrating linear regression and random forest. Cross-validation on the training dataset and prediction on the test dataset were conducted to evaluate the model performance.

Results and Discussion:
This study presents the first quantitative structure-activity relationship (QSAR) model for predicting in vitro pulmonary permeability. Based on a sequential feature selection algorithm, there were seven descriptors identified as informative features for predicting Papp values, such as topological polar surface area (TopoPSA) which was the most common physicochemical properties related to permeability. The final model based on the seven identified features performed well with correlation coefficients of 0.932, 0.803 and 0.859 for model fitting, 10-fold cross-validation and independent test, respectively. Altogether, the ensemble model based on the seven features is a potentially useful model to predict pulmonary permeability. In the future, we would follow the Organisation for Economic Co-operation and Development (OECD) guideline for validation of QSAR model to determine the applicability domain of the developed model. The model is expected to be useful for drug development and chemical risk assessment.

Keywords: Ensemble learning, Calu-3, Pulmonary permeability, Airway epithelial barrier

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TOXICOGENOMIC ANALYSIS OF BERBERINE'S PROTECTIVE ROLE IN TOXIC METALS INDUCED ALZHEIMER'S DISEASE

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ABSTRACT

Introduction:
Environmentally relevant toxic metals are reported as neurodegenerative disorders progenitor, playing a role in the precipitation of abnormal β-amyloid protein and hyperphosphorylated tau, the hallmarks of Alzheimer's disease (AD). The current therapies confer partial protection.d alternative approaches targeting phytochemicals, such as berberine have been proposed as an additional form of treatment.

Objective:
The aim of this study was to examine the toxicogenomic basis for the positive effect of berberine against environmentally relevant toxic metals induced AD, applying data analysis.

Methods:
The Comparative Toxicogenomic Database retrieved the set of genes common to lead, cadmium, arsenic and methylmercury linked with AD development and the set of genes by which berberine exerts a therapeutic mode of action in AD. *GeneMania* prediction server revealed detailed gene interactions, while *Metascape* analysed protein-protein interaction enrichment (PPIE). *SwissADME* evaluated physicochemical properties of berberine.

Results and Discussion:
Ten of the seventeen genes related to berberine therapeutic effects in AD are common to metal-induced AD: ACHE, APP, BAX, BCL2, CASP3, HMOX1, IL1B, MAPT, SOD2, TNF. Berberine exerts antagonistic effect to these genes. Selected genes' interaction network analysis revealed server predicted interactions (46.70%) and physical interactions (18.66%) as the most represented. The inference of enriched biological processes showed apoptotic signaling pathway, positive regulation of organelle organization and response to oxidative stress as the most prominent pathways involved in berberine protective action towards toxic metals. PPIE analysis showed regulation of apoptotic signaling pathway as the main gene ontology process potentially targeted with berberine. Physicochemical properties and pharmacokinetics of berberine are in accordance with the hypothesis of its beneficial properties in AD due to high gastrointestinal absorption and capability to pass blood-brain barrier.

Keywords: toxic metals, berberine, Alzheimer's disease, toxicogenomics

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Hussien, H.M., Abd-Ekmegied, A., Ghareeb, D.A., et al. (2018). Neuroprotective effect of berberine against environmental heavy metals-induced neurotoxicity and Alzheimer's-like disease in rats. Food Chem Toxicol, 111, 432-444. DOI: 10.1016/j.fct.2017.11.025

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PART VI: ABSTRACTS OF THE POSTER PRESENTATIONS

(e) Mechanistic Toxicology

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SUPEROXIDE DISMUTASE ACTIVITY IN THE BLOOD OF WISTAR RATS AFTER SUBACUTE EXPOSURE TO LOW LEVELS OF LEAD

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ABSTRACT

Introduction:
Lead (Pb) is toxic metal widely distributed in environment. One of the main mechanisms of its toxicity is induction of oxidative stress, by stimulation of free radicals production and inhibition of antioxidant enzymes. Since most research up to date has focused on the effects of higher Pb exposure, there is insufficient data available to form a dose-response relationship on low levels of Pb exposure scenario.

Objective:
The aim of this study was to investigate superoxide dismutase (SOD) activity in blood of Wistar rats, in low Pb dose exposure scenario and to perform dose response modeling.

Methods:
Six groups (male Wistar rats, n=6), received 0.1; 0.5; 1; 3; 7; 15; mg Pb/kg body weight/day for 28 days by oral gavage, while control group was untreated. All animals were sacrificed 24h after treatment and serum was used for determination of SOD activity. Statistical analysis was performed using SPSS 18.0, IBM, Armonk, NY, USA. Dose-response modeling was performed using PROASTweb software. The study was approved by the Ethic Committee (No. 323-07-11822/2018-05).

Results and Discussion:
Lead induced a significant decrease of serum SOD in all treated groups compared to the control, indicating that no observed adversed effect level (NOAEL) dose for the SOD activity is lower than the lowest dose used in the experiment, 0.1 mg Pb/kg/day. Dose response modeling was performed and confidence interval was determined using the model averaging method. For an effect dose of 5%, the proposed confidence interval was BMDL5 (2.5e-05 mg Pb/kg/day) and BMDU5 (12.6 mg Pb/kg/day). SOD has been proposed to play a key role in protecting cells from the toxic effects of superoxide anion radical. Our results demonstrated dose response inhibition of SOD in all treated groups that might be explained by direct inhibition of this enzyme by Pb or by the ability of Pb to replace metals that serve as enzyme co-factors. These results show that a low dose of Pb affects SOD function after 28 days exposure in Wistar rats, indicating that the decrease of SOD in the blood might be a sensitive indicator of Pb exposure.

Keywords: Pb toxicity, low doses exposure, dose response modeling, antioxidant enzyme

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ANTITUMOR ACTIVITIES OF PHENYLTIN(IV) DITHIOCARBAMATE COMPOUNDS IN HUMAN ERYTHROLEUKAEMIA CELL LINE K562

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ABSTRACT

Introduction:
The success of the first clinical metal-based drug, cisplatin, has brought the attention to develop other metallopharmaceutical drugs with lower toxicity and fewer side effects. Over the years, organotin (IV) compounds have been synthesized, characterized and reported in portraying effective antitumor effects in their own stable state of physical and chemical properties.

Objective:
To study the antitumor activities in which apoptosis induced cytotoxicity of di-,tri-phenyltin(IV) dithiocarbamate compounds via mitochondria-mediated pathway in human erythroleukaemia cells K562.

Methods:
Cytotoxicity effect and the mode of cell death were determined by MTT and Annexin V-FITC/PI assay, respectively. Cell cycle arrest and oxidative stress were identified by cell cycle analysis and N-acetyl-L-cysteine (NAC) and dihydroethidium (HE) staining assays, resepectively. Loss of mitochondrial membrane potential was assessed by tetramethylrhodamine ethyl ester (TMRE) staining assay.

Results and Discussion:
Phenyltin(IV) dithiocarbamate compounds inhibited K562 cell lines growth with a lower IC50 values, ranging from 0.55 μM to 6μM. The respective IC50 value of all compounds induced 46% to 69% apoptotic cell death, characterised by modulation of mitochondria pathway and production of reactive oxygen species. Moreover, the ability of compound 2 to arrest S phase, suggests that organotin (IV) compounds are DNA-targeted, which in line with most chemotherapeutic drugs target. The cells were being pre-treated with N-acetyl-L-cysteine (NAC) prior to the induction of organotin (IV) compound to identify the role of oxidative stress. Indeed, by the NAC pre-treatment, the apoptotic cells were significantly dropped as compared to the non-induction of NAC. Organotin (IV) compounds exhibit potent cytotoxic effect and induce apoptosis through mitochondrial pathway, attaining a higher potential to be developed as metallopharmaceutical antitumor drugs.

Keywords: organotin, dithiocarbamate, cytotoxicity, apoptosis, antitumor

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PART VI: ABSTRACTS OF THE POSTER PRESENTATIONS

(f) Risk Assessment & Others

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CARCINOGENIC AND ECOLOGICAL RISK ASESSMENT OF HEAVY METALS IN EGGS AND SOILS NEAR A GOLD MINE IN THAILAND

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ABSTRACT

Introduction:
Gold mining is a major activity of concern as it causes increasing heavy metals contamination in the environment, globally. Various farming activites surrounded the largest gold mining in Northern Thailand that had been in operation for 16 years and decommissioned since 2016. However, evaluation of heavy metals impact on health and ecological risk in the surrounding area was limited.

Objective:
To determine total mercury (THg), lead (Pb) and cadmium (Cd) concentrations in the eggs and soils collected from poultry farms to assess carcinogenic and ecological risks.

Methods:
Thirty chiken eggs and six soil samples from six farms within <25 km radius of a gold mining area were analyszed for heavy metals contaminations (EPA Method 200.8 and Method 3050B). Spearman's rank correlation coefficient was used to determine the relationship between heavy metal contamination in eggs and soil samples. The contamination factor (CF) and potential ecological risk index (RI) were calculated to assess soil contamination and human health risk assessment was based on carcinogenic risk.

Results and Discussion:
Pb average level in eggs correlated with the level in soil ($P < 0.05$). Potential ecological risk (ER) index coefficient were ER(Cd)>ER(THg)>ER(Pb). The pollution degree of Cd for ER was 89.89 and the RI was 95.69, indicating potential ecological risk in this area. The soil CFs were Pb(1.22)>Cd(1.07)>THg(0.12), indicating enrichment of Pb and Cd in this area. The incremental lifetime cancer risk (ILCR) of both Pb and Cd exceeded 0.0001 in all age groups, indicating significant health effects for the cancer risk. The ILCR of Pb and Cd were highest in 13-18 years old and 18-35 years old groups. Human cancer risk was well correlated with both Pb and Cd levels in chicken eggs from poultry farms near the gold mining area. The long-term health surveillance for eggs and environment, and safety policy on farming nearby gold mining area must be introduced.

Keywords: Eggs, Soil, Heavy Metals, Gold mining, Carcinogenic

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UPTAKE OF CARBOXYL-POLYETHYLENE GLYCOL-FUNCTIONALISED GOLD NANOPARTICLES INTO SPHEROIDS

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ABSTRACT

Introduction:
Drug discovery is hindered by non-representative monolayer in vitro models. Three-dimensional (3D) multicellular tumor spheroids are a more appropriate and representative platform. Complementarily, nanomedicines show theragnostic potential. Health and safety profiles of engineered nanomaterials are also under scrutiny – all of the above stand to be advanced by the findings from this study.

Objective:
Establishment of a 3D A549 (human lung carcinoma cell line) drug discovery and testing platform to elucidate uptake mechanisms employed by carboxyl-polyethylene glycol-functionalised gold nanoparticles (PCOOH-AuNPs).

Methods:
Liquid-overlay A549 spheroids' uptake mechanisms were assessed by counting internalised PCOOH-AuNPs using CytoViva® hyperspectral imaging of 5 µm spheroid sections, post-incubation with uptake inhibitors: sodium azide, dynasore, 5-(N-ethyl-N-isopropyl) amiloride, genistein, and chlorpromazine. Cell growth, as well as PCOOH-AuNP and inhibitor cytotoxicities, were assessed using lactate dehydrogenase release. Spheroid morphology was assessed via microscopy and live/dead staining.

Results and Discussion:
Cytotoxicity was absent for all exposure groups (PCOOH-AuNPs: 2 and 24 h; inhibitors: 3 h). Clathrin-mediated endocytosis (CME) was noted as the primary endocytic mechanism, 33.5%–54.8% of PCOOH-AuNPs being taken up this way, meaning the NPs are largely trafficked towards a degradative fate in the lysosome. Mean penetration into spheroids of 4.5 µm indicated low transcytosis. Lysosomal membrane permeabilisation could be a desirable possible mechanism of action. Findings enable reproducible 3D in vitro NP testing and inform future design of AuNPs with improved therapeutic profiles.

Keywords: alveolar carcinoma, clathrin-mediated endocytosis, gold nanoparticles, uptake, spheroids

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15 YEARS OF THE IBEROAMERICAN NETWORK OF TOXICOLOGY AND CHEMICAL SAFETY

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ABSTRACT

Introduction:
The Iberoamerican Network of Toxicology and Chemical Safety (RITSQ), began 15 years ago due to the initiative and the close and effective collaboration between Dr. Silvia Barros, from the University of São Paulo, in Brazil and Dr. Eduardo de la Peña, at the time president of the Spanish Association of Toxicology. The first meeting was held in Santiago, Chile, in August 2006 during the Latin American Congress of Toxicology (ALATOX).

Objective:
Here we present an overview of the activities of RITSQ during these fifteen years.

Methods:
We have searched the records of RITSQ to highlight the main activities during these years.

Results and Discussion:
After the initial meeting in 2006, in Santiago, Chile, RITSQ set up a web page (http://ritsq.org) with objectives and information on activities in the field of toxicology. The page and its information is open and freely available. We publish information on congresses and meetings, especially those organized in Iberoamerica (Latin America, Portugal and Spain). We also present posters with our information at congresses and meetings attended by our members. The number of visits to our webpage has continually increased throughout the years reaching 69,902 users, 101,515 sessions and a total of 206,668 visits.

Keywords: RITSQ, toxicology collaboration and networking

References:
Not applicable or not provided by author

PART VII: CTDC12 INVITATION ANNOUNCEMENT

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CTDC Meetings

Congress of Toxicology in Developing Countries

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CTDC11 ABSTRACT BOOK