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COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH

CSIR-INDIAN INSTITUTE OF TOXICOLOGY RESEARCH

CSIR-IITR, Lucknow is the only multidisciplinary research institute in the field of toxicology in South East Asia with the motto:

"Safety to environment & health and service to industry".

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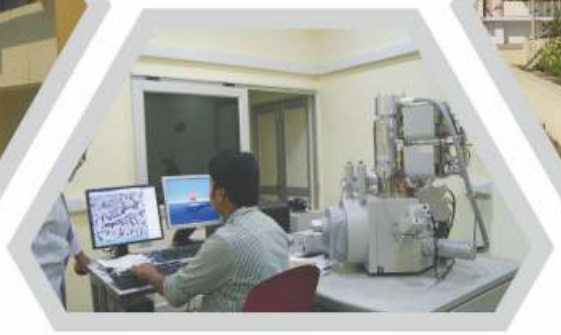

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Professor Alok Dhawan takes charge as Director, CSIR-IITR, Lucknow

Professor Alok Dhawan
FNASc, ATS, FAEB, FINS
Director, CSIR- IITR

Professor Alok Dhawan has assumed charge of Director, CSIR-Indian Institute of Toxicology Research, Lucknow in the forenoon of June 24, 2015. He was earlier Director, Institute of Life Sciences, Ahmedabad University, Gujarat. He obtained his Ph.D. Biochemistry from University of Lucknow, India in 1991. Professor Dhawan is an accomplished scientist and started the area of nanomaterial toxicology in India and published a guidance document on the safe use of nanomaterials. As scientist at CSIR-IITR, he spearheaded the alternate to animal models in toxicology programme in the country. He also developed *in silico* models for toxicity assessment and used them for understanding the mechanism of toxicants and nanomaterials. His work in the area of nanomaterial toxicology brought India to the global map through Indo-UK collaboration and the flagship European Union programme (NanoValid) under the EU-FP7. Professor Dhawan has several honours and awards to his credit including the INSA Young Scientist Medal in 1994, CSIR Young Scientist Award in 1999 the Shakuntala Amir Chand Prize of ICMR in 2002 and the Vigyan Ratna by the Council of Science and Technology, UP in 2011. He founded the Indian Nanoscience Society in 2007. In recognition of his work he has been elected Fellow, The National Academy of Sciences, India; Fellow, The Academy of Toxicological Sciences, USA; Fellow, The Academy of Environmental Biology; Fellow, Academy of Science for Animal Welfare; Fellow—Society of Toxicology (India); Founder Fellow, Indian Nanoscience Society; Fellow, Gujarat Science Academy; Vice President—Environmental Mutagen Society of India (2006-07); Member—National Academy of Medical Sciences. He has to his credit over 100 publications in peer reviewed international journals, several reviews/book chapters, four patents, one copyright. He has edited two books. After taking charge, he addressed the scientists, staff and students of the institute and encouraged them to rededicate and orient themselves to the larger goals of nation building. He also emphasized that CSIR-IITR should take the lead in developing capabilities to assess the safety of smart materials and new biologics. He lauded the efforts made by the previous Directors in bringing the Institute to international glory and pledged that it would only go higher with the dynamism of the scientists and students.

Events

National Science Day Celebrated

Anaemia, though widespread, has not received the attention it deserves as a public health concern among the common man and the educated class. This fact was revealed by Dr A. K. Tripathi, Prof and Head, Department of Clinical Haematology, KGMU,

National Science Day celebrations

while delivering a popular lecture entitled, **Anaemia – An unmet challenge**. He apprised the audience that about 1/3rd of the world's population remains anaemic and more than 70% of children below 3 yrs in India are anaemic. The most important cause for this is Iron deficiency and this is now being addressed by policy planners. Dr Tripathi explained the causes, symptoms, associated conditions and therapy for combating anaemia in a very simple and

Prof. A. K. Tripathi, delivering popular lecture

lucid language that could be easily understood by the audience which was a mix of students, scientists, and technical staff. Earlier, welcoming the gathering, Dr C. S. Nautiyal, Director, CSIR – IITR, said that Science Day is celebrated throughout the country to commemorate the discovery of the Raman Effect and to popularize science and take it to the public. The institute also celebrated the day as an Open Day, throwing its doors open to common citizenry to experience cutting edge science first hand.

Dr Poonam Kakkar, Convener – National Science Day Celebration Committee introduced the speaker and Dr Mukul Das, Chairman of the committee proposed the vote of thanks.

Students participating in National Science Day function

CSIT-IITR Celebrated World Environment Day

CSIR – Indian Institute of Toxicology Research celebrated the World Environment Day on 05 Jun 2015. Dr C. S. Nautiyal, Director, CSIR–IITR welcomed the gathering. Prof. K. P. Gopinathan, INSA Honorary Professor, Indian Institute of Science, Bengaluru was the Chief Guest and delivered the XIX Dr C. R. Krishna Murti Memorial Oration. His talk on "The Great Silk Route Passes through Safe Environment" apprised the audience of the many beneficial roles that insects can play in improving human life. Many insects like silk worms, honey bees, Lac insects etc. have been exploited by man for their commercial value. Another beneficial use of insects is in the application of spider silk for making bullet proof jackets. Dr Gopinathan also

Dr C. S. Nautiyal, Director, CSIR–IITR welcoming the guests

stressed upon the importance of better public health management and remedying environmental problems tackling for more effectively the scourge of infectious diseases in the country. The function was presided over by Dr V. P. Kamboj, Former Director, Central Drug Research Institute, Lucknow. He opined that the theme for the World Environment Day Celebrations 2015, as chosen by the UN, Consumption Vs Production was totally apt in the present scenario of depleting natural resources. Referring to the Swach Bharat Mission, he said, the onus is on each one of us is to ensure cleanliness of our surroundings which in turn will contribute to a clean and green environment. The report on the air quality for the pre-monsoon period in the city of Lucknow was released on the occasion by Dr V.P. Kamboj. The study was carried out during the months of April-May, 2015 to assess the status of air quality by monitoring and assessment of some

Release of Vish Vigyan sandesh (L-R) Dr Poonam Kakkar, Dr K.C. Gupta, Dr V.P. Kamboj, Prof. K.P. Gopinathan, Dr C.S. Nautiyal and Er. A.H. Khan

selected air pollutants namely Respirable Particulate Matter (RSPM or PM10), Fine particles (PM2.5), Sulphur dioxide (SO_2), Oxides of Nitrogen (NOx) and trace metals-Lead (Pb) and Nickel (Ni) and noise level at 9 representative locations, categorized as residential (four), commercial (four)

Children participating in Painting competion

A child receiving prize from Prof. K. P. Gopinathan

A view of audience

and industrial (one) areas in Lucknow city. The average values of PM10 and PM2.5 irrespective of locations were found to be above the permissible limit (100 µg/m^3 for PM10 and 60 µg/m^3 for PM2.5 prescribed by MoEF), while that of SO_2 and NOx was found to be below the permissible limit. Noise levels during day and night time were found to be in the range of 68.9 to 74.8 dB (A) and 51.7 to 69.4 dB (A) respectively which was above the respective permissible limits except in industrial area. Dr K.C. Gupta released the in-house magazine, Vish Vigya Sandesh. CSIR – IITR conducted a painting competition for school students in two age groups on this occasion. In the junior group, the first prize went to Anishaa Pandey, the second to Unnati Gupta and the third to Utkarsh Gopal. In the senior category, the first, second and third prizes were bagged by Riyan, Zaina Qasim and Neharika respectively. The prizes to the children were given away by Prof. Gopinathan. The programme concluded with the vote of thanks by Dr Poonam Kakkar.

National Technology Day Celebrated

The National Technology Day was celebrated with great enthusiasm by the scientists of CSIR-Indian Institute of Toxicology Research (IITR) on May 11, 2015. While welcoming the chief guest, Prof. P.K. Seth, CEO, Biotech Park, Lucknow, Dr C.S. Nautiyal, Director, CSIR-IITR spoke on the significance of National Technology Day and why it is celebrated every year. Dr Poonam Kakkar, introduced Prof. Seth to the audience. In his lecture entitled “New innovative devices for health care” Prof. Seth gave examples of these devices developed by innovators with a passion to become entrepreneurs. He began his lecture by describing 3-nethra, an eye pre-screening device which is used for rapid screening of patients with retinopathy, cataract, glaucoma and refraction problems. This device has been developed by Forus Health, Bangalore. The next device he mentioned pertained to diagnosis of anemia. The device measures indirectly the blood oxygen levels and determines anemia. Further he described a device

Celebration of National Technology day sitting on dais (L-R) Dr Mukul Das, Dr P.K. Seth, Dr C.S. Nautial and Dr Poonam Kakkar

named Abhaya, which transmits panic and fear signals through a sensor and triggers an emergency call. This device has been designed by students of Cochin University of Science & Technology, Cochin. He further dwelt on the medical devices developed under Stanford India Biodesign programme (SIB) in

Dr P.K. Seth delivering Technology Day Lecture

which the participants are from AIIMS, New Delhi, IIT, New Delhi and Stanford University, USA. A few devices developed by this group include Limb Immobiliser, a Resuscitation Device for babies who develop asphyxia after birth and Sohum – a hearing screening device to screen neonates for hearing impairment with high sensitivity and specificity. While concluding his lecture, Prof. Seth said that a country can progress only if we synergise our efforts in bringing together the best competencies of public funded R&D institutions like CSIR, academia and private industries. Dr Mukul Das proposed the vote of thanks.

CSIR-IITR Research Highlights

Prenatal exposure of cypermethrin induces similar alterations in xenobiotic-metabolizing cytochrome P450s and rate-limiting enzymes of neurotransmitter synthesis in brain regions of rat offsprings during postnatal development.

[Singh A, Mudawal A, Maurya P, Jain R, Nair S, Shukla RK, Yadav S, Singh D, Khanna VK, Chaturvedi RK, Mudiam MK, Sethumadhavan R, Siddiqi MI, Parmar D. Mol Neurobiol. 2015 Jun 27. (Epub ahead of print) DOI 10.1007/s12035-015-9307-y]

Oral administration of low doses of cypermethrin to pregnant Wistar rats led to a dose-dependent differences in the induction of xenobiotic-metabolizing cytochrome P450s (CYPs) messenger RNA (mRNA) and protein in brain regions isolated from the offsprings postnatally at 3 weeks that persisted up to adulthood. Similar alterations were observed in the expression of rate-limiting enzymes of neurotransmitter synthesis in brain regions of rat offsprings. These persistent changes were associated with alterations in circulating levels of growth hormone (GH), cognitive functions, and accumulation of cypermethrin and its metabolites in brain regions of exposed offsprings. Though molecular docking studies failed to identify similarities between the docked conformations of cypermethrin with CYPs and neurotransmitter receptors, *in silico* analysis identified regulatory sequences of CYPs in the promoter region of rate-limiting enzymes of neurotransmitter synthesis. Further, rechallenge of the prenatally exposed offsprings at adulthood with cypermethrin (p.o. 10 mg/kg × 6 days) led to a greater magnitude of alterations in the expression of CYPs and rate-limiting enzymes of neurotransmitter synthesis in different brain regions. These alterations were associated with a greater magnitude of decrease in the circulating levels of GH and cognitive functions in rechallenged offsprings. Data has led us to suggest that due to the immaturity of CYPs in fetus or during early development, even the low-level exposure of cypermethrin may be sufficient to interact with the CYPs, which in turn affect the neurotransmission processes and may help in explaining the developmental neurotoxicity of cypermethrin.

Bucky tubes induce oxidative stress mediated cell death in human lung cells.

[Singhal J, Singh SP, Karuppiah S, Pandey AK. Biomed Res Int. 2015;2015:560768.]

Unique physicochemical properties of carbon nanomaterials (CNMs) have opened a new era for therapeutics and diagnosis (known as theranostics) of various diseases. This exponential increase in application makes them important for toxicology studies. The present study was aimed at exploring the toxic potential of one of the CNMs, that is, bucky tubes (BTs), in human lung adenocarcinoma (A549) cell line. BTs were characterised by electron microscopy (TEM), dynamic light scattering (DLS), Fourier transform spectroscopy (FTIR), and X-ray diffraction (XRD). Flow cytometric study showed a concentration and time dependent increase in intracellular internalization as well as reduction in cell viability upon exposure to BTs. However, a

significant increase in intracellular reactive oxygen species (ROS) production was observed as evident by increased fluorescence intensity of 2',7'-dichlorofluorescein (DCF). BTs induced oxidative stress in cells as evident by depletion in glutathione with concomitant increase in lipid peroxidation with increasing concentrations. A significant increase in micronucleus formation and apoptotic cell population and loss of mitochondrial membrane potential (MMP) as compared to control were observed. Moreover, in the present study, BTs were found to be mild toxic and it is encouraging to conclude that BTs having outer diameter in the range of 7-12 nm and length 0.5-10 µm can be used for theranostics.

Predicting the hazardous dose of industrial chemicals in warm-blooded species using machine learning-based modelling approaches.

[Gupta S, Basant N, Singh KP. SAR QSAR Environ Res. 2015 Jun 18:1-20.]

The hazardous dose of a chemical (HD_{50}) is an emerging and acceptable test statistic for the safety/risk assessment of chemicals. Since it is derived using the experimental toxicity values of the chemical in several test species, it is highly cumbersome, time and resource intensive. In this study, three machine learning-based QSARs were established for predicting the HD_{50} of chemicals in warm-blooded species following the OECD guidelines. A data set comprising HD_{50} values of 957 chemicals was used to develop SDT, DTF and DTB QSAR models. The diversity in chemical structures and nonlinearity in the data were verified. Several validation coefficients were derived to test the predictive and generalization abilities of the constructed QSARs. The chi-path descriptors were identified as the most influential in three QSARs. The DTF and DTB performed relatively better than SDT model and yielded r2 values of 0.928 and 0.959 between the measured and predicted HD_{50} values in the complete data set. Substructure alerts responsible for the toxicity of the chemicals were identified. The results suggest the appropriateness of the developed QSARs for reliably predicting the HD_{50} values of chemicals, and they can be used for screening of new chemicals for their safety/risk assessment for regulatory purposes.

Chromium oxide nanoparticle-induced genotoxicity and p53-dependent apoptosis in human lung alveolar cells.

[Senapati VA, Jain AK, Gupta GS, Pandey AK, Dhawan A. J Appl Toxicol. 2015 Jun 18. doi: 10.1002/jat.3174.]

Chromium oxide (Cr_2O_3) nanoparticles (NPs) are being increasingly used as a catalyst for aromatic compound manufacture, abrading agents and as pigments (e.g., Viridian). Owing to increased applications, it is important to study the biological effects of Cr_2O_3 NPs on human health. The lung is one of the main exposure routes to nanomaterials; therefore, the present study was designed to determine the genotoxic and apoptotic effect of Cr_2O_3 NPs in human lung epithelial cells (A549). The study also elucidated the molecular mechanism of its toxicity. Cr_2O_3 NPs led to DNA damage, which was deduced by comet assay and cytokinesis block micronucleus assay. The damage could be mediated by the increased levels of reactive oxygen species. Further, the oxygen species led to a decrease in mitochondrial membrane potential and an increase in the ratio of BAX/Bcl-2 leading to mitochondria-mediated apoptosis induced by Cr_2O_3 NPs, which ultimately leads to cell death. Hence, there is a need of regulations to be imposed in NP usage. The study provided insight into the caspase-dependent mechanistic pathway of apoptosis.

Association of polymorphism of neuronal nitric oxide synthase gene with risk to Parkinson's disease.

[Gupta SP, Kamal R, Mishra SK, Singh MK, Shukla R, Singh MP. Mol Neurobiol. 2015 Jun 17. (Epub ahead of print) doi: 10.1007/s12035-015-9274-3]

Environmental factors are implicated in aging as well as genetic predisposition-induced Parkinson's disease (PD) pathogenesis. Wrongdoers increase oxidative stress and nitrosative burden, which eventually degenerate the nigrostriatal dopaminergic neurons. Inhibition of the expression of nitric oxide synthase (NOS), an enzyme responsible for nitric oxide (NO) biosynthesis, prevents the demise of the nigrostriatal dopaminergic neurons. Polymorphism of NOS is thus expected to alter PD susceptibility. The study therefore aimed to examine an association of neuronal NOS (nNOS) gene polymorphism with nitrite, an indicator of nitrosative load; lipid peroxidation, an index of oxidative stress and PD susceptibility. An age-matched case-control study was performed in the north Indian residents enrolled at the Neurology Department of the King George's Medical University, Lucknow, India. While nNOS exon 29 TT variant genotype [odds ratio (OR) = 2.20, 95% CI = 1.08-5.34, P = 0.040], combined TT and CT variants [OR = 1.68, 95% CI = 1.05-2.69, P = 0.031] and T allele [OR = 1.58, 95% CI = 1.10-2.28, P = 0.014] were found to be significantly associated with PD susceptibility, no association

between nNOS exon 18 [OR for TT carriers = 1.97, 95% CI = 0.89-4.20, P = 0.09 and OR for T allele = 1.35, 95% CI = 0.94-1.93, P = 0.098] and PD risk was observed. Lipid peroxidation was augmented in all patients irrespective of their genotype. While genotype independent increase in nitrite content was observed in PD patients of exon 29 polymorphic groups, only heterozygous variant genotype of exon 18 was associated with augmentation in nitrite level as compared with respective control. The results obtained thus demonstrate that selected nNOS polymorphisms do not significantly contribute to PD risk in north Indian population.

C-Phycocyanin protects against acute tributyltin chloride neurotoxicity by modulating glial cell activity along with its anti-oxidant and anti-inflammatory property: A comparative efficacy evaluation with N-acetyl cysteine in adult rat brain.

[Mitra S, Siddiqui WA, Khandelwal S. Chem Biol Interact. 2015 Jun 14;238:138-150.]

Spirulina is a widely used health supplement and is a dietary source of C-Phycocyanin (CPC), a potent anti-oxidant. Authors have previously reported the neurotoxic potential of tributyltin chloride (TBTC), an environmental pollutant and potent biocide. In this study, Authors have evaluated the protective efficacy of CPC against TBTC induced neurotoxicity. To evaluate the extent of neuroprotection offered by CPC, its efficacy was compared with the degree of protection offered by N-acetylcysteine (NAC) (a well known neuroprotective drug, taken as a positive control). Male Wistar rats (28day old) were administered with 20mg/kg TBTC (oral) and 50mg/kg CPC or 50mg/kg NAC (i.p.), alone or in combination, and various parameters were evaluated. These include blood-brain barrier (BBB) damage; redox parameters (ROS, GSH, redox pathway associated enzymes, oxidative stress markers); inflammatory, cellular, and stress markers; apoptotic proteins and *in situ* cell death assay (TUNEL). Authors observed increased CPC availability in cortical tissue following its administration. Although BBB associated proteins like claudin-5, p-glycoprotein and ZO-1 were restored, CPC/NAC failed to protect against TBTC induced overall BBB permeability (Evans blue extravasation). Both CPC and NAC remarkably reduced oxidative stress and inflammation. NAC effectively modulated redox pathway associated enzymes whereas CPC countered ROS levels efficiently. Interestingly, CPC and NAC were equivalently capable of reducing apoptotic markers, astroglial activation and cell death. This study illustrates the various pathways involved in CPC mediated neuroprotection against this environmental neurotoxicant and highlights its capability to modulate glial cell activity.

Overexpression of hsp27 rescued neuronal cell death and reduction in life- and health-span in *Drosophila melanogaster* against prolonged exposure to dichlorvos.

[Pandey A, Saini S, Khatoon R, Sharma D, Narayan G, Kar Chowdhuri D. Mol Neurobiol. 2015 Jun 3. (Epub ahead of print) DOI: 10.1007/s12035-015-9221-3]

Long-term exposure to dichlorvos (O,O-dimethyl-2,2-dichlorovinyl phosphate (DDVP), an organophosphate pesticide) is reported to exert neurotoxicity, i.e., generation of reactive oxygen species (ROS), oxidative damage, and neuronal cell death along with life- and health-span reduction in nontarget organisms including humans. However, studies on genetic modulation towards neuroprotection against prolonged DDVP exposure are elusive. Hsp27 (a small heat shock protein) is involved in various cellular processes and thus has attained emphasis as a therapeutic target. Authors aimed to examine the protective effect of hsp27 overexpression against prolonged DDVP exposure using an *in vivo* model *Drosophila melanogaster*. Flies were exposed to 15.0 ng/ml DDVP for a prolonged period to examine neuronal cell death, locomotor performance, and lifespan. After prolonged exposure, cell death, ROS level, glutathione depletion, nicotinamide adenine dinucleotide phosphate level (NADPH), glucose-6-phosphate dehydrogenase (G6PD), and thioredoxin reductase (TrxR) activities were examined in fly brain tissues at different days of age (days 10, 20, and 30). Flies with ubiquitous overexpression of hsp27 showed better resistance (improved lifespan and locomotor performance) in comparison to that targeted to motor neurons and nervous system. These flies also exhibited lesser intracellular ROS level and glutathione depletion by restoring G6PD activity, NADPH level, and TrxR activity in their brains thereby resisted neuronal cell death. Conversely, hsp27 knockdown flies exhibited reversal of the above endpoints. The study evidenced the neuroprotective efficacy of hsp27 overexpression against prolonged DDVP exposure and favored Hsp27 as a therapeutic target towards achieving better organismal (including human) health against long-term chemical exposure.

Bisphenol-A mediated inhibition of hippocampal neurogenesis attenuated by curcumin via canonical wnt pathway.

[Tiwari SK, Agarwal S, Tripathi A, Chaturvedi RK. Mol Neurobiol. 2015 May 12. (Epub ahead of print) doi: 10.1007/s12035-015-9197-z]

Bisphenol A (BPA) is an environmental xenoestrogenic endocrine disruptor, utilized for production of consumer products, and exerts adverse effects on the developing nervous system. Recently, authors found that BPA impairs the finely tuned dynamic processes of neurogenesis (generation of new neurons) in the hippocampus of the developing rat brain. Curcumin is a natural polyphenolic compound, which provides neuroprotection against various environmental neurotoxicants and in the cellular and animal models of neurodegenerative disorders. Here, authors have assessed the neuroprotective efficacy of curcumin against BPA-mediated reduced neurogenesis and the underlying cellular and molecular mechanism(s). Both *in vitro* and *in vivo* studies showed that curcumin protects against BPA-induced hippocampal neurotoxicity. Curcumin protects against BPA-mediated reduced neural stem cells (NSC) proliferation and neuronal differentiation and enhanced neurodegeneration. Curcumin also enhances the expression/levels of neurogenic and the Wnt pathway genes/proteins, which were reduced due to BPA exposure in the hippocampus. Curcumin-mediated neuroprotection against BPA-induced neurotoxicity involved activation of the Wnt/β-catenin signaling pathway, which was confirmed by the use of Wnt specific activators (LiCl and GSK-3β siRNA) and inhibitor (Dkk-1). BPA-mediated increased β-catenin phosphorylation, decreased GSK-3β levels, and β-catenin nuclear translocation were significantly reversed by curcumin, leading to enhanced neurogenesis. Curcumin-induced protective effects on neurogenesis were blocked by Dkk-1 in NSC culture treated with BPA. Curcumin-mediated enhanced neurogenesis was correlated well with improved learning and memory in BPA-treated rats. Overall, author's results conclude that curcumin provides neuroprotection against BPA-mediated impaired neurogenesis via activation of the Wnt/β-catenin signaling pathway.

Activity-guided chemo toxic profiling of *Cassia occidentalis* (CO) seeds: Detection of toxic compounds in body fluids of CO-exposed patients and experimental rats.

[Panigrahi GK, Ch R, Mudiam MK, Vashishtha VM, Raisuddin S, Das M. Chem Res Toxicol. 2015 Jun 15;28(6):1120-32.]

Authors' prior studies have shown an association between the deaths of children and consumption of *Cassia occidentalis* (CO) seeds. However, the chemicals responsible for the CO poisoning are not known. Therefore, the present study was designed to identify the key moieties in CO seeds and their cytotoxicity in rat primary hepatocytes and HepG2 cells. Activity-guided sequential extraction and fractionation of the seeds followed by GC-MS analysis identified the toxic compounds in the CO seeds. These identified compounds were subsequently detected and quantified in blood and urine samples from CO-exposed rats and CO poisoning human study cases. GC-MS analysis of different fractions of methanol extracts of CO seeds revealed the presence of five anthraquinones (AQs), viz. physcion, emodin, rhein, aloe-emodin, and chrysophanol. Interestingly, these AQs were detected in serum and urine samples from the study cases and CO-exposed rats. Cytotoxicity analysis of the above AQs in rat primary hepatocytes and HepG2 cells revealed that rhein is the most toxic moiety, followed by emodin, aloe-emodin, physcion, and chrysophanol. These studies indicate that AQ aglycones are responsible for producing toxicity, which may be associated with symptoms of hepatomyoencephalopathy in CO poisoning cases.

Nonlinear QSAR modeling for predicting cytotoxicity of ionic liquids in leukemia rat cell line: An aid to green chemicals designing.

[Gupta S, Basant N, Singh KP. Environ Sci Pollut Res Int. 2015 Apr 28. (Epub ahead of print) doi:10.1007/s11356-015-4526-3.]

Safety assessment and designing of safer ionic liquids (ILs) are among the priorities of the chemists and toxicologists today. Computational approaches have been considered as appropriate methods for prior safety assessment of chemicals and tools to aid in structural designing. The present study is an attempt to investigate the chemical attributes of a wide variety of ILs towards their cytotoxicity in leukemia rat cell line IPC-81 through the development of nonlinear quantitative structure-activity relationship (QSAR) models in the light of the OECD principles for QSAR development. Here, the cascade correlation network (CCN), probabilistic neural network (PNN), and generalized regression neural networks (GRNN) QSAR models were established for the discrimination of ILs in four categories of cytotoxicity and their end-point prediction using few simple descriptors. The

diversity and nonlinearity of the considered dataset were evaluated through computing the Euclidean distance and Brock-Dechert-Scheinkman statistics. The constructed QSAR models were validated with external test data. The predictive power of these models was established through a variety of stringent parameters recommended in QSAR literature. The classification QSARs rendered the accuracy of >86%, and the regression models yielded correlation (R 2) of >0.90 in test data. The developed QSAR models exhibited high statistical confidence and identified the structural elements of the ILs responsible for their cytotoxicity and, hence, could be useful tools in structural designing of safer and green ILs.

N-acetylcysteine effectively mitigates cadmium-induced oxidative damage and cell death in Leydig cells *in vitro*.

[Khanna S, Mitra S, Lakhera PC, Khandelwal S. Drug Chem Toxicol. 2015 Apr 17:1-7. (Epub ahead of print) doi:10.3109/01480545.2015.1028068]

Cadmium (Cd) is known to cause severe damage to various organs including lung, liver, kidney, brain and reproductive system. Several studies have reported the induction of oxidative stress pathways following Cd exposure. Since oxidative stress is also deemed responsible for inducing male infertility, a growing worldwide concern, authors tried to understand whether the antioxidant N-acetylcysteine (NAC) can be a potential therapeutic agent to counter Cd toxicity using primary Leydig cells. This study highlights the initial cellular alterations which culminate in cell death induction. Primary Leydig cells were isolated from 28-day-old male Wistar rats, exposed to various concentrations of Cd *in vitro* and biochemical and cell death parameters were evaluated to understand the effect of Cd. NAC pre-treatment was done to understand its protective efficacy. Following Cd exposure to Leydig cells *in vitro*, authors found simultaneous intracellular calcium (Ca2+) increase and reduction in mitochondrial membrane polarization at 30 min, followed by significant induction of reactive oxygen species and MAPK-extracellular-regulated kinases with concurrent glutathione depletion at 1 h, and significant cell death (both necrotic and apoptotic) at 6 and 18 h, respectively. Pre-treatment with NAC abrogated all these toxic manifestations and showed significantly reduced cell death. NAC also rescued the expression of 3-βHSD, a major steroidogenic protein. Taken together, these data illustrated that NAC can be used as a potential protective agent against Cd-induced testicular toxicity, especially with regards to oxidative stress-induced Leydig cell toxicity.

Trans-blood brain barrier delivery of dopamine-loaded nanoparticles reverses functional deficits in parkinsonian rats.

[Pahuja R, Seth K, Shukla A, Shukla RK, Bhatnagar P, Chauhan LK, Saxena PN, Arun J, Chaudhari BP, Patel DK, Singh SP, Shukla R, Khanna VK, Kumar P, Chaturvedi RK, Gupta KC. ACS Nano. 2015 May 26;9(5):4850-71.]

Sustained and safe delivery of dopamine across the blood brain barrier (BBB) is a major hurdle for successful therapy in Parkinson's disease (PD), a neurodegenerative disorder. Therefore, in the present study authors designed neurotransmitter dopamine-loaded PLGA nanoparticles (DA NPs) to deliver dopamine to the brain. These nanoparticles slowly and constantly released dopamine, showed reduced clearance of dopamine in plasma, reduced quinone adduct formation, and decreased dopamine autoxidation. DA NPs were internalized in dopaminergic SH-SY5Y cells and dopaminergic neurons in the substantia nigra and striatum, regions affected in PD. Treatment with DA NPs did not cause reduction in cell viability and morphological deterioration in SH-SY5Y, as compared to bulk dopamine-treated cells, which showed reduced viability. Herein, authors report that these NPs were able to cross the BBB and capillary endothelium in the striatum and substantia nigra in a 6-hydroxydopamine (6-OHDA)-induced rat model of PD. Systemic intravenous administration of DA NPs caused significantly increased levels of dopamine and its metabolites and reduced dopamine-D2 receptor supersensitivity in the striatum of parkinsonian rats. Further, DA NPs significantly recovered neurobehavioral abnormalities in 6-OHDA-induced parkinsonian rats. Dopamine delivered through NPs did not cause additional generation of ROS, dopaminergic neuron degeneration, and ultrastructural changes in the striatum and substantia nigra as compared to 6-OHDA-lesioned rats. Interestingly, dopamine delivery through nanoformulation neither caused alterations in the heart rate and blood pressure nor showed any abrupt pathological change in the brain and other peripheral organs. These results suggest that NPs delivered dopamine into the brain, reduced dopamine autoxidation-mediated toxicity, and ultimately reversed neurochemical and neurobehavioral deficits in parkinsonian rats.

Role of type I & type II reactions in DNA damage and activation of caspase 3 via mitochondrial pathway induced by photosensitized benzophenone.

[Amar SK, Goyal S, Mujtaba SF, Dwivedi A, Kushwaha HN, Verma A, Chopra D, Chaturvedi RK, Ray RS. Toxicol Lett. 2015 Jun 1;235(2):84-95.]

Sunscreen users have been increased, since excessive sun exposure increased the risk of skin diseases. Benzophenone (BP) and its derivatives are commonly used in sunscreens as UV blocker. Its photosafety is concern for human health. Authors study showed the role of type-I and type-II radicals in activation of caspase 3 and phototoxicity of BP under sunlight/UV radiation. BP photodegraded and formed two photoproducts. BP generates reactive oxygen species (ROS) singlet oxygen ($(1)O_2$), superoxide anion ($O_2^{\cdot}(-)$) and hydroxyl radical ($^{\cdot}OH$) through type-I and type-II photodynamic mechanisms. Photocytotoxicity significantly reduced cell viability under sunlight, UVB and UVA. DCF fluorescence confirmed intracellular ROS generation. BP showed single strand DNA breakage, further proved by cyclobutane pyrimidine dimmers (CPDs) formation. Lipid peroxidation and LDH leakage were enhanced by BP. P21 dependent cell cycle study showed sub G1 population which advocates apoptotic cell death, confirmed through AO/EB and annexin V/PI staining. BP decreased mitochondrial membrane potential, death protein released and activated caspase. Authors proposed cytochrome c regulated caspase 3 dependent apoptosis in HaCaT cell line through down regulation of Bcl2/Bax ratio. Phototoxicity potential of its photoproducts is essential to understand its total environmental fate. Hence, authors conclude that BP may replace from cosmetics preparation of topical application.

Nitrous oxide related behavioral and histopathological changes may be related to oxidative stress.

[Singh SK, Misra UK, Kalita J, Bora HK, Murthy RC. Neurotoxicology. 2015 May;48:44-9.]

Nitrous oxide (N_2O) toxicity can result in myelin loss and hyperhomocysteinemia similar to cobalamin (Cbl) deficiency. Studies on N_2O exposure can help in understanding the mechanism of demyelination. In view of paucity of studies on N_2O toxicity in rats this study was undertaken. Six male wistar rats were exposed to 1.5L/min N2O with 1:1 O_2 for 90min daily for 1 month. After 1-month exposure blood homocysteine (HCY) and oxidative stress parameters glutathione (GSH) and total antioxidant capacity (TAC) were measured. Brain and spinal cord was subjected to histopathological examination. The neurobehavioral changes, oxidative stress parameters and histopathological changes were correlated with serum B12 and HCY level. After 1-month exposure, the rats appeared sluggish, lethargic and developed predominantly hind limb weakness for 1-1.5h. In the exposed group, the total distance traveled (2001.66±118.27cm; p=0.037), time moving (80.16±5.7s; p=0.028), number of rearing (10.33±1.45; p=0.014) and grip strength (1042.40±51.3N; p=0.041) were significantly decreased whereas, resting time significantly increased (219.83±5.7s; p=0.030) compared to controls. Serum HCY level was significantly increased (20.56±1.296µm/ml; p=0.0007) in the exposed group. However, serum B12 and folic acid levels were not significantly different. GSH significantly decreased (2.21±0.60mg/dl; p=0.018) along with TAC (0.76±0.16 Trolox_Eq_mmol/l; p=0.036). The histopathological studies revealed shrinkage and vacuolation of neurons in cerebral cortex, focal myelin loss, vacuolation in subcortical white matter and spinal cord. N_2O exposure results in behavioral alterations, hyperhomocysteinemia, cortical and spinal cord demyelination which were associated with decrease GSH and TAC highlighting pathophysiological role of oxidative stress.

Minocycline rescues from zinc-induced nigrostriatal dopaminergic neurodegeneration: Biochemical and molecular interventions.

[Kumar V, Singh BK, Chauhan AK, Singh D, Patel DK, Singh C. Mol Neurobiol. 2015 Mar 13. (Epub ahead of print) doi: 10.1007/s12035-015-9137-y]

Accumulation of zinc (Zn) in dopaminergic neurons is implicated in Parkinson's disease (PD), and microglial activation plays a critical role in toxin-induced parkinsonism. Oxidative stress is accused in Zn-induced dopaminergic neurodegeneration; however, its connection with microglial activation is still not known. This study was undertaken to elucidate the role and underlying mechanism of microglial activation in Zn-induced nigrostriatal dopaminergic neurodegeneration. Male Wistar rats were treated intraperitoneally with/without zinc sulphate (20 mg/kg) in the presence/absence of minocycline (30 mg/kg), a microglial activation inhibitor, for 2-12 weeks. While neurobehavioral and biochemical indexes of PD and number of dopaminergic neurons were reduced, the number of microglial cells was increased in the substantia nigra of the Zn-exposed animals. Similarly, Zn elevated lipid peroxidation (LPO) and activities of superoxide

dismutase (SOD) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; however, catalase activity was reduced. Besides, Zn increased an association of NADPH oxidase subunit p67phox with membrane, cytochrome c release from the mitochondria and cleavage of pro-caspase 3. Zn attenuated the expression of tyrosine hydroxylase (TH) and vesicular monoamine transporter-2 (VMAT-2) while augmented the expression of dopamine transporter (DAT) and heme oxygenase-1 (HO-1). Minocycline alleviated Zn-induced behavioural impairments, loss of TH-positive neurons, activated microglial cells and biochemical indexes and modulated the expression of studied genes/proteins towards normalcy. The results demonstrate that minocycline reduces the number of activated microglial cells and oxidative stress, which rescue from Zn-induced changes in the expression of monoamine transporter and nigrostriatal dopaminergic neurodegeneration

Critical role of the miR-200 family in regulating differentiation and proliferation of neurons.

[Pandey A, Singh P, Jauhari A, Singh T, Khan F, Pant AB, Parmar D, Yadav S. J Neurochem. 2015 Jun;133(5):640-52.]

The generation of differentiated and functional neurons is a complex process, which requires coordinated expression of several proteins and microRNAs (miRNAs). The present study using nerve growth factor (NGF)-differentiated PC12 cells led to the identification of miR-200, miR-221/222 and miR-34 families as major up-regulated miRNAs in fully differentiated neurons. Similar to PC12 cells, induction of miR-200 family was observed in differentiating neural stem cells, demonstrating a direct role of miR-200 family in neuronal differentiation. Over-expression of miR-200 induced neurite formation in PC12 cells and regulated neuronal markers in favour of differentiation. However, inhibition of miR-200 induced proliferation of PC12 cells. In differentiating PC12 cells and neural stem cells, an inverse relationship was observed between expression of reprogramming transcription factors (SOX2, KLF4, NANOG, OCT4 and PAX6) and miR-200. Over-expression of miR-200 in PC12 cells significantly down-regulated mRNA and protein levels of SOX2 and KLF4. Moreover, authors observed two phases of dramatic down-regulation of miR-200 expression in developing rat brains correlating with periods of neuronal proliferation. In conclusion, author's results indicate that increased expression of the miR-200 family promotes neuronal differentiation, while decreased expression of the miR-200 family promotes neuronal proliferation by targeting SOX2 and KLF4

Efficacy of methuselah gene mutation toward tolerance of dichlorvos exposure in *Drosophila melanogaster*.

[Pandey A, Khatoon R, Saini S, Vimal D, Patel DK, Narayan G, Chowdhuri DK. Free Radic Biol Med. 2015 Jun;83:54-65.]

Adverse reports on the exposure of organisms to dichlorvos (DDVP; an organophosphate insecticide) necessitate studies of organismal resistance/tolerance by way of pharmacological or genetic means. In the context of genetic modulation, a mutation in methuselah (mth; encodes a class II G-protein-coupled receptor (GPCR)) is reported to extend (~35%) the life span of *Drosophila melanogaster* and enhance their resistance to oxidative stress induced by paraquat exposure (short term, high level). A lack of studies on organismal tolerance of DDVP by genetic modulation prompted us to examine the protective efficacy of mth mutation in exposed Drosophila. Flies were exposed to 1.5 and 15.0 ng/ml DDVP for 12-48 h to examine oxidative stress endpoints and chemical resistance. After prolonged exposure of flies to DDVP, antioxidant enzyme activities, oxidative stress, glutathione content, and locomotor performance were assayed at various days (0, 10, 20, 30, 40, 50) of age. Flies with the mth mutation (mth(1)) showed improved chemical resistance and rescued redox impairment after acute DDVP exposure. Exposed mth(1) flies exhibited improved life span along with enhanced antioxidant enzyme activities and rescued oxidative perturbations and locomotor insufficiency up to middle age (~20 days) over similarly exposed w(1118) flies. However, at late (≥30 days) age, these benefits were undermined. Further, similarly exposed mth-knockdown flies showed effects similar to those observed in mth(1) flies. This study provides evidence of tolerance in organisms carrying a mth mutation against prolonged DDVP exposure and further warrants examination of similar class II GPCR signaling facets toward better organismal health.

The manganese-salen compound EUK-134 and N-acetyl cysteine rescue from zinc- and paraquat-induced toxicity in rat polymorphonuclear leukocytes.

[Kumar A, Shukla S, Chauhan AK, Singh D, Pandey HP, Singh C. Chem Biol Interact. 2015 Apr 25;231:18-26.]

Oxidative stress is implicated in toxicant-induced inflammation leading to chronic diseases. Polymorphonuclear leukocytes (PMNs) offer the first line of defense against infection in the mammals and protect against inflammation-mediated pathological anomalies. Conversely, activated PMNs contribute to the oxidative stress-mediated damage and inflammation. The study aimed to investigate the status of oxidative stress and antioxidant defense system in the PMNs of rats treated with/without zinc (Zn) and/or paraquat (PQ) in the presence or absence of a synthetic superoxide dismutase/ catalase mimetic, a manganese-salen compound-EUK-134 and/or a glutathione precursor, N-acetyl cysteine (NAC). While Zn and/or PQ elevated the total free radical generation, lipid peroxidation (LPO) and catalytic activity of myeloperoxidase (MPO), superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione S-transferase alpha 4-4 (GSTA4-4), a pronounced decrease in reduced glutathione (GSH) and glutathione reductase (GR) activity was also observed. Zn and/or PQ augmented the expression of metallothionein-I and II and GSTA4-4. Pre-treatment of EUK-134 or NAC alone altered the level of total free radical generation, LPO, GSH content and catalytic activity of MPO, SOD, GR and GPx and the expression of metallothionein I and II towards normalcy. The alterations were more pronounced in the PMNs of rats treated with EUK-134 and NAC in combination. Catalytic activity/expression of GSTA4-4 remained unchanged in the PMNs of EUK-134 or NAC treated rats. The results demonstrate that EUK-134 and NAC protect PMNs from the toxic effects of Zn and PQ in rats and also suggest that metallothioneins I/II might contribute to antioxidant defense under GSH depleted conditions.

Resveratrol protects from toxin-induced parkinsonism: Plethora of proofs hitherto petty translational value.

[Ur Rasheed MS, Tripathi MK, Mishra AK, Shukla S, Singh MP. Mol Neurobiol. 2015 Feb 18. (Epub ahead of print) doi: 10.1007/s12035-015-9124-3]

Parkinson's disease (PD) is a mysterious, chronic, multi-factorial and progressive disorder of the nervous system that is characterized by the selective loss of dopamine-producing cells of the substantia nigra leading to dopamine deficiency in the striatum. PD is exemplified by oxidative stress, α-synuclein accumulation, mitochondrial dysfunction, defective ubiquitin proteasome system, aberrant autophagy, inflammation, and atypical apoptosis, which eventually lead to slowness of movement, resting tremor, stiffness, and loss of balance. Despite incomprehensible etiology, timely diagnosis, and permanent cure, a handful of synthetic and natural agents rescue from the symptomatic features and delay disease progression. At low doses, a natural polyphenol, trans-3,5,4'-trihydroxystilbene (resveratrol), delays neurodegeneration in the cellular and animal models and lessens oxidative stress, mitochondrial dysfunction, aberrant apoptosis, and defective autophagy. The present article explains neuroprotective efficacy, advantages, and downsides of resveratrol in the conventional and preclinical models. This piece of writing also examines its probable neuroprotective mechanisms and constraints of realistic recital in clinical investigations and likely endeavors to minimize apprehensions.

Application of nano-sized multi-template imprinted polymer for simultaneous extraction of polycyclic aromatic hydrocarbon metabolites in urine samples followed by ultra-high performance liquid chromatographic analysis.

[Chauhan A, Bhatia T, Singh A, Saxena PN, Kesavchandran C, Mudiam MK. J Chromatogr B Analyt Technol Biomed Life Sci. 2015 Mar 15;985:110-8.]

Nano-sized molecularly imprinted polymer (nMIP) was synthesized through precipitation polymerization method and used it as solid phase extraction (SPE) sorbent for the selective and simultaneous extraction of hydroxylated metabolites of polycyclic aromatic hydrocarbons (PAHs) from urine followed by ultra-high performance liquid chromatography (UHPLC) analysis coupled with the fluorescent detector (FLD). Multi-template imprinting approach was used in the synthesis of nMIP by taking 1-naphthol, 9-phenanthrol and 9-hydroxyfluorene as templates, methacrylic acid (MAA) as a monomer, ethyleneglycoldimethacrylate (EGDMA) as a crosslinker and AIBN as an initiator. The synthesized nMIP exhibit the highest degree of binding affinity in comparison to non-imprinted polymer (NIP), and its binding affinity found to be in the range of 50-90% for all five metabolites tested. Method exhibits good linearity over a range of

concentrations of metabolites with a R(2) value ranges from 0.9789 to 0.9921. Limit of detection (LOD) and limit of quantitation (LOQ) in urine samples were found to be in the range of 0.33-2.6 and 0.99-8ngmL(-1), respectively. Precision study shows that intra and inter-day precision was found to be less than 10%. The application of nMIP as SPE sorbent offers an effective and selective affinity towards the PAH metabolite's and found to be an alternative to the conventional sorbent for PAH metabolite's extraction from the biological samples. The developed nMIP offers wide advantages like simultaneous determination of PAH metabolites with improved sensitivity and found to be cost-effective for the routine analysis.

Bromelain nanoparticles protect against 7, 12-dimethylbenz[a]anthracene induced skin carcinogenesis in mouse model.

[Bhatnagar P, Pant AB, Shukla Y, Chaudhari B, Kumar P, Gupta KC. Eur J Pharm Biopharm. 2015 Apr;91:35-46.]

Conventional cancer chemotherapy leads to severe side effects, which limits its use. Nanoparticles (NPs) based delivery systems offer an effective alternative. Several evidences highlight the importance of Bromelain (BL), a proteolytic enzyme, as an anti-tumor agent which however has been limited due to the requirement of high doses at the tumor site. Therefore, authors illustrate the development of BL loaded poly (lactic-co-glycolic acid) NPs that show enhanced anti-tumor effects compared to free BL. The formulated NPs with a mean particle size of 130.4 ± 8.81 nm exhibited sustained release of BL. Subsequent investigation revealed enhanced anti-tumor ability of NPs in 2-stage skin tumorigenesis mice model. Reduction in average number of tumors (~ 2.3 folds), delay in tumorigenesis (~ 2 weeks), percent tumorigenesis (~ 4 folds), and percent mortality rate as well as a reduction in the average tumor volume (~ 2.5 folds) in mice as compared to free BL were observed. The NPs were found to be superior in exerting chemopreventive effects over chemotherapeutic effects at 10 fold reduced dose than free BL, validated by the enhanced ability of NPs (~ 1.8 folds) to protect the DNA from induced damage. The effects were also supported by histopathological evaluations. NPs were also capable of modulating the expression of pro-apoptotic (P53, Bax) and anti-apoptotic (Bcl2) proteins. Therefore, authors' findings demonstrate that developed NPs formulation could be used to improve the efficacy of chemotherapy by exerting chemo-preventive effects against induced carcinogenesis at lower dosages.

Effect of prenatal exposure of lindane on alterations in the expression of cerebral cytochrome P450s and neurotransmitter receptors in brain regions.

[Srivastava S, Singh A, Shukla RK, Khanna VK, Parmar D. Food Chem Toxicol. 2015 Mar;77:74-81.]

Prenatal exposure to low doses (0.0625- or 0.125- or 0.25 mg/kg b. wt., orally) of lindane, an organo-chlorine insecticide, from gestation day (GD) 5-21 was found to produce a dose-dependent increase in the mRNA expression of cytochrome P450s (CYPs) and associated transcription factors in frontal cortex, cerebellum and corpus striatum isolated from the offsprings. Though the increase in the expression persisted up to postnatal day 60, the increase was significant at postnatal days 21-, and 45- in the offsprings exposed prenatally to relatively higher doses (0.125- or 0.25 mg/kg) of lindane and even up to postnatal day 60 in the offsprings exposed prenatally to the highest dose of lindane. A similar increase in the expression of dopamine D2, 5HT2A and GABAA receptors and associated neurotransmitter receptor binding was observed in the brain regions of the exposed offsprings. Scatchard analysis also suggested an increase in the levels of these neurotransmitter receptors in offsprings prenatally exposed to lindane. The data indicating similarities in the alterations of neurotransmitter receptors and CYPs in brain regions in prenatally exposed offsprings have suggested that neurotransmission processes and CYPs are closely linked that will eventually help in understanding the developmental neurotoxicity of lindane.

Fast agitated directly suspended droplet microextraction technique for the rapid analysis of eighteen organophosphorus pesticides in human blood.

[Kumari R, Patel DK, Panchal S, Jha RR, Satyanarayana GN, Asati A, Ansari NG, Pathak MK, Kesavachandran C, Murthy RC. J Chromatogr A. 2015 Jan 16;1377:27-34.]

A new sample preparation technique named as fast agitated directly suspended droplet microextraction (FA-DSDME) was proposed as an improved version of directly suspended droplet microextraction (DSDME) for the extraction and pre-concentration of wide-range organophosphorus pesticides (OPPs) from human blood prior to liquid chromatography tandem mass spectrometric (LC-MS/MS) analysis. In this method, instead of protecting the unwanted rupturing of extraction droplet (organic solvent), it

was deliberately splintered into fine droplets by providing automated high-speed agitation to the biphasic extraction system (extraction solvent and sample solution). Fine organic droplets were then recollected into one, not by using a centrifuge machine but just by giving a very slow stirring to the bottom of the extraction system. The present method has surmounted the problem of prolonged extraction time associated with old DSDME. Under optimum extraction conditions, the method showed good sensitivity with low detection limits ranging from 0.0009 to 0.122µgL(-1). Mean recoveries were achieved in the range of 86-109% at three levels of spiking concentration (low, middle and high) from linearity range of individual analyte. Intra-day and inter-day precisions were ≤4.68 and ≤9.57 (%RSD) respectively. Enrichment factor (EF) for each analyte varied from 30 to 132 which prove the ability of this technique to pre-concentrate the extracted analytes up to a good extent. The sample matrices have shown an insignificant influence on method's sensitivity. The proposed method may find immense use in epidemiological, toxicological, regulatory and forensic laboratories.

Superoxide mediated photomodification and DNA damage induced apoptosis by Benz(a)anthracene via mitochondrial mediated pathway.

[Mujtaba SF, Dwivedi A, Yadav N, Ch R, Kushwaha HN, Mudiam MK, Singh G, Ray RS. J Photochem Photobiol B. 2015 Jan;142:92-102.]

Benz(a)anthracene (BA) is an ubiquitous environmental pollutant of polycyclic aromatic hydrocarbon's (PAHs) family. Authors showed superoxide (O_2(-)) catalyzed BA photo modification and apoptosis in HaCaT keratinocytes under sunlight exposure. O_2(-) generation was confirmed by quenching through superoxide dismutase (SOD). BA induced photocytotoxicity were investigated through MTT and NRU assay. Authors proposed DNA insults such as single and double strand breakage and CPDs formation which results in cell cycle arrest and apoptosis by photosensitized BA. BA induced apoptosis was caspase dependent and occurred through a mitochondrial pathway. Reduction of mitochondrial membrane potential, translocation of Bax to mitochondria and cytochrome c release favors involvement of mitochondria in BA phototoxicity. AO/EB double staining and TEM analysis also support apoptotic cell death. Authors propose a p21 regulated apoptosis via expression of Bax, and cleaved PARP under sunlight exposure. Thus, authors conclude that it is imperative to avoid solar radiation during peak hr (between 11A.M. and 3P.M.) when the amount of solar radiation is high, in the light of DNA damage which may lead to mutation or skin cancer through photosensitized BA under sunlight exposure. Concomitantly, investigation is urgently required for the photosafety of BA photoproducts reaching in the environment through photomodification.

Combinatorial chemopreventive effect of butyric acid, nicotinamide and calcium glucarate against the 7,12-dimethylbenz(a) anthracene induced mouse skin tumorigenesis attained by enhancing the induction of intrinsic apoptotic events.

[Tiwari P, Sahay S, Pandey M, Qadri SS, Gupta KP. Chem Biol Interact. 2015 Jan 25;226:1-11.]

Authors explored the basis of the combinatorial chemopreventive effect of butyric acid (BA), nicotinamide (NA) and calcium glucarate (CAG) on mouse skin exposed to 7,12-dimethylbenz(a) anthracene (DMBA). They studied the effects of topical application of DMBA in the presence or absence of BA, NA and CAG on the regulators of apoptosis. DMBA treatment suppressed Bax, Bax/Bcl-2 ratio, release of cyt c, Apaf1, caspase-9, -3 mediated apoptosis. Downregulation of p21 and upregulation of Bcl-2, mut p53 were also observed in only DMBA treated mice. Simultaneous application of BA, NA and CAG induced a mitochondria-mediated apoptosis, characterized by a rise in the Bax, Bax/Bcl-2 ratio, release of cyt c, upregulation of Apaf1 with down-stream activation of caspase-9, -3. Furthermore treatment with BA, NA and CAG demonstrated an upregulation of p21 and downregulation of Bcl-2, mut p53. But this effect was enhanced in the presence of all the three compounds together in combination. Chemoprevention by a combination of BA, NA and CAG by inducing the apoptosis, the natural cell death, suggest the importance of the potential combinational strategies capable of preventing skin tumor development.

MiRNA profiling provides insights on adverse effects of Cr(VI) in the midgut tissues of *Drosophila melanogaster*.

[Chandra S, Pandey A, Chowdhuri DK. J Hazard Mater. 2015 Feb 11;283:558-67.]

Cr(VI), a well-known environmental chemical, is reported to cause various adverse effects on exposed organisms including genomic instability and carcinogenesis. Despite available information on the underlying mechanism of Cr(VI) induced

toxicity, studies regarding toxicity modulation by epigenetic mechanisms are limited. It was therefore, hypothesized that the global miRNA profiling in Cr(VI) exposed Drosophila, a genetically tractable model organism, will provide information about mis-regulated miRNAs along with their targeted genes and relevant processes. Third instar larvae of *Drosophila melanogaster* (Oregon R(+)) were exposed to 5.0-20.0 µg/ml of Cr(VI) for 24 and 48 h. Following miRNA profile analysis on an Agilent platform, 28 of the 36 differentially expressed miRNAs were found to be significantly mis-regulated targeting major biological processes viz., DNA damage repair, oxidation-reduction processes, development and differentiation. Down-regulation of mus309 and mus312 under DNA repair, acon to oxidation-reduction and pyd to stress activated MAPK cascade respectively belonging to these gene ontology classes concurrent with up-regulation of dme-miR-314-3p, dme-miR-79-3p and dme-miR-12-5p confirm their functional involvement against Cr(VI) exposure. These findings assume significance since majority of the target genes in Drosophila have functional homologues in humans. The study further recommends Drosophila as a model to explore the role of miRNAs in xenobiotic induced toxicity.

Benzanthrone induced immunotoxicity via oxidative stress and inflammatory mediators in Balb/c mice.

[Tewari P, Roy R, Mishra S, Mandal P, Yadav A, Chaudhari BP, Chaturvedi RK, Dwivedi PD, Tripathi A, Das M. Immunobiology. 2015 Mar;220(3):369-81.]

Benzanthrone (BA) is an important dye intermediate which is used in the manufacturing of several polycyclic vat and disperse dyes in textile industries. Several studies have indicated that the general population is also exposed to BA owing to its release from furnace effluents and automobile exhausts in the environment. In several clinical studies, it has been shown that workers exposed to BA developed itching, burning sensation, erythema and hyperpigmentation of the skin, which could be an outcome of the dysregulated immune response. In this study, authors have used female Balb/c mice as a model to study the immuno-inflammatory changes after systemic administration of BA (7.5mg/kgb.w. and 15mg/kgb.w.) for one week. BA exposed animals exhibited the signs of intense systemic inflammation as evident by enhanced DTH response, MPO activity, hyperplastic and dysplastic histopathological organization of spleen and lung tissue. Splenic evaluation revealed enhanced oxidative stress, upregulation of prominent inflammatory markers like iNOS and COX-2 and DNA damage. In coherence with the observed immuno-inflammatory alterations, the levels of several inflammatory and regulatory cytokines (IL-17, TNF-α, IFN-γ, IL-1, IL-10, IL-4) were significantly enhanced in serum as well as the spleen. In addition, BA administration significantly induced the activation of ERK1/2, p38, JNK MAPKs and their downstream transcription factors AP-1 (c-fos, c-jun), NF-κB and Nrf2 which comprise important mechanistic pathways involved in inflammatory manifestations. These results suggest the immunotoxic nature of the BA and have implications for the risk assessment and management of occupational workers, and even common masses considering its presence as an environmental contaminant.

Gene-environment interactions in determining differences in genetic susceptibility to cancer in subsites of the head and neck.

[Maurya SS, Katiyar T, Dhawan A, Singh S, Jain SK, Pant MC, Parmar D. Environ Mol Mutagen. 2015 Apr;56(3):313-21.]

Genetic differences in susceptibility to cancer in subsites of the head and neck were investigated in a case-control study involving 750 cases of cancers of the oral cavity, larynx, or pharynx, and an equal number of healthy controls. The prevalence of variant genotypes of cytochrome P450 (CYP) 1A1, 1B1, 2E1, or glutathione-S-transferase M1 (null) in cases suggests that polymorphisms in drug metabolizing enzymes (DMEs) modify cancer risk within subsites of the head and neck. Tobacco or alcohol use was found to increase the risk in cases of laryngeal, pharyngeal, or oral cavity cancers. Interaction between genetic variation in DMEs and tobacco smoke (or smoking) exposures conferred significant risk for laryngeal cancer. Likewise, strong associations of the polymorphic genotypes of DMEs with cases of pharyngeal and oral cavity cancer who were tobacco chewers or alcohol users demonstrate that gene-environment interactions may explain differences in genetic susceptibility for cancers of the oral cavity, larynx, and pharynx.

Simultaneous determination of acetaminophen and synthetic color(s) by derivative spectroscopy in syrup formulations and validation by HPLC: Exposure risk of colors to children.

[Rastogi SD, Dixit S, Tripathi A, Das M. AAPS PharmSciTech. 2015 Jun;16(3):505-17.]

Color additives are used in pediatric syrup

formulations as an excipient; though not pre-requisite, but pediatric syrup formulations are normally colored. An attempt has been made to measure simultaneously the single drug, acetaminophen (AT), along with the colors, carmoisine (CA), erythrosine (ET), and sunset yellow FCF (SSY) added in it by three derivative spectroscopy methods namely, 1st order, ratio, and differential derivative methods. Moreover, evaluation has been made for the exposure assessment of the colors added as excipient because some colors have been reported to cause allergic reactions and hypersensitivity in children. The present methods provide simple, accurate, and reproducible quantitative determination of the drug, AT, along with the color in synthetic mixtures and commercial drug formulations without any interference. The limit of detection varied from 0.0001-0.31 µg/ml while limit of quantification ranged from 0.002-1.04 µg/ml in all the three methods. The calibration curve of all the three derivative methods exhibited good linear relationship with excellent regression coefficients (0.9986-1.000). Both intra-day and inter-day precisions showed %RSD value less than 2% while the percentage recovery was found between 96.8-103.8%. The sensitivity of the proposed methods is almost comparable to HPLC and thus, can be used for determination of drug AT, and color simultaneously in pharmaceutical formulation on routine basis. The present methods also showed that colors like SSY and ET are saturating more than 50% of acceptable daily intake (ADI) value which is alarming and needs to be considered for modification by regulatory authorities to safeguard the health of children.

Toxicological mode of action of ZnO nanoparticles: Impact on immune cells.

[Roy R, Das M, Dwivedi PD. Mol Immunol. 2015 Feb;63(2):184-92.]

The use of nanoscale materials is growing exponentially as concerns rise about the human hazards to it. It is assumed that living beings are coevolved with nanoparticles ever since the origin of life on earth and therefore, they must have developed the defense and toxicity mitigating mechanisms for nanoparticles. Although having peculiar properties these new materials also present new health risks upon interacting with biological systems. Zinc oxide is the most widely used nanoparticles among various nanomaterials. Recently, these nanoparticles have been shown to specifically kill cancerous cells; therefore, it is believed that these nanoparticles may be used as an alternative anti-tumor agent. However, it is also known that these nanoparticles pose several deleterious effects to living beings. It is therefore critical to understand the nature and origin of the toxicity imposed by these nanomaterials. Keeping these points in mind the present review provides updated information on various aspects of toxicities induced by these engineered nanoparticles.

Size dependent toxicity of zinc oxide nano-particles in soil nematode *Caenorhabditis elegans.*

[Khare P, Sonane M, Nagar Y, Moin N, Ali S, Gupta KC, Satish A. Nanotoxicology. 2015 May;9(4):423-32.]

Zinc oxide nano-particles (ZnO NPs), with their unique physico-chemical properties conferred by various size formulations, are extensively used in consumer products. The enormous usage coupled with their release to the environment demands risk assessment of ZnO NPs on health and the environment. Toxicity of ZnO NPs is well understood in comparison to the bulk ZnO. However, toxicity in relation to the NP size is poorly understood. In this context, authors examined the adverse effects of different sizes (35 nm, 50 nm and 100 nm) of ZnO NPs in soil nematode *C. elegans* along with bulk ZnO and ZnCl2. Here, authors show that growth, reproduction and behavior of worms were adversely affected by ZnO NPs in a size dependent manner. Further, exposure to ZnO NPs caused modulation of expression/function of genes associated with Insulin/IGF-like signaling pathway and/or stress response pathway in a size dependent manner in exposed worms. The expression of pro-apoptotic gene and suppression of anti-apoptotic genes, together with increased numbers of cell corpses in the germ line, indicated that apoptosis was also dependent on the size of the ZnO NP. Taken together, authors study provides evidence that exposure to ZnO NPs disrupts various physiological processes and causes apoptosis in the germ-line even at very low concentration in a size dependent manner. Authors finding suggests the inclusion of size as an additional measure for the cautious monitoring of ZnO NP disposal into the environment.

Differentiating neurons derived from human umbilical cord blood stem cells work as a test system for developmental neurotoxicity.

[Kashyap MP, Kumar V, Singh AK, Tripathi VK, Jahan S, Pandey A, Srivastava RK, Khanna VK, Pant AB. Mol Neurobiol. 2015 Apr;51(2):791-807.]

Differentiating neuronal cells derived from human umbilical cord blood stem cells have been used as an *in vitro* tool for the assessment of developmental neurotoxicity of monocrotophos (MCP), an organophosphate pesticide. The differentiating cells were exposed to MCP during the different stages of maturation, viz., days 2, 4, and 8, and changes in the makers of cell proliferation, neuronal differentiation, neuronal injuries, and receptors were studied. Authors found significant upregulation in the different MAPKs, apoptosis, and neurogenesis markers and downregulation in the cell proliferation markers during neuronal differentiation. Authors further identified significant upregulation in the expression of different MAPKs and proteins involved in oxidative stress, apoptosis, and calpain pathways in the mid-differentiating cells exposed to MCP. The upregulated levels of these proteins seem to be the main cause of alteration during the differentiation process towards apoptosis as a fine-tune of pro-apoptotic and anti-apoptotic proteins are desirable for the process of differentiation without apoptosis. The decreased acetylcholinesterase activity, dopaminergic, and cholinergic receptors and increased acetylcholine levels in the differentiating neuronal cells indicate the vulnerability of these cells towards MCP-induced neurotoxicity. Authors data confirms that differentiating neuronal cells derived from human umbilical cord stem cells could be used as a powerful tool to assess the developmental neurotoxicity in human beings.

Aberrant autophagy and parkinsonism: Does correction rescue from disease progression?

[Mishra AK, ur Rasheed MS, Shukla S, Tripathi MK, Dixit A, Singh MP. Mol Neurobiol. 2015 Jun;51(3):893-908.]

Information generated from animal models, genome sequencing, and high-throughput technologies provide valuable sequence of events to understand the Parkinson's disease (PD) pathogenesis. A dynamic equilibrium between biosynthesis and biodegradation of sub-cellular components by ubiquitin proteasome system and autophagy is found to be responsible for sustaining the homeostasis of tyrosine hydroxylase-positive neurons. Autophagy degrades and eliminates α-synuclein, Parkin, ubiquitin, etc., proteins along with damaged cellular components to maintain the homeostasis of the nigrostriatal dopaminergic neurons. Aberrant type II apoptosis is widely implicated in dopaminergic neurodegeneration leading to PD. The current article reviews the elementary role of autophagy in the degradation and elimination of superfluous and aggregated proteins and impaired mitochondria. The article also recapitulates the information, which implicated the role of aberrant autophagy in toxin-induced parkinsonism. Moreover, the review sheds light on whether or not targeting the defective autophagy could reinstate the normal functioning of dopaminergic neurons, which could ultimately rescue from PD pathogenesis.

Research Digest

Widely used food additive promotes colitis, obesity and metabolic syndrome

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Emulsifiers, which are added to most processed foods to aid texture and extend shelf life, can alter the gut microbiota composition and localization to induce intestinal inflammation that promotes the development of inflammatory bowel disease and metabolic syndrome, new research shows. The research, published Feb. 25 in Nature, was led by Georgia State University Institute for Biomedical Sciences' researchers Drs. Benoit Chassaing and Andrew T. Gewirtz, and included contributions from Emory University, Cornell University and Bar-Ilan University in Israel. Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, afflicts millions of people and is often severe and debilitating. Metabolic syndrome is a group of very common obesity-related disorders that can lead to type-2 diabetes, cardiovascular and/or liver diseases. Incidence of IBD and metabolic syndrome has been markedly increasing since the mid-20th century. The term "gut microbiota" refers to the diverse population of 100 trillion bacteria that inhabit the intestinal tract. Gut microbiota are disturbed in IBD and metabolic syndrome. Chassaing and Gewirtz's findings suggest emulsifiers might be partially responsible for this disturbance and the increased incidence of these diseases. "A key feature of these modern plagues is alteration of the gut microbiota in a manner that promotes inflammation," says Gewirtz. "The dramatic increase in these diseases has occurred despite consistent human genetics, suggesting a pivotal role for an environmental factor," says Chassaing. "Food interacts intimately with the microbiota so we considered what modern additions to the food supply might possibly make gut bacteria more pro-inflammatory." Addition of emulsifiers to food seemed to fit the time frame and had been shown to promote bacterial translocation across epithelial cells. Chassaing and Gewirtz hypothesized that emulsifiers might affect the gut microbiota to promote these inflammatory diseases and designed experiments in mice to test this possibility. The team fed mice two very commonly used emulsifiers, polysorbate 80 and carboxymethylcellulsose, at doses seeking to model the broad consumption of the numerous emulsifiers that are incorporated into almost all processed foods. They observed that emulsifier consumption changed the species composition of the gut microbiota and did so in a manner that made it more pro-inflammatory. The altered microbiota had enhanced capacity to digest and infiltrate the dense mucus layer that lines the intestine, which is normally, largely devoid of bacteria. Alterations in bacterial species resulted in bacteria expressing more flagellin and lipopolysaccharide, which can activate proinflammatory gene expression by the immune system. Such changes in bacteria triggered chronic colitis in mice genetically prone to this disorder, due to abnormal immune systems. In contrast, in mice with normal immune systems, emulsifiers induced low-grade or mild intestinal inflammation and metabolic syndrome, characterized by increased levels of food consumption, obesity, hyperglycemia and insulin resistance. The effects of emulsifier consumption were eliminated in germ-free mice, which lack a microbiota. Transplant of microbiota from emulsifiers-treated mice to germ-free mice was sufficient to transfer some parameters of low-grade inflammation and metabolic syndrome, indicating a central role for the microbiota in mediating the adverse effect of emulsifiers. The team is now testing additional emulsifiers and designing experiments to investigate how emulsifiers affect humans. If similar results are obtained, it would indicate a role for this class of food additive in driving the epidemic of obesity, its inter-related consequences and a range of diseases associated with chronic gut inflammation. While detailed mechanisms underlying the effect of emulsifiers on metabolism remain under study, the team points out that avoiding excess food consumption is of paramount importance. "We do not disagree with the commonly held assumption that over-eating is a central cause of obesity and metabolic syndrome," Gewirtz says. "Rather, our findings reinforce the concept suggested by earlier work that low-grade inflammation resulting from an altered microbiota can be an underlying cause of excess eating." The team notes that the results of their study suggest that current means of testing and approving food additives may not be adequate to prevent use of chemicals that promote diseases driven by low-grade inflammation and/or which will cause disease primarily in susceptible hosts.

The multifaceted role of curcumin in cancer prevention and treatment

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Despite significant advances in treatment modalities over the last decade, neither the incidence of the disease nor the mortality due to cancer has altered in the last thirty years. Available anti-cancer drugs exhibit limited efficacy, associated with severe side effects, and are also expensive. Thus identification of pharmacological agents that do not have these disadvantages is required. Curcumin, a polyphenolic compound derived from turmeric (*Curcumin longa*), is one such agent that has been extensively studied over the last three to four decades for its potential anti-inflammatory and/or anti-cancer effects. Curcumin has been found to suppress initiation, progression, and metastasis of a variety of tumors. These anti-cancer effects are predominantly mediated through its negative regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other oncogenic molecules. It also abrogates proliferation of cancer cells by arresting them at different phases of the cell cycle and/or by inducing their apoptosis. The current review focuses on the diverse molecular targets modulated by curcumin that contribute to its efficacy against various human cancers.

Shift work can affect your health

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Shiftwork is an occupational health risk of growing significance because it is becoming more common and because of its potential influence on health outcomes, possibly increasing health differences between workers of higher vs lower socioeconomic status. A new study from the University of Wisconsin School of Medicine and Public Health determined that employees who work shifts outside of a 9-to-5 schedule are more likely to be overweight and experience sleep problems, and possibly more likely to develop metabolic disorders, such as diabetes, compared to workers following traditional work schedules. The study is published in Sleep Health, journal of the National Sleep Foundation. “Shiftwork employees are particularly vulnerable to experiencing sleep problems as their jobs require them to work night, flex, extended, or rotating shifts,” explained lead investigator Marjory Givens, PhD, an Associate Scientist with the University of Wisconsin School of Medicine and Public Health. “Shiftworkers are more commonly men, minorities, and individuals with lower educational attainment and typically work in hospital settings, production, or shipping industries.” The investigators used cross-sectional data from the Survey of the Health of Wisconsin (SHOW) collected from 2008-2012. SHOW is a population-based health examination survey that includes home- and clinic-based interviews and physical examinations. In this analysis, 1593 participants were assessed using measures from the physical examination to calculate body mass index and determine obesity or overweight status. Type-2 diabetes (T2D) was assessed in 1400 subjects using either self-report of physician-diagnosed T2D or glycated hemoglobin (HbA1c) equal to or greater than 6.5% as determined from a blood sample obtained at the physical examination. Shiftworkers were significantly more likely than traditional schedule workers to be overweight (47.9% vs. 34.7%). They also experienced more sleep problems such as insomnia (23.6% vs. 16.3%), insufficient sleep (53.0% vs. 42.9%), or excessive wake-time sleepiness (31.8% vs. 24.4%). Since shiftwork and sleep problems have both been implicated in poor metabolic health, this study asked whether sleep problems may play a role in shiftworker health disparities. Dr Givens and her colleagues found that experiencing sleep problems was positively associated with being overweight/obese or diabetic. Moreover, even though sleep problems did not fully explain the relation between shiftwork and overweight or diabetes, these association appear to be stronger among shiftworkers who were not able to obtain sufficient sleep (less than seven hours per day), suggesting that the adverse metabolic consequences of shiftwork could be partially alleviated by sufficient sleep. Two particular strengths of this study are that it draws from a general population sample and primary outcomes (overweight and diabetes status) were defined according to objective markers (measured weight, height, and HbA1c). Potential limitations include unmeasured confounding factors, the potential for systematic biases in self-reports of sleep duration and sleep quality, and an inability to determine a causal relationship due to the cross-sectional nature of the study. According to Dr Givens, “This study adds to a growing body of literature calling attention to the metabolic health burden commonly experienced by shiftworkers and suggests that obtaining sufficient sleep could lessen this burden. More research in this area could inform workplace wellness or healthcare provider interventions on the role of sleep in addressing shiftworker health disparities.”

Earlier menopause linked to everyday chemical exposures

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Women whose bodies have high levels of chemicals found in plastics, personal-care products, common household items and the environment experience menopause two to four years earlier than women with lower levels of these chemicals, according to a new study at Washington University School of Medicine in St. Louis. The researchers looked at levels in blood and urine of 111 chemicals that are suspected of interfering with the natural production and distribution of hormones in the body. While several smaller studies have examined the link between so-called endocrine-disrupting chemicals and menopause, the new research is the first to broadly explore the association between menopause and individual chemicals on a large scale, using a nationally representative sample of patients across the United States. "Chemicals linked to earlier menopause may lead to an early decline in ovarian function, and our results suggest we as a society should be concerned," said senior author Amber Cooper, MD, an assistant professor of obstetrics and gynecology. A decline in ovarian function not only can adversely affect fertility but also can lead to earlier development of heart disease, osteoporosis and other health problems. Other problems already linked to the chemicals include certain cancers, metabolic syndrome and, in younger females, early puberty. "Many of these chemical exposures are beyond our control because they are in the soil, water and air," Cooper said. "But we can educate ourselves about our day-to-day chemical exposures and become more aware of the plastics and other household products we use." For example, Cooper recommends that people microwave food in glass or paper containers instead of in plastic and try to learn more about the ingredients in cosmetics, personal-care products and food packaging they use every day. Although many of the chemicals included in the study have been banned from U.S. production because of their negative health effects, they still are produced globally and are pervasive in the environment. In the study, Cooper and researchers at the University of Missouri-Kansas City School of Medicine and the Wadsworth Center at the State University of New York at Albany analyzed data collected from 1999-2008 as part of the National Health and Nutrition Examination Survey, conducted by the U.S. Centers for Disease Control and Prevention. The survey included data from 31,575 people, including 1,442 menopausal women who had been tested for levels of endocrine-disrupting chemicals. The average age of these women was 61, and none was using estrogen-replacement therapies or had had surgery to remove ovaries. The survey was designed so that the women who had undergone chemical testing would represent a population of almost 9 million menopausal women. The women's blood and urine samples were analyzed for exposures to 111 mostly man-made chemicals, which included known reproductive toxins and/or those that take more than a year to break down. Chemicals from the following categories were analyzed in the survey: dioxins/furans (industrial combustion byproducts); phthalates (found in plastics, common household items, pharmaceuticals and personal-care products including lotions, perfumes, makeup, nail polish, liquid soap and hair spray); phytoestrogens (plant-derived estrogens); polychlorinated biphenyls (PCBs, coolants); phenolic derivatives (phenols, industrial pollutants); organophosphate pesticides; surfactants; and polycyclic aromatic hydrocarbons (combustion products). The researchers identified 15 chemicals—nine PCBs, three pesticides, two phthalates and a furan (a toxic chemical)—that warrant closer evaluation because they were significantly associated with earlier ages of menopause and potentially have detrimental effects on ovarian function. "Earlier menopause can alter the quality of a woman's life and has profound implications for fertility, health and our society," Cooper said. "Understanding how the environment affects health is complex. This study doesn't prove causation, but the associations raise a red flag and support the need for future research."

Tainted love: Bees prefer food laced with harmful pesticides

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This is the latest twist in the tale of neonicotinoid pesticides and their disputed effects on bee health. Given a choice, honeybees and a species of bumblebee preferred sugar solutions containing neonicotinoids. Since late 2013, the use of three neonicotinoids – clothianidin, imidacloprid, and thiamethoxam – has been restricted in the EU, as part of a two-year moratorium following mounting evidence that these compounds harm bees. The EU's restrictions have been disputed by agrichemical companies and national governments who have questioned the validity of studies showing the effects of neonicotinoids on bees.

Overdose by choice?

"An assumption of those defending the use of neonicotinoids has been that bees could avoid neonicotinoids in nectar if they had other options," says Geraldine Wright of Newcastle University in the UK. To tests the assumption, her team offered honeybees and a species of bumblebee a choice of sugar solutions, where some contained neonicotinoids at levels similar to those found in the nectar of treated crop plants. They found that buff-tailed bumblebees and honeybees had a preference for some of the pesticide-tainted solutions. Some bumblebees preferred these solutions by as much as 40 per cent, compared with the untainted solutions, while honeybees showed preferences of up to 15 per cent, both depending on the specific compound and its concentration. Bees preferred imidacloprid and thiamethoxam, but had no preference for clothianidin, says Wright. "This is really odd and interesting," says Dave Goulson of the University of Sussex, UK. "It might result in bees getting much higher doses of these pesticides than we had previously realised."

Wild bees beware

Another experiment published this week suggests that neonicotinoids really do have a harmful impact on bees. This latest experiment focussed on wild bee species, and used agricultural plots in an attempt to accurately mimic the way that neonicotinoids are used by farmers. The team that carried out the research used Elado, a commercial insecticide that contains clothianidin, in field tests in spring and summer of 2013. "One important condition for the study was that it should be realistic for southern Swedish oilseed rape farmers. The fields were managed by individual farmers, just as they would if the study was not conducted," says lead author Maj Rundlöf of Lund University in Sweden. She says her study is unique in its realistic field conditions – many previous studies have been criticised for using bees artificially exposed to neonicotinoids, which doesn't reflect real-world scenarios.

Field questions

The team found that, compared with untreated plots, at the treated sites there were reductions in wild bee density, solitary bee nesting and bumblebee reproduction. Bumblebees and solitary bees are important pollinators, and bumblebees are more important than honeybees for crops like tomatoes, blueberries, raspberries and runner beans. While these effects were observed in wild bees, no significant impact was seen in honeybees, the subject of many previous studies. "We think that our results indicate at least a short-term population effect for the wild bees. Whether this also translates into long-term population consequences is still an open question," says Rundlöf. This is the best field study so far, says Goulson. "It confirms what many of us have been saying for a while – that these chemicals are harmful to wild bees. In my opinion, it is no longer credible to claim otherwise." But Linda Field of Rothamsted Research in Hertfordshire, UK, says she doesn't think this study is enough to put an end to the argument. "We simply need more data before we can really say what the risks are," says Field.

First evidence of how parents' lives could change children's DNA

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For the first time, scientists have discovered a mechanism in humans that could explain how your lifestyle choices may impact your children and grandchildren's genes. Mounting evidence suggests that environmental factors such as smoking, diet and stress, can leave their mark on the genes of your children and grandchildren. For example, girls born to Dutch women who were pregnant during a long famine at the end of the second world war had twice the usual risk of developing schizophrenia. Likewise, male mice that experience early life stress give rise to two generations of offspring that have increased depression and anxiety, despite being raised in a caring environment. This has puzzled many geneticists, as genetic information contained in sperm and eggs is not supposed to be affected by the environment, a principle called the August Weismann barrier. But we also know the activity of our own genes can be changed by our environment, through epigenetic mechanisms. These normally work by turning a gene on or off by adding or subtracting a methyl group to or from its DNA. These methyl groups can inactivate genes by making their DNA curl up, so that enzymes can no longer access the gene and read its instructions. Such epigenetic mechanisms are high on the list of suspects when it comes to explaining how environmental factors that affect parents can later influence their children, such as in the Dutch second world war study, but just how these epigenetic changes might be passed on to future generations is a mystery. Although there is evidence from mice that these changes can be inherited, classical genetics says this shouldn't be possible because epigenetic marks on sperm and eggs are wiped clean after fertilisation. But now, for the first time, researchers have observed some human genes evading this clean-up process.

Escaping genes

Azim Surani at Cambridge University and colleagues have demonstrated that some genes in the developing fetus escape the cleaning mechanism. Surani's team analysed methylation patterns in a type of fetal cell that later forms a fetus's own sperm or eggs. We would expect these cells to have been wiped clean when the fetus's epigenome was reset at the early embryo stage. "However, about 2 to 5 per cent of methylation across the genome escaped this reprogramming," says Surani. Any methylation in these areas of the genome might therefore impact future generations – and could provide the missing clue for how a person can pass on hereditary changes caused by their environment to their children and grandchildren.

Schizophrenia and obesity

Because this is only a small proportion of the genome, Surani says most epigenetic changes brought about by our environment are very unlikely to affect future generations, but that there may be a small window of opportunity for some of these to be passed on. A closer look at these "escapees" showed they were mostly genes implicated in brain conditions such as bipolar disorder and schizophrenia, as well as genes involved in metabolic disorders such as obesity. Surani says he is cautious about drawing any further conclusion as to whether or not these have any functional significance for the health of future generations until they have discovered more about how these genes manage to evade reprogramming and why. Marcus Pembrey, emeritus professor of paediatric genetics at University College London's Institute of Child Health, says that the escapees look very intriguing. Although there is a long way to go in our understanding of transgenerational effects, "I think we can say the August Weismann barrier has been well and truly breached," he says.

विज्ञान परिक्रमा

(साभार जी न्यूज़ विज्ञान समाचार)

नासा के आंकड़ों ने दिखाया, बारिश के पानी से भारतीय बचा सकते हैं पैसा

भारत में सब्जियों की सिंचाई के लिए संग्रहित रेनवाटर पानी के बिल को घटा सकता है, कैलोरी की मात्रा में इजाफा कर सकता है और यहां तक कि आमदनी का दूसरा जरिया हो सकता है। नासा के उपग्रह के आंकड़ों का अध्ययन करने वाले वैज्ञानिकों ने यह बात कही है। अध्ययन नासा और जापान अंतरिक्ष अन्वेषण एजेंसी के बीच का संयुक्त अभियान ऊष्णकटिबंधीय वर्षाजल आंकलन मिशन (टीआरएमएम) के आंकड़ों पर आधारित है। इसमें 1997 और 2015 के बीच उष्णकटबंध और उपउष्णकटिबंध खेत्र में वर्षाजल का आंकलन किया गया है। यूटा यूनिवर्सिटी में सिविल इंजीनियरिंग विभाग में अध्ययन सहायक डेन स्टोउट ने बताया, 'भारत को अपने सभी बाशिंदों को पीने योग्य पानी मुहैया कराने में दिक्कतें आती है। हमने अपेक्षाकृत छोटे टैंक में जल संग्रह पर विचार किया और रोचक है कि भारतीय लोग सरल और सहज तीरके से यह कर सकते हैं। वर्षाजल संचय कोई नयी अवधारणा नहीं है लेकिन अध्ययनकर्ताओं का मानना है कि भारत में इस संसाधन का ज्यादा दोहन नहीं हुआ है। नये अध्ययन में टीम ने इस संभावना को खंगाला कि क्या भारतीय सस्ते 200 गैनल टैंक को सघन शहरी इलकों में मसलन भारत के तेजी से बढ़ रहे शहरों में लगा सकते हैं। अर्बन वाटर जर्नल में प्रकाशति अध्ययन में कहा गया है कि इससे भारत में पैसा बचाने और जीवन की गुणवत्ता बढ़ाने में मदद मिल सकती है।

'तेल, गैस के लिए की जाने वाली खुदाई से है भूकंप का संबंध'

एक नए अध्ययन में दावा किया गया है कि 2009 के बाद से मध्य और पूर्वी अमेरिका में भूकंपों की संख्या में हुई नाटकीय वृद्धि का संबंध तेल एवं गैस निकालने में इस्तेमाल किए जाने वाले इंजेक्शन वाले (द्रव) पदार्थ निकालने वाले कुएं

उपकरणों से हैं। अध्ययनकर्ता समूह का नेतृत्व करने वाले यूनिवर्सिटी ऑफ कोलोराडों बोल्डर के पीएचडी छात्र मैथ्यू विंगगार्टन ने बताया कि 1970 के दशक में जहां इससे जुड़े भूकंपो की संख्या कुछ ही थी वहीं 2014 में इनकी संख्या 650 से अधिक हो गयी। अध्ययनकर्ताओं के अनुसार 2011 और 2012 में कई विनाशकारी भूकंप आए जिनकी तीव्रता 4.7 से 5.6 के बीच थी। ये भूकंप ओकलाहोमा के प्राग, कोलोराडो के त्रिनिदादा, टेक्सास के टिंपसन और अरकंसास के गाई में आए थे। विंगगार्टन ने कहा, 'पहली बार एक व्यापक, लगभग राष्ट्रीय सतर पर इंजेक्शन वेल और भूकंप के बीच परस्पर संबंधों का अध्ययन किया गया है।' साइंस पत्रिका में प्रकाशित किए गए अध्ययन के अनुसार इंजेक्शन वेल से तेल या गैस भंडारों में बड़े दबाव परिवर्तन का निर्माण होता है जिसके कारण बाद में भूकंप की स्थितियां पैदा होती हैं।'

अब भारत में वायरलेस उपकरण से होगी स्तन कैंसर की पहचार

गहज पांच मिनट में स्तन कैंसर का परीक्षण करने और स्मार्ट फोन या टैबलेट पर परीक्षणों के नतीजे उपब्ध कराने में सक्षम एक छोटे और वायरलेस उपकरण को अमेरिका और भारत में लॉन्च किया जाएगा। एक शीर्ष अमेरिकी अधिकारी ने यह जानकारी दी। अमेरिका की वाणिज्य मंत्री पैनी प्रित्जेकर ने कोलंबिया विश्वविद्यालय के छात्रों को बताया कि यह उपकरण अमेरिकी वाणिज्य विभाग के आर्थिक विकास प्राशासन के 10 लाख डॉलर के उस निवेश का परिणाम है, जो उसने लाइफ साइंस शोध को बाजार में लाने के लिए अवधारण प्रमाणन केंद्र में किया था। प्रित्जेकर ने न्यूयार्क में आयोजित करने वाले ड्रैक्सेल विश्वविद्यालय के वैज्ञानिकों ने 'आईब्रेस्ट एग्जाम' नाम छोटा सा वायरलेस उपकरण तैयार किया है, जो कि स्तन कैंसर का स्कैनर है। इस उपकरण की मदद से कोई भी डॉक्टर या स्वास्थ्यकर्मी पांच मिनट के भीतर यह परीक्षण कर सकता है और फिर इसके नतीजे स्मार्ट फोन या टैबलेट पर हासिल कर सकता है। उन्होंने कहा, 'हमें उम्मीद है कि यह उत्पाद अमेरिका और भारत में व्यवसायिक प्रयोग के लिए उपलब्ध हो सकेगा। यह एक शहरी केंद्र, अकादमिक नवोन्मेषियों और सार्वजनिक वित्त पोषण के बीच गहरे तालमेल का नतीजा है।'

स्मार्टफोन से आंखों के कैंसर का पता लगाना मुमकिन

अपने स्मार्टफोन में प्रयुक्त कैमर से पांच साल से कम उम्र के बच्चों की आंखों में पाये जाने वाले कैंसर के एक प्रकार की पहचान की जा सकती है। ब्रिटेन के विशेषज्ञों ने इस बात की

तस्दीक की है। बाल्यावस्था में होने वाले कैंसर पर काम करने वाली संस्था चाइल्डहुड आई कैंसर ट्रस्ट ने कहा कि स्मार्टफोन के कैमरा के फ्लैश से कैंसर के एक प्रकार रेटिनोब्लास्टोमा के कारण छोटे बच्चों की आंखों में बन रहे टूयूमर का पता लगाया जा सकता है। इस प्रकार के कैंसर के बच्चों की आंखों की रौशनी जा सकती है। यहां तक कि उनकी मृत्यु भी हो सकती है। इसके लक्षणों का आसानी से पता नहीं लगाया जा सकता। हॉफिंगटन पोस्ट की एक रिपोर्ट के अनुसार जब किसी बच्चें की आंख के अंदर किसी ट्यूमर का विकास होता है तो फ्लैश ऑन कर लिये गये फोटो में पुतली का रंग परावर्तित होकर सफेद दिख सकता है। अगर शुरूआत में इसका पता लगा लिया गया तो एक बच्चे की जान बचायी जा सकती है। संस्था ने बताया कि स्मार्टफोन तकनीक से पहले ही कैंसर से पीड़ित एक चार माह की बच्ची को बचाया जा चुका है। पिछले साल उसकी मां ने गौर किया कि स्मार्टफोन से फोटो खींचने पर उसकी बच्ची की आंखों में उजलापन दिखाई दे रहा था। उसने तत्काल एक विशेषज्ञ से सलाह ली जिसने ये कहा कि बच्ची को रेटिनोब्लास्टोमा है। डॉक्टरों ने साहसिक निर्णय लेते हुए बच्ची की प्रभावित आंख को हटा दिया । आज बच्ची पूरी तरह ठीक हो गयी है और हाल ही में उसने अपना पहला जन्मदिन मनाया है।

'चीन में हर सालवायु प्रदूषण से मरते हैं 5 लाख लोग'

चीन में वायु प्रदूषण पर आधारित एक डाक्यूमेंटरी में दावा किया गया है कि इस देश में वायु प्रदूषण के कारण हर साल करीब 5 लाख लोगों की मौत समयपूर्व हो जती है। पूर्व सीसीटीवी एंकर चाई जिंग द्वारा तैयार एक वीडिया इंटरनेट पर वायल हो गया है। आलोचकों का कहना है कि उनके इस दावे के पीछे कोई वैज्ञानिक आधार नहीं है। इस डॉक्यूमेंट्री में जमीनी स्तर पर पड़ताल और अधिकारियों, वैज्ञानिकों एवं आम लोगों से साक्षात्कार के आधार पर यह दावा किया गया है। नासा से मिली उपग्रह की तस्वीरों से पता चलता है कि उत्तरी चीन में पिछले एक दशक के दौरान वायु की गुणवत्ता काफी खराब हुई है। पूर्व स्वास्थ्य मंत्री चेन झू के हवाले से कहा गया है कि चीन में हर साल वायु प्रदूषण से करीब पांच लाख लोगों की मौत समय से पहले हो जाती है।

ओजोन परत के लिए घातक गैसों की मात्रा बढ़ी

शोधकर्ताओं ने चेतावनी दी है कि कुछ निश्चित रसायनों की वजह से ओजोन परत के समक्ष नई चुनौती पैदा हो गई है। इन रसायनों की वजह से ओजोन परत के क्षय होने का खतरा बढ़ गया है। ये ऐसे रसायन हैं, जिनके नियंत्रण का उल्लेख ओजोन परत के बचाव के लिए तैयार संयुक्त राष्ट्र संधि के मसौदे में नहीं है। शोध के मुताबिक, इस तरह के क्षणभंगुर अवयवों (वीएसएलएस) की मात्रा वायुमंडल में तेजी से बढ़ रही है। ब्रिटेन में यूनिवर्सिटी ऑफ लीड्स के मुख्य शोधकर्ता लेखक रायन हुसैनी के मुताबिल वीएसएलएस में प्राकृतिक और औद्योगिक दोनों तरह के स्रोत शामिल हो सकते हैं। वीएसएलएस पर नियंत्रण को संयुक्त राष्ट्र मोंट्रियल प्रोटोकॉल के दायरे में नही लाया गया है, क्योंकि ऐसा माना जाता रहा है कि इन रसायनों से ओजोन परत को मामूली क्षति पहुंचती है। हुसैनी ने आगे कहा कि लेकिन अब शोध में हमने यह पता लगाया है कि इनमें से कुछ रसायनों की मात्रा पर्यावरण में तेजी से बढ़ रही है और यदि इन्हें इसी तरह बढ़ने दिया गया तो ये मोंट्रियल प्रोटोकॉल के कारण ओजोन परत को होने वाले लाभ को प्रभावहीन कर देंगे। शोधकर्ताओं ने इस शोध के तहत होजोन परत और जलवायु पर वीएसएलएस के प्रभाव का पता लगाने के लिए पर्यावरण के 3डी कंप्यूटर मॉडल का इस्तेमाल किया। शोधकर्ताओं ने पाया कि क्लोरोफ्लूरोकार्बन (सीएफसी) जैसी वायुमंडल में

अधिक देर तक रहने वाले गैसों की तुलना में वीएसएलएस से ओजोन परत के क्षय को कम क्षति पहुंचती है। इस शोध को 'नेचर जियोसाइंस' पत्रिका में प्रकाशित किया गया है।

समुद्र से निकलने वाले कार्बन ने तापमान बढ़ाया : अध्ययन

महासागर के जलवायु परिवर्तन पर पड़े असर के बारे में एक अध्ययन के मुताबिक भारी मात्रा में सागर से निकलने वाले कार्बन डाइऑक्साइड ने आखिरी हिम युग को खत्म किया था। अध्ययन के मुताबिक दक्षिणी सागर में गहराई में एक अलग–थलग स्थान पर एकत्रित कार्बन वायुमंडल में दोबारा चला गया जिससे कार्बन डाइआक्साइड में वृद्धि हुई और वैश्विक तापमान में बढ़ोत्तरी हुई। अध्ययनकर्ताओं ने बताया कि सागर में वायुमंडल की तुलना में करीब 60 गुना अधिक कार्बन अभी जमा है। यह कार्बन बहुत तेजी से इन दोनों के बीच स्थानांतरित हो सकता है। यह अध्ययन नेचर जर्नल में प्रकाशित हुआ है।

गुस्सा आना अपके बेहत सेहतमंद होने की निशानी है?

आमतौर पर यह माना जाता है कि क्रोध तन और मन दोनों के लिए नुकसानदायक होता है, लेकिन शोधकर्ताओं का कहना है कि कुछ संस्कृतियों में गुस्सा बुरे नहीं बल्कि अच्छे स्वास्थ्य का संकेत होता है। अध्ययन में पता चला है कि अत्यधिक क्रोध को जापानी लोग बेहतर जैविक स्वास्थ्य से जोड़कर देखते हैं। यूनिवर्सिटी ऑफ मिशिगन के मनोविज्ञानी शिनोबु किताियामा के मुताबिक, क्रोध को बुरे स्वास्थ्य से जोड़कर देखना आमतौर पर पश्चिमी संस्कृति का हिस्सा है, जाहं गुस्से को निराशा, निर्धनता, निम्न जीवन स्तर और उन सभी कारकों से जोड़कर देखा जाता है, जो स्वास्थ्य को नुकसान पहुंचाते हैं। शोधकर्ताओं ने अमेरिका और जापान में एकत्र किए गए आंकड़ों का अध्ययन किया। उन्होंने अच्छे स्वास्थ्य के स्तर को मापने के लिए उत्तेजना और हृदय से जुड़ी गतिविधियों का अध्ययन किया, जिन्हें पूर्व में किए गए शोधों में क्रोध की भावना से जोड़कर देखा जाता रहा है। अध्ययन में पाया गया कि अमेरिका में अत्यधिक क्रोध को जैविक स्वास्थ्य के लिए हानिकारक माना जाता है, जैसा कि पूर्व के शोधों में भी कहा गया है। वहीं, जापान में अत्यधिक क्रोध को जैविक स्वास्थ्य के खतरे के स्तर में गिरावट लाने और अच्छे स्वास्थ्य की निशानी से जोड़कर देखा जाता है। किताियामा ने कहा, इन अध्ययनों से पता चलता है कि सामाजिक–सांस्कृतिक कारक भी जैविक प्रक्रियाओं को महत्वपूर्ण ढंग से प्रभावित करते हैं। यह अध्ययन जर्नल साइकोलॉजिकल साइंस में प्रकाशित हुआ है।

बारिश होने के बाद मिट्टी से क्यों आती है सोंधी खुशबू?

बारिश की बूंदों के जमीन पर गिरने के बाद मिट्टी की सोंधी खुशबू किसे अच्छी नहीं लगती, लेकिन क्या आपने कभी सोचा है कि यह खुशबू आखिर आती कहां से है। इस सवाल का जवाब वैज्ञानिकों ने ढूंढ लिया है। दरअसल, जमीन को स्पर्श करने से पहले बारिश की बूंदों में कोई खुशबू नहीं होती, लेकिन जैसे ही यह धूलकणों से मिलती है, हम एक सोंधी सी खुशबू महसूस करते हैं। इस खुशबू को 'पेट्रिकोर' कहते हैं, जो ग्रीक भाषा के शब्द पेट्रा से बना है, जिसका अर्थ स्ओन या आईकर होता है, और माना जाता है कि यह वही तरल है, जो ईश्वर की नसों में रक्त के रूप में बहता है। कैंब्रिज में मैसाचुसेट्स इंस्टीट्यूट ऑफ टैक्नोलॉजी में मैकेनिकल इंजीनियरिंग के सहायक प्रोफेसर कुलेन बुई ने कहा, ''दरअसल, पौधों द्वारा उत्सर्जित किए गए कुछ तैलीय पदार्थ व बैक्टीरिया द्वारा उत्सर्जित कुछ विशेष रसायन बारिश की बूंदों के साथ प्रतिक्रिया करती हैं, जिसके परिणामस्वरूप हम ऐसी सोंधी खुशबू महसूस करते हैं।'' बारिशकी बूंदें जैसे ही जमीन पर छिद्रयुक्त सतह पर गिरती है, वह हवा के छोटे–छोटे बुलबुलों में तब्दील हो जाती है। बुलबुले फूटने के पहले ऊपर की ओर बढ़ते हैं और हवा में बेहद छोटे–छोटे कणों को बाहर निकालते हैं, जिसे 'एरोसॉल' कहते हैं। शोधकर्ताओं के मुताबिक यही एरोसॉल सोंधी–सोंधी खुशबू बिखेरते हैं, जो हमारा चित्त प्रसन्न कर देती है। यह निष्कर्ष पत्रिका 'नेचर कम्युनिकेशन' में प्रकाशित हुआ है।

Editor

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Any feedback on this publication is welcome
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