ISSN: 0970-437X

Toxicology Research Bulletin

Vol. 32 Number 1, 2012

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CSIR-Indian Institute of Toxicology Research
(Council of Scientific and Industrial Research)
Lucknow, India

EVENTS

National Science Day

Indian Institute of Toxicology Research (IITR), Lucknow celebrated its twenty first National Science Day on 28th February, 2012. Dr Mukul Das, Chief Scientist and Chairman, National Science Day Committee welcomed the chief guest, Padma Shri Prof. Mansoor Hasan, a renowned cardiologist from Sahara India Medical Institute, Lucknow and children from various schools who had come to attend the function. He gave the genesis of the National Science Day. He also emphasized the purpose of celebrating this day, the purpose is to popularize science and inculcate a scientific temper in young minds. On this occasion a publication in Hindi entitled "Vish Vigyan Sandesh" was released by Prof. Mansoor Hasan. Earlier Prof. Hasan inaugurated an exhibition depicting few activities of the institute through exhibits. The major exhibits were:

(1) Demonstration of colour detection kit (CD-strip), developed by IITR for the detection of a non-permitted, carcinogenic oil soluble dye, butter yellow in mustard oil. Food stuffs coloured with various permitted and non permitted colours were displayed and the students were made aware of the possible health risk associated with these colours.

(2) The criteria involved in safety evaluation of plastic and polymeric materials and biosafety assessment studies of plastic and polymeric products were explained to the visitors.

(3) Noise level monitor for recording of noise levels, air quality monitor for CO, CO_2, PM, Temp. and pH; fine particulate sampler for PM 2.5, respirable dust sampler for monitoring of air pollutants namely, SPM, RSPM, SO_2 and NOx was demonstrated.

(4) Portable water analysis kit for chemical and bacteriological analysis of water samples was demonstrated. A kit (Arsenator) for detection of arsenic in water samples was also demonstrated

(5) Herbal Research Section demonstrated:

- viz-SOD mimetic activity, lipid peroxidation inhibition assay and ABTS, declolourization assays.
- Medicinal value and constituents along with safety studies of Mahayogiraj, Gugglu, Arogya Vardhani Vati and Maha Laxmi Vilas Rasa through slide show.
- Chemical finger printing of *Oroxylum indicum* through UV visualizer.

(6) Lung Function measurement was done for 60 subjects visiting the stall, this included vital capacity FVC and FEV1. The results were handed over to the subjects. Body fat analysis though bio-electric impedance instrument was also displayed.

Prof. Hasan gave a popular lecture entitled "CAD a gathering storm-An impending Tsunami". He said that Cardio-Vascular Diseases (CAD) are coming to India like a Tsunami, and by the year 2020 India will be at the topmost position in terms of cardiac and diabetic patients. He discussed in detail about the global burden of Cardio-Vascular Diseases. While discussing about CVD in Asian countries, he said that the proportion of CAD among individuals (Asians) less

Prof. Mansoor Hasan inaugurating the exhibition

Prof. Mansoor Hasan visiting the exhibition

Children from local schools at the exhibition

Release of Hindi Patrika "Vish Vigyan Sandesh"

than 40 years is 12-16% while the same among whites is 2-5%. The CAD prevalence in India among the urban population has shown a 9-fold increase while the same among rural population showed a 2-fold increase. The overall greatest increase was in the younger age group (20-39 years). He also spoke on the methods of reducing the global burden of CAD. He discussed about recent advances in diagnostic techniques of cardiac diseases. He concluded his lecture by quoting the lines "Medicine is a science of uncertainty and an art of probability". At the end Dr Poonam Kakkar, Senior Principal Scientist, IITR and convener of the function proposed the vote of thanks.

National Technology Day Celebrated at IITR

Indian Institute of Toxicology Research, Lucknow celebrated National Technology Day on May 11, 2012. The function was organized in the IITR auditorium. While welcoming the guest Sri Sunil Dutt Awasthi, Assistant General Manager, New Product Introduction & Technical Services Tata Motors Ltd., Lucknow, Dr Mukul Das said that National Technology Day is celebrated to mark the centenary of Shakti, the nuclear test carried at Pokhran on May 11, 1998. He further said that IITR has also been involved in development of technologies which were utilized in several disasters which India faced in the past like the Gujarat earthquake, super cyclone in Odisha and the Epidemic dropsy in Delhi and Lucknow.

From left to right: Dr Mukul Das (Chief Scientist IITR), Sri S.D. Awasthi (AGM Tata Motors Ltd.), Dr K.C. Gupta (Director IITR), Shri B.D. Bhattacharji (Senior Principal Scientist IITR)

Shri S.D. Awasthi spoke on "Going Green in Auto Industry". In his talk Shri Awasthi stressed on the need for vehicles with a) improved efficiency, b) low emission level, and c) effective public transportation system. He said that people are becoming much more protective of the environment and many green movements have been initiated in India including the one by Tata Motors Ltd. He further said that the journey to sustainable transportation solutions will be through the use of Hybrid vehicles which use Biodiesel blend, hydrogen-CNG and ethanol-gasoline. The long term aim will be to use fuel cell (or electric) vehicles. Tata motors have introduced diesel series hybrid buses with high efficiency diesel engine with Common Rail Direct Injection (CRDI) Technology. These vehicles improved the fuel economy by more than 40% and have lower emission due to lower engine transient operation. Mr. B.D. Bhattacharji Senior Principal Scientist, IITR proposed the vote of thanks.

World Environment Day

Indian Institute of Toxicology Research, Lucknow celebrated World Environment Day on June 5, 2012. Dr KC Gupta, Director, IITR welcomed the guests. He said that we celebrate World Environment Day to show our gratefulness to Mother Nature. The theme of 2012 World Environment Day was "Green Economy: Does it include YOU?" World Environment Day celebration began in 1972 and has grown to become the one of the main vehicles through which the UN stimulates worldwide awareness of the environment and encourages political attention and action. Through this celebration we are able to personalize environmental issues and enable everyone to realize not only their responsibility, but also their power to become agents for change in support of sustainable and equitable development. World Environment Day is also a day for people from all walks of life to come together to ensure a cleaner, greener and brighter outlook for themselves and future generations. He told that 2012 is declared as International Year for Sustainable Development and 2011-2020 is United Nations decade for biodiversity. He again told that in India appreciable amount of work has been done to exploit the use of Solar Energy. Karnataka is in the top in terms of production and use of Solar Energy. The Environmental Status Report of Lucknow was released by Prof HN Verma, Pro-Vice Chancellor, Jaipur National University, Jaipur, chief guest of the function. This study was carried out during the months of March-May, 2012 to see the status of air quality by monitoring and assessment of some selected air pollutants namely Respirable Particulate Matter (RSPM or PM_{10}), Fine Particulates ($PM_{2.5}$), Sulphur dioxide (SO_2), Nitrogen dioxide (NO_2), and Trace metals- Iron (Fe), Nickel (Ni), Chromium (Cr), Zinc (Zn), Lead (Pb), Manganese (Mn) and Cobalt (Co) and noise level at 9 representative locations, categorized as residential (four), commercial (four) and industrial (one) areas in Lucknow city. The results revealed

Children participating in painting competition

Prize wining posters

the 24 hours concentration of PM_{10} in the range of 113.0 to 396.2 µg/m³ with an average of 231.9µg/m³. The corresponding 24 hours values of $PM_{2.5}$ ranged between 59.8 to 175.4µg/m³ with an average of 89.3 µg/m³. The average values of PM_{10} and $PM_{2.5}$ irrespective of locations were found to be above the permissible limit (PM_{10}= 100 µg/m³ and $PM_{2.5}$= 60 µg/m³) prescribed by MoEF. 24 hours concentration of SO_2 and NOx were found in the range of 9.8 to 24.9 and 21.6 to 61.5 µg/m³ with an average concentration of 17.5 and 37.3 µg/m³ respectively and all the values were below the permissible limits (80 µg/m³). The mean level of trace metals were found Fe = 1502.92, Ni = 14.00, Cr = 39.39, Pb = 34.45, Zn = 150.11, Mn = 113.34 and Co = 4.15 ng/m³. Noise levels during day and night time were found in the range of 62.5 to 73.7 dB (A) and 52.6 to 66.9 dB (A) which was above the respective permissible limits except in industrial area.

Dr Mukul Das, Chief Scientist, IITR gave the genesis of Dr Krishna Murti Memorial Oration and introduced Prof. Verma. Prof. Verma delivered the Dr Krishna Murti Memorial Oration. The title of the oration was "Environmental Hazards Concerns about Cell Phone and Microwave Exposures"

Dr KC Gupta, Director welcoming the guests

He said that a relation between the environment and human health has been observed for centuries. Hippocrates (460-377 BC) for the first time showed connection between disease and environmental conditions - water and seasons. Malaria and yellow fever diseases were found to be more common in swampy areas 2000 years later Ramazzini (1633-1714) associated adverse health outcomes with chemicals, dust, metals and other agents The potters, the mirror makers, the gold smiths and others were exposed to lead poisoning and the dangers of mercury. John Snow (1813-1858) showed that cholera was water borne disease. Currently numerous chemical exposures and industrial processes are causally associated with human cancer. A large number of researches in recent years have added to our understanding of how the environmental exposures can contribute to disability and premature death. Many of the environmental exposures are involuntary for example exposure to environmental tobacco smoke. Infants exposed to environmental tobacco smoke are particularly susceptible to bronchitis, pneumonia and asthma. Tobacco smoke has been declared as a human carcinogen and contains over 250 toxic chemicals. Exposure to environmental tobacco smoke increases the risk of coronary heart disease. Many studies have focused on how human health is influenced by environmental factors. The environmental issues surrounding mobile phones are proving to be a sizeable challenge. The experimental studies carried out at JNU, Delhi and Jaipur National University, Jaipur have shown the potential harmful effects of electromagnetic fields and radiation exposures. The mobile and microwave radiation were found to have adverse effects on brain and reproductive systems of male Wistar rats. After cell phone exposure, the sperm cells showed distortion, decrease in sperm count and affects on the rat sperm cell cycle. Mobile phone and Microwave exposure also cause DNA damage in brain cells. Apoptosis in rat testis after microwave exposure has also been observed. Thus, cell phone and microwave radiations may cause many health problems several other eco-impacts and bad effects of mobile phones have also been reported in literature. Many physiological, environmental and sociological effects have been noticed due to the use of mobile phones. However, the radiation and thermal effects are directly related to the time one spends on talking on the cell phones. Children have been found to be more vulnerable as compared to adults. The excessive use of mobile phone thus needs to be reduced as far as possible.

Release of the Pre Mansoon Environmental Status Report of Lucknow

Winners of the painting competition

Prof. RK Sharma, Director, Sanjay Gandhi Post Graduate Institute of medical Sciences, Lucknow gave the Presidential Address. He said he is very concerned about the environmental hazards. He raised the concern that how prosperity has affected our wellness and happiness? Pollution is the result of prosperity. We are aware that cosmetics contain many chemicals injurious for health. Cell phones disturbs the privacy of individuals. He said when we talk of environmental friendly technologies, we do not have to learn these technologies, we lived with these technologies and we have to practice these. He said that this is the high time we should be aware of environmental concerns before the earth becomes like Venus. Mr. AH Khan proposed the vote of thanks.

CSIR-IITR RESEARCH HIGHLIGHTS

Evaluation of cytotoxic, oxidative stress, proinflammatory and genotoxic responses of micro- and nano-particles of dolomite on human lung epithelial cells A(549).

[Patil G, Khan MI, Patel DK, Sultana S, Prasad R, Ahmad I. Environ Toxicol Pharmacol. 2012 Jun 8;34(2):436-445.]

Dolomite is a natural mineral of great industrial importance and used worldwide, thus millions of workers are at risk of occupational exposure. Its toxicity is however, meagerly documented. In the present investigation, a dolomite powder obtained from its milling unit was analyzed by some standard methods namely, optical microscopy, transmission electron microscopy and dynamic light scattering. Results showed that dolomite powder contained particles of different shapes and size micro particles (MPs) and nanoparticles (NPs), suggesting potential occupational exposure of these particles. An attempt was therefore, made to investigate dolomite toxicity in a particle size-dependent manner in human lung epithelial cells A(549). The comparative toxicity evaluation of MPs and NPs was carried out by assessing their effects on cell viability, membrane damage, glutathione, reactive oxygen species (ROS), lipid per oxidation (LPO), micronucleus (MN) and pro-inflammatory cytokines, namely tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6). These markers of cytotoxicity, genotoxicity and inflammation were assayed in cells exposed to MPs and NPs in a dose-and time-dependent manner. Invariably, their toxic effects were dose-and time-dependent while NPs in general were significantly more toxic. Notably, NPs caused oxidative stress, genotoxicity and inflammatory responses, as seen by significant induction of ROS, LPO, MN, TNF-α, IL-1β and IL-6. Thus, the study tends to suggest that separate health safety standards would be required for micrometer and nanometer scale particles of dolomite.

Rodent models and contemporary molecular techniques: notable feats yet incomplete explanations of Parkinson's disease pathogenesis.

[Yadav S, Dixit A, Agrawal S, Singh A, Srivastava G, Singh AK, Srivastava PK, Prakash O, Singh MP. Mol Neurobiol. 2012 Jun 27 doi:10.1007/s12035-012-8291-8. (Epub ahead of print)]

Rodent models and molecular tools, mainly omics and RNA interference, have been rigorously used to decode the intangible etiology and pathogenesis of Parkinson's disease (PD). Although convention of contemporary molecular techniques and multiple rodent models paved imperative leads in deciphering the role of putative causative factors and sequential events leading to PD, complete and clear-cut mechanisms of pathogenesis are still hard to pin down. The current article reviews the implications and pros and cons of rodent models and molecular tools in understanding the molecular and cellular bases of PD pathogenesis based on the existing literature. Probable rationales for short of comprehensive leads and future possibilities in spite of the extensive applications of molecular tools and rodent models have also been discussed.

Optimization of nitrate reduction by EDTA catalyzed zero-valent bimetallic nanoparticles in aqueous medium.

[Singh KP, Singh AK, Gupta S. Environ Sci Pollut Res Int. 2012 Jun 8 doi:10.1007/s11356-012-1005-y. (Epub ahead of print)]

The present study aims to investigate the EDTA catalyzed reduction of nitrate (NO^{3-}) by zero-valent bimetallic (Fe-Ag) nanoparticles (ZVBMNPs) in aqueous medium and to enumerate the effect of temperature, solution pH, ZVBMNPs dose and EDTA concentration on NO^{3-} reduction. Batch experimental data were generated using a four-factor Box-Behnken design. Optimization modeling was performed using the response surface method for maximizing the reduction of NO^{3-} by ZVBMNPs. Significance of the independent variables and their interactions were tested by the analysis of variance and t test statistics. The model predicted maximum reduction capacity (340.15 mg/g NO^{3-}) under the optimum conditions of temperature, 60°C; pH 4; dose, 1.0/g; and EDTA concentration, 2.0 mmol/l was very close to the experimental value (338.62 mg/g) and about 16 % higher than the experimentally determined capacity (291.32 mg/g). Study demonstrated that ZVBMNPs had higher reduction efficiency than Fe(0) nanoparticles for NO^{3-}. EDTA significantly enhanced the NO^{3-} reduction by ZVBMNPs. The EDTA catalyzed reduction of NO^{3-} by ZVBMNPs can be employed for the effective decontamination of water.

Development, validation and comparison of two microextraction techniques for the rapid and sensitive determination of pregabalin in urine and pharmaceutical formulations after ethyl chloroformate derivatization followed by gas chromatography-mass spectrometric analysis.

[Mudiam MK, Chauhan A, Jain R, Ch R, Fatima G, Malhotra E, Murthy RC. J Pharm Biomed Anal. 2012 May 11. (Epub ahead of print)]

The present article reports first time the use of solid-phase micro-extraction (SPME) and dispersive liquid-liquid micro-extraction (DLLME) to extract pregabalin (PRG) from urine and pharmaceutical formulations followed by GC-MS analysis after ethyl chloroformate (ECF) derivatization. PRG is an antiepileptic and analgesic drug, which is a structural analogue of γ-amino-butyric acid (GABA). It is approved by Food and Drug Administration (FDA) for the treatment of central nervous system (CNS) disorders and neuropathic pain. Initially PRG was derivatized with ECF in the presence of pyridine at room temperature for 30s. Experimental parameters were investigated for derivatization, SPME and DLLME conditions. The limit of detection (LOD) and limit of quantitation (LOQ) were found to be 0.019 µg/ml and 0.063 µg/ml for SPME and 0.022 µg/ml and 0.075 µg/ml for DLLME respectively. The percentage recovery, in case of SPME was in the range of 83-98% while for DLLME it is in the range of 84-98%. The intra and inter-day precisions were found to be less than 6%. The developed methods after ECF derivatization were found to be simple, fast, efficient and inexpensive. DLLME has several advantages like lesser extraction time and cost effectiveness as compared to SPME. The developed methods may find wide application for the routine determination of PRG in biological as well as in quality control samples of pharmaceutical formulations.

Biosorption of arsenic from aqueous solution using dye waste.

[Nigam S, Vankar PS, Gopal K. Environ Sci Pollut Res Int. 2012 Jun 2 doi:10.1007/s11356-012-0966-1. (Epub ahead of print)]

The purpose of this study is to examine on removal of arsenic from water by biosorption through potential application of herbal dye wastes. Four different flower dye residues (after extraction of natural dye) viz. *Hibiscus rosasinensis, Rosa rosa, Tagetes erecta,* and *Canna indica* were utilized successfully for the removal of arsenic from aqueous solution. Batch studies were carried out for various parameters viz. pH, sorbent dose, contact time, initial metal ion concentration, and temperature. Data were utilized for isothermal, kinetic, and thermodynamic studies. Scanning electron microscopy (SEM), energy-dispersive x-ray spectroscopy (EDAX), and Fourier transform infrared (FTIR) analyses of biomass were performed. The results showed that 1 g/100 ml for 5.0-5.5 h contact time at pH 6.0-7.5 with agitation rate 150 rpm provided 98, 96, 92, and 85 % maximum absorption of arsenic by *R. rosa, H. rosasinensis, T. erecta,* and *C. indica,* respectively, at initial concentration of 500 ppb. Data followed Langmuir isotherm showing sorption to be monolayer on heterogeneous surface of biosorbent. Negative values of ΔG° indicated spontaneous nature, whereas ΔH° indicate exothermic nature of system followed by pseudo-first-order adsorption kinetics. FTIR results showed apparent changes in functional group regions after metal chelation. SEM and EDAX analyses showed the changes in surface morphology of all test biosorbents. Herbal dye wastes, used as biosorbent, exhibited significant (85-98%) removal of arsenic from aqueous solution. Hence, these biosorbents are cost-effective, easily available, eco-friendly, and comparatively more effective than other biosorbents already in use. These may be used to remove arsenic and other toxic metals from water.

Organochlorine pesticide, endosulfan induced cellular and organismal response in *Drosophila melanogaster*.

[Sharma A, Mishra M, Shukla AK, Kumar R, Abdin MZ, Chowdhuri DK. J Hazard Mater. 2012 Jun 30;221-222:275-87.]

The effect of endosulfan (0.02-2.0 µg/mL) to *Drosophila melanogaster* (Oregon R^+) at the cellular and organismal levels was examined. Third instar larvae of *D. melanogaster* and the strains transgenic for hsp70, hsp83 and hsp26 were exposed to endosulfan through food for 12-48h to examine the heat shock proteins (hsps), reactive oxygen species (ROS) generation, anti-oxidant stress markers and xenobiotic metabolism enzymes. Authors observed a concentration- and time-dependent significant induction of only small hsps (hsp23>hsp22) in the exposed organism in concurrence with a significant induction of ROS generation, oxidative stress and xenobiotic metabolism markers. Sub-organismal response was to be propagated towards organismal response, i.e., delay in the emergence of flies and decreased locomotor behaviour. Organisms with diminished locomotion also exhibited significantly lowered acetylcholinesterase activity. A significant positive correlation observed among ROS generation and different cellular endpoints (small hsps, oxidative stress markers, cytochrome P450 activities) in the exposed organism indicate a modulatory role of ROS in endosulfan-mediated cellular toxicity. The study thus suggests that the adverse effects of endosulfan in exposed Drosophila are manifested both at cellular and organismal levels and recommends Drosophila as an alternative animal model for screening the risk caused by environmental chemicals.

A comprehensive review of legume allergy.

[Verma AK, Kumar S, Das M, Dwivedi PD. Clin Rev Allergy Immunol. 2012 May 4. doi:10.1007/s12016-012-8310-6 (Epub ahead of print)]

Legumes belonging to Fabaceae family of the order Fabales

are a rich and important source of proteins and many essential elements. Due to its nutritious elements, these are preferably included in human diet in most part of the world. But, unfortunately, IgE binding proteins have been identified in majority of legumes, and allergenic response to these legumes may range from mild skin reactions to life-threatening anaphylactic reaction. Overall, allergenicity due to consumption of legumes in decreasing order may be peanut, soybean, lentil, chickpea, pea, mung bean, and red gram. So far, several allergens from different legumes have been identified and characterized. Most of identified allergens belong to storage proteins family, profilins, or the pathogenesis-related proteins. Legumes also have property of immunological cross-reactivity among themselves and from other sources that also increases the severity of allergenic response to a particular legume. This review summarizes the currently available knowledge on legume allergy and describes the allergenic problems associated with different legumes. It also tries to explore about the legume allergens identified so far by different scientific groups. The culmination of knowledge about identification and characterization of allergens from different legumes will be helpful in diagnosis and treatment of allergy, for development of novel therapeutic strategies, for strict avoidance of particular legume in diet by susceptible individual and also to produce hypoallergenic cultivars of leguminous crop through conventional breeding or genetic modification.

Linear and nonlinear modeling approaches for urban air quality prediction.

[Singh KP, Gupta S, Kumar A, Shukla SP. Sci Total Environ. 2012 Jun 1;426:244-55.]

In this study, linear and nonlinear modeling was performed to predict the urban air quality of the Lucknow city (India). Partial least squares regression (PLSR), multivariate polynomial regression (MPR), and artificial neural network (ANN) approach-based models were constructed to predict the respirable suspended particulate matter (RSPM), SO_2, and NO_2 in the air using the meteorological (air temperature, relative humidity, wind speed) and air quality monitoring data [SPM, NO_2, SO_2 of five years (2005-2009)]. Three different ANN models, viz. multilayer perceptron network (MLPN), radial-basis function network (RBFN), and generalized regression neural network (GRNN) were developed. All the five different models were compared for their generalization and prediction abilities using statistical criteria parameters, viz. correlation coefficient (R), standard error of prediction (SEP), mean absolute error (MAE), root mean squared error (RMSE), bias, accuracy factor (A(f)), and Nash-Sutcliffe coefficient of efficiency (E(f)). Nonlinear models (MPR, ANNs) performed relatively better than the linear PLSR models, whereas, performance of the ANN models was better than the low-order nonlinear MPR models. Although, performance of all the three ANN models were comparable, the GRNN over performed the other two variants. The optimal GRNN models for RSPM, NO_2, and SO_2 yielded high correlation (between measured and model predicted values) of 0.933, 0.893, and 0.885; 0.833, 0.602, and 0.596; and 0.932, 0.768 and 0.729, respectively for the training, validation and test sets. The sensitivity analysis performed to evaluate the importance of the input variables in optimal GRNN revealed that SO_2 was the most influencing parameter in RSPM model, whereas, SPM was the most important input variable in other two models. The ANN models may be useful tools in the air quality predictions.

Cypermethrin alters the expression profile of mRNAs in the adult rat striatum: a putative mechanism of postnatal pre-exposure followed by adulthood re-exposure-enhanced neurodegeneration.

[Tiwari MN, Singh AK, Agrawal S, Gupta SP, Jyoti A, Shanker R, Prakash O, Singh MP. Neurotox Res. 2012 Apr 21 doi:10.1007/s12640-012-9317-8. (Epub ahead of print)]

This study was undertaken to investigate the effect of cypermethrin on the expression patterns of mRNAs in the striatum of adulthood alone and postnatal pre-exposed followed by adulthood re-exposed rats using discover chips rat microarrays. The expression patterns of V-akt murine thymoma viral oncogene homolog 1, B-cell lymphoma 2 (BCL-2), BCL-2-associated X protein, caspase 1, caspase 9, death-associated protein 3 and interleukin-1â were validated by the qRT-PCR. The expressions of inducible nitric oxide synthase (iNOS) and major histocompatibility complex (MHC) II were assessed immunohistochemically; however, tumour protein p53 and cytochrome c (mitochondrial and cytosolic) expressions were checked at protein level by western blotting. Cypermethrin differentially regulated 65 transcripts at one or the other stage of exposure and 21 transcripts exhibited more pronounced alterations in the postnatal pre-exposed and adulthood re-challenged rats. The results of qRT-PCR were in accordance with the microarray observations and the expressions of iNOS, p53 and cytosolic cytochrome c and MHC II positivity were increased while the level of mitochondrial cytochrome c was reduced in adulthood treated animals. The effects were more pronounced in the postnatal pre-exposed followed by adulthood re-exposed rats. The results obtained thus suggest that multiple

pathways are involved in the neuro-degeneration as well as in enhancing the vulnerability of neurons in cypermethrin pre-exposed postnatal animals upon re-exposure during adulthood.

Natural terpenes prevent mitochondrial dysfunction, oxidative stress and release of apoptotic proteins during nimesulide-hepatotoxicity in rats.

[Singh BK, Tripathi M, Chaudhari BP, Pandey PK, Kakkar P. PLoS One. 2012;7(4):e34200.]

Nimesulide, an anti-inflammatory and analgesic drug, is reported to cause severe hepatotoxicity. In this study, molecular mechanisms involved in deranged oxidant-antioxidant homeostasis and mitochondrial dysfunction during nimesulide-induced hepatotoxicity and its attenuation by plant derived terpenes, camphene and geraniol has been explored in male Sprague-Dawley rats. Hepatotoxicity due to nimesulide (80 mg/kg BW) was evident from elevated SGPT, SGOT, bilirubin and histo-pathological changes. Antioxidants and key redox enzymes (iNOS, mtNOS, Cu/Zn-SOD, Mn-SOD, GPx and GR) were altered significantly as assessed by their mRNA expression, Immunoblot analysis and enzyme activities. Redox imbalance along with oxidative stress was evident from decreased NAD(P)H and GSH (56% and 74% respectively; $P<0.001$), increased superoxide and secondary ROS/RNS generation along with oxidative damage to cellular macromolecules. Nimesulide reduced mitochondrial activity, depolarized mitochondria and caused membrane permeability transition (MPT) followed by release of apoptotic proteins (AIF; apoptosis inducing factor, EndoG; endonuclease G, and Cyto c; cytochrome c). It also significantly activated caspase-9 and caspase-3 and increased oxidative DNA damage (level of 8-Oxoguanine glycosylase; $P<0.05$). A combination of camphene and geraniol (CG; 1:1), when pre-administered in rats (10 mg/kg BW), accorded protection against nimesulide hepatotoxicity *in vivo*, as evident from normalized serum biomarkers and histopathology. mRNA expression and activity of key antioxidant and redox enzymes along with oxidative stress were also normalized due to CG pre-treatment. Downstream effects like decreased mitochondrial swelling, inhibition in release of apoptotic proteins, prevention of mitochondrial depolarization along with reduction in oxidized NAD(P)H and increased mitochondrial electron flow further supported protective action of selected terpenes against nimesulide toxicity. Therefore CG, a combination of natural terpenes prevented nimesulide induced cellular damage and ensuing hepatotoxicity.

Low density solvent based dispersive liquid-liquid microextraction with gas chromatography-electron capture detection for the determination of cypermethrin in tissues and blood of cypermethrin treated rats.

[Mudiam MK, Jain R, Maurya SK, Khan HA, Bandyopadhyay S, Murthy RC. J Chromatogr B Analyt Technol Biomed Life Sci. 2012 May 1;895-896:65-70.]

A simple and rapid method to determine the cypermethrin (CYP) insecticide in rat tissues (kidney, liver and brain) and blood has been developed for the first time using low density solvent-dispersive liquid-liquid microextraction (LDS-DLLME) followed by gas chromatography-electron capture detector (GC-ECD) analysis. Initially, tissue samples containing CYP were homogenized in acetone. Subsequently, homogenate was mixed with n-hexane (extraction solvent) and the mixture was rapidly injected into water. The upper n-hexane layer was collected in a separate micro tube and injected into GC-ECD for analysis. Blood samples were diluted with ultrapure water and subjected to DLLME through similar procedure. Parameters such as type and volume of disperser and extraction solvent, salting out effect and extraction time, which can affect the extraction efficiency of DLLME, was optimized. Method was validated by investigating linearity, precision, recovery, limit of detection (LOD) and quantification (LOQ). LODs in tissue were in the range of 0.043-0.314 ng/mg and for blood it was 8.6 ng/ mL with a signal to noise ratio of 3:1. LOQs in tissue were in the range of 0.143-1.03 ng/mg and for blood it was 28.3 ng/mL with a signal to noise ratio of 10:1. Mean recoveries of CYP at three different concentration levels in all the matrices were found to be in the range of 81.6-103.67%. The results show that, LDS-DLLME coupled with GC-ECD offers a simple, rapid and efficient technique for extraction and determination of CYP in rat tissues and blood samples, which in turn would be useful for toxicological studies of CYP.

Role of ErbB2 mediated AKT and MAPK pathway in gall bladder cell proliferation induced by argemone oil and butter yellow. Argemone oil and butter yellow induced gall bladder cell proliferation.

[Mishra V, Ansari KM, Khanna R, Das M. Cell Biol Toxicol. 2012 Jun;28(3):149-59.]

The effect of non cytotoxic doses of argemone oil (AO) and butter yellow (BY), the common adulterants in edible oil, on free radical generation and signaling pathway for cell proliferation in primary cells of gall bladder (GB) was undertaken. AO and BY showed no cytotoxicity at

0.1 µl/ml and 0.1 µg/ml concentration, respectively. AO caused significant increase in ROS after 30 min and RNS after 24 h in GB cells while no change was observed following BY treatment. Enhanced level of COX-2 was observed following AO (0.1 µl/ml) and BY (0.1 µg/ml) treatment to cells for 24 h. AO treatment caused phosphorylation of ErbB2, AKT, ERK, and JNK along with increased thymidine uptake indicating cell proliferation ability in GB cells. BY treatment also showed significant expression of these proteins with the exception of phosphorylated JNK. These results suggest that AO and BY have cell proliferative potential in GB cells following up-regulation of COX-2 and ErbB2; however, their downstream signaling molecules and free radical generation have differential response, indicating that the mechanism of proliferation is different for both compounds and may have relevance in gall bladder cancer.

Lupeol protects against acetaminophen-induced oxidative stress and cell death in rat primary hepatocytes.

[Kumari A, Kakkar P. Food Chem Toxicol. 2012 May;50(5):1781-9.]

Drug induced hepatotoxicity is a major problem where phytochemicals hold promise for its abrogation. This study was carried out to explore cytoprotective potential of lupeol, a triterpene, against acetaminophen (AAP)-induced toxicity in rat hepatocytes. AAP exposure significantly ($p<0.05$) reduced cell viability, disturbed Bcl-2 family pro/anti-apoptotic protein balance, increased ROS production and altered redox homeostasis. It also induced mitochondria-mediated hepatocellular injury by significant mitochondrial depolarization, caspase-9/3 activation and subsequent DNA fragmentation. Results suggest that lupeol pre-treatment effectively restored antioxidant enzyme levels, decreased lipid per oxidation, inhibited ROS generation and depolarization of mitochondria. Lupeol also attenuated mitochondria-mediated signaling pathway and DNA damage as evident from TUNEL assay and cell cycle studies leading to prevention of cytotoxicity. This study confirms the efficacy of lupeol, a food derived antioxidant, in abrogating ROS generation, maintaining redox balance and providing significant protection against mitochondria-mediated cell death during AAP-induced toxicity.

Zinc oxide nanoparticles induce oxidative DNA damage and ROS-triggered mitochondria mediated apoptosis in human liver cells (HepG2).

[Sharma V, Anderson D, Dhawan A. Apoptosis. 2012 Aug;17(8):852-70.]

The wide scale use of Zinc oxide (ZnO) nanoparticles in the world consumer market makes human beings more prone to the exposure to ZnO nanoparticles and its adverse effects. The liver, which is the primary organ of metabolism, might act as a major target organ for ZnO nanoparticles after they gain entry into the body through any of the possible routes. Therefore, the aim of the present study was to assess the apoptotic and genotoxic potential of ZnO nanoparticles in human liver cells (HepG2) and the underlying molecular mechanism of its cellular toxicity. The role of dissolution in the toxicity of ZnO nanoparticles was also investigated. Results demonstrate that HepG2 cells exposed to 14-20 µg/ml ZnO nanoparticles for 12 h showed a decrease in cell viability and the mode of cell death induced by ZnO nanoparticles was apoptosis. They also induced DNA damage which was mediated by oxidative stress as evidenced by an increase in Fpg sensitive sites. Reactive oxygen species triggered a decrease in mitochondria membrane potential and an increase in the ratio of Bax/Bcl2 leading to mitochondria mediated pathway involved in apoptosis. In addition, ZnO nanoparticles activated JNK, p38 and induced p53(Ser15) phosphorylation. However, apoptosis was found to be independent of JNK and p38 pathways. This study investigating the effects of ZnO nanoparticles in human liver cells has provided valuable insights into the mechanism of toxicity induced by ZnO nanoparticles.

Involvement of dopaminergic and serotonergic systems in the neurobehavioral toxicity of lambda-cyhalothrin in developing rats.

[Ansari RW, Shukla RK, Yadav RS, Seth K, Pant AB, Singh D, Agrawal AK, Islam F, Khanna VK. Toxicol Lett. 2012 May 20;211(1):1-9.]

In view of extensive uses of lambda-cyhalothrin, a new generation type II synthetic pyrethroid, human exposure is quite imminent. The present study has therefore been carried out to investigate effect of lambda-cyhalothrin on brain dopaminergic and serotonergic systems and functional alterations associated with them. Post-lactational exposure to lambda-cyhalothrin (1.0 mg/kg or 3.0 mg/kg body weight, p.o.) from PD22 to PD49 caused a significant decrease in the motor activity and rota-rod performance in rats on PD50 as compared to controls. Decrease in motor activity in lambda-cyhalothrin treated rats was found to persist 15 days after withdrawal of exposure on PD65 while a trend of recovery in rota-rod performance was observed. A decrease in the binding of ^{3}H-Spiperone, known to label dopamine-D2 receptors in corpus striatum associated with decreased expression of tyrosine hydroxylase (TH)-immuno-reactivity and TH protein was observed in lambda-cyhalothrin treated rats on PD50 and PD65 compared to

controls. Increase in the binding of ^{3}H-Ketanserin, known to label serotonin-2A receptors in frontal cortex was observed in lambda-cyhalothrin exposed rats on PD50 and PD65 as compared to respective controls. The changes were more marked in rats exposed to lambda-cyhalothrin at a higher dose (3.0 mg/kg) and persisted even 15 days after withdrawal of exposure. The results exhibit vulnerability of developing rats to lambda-cyhalothrin and suggest that striatal dopaminergic system is a target of lambda-cyhalothrin. Involvement of serotonin-2A receptors in the neurotoxicity of lambda-cyhalothrin is also suggested. The results further indicate that neurobehavioral changes may be more intense in case exposure to lambda-cyhalothrin continues.

Resveratrol potentiates cytochrome P450 2 d22-mediated neuroprotection in maneb- and paraquat-induced Parkinsonism in the mouse.

[Srivastava G, Dixit A, Yadav S, Patel DK, Prakash O, Singh MP. Free Radic Biol Med. 2012 Apr 15;52(8):1294-306.]

A strong association between polymorphisms of the cytochrome P450 (CYP/Cyp) 2D6 gene and risk to Parkinson's disease (PD) is well established. The present study investigated the neuroprotective potential of Cyp2d22, a mouse ortholog of human CYP2D6, in maneb- and paraquat-induced Parkinsonism and the mechanisms involved therein along with the effects of resveratrol on various parameters associated with Cyp2d22-mediated neuroprotection. The animals were treated intraperitoneally with resveratrol (10mg/kg, daily) and paraquat (10mg/kg) alone or in combination with maneb (30 mg/kg), twice a week, for 9 weeks, along with their respective controls. The subsets of animals were also treated intraperitoneally with a Cyp2d22 inhibitor, ketoconazole (100mg/kg, daily). Maneb and paraquat reduced Cyp2d22 and vesicular monoamine transporter type 2 (VMAT-2) expressions, the number of tyrosine hydroxylase-positive cells, and dopamine content and increased paraquat accumulation in the nigrostriatal tissues, oxidative stress, microglial activation, neuroinflammation, and apoptosis. Cyp2d22 inhibitor significantly exacerbated all these neurodegenerative indexes. Resveratrol co treatment, partially but significantly, ameliorated the neurodegenerative changes by altering Cyp2d22 expression and paraquat accumulation. The results obtained in the study demonstrate that Cyp2d22 offers neuroprotection in maneb- and paraquat-induced dopaminergic neurodegeneration and resveratrol enhances its neuroprotective credentials by influencing Cyp2d22 expression and paraquat accumulation.

Cholinergic dysfunctions and enhanced oxidative stress in the neurobehavioral toxicity of lambda-cyhalothrin in developing rats.

[Ansari RW, Shukla RK, Yadav RS, Seth K, Pant AB, Singh D, Agrawal AK, Islam F, Khanna VK. Neurotox Res. 2012 Feb 11 doi:10.1007/s12640-012-9313-z. (Epub ahead of print)]

This study is focused on understanding the mechanism of neurobehavioral toxicity of lambda-cyhalothrin, a new generation type II synthetic pyrethroid in developing rats following their exposure from post-lactational day (PLD) 22 to PLD49 and investigate whether neurobehavioral alterations are transient or persistent. Post-lactational exposure to lambda-cyhalothrin (1.0 or 3.0 mg/kg body weight, p.o.) affected grip strength and learning activity in rats on PLD50 and the persistent impairment of grip strength and learning was observed at 15 days after withdrawal of exposure on PLD65. A decrease in the binding of muscarinic-cholinergic receptors in frontocortical, hippocampal, and cerebellar membranes associated with decreased expression of choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) in hippocampus was observed following exposure to lambda-cyhalothrin on PLD50 and PLD65. Exposure to lambda-cyhalothrin was also found to increase the expression of growth-associated protein-43 in hippocampus of rats on PLD50 and PLD65 as compared to controls. A significant increase in lipid per oxidation and protein carbonyl levels and decreased levels of reduced glutathione and activity of superoxide dismutase, catalase, and glutathione peroxidase in brain regions of lambda-cyhalothrin exposed rats were distinctly observed indicating increased oxidative stress. Inhibition of ChAT and AChE activity may cause down-regulation of muscarinic-cholinergic receptors consequently impairing learning activity in developing rats exposed to lambda-cyhalothrin. The data further indicate that long-term exposure to lambda-cyhalothrin at low doses may be detrimental and changes in selected behavioral and neurochemical end points may persist if exposure to lambda-cyhalothrin continues.

Lupeol prevents acetaminophen-induced *in vivo* hepatotoxicity by altering the Bax/Bcl-2 and oxidative stress-mediated mitochondrial signaling cascade.

[Kumari A, Kakkar P. Life Sci. 2012 Apr 20;90(15-16): 561-70.]

Lupeol, a triterpene, possesses numerous pharmacological activities, including anti-malarial, anti-arthritic and anti-carcinogenic properties. The present study was conducted

to explore the hepatoprotective potential of lupeol against acetaminophen (AAP)-induced hepatotoxicity in Wistar rats. Rats were given a prophylactic treatment of lupeol (150 mg/kg body weight, p.o., for 30 consecutive days) with a co-administration of AAP (1 g/kg body weight). The modulatory effects of lupeol on AAP-induced hepatotoxicity were investigated by assaying oxidative stress biomarkers, serum liver toxicity markers, pro/anti apoptotic proteins, DNA fragmentation and by the histopathological examination of the liver. Lupeol significantly prevented hepatic damage as evident from the histopathological studies and significant decline in serum trans-aminases. The alterations in cellular redox status ($p<0.01$) and antioxidant enzyme activities together with the enhanced lipid peroxidation and protein carbonyl levels were also observed in the AAP-treated rats. In addition, significant ROS generation and mitochondrial depolarization were observed in this group. Co-administration of lupeol significantly decreased the level of serum transaminases, MDA and protein carbonyl content. It also prevented ROS generation and mitochondrial depolarization. Furthermore, lupeol enhanced the mitochondrial antioxidant and redox status and inhibited DNA damage and cell death by preventing the down regulation of Bcl-2, up regulation of Bax, release of cytochrome c and the activation of caspase 9/3. The conclusion of this study is that lupeol when co-administered with AAP effectively reduces oxidative stress and prevents AAP-induced hepatotoxicity by inhibiting critical control points of apoptosis.

Chickpea (*Cicer arietinum*) proteins induce allergic responses in nasobronchial allergic patients and BALB/c mice.

[Verma AK, Kumar S, Tripathi A, Chaudhari BP, Das M, Dwivedi PD. Toxicol Lett. 2012 Apr 5;210(1):24-33.]

Allergy to chickpea or Garbanzo bean (*Cicer arietinum*) has been reported in the Indian population. Little information is found regarding allergenic events involved in the chickpea allergy; therefore, chickpea allergenicity assessment was undertaken. *In vivo* and *ex vivo* studies were carried out using BALB/c mice. Chickpea skin prick test positive patients have been used to extend this study in humans. Identification of allergens was carried out by simulated gastric fluids assay for pepsin resistant polypeptides and validated by IgE western blotting using chickpea sensitive humans and sensitized mice sera. The data have shown the occurrence of a systemic anaphylactic reaction resulting in reduced body temperature after challenge along with significantly increased levels of IgE, IgG1, MMCP-1, CCL-2 as well as histamine. Further, increased Th1/Th2 (mixed) cytokine response was observed in spleen cell culture supernatants. Jejunum, lungs and spleen showed prominent histopathological changes specific for allergic inflammation. Immunoblotting with pooled sera of either sensitized mice or human sera recognized seven similar IgE binding polypeptides that may be responsible for chickpea induced hypersensitivity reactions. This study has addressed the allergenic manifestations associated with chickpea consumption and identifies the proteins responsible for allergenicity which may prove useful in diagnosis and management of allergenicity of legumes especially chickpea.

Evaluation of bactericidal efficacy of silver ions on *Escherichia coli* for drinking water disinfection.

[Pathak SP, Gopal K. Environ Sci Pollut Res Int. 2012 Jul;19(6):2285-90.]

The purpose of this study is the development of a suitable process for the disinfection of drinking water by evaluating bactericidal efficacy of silver ions from silver electrodes. A prototype of a silver ionizer with silver electrodes and control unit has been fabricated. Silver ions from silver electrodes in water samples were estimated with an atomic absorption spectrophotometer. A fresh culture of *Escherichia coli* ($1.75\times10(3)$ c.f.u./ml) was exposed to 1, 2, 5, 10 and 20 ppb of silver ions in 100 ml of autoclaved tap water for 60 min. The effect of different pH and temperatures on bactericidal efficacy was observed at constant silver ion concentration (5 ppb) and contact time of 30 min. The maximum bactericidal activity (100%) was observed at 20 ppb of silver ion concentration indicating total disinfection after 20 min while minimum bactericidal activity (25%) was observed after 10 min at 01 ppb of silver ions. Likewise, 100% bactericidal activity was noticed with 2, 5 and 10 ppb of silver ions after 60, 50 and 40 min, respectively. Bactericidal activity at pH 5, 6, 7, 8 and 9 was observed at 79.9%, 79.8%, 80.5%, 100% and 100%, respectively, whereas it was 80.4%, 88.3%, 100%, 100% and 100% at 10°C, 20°C, 30°C, 40°C and 50°C, respectively. The findings of this study revealed that very low concentrations of silver ions at pH 8-9 and temperature >20°C have bactericidal efficacy for total disinfection of drinking water. Silver ionization is suitable for water disinfection and an appropriate alternative to chlorination which forms carcinogenic disinfection by-products.

Modeling and optimization of reductive degradation of chloramphenicol in aqueous solution by zero-valent bimetallic nanoparticles.

[Singh KP, Singh AK, Gupta S, Rai P. Environ Sci Pollut Res Int. 2012 Jul;19(6):2063-78.]

The present study aims to investigate the individual and

combined effects of temperature, pH, zero-valent bimetallic nanoparticles (ZVBMNPs) dose, and chloramphenicol (CP) concentration on the reductive degradation of CP using ZVBMNPs in aqueous medium. Iron-silver ZVBMNPs were synthesized. Batch experimental data were generated using a four-factor statistical experimental design. CP reduction by ZVBMNPs was optimized using the response surface modeling (RSM) and artificial neural network-genetic algorithm (ANN-GA) approaches. The RSM and ANN methodologies were also compared for their predictive and generalization abilities using the same training and validation data set. Reductive by-products of CP were identified using liquid chromatography-mass spectrometry technique. The optimized process variables (RSM and ANN-GA approaches) yielded CP reduction capacity of 57.37 and 57.10 mg/g, respectively, as compared to the experimental value of 54.0 mg/g with un-optimized variables. The ANN-GA and RSM methodologies yielded comparable results and helped to achieve a higher reduction (>6%) of CP by the ZVBMNPs as compared to the experimental value. The root mean squared error, relative standard error of prediction and correlation coefficient between the measured and model-predicted values of response variable were 1.34, 3.79, and 0.964 for RSM and 0.03, 0.07, and 0.999 for ANN models for the training and 1.39, 3.47, and 0.996 for RSM and 1.25, 3.11, and 0.990 for ANN models for the validation set. Predictive and generalization abilities of both the RSM and ANN models were comparable. The synthesized ZVBMNPs may be used for an efficient reductive removal of CP from the water.

Bio-capture of *S. Typhimurium* from surface water by aptamer for culture-free quantification.

[Singh G, Vajpayee P, Rani N, Jyoti A, Gupta KC, Shanker R. Ecotoxicol Environ Saf. 2012 Apr;78:320-6.]

In this study, a DNA aptamer was used to bio-capture *Salmonella enterica serovar Typhimurium* from surface water collected from highly endemic zone prior to culture-free detection through Molecular-Beacon based real-time PCR assay targeting invA gene. The assay could detect *S. Typhimurium* cells (1 CFU/PCR or 100 CFU/ml) selectively captured by serovar specific DNA aptamer. The observations indicate that all the water samples (n=40) collected from the river Gomti were contaminated by *S. Typhimurium* (31400-1 × 10(7) CFU/100 ml). The pre-analytical step in the form of serovar specific DNA aptamer based bio-capture of the bacterial cell was found to enhance the sensitivity of the florescent probe based real-time PCR assay during detection of *S. Typhimurium* in environmental samples exhibiting natural PCR inhibitors and high background bacterial flora. The assay could be used for the regular monitoring of surface waters for forecasting and management of non-typhoidal Salmonellosis in south Asia.

Mechanism of inhibition of the ATPase domain of human topoisomerase IIα by 1,4-benzoquinone, 1,2-naphthoquinone, 1,4-naphthoquinone, and 9,10-phenanthroquinone.

[Gurbani D, Kukshal V, Laubenthal J, Kumar A, Pandey A, Tripathi S, Arora A, Jain SK, Ramachandran R, Anderson D, Dhawan A. Toxicol Sci. 2012 Apr;126(2):372-90.]

The inhibition of human topoisomerase IIα (Hu-TopoIIα), a major enzyme involved in maintaining DNA topology, repair, and chromosome condensation/decondensation results in loss of genomic integrity. In the present study, the inhibition of ATPase domain of Hu-TopoIIα as a possible mechanism of genotoxicity of 1,4-benzoquinone (BQ), hydroquinone (HQ), naphthoquinone (1,2-NQ and 1,4-NQ), and 9,10-phenanthroquinone (9,10-PQ) was investigated. *In silico* modeling predicted that 1,4-BQ, 1,2-NQ, 1,4-NQ, and 9,10-PQ could interact with Ser-148, Ser-149, Asn-150, and Asn-91 residues of the ATPase domain of Hu-TopoIIα. Biochemical inhibition assays with the purified ATPase domain of Hu-TopoIIα revealed that 1,4-BQ is the most potent inhibitor followed by 1,4-NQ > 1,2-NQ > 9,10-PQ > HQ. Ligand-binding studies using isothermal titration calorimetry revealed that 1,4-BQ, HQ, 1,4-NQ, 1,2-NQ, and 9,10-PQ enter into four sequentially binding site models inside the domain. 1,4-BQ exhibited the strongest binding, followed by 1,4-NQ > 1,2-NQ > 9,10-PQ > HQ, as revealed by their average K(d) values. The cellular fate of such inhibition was further evidenced by an increase in the number of Hu-TopoIIα-DNA cleavage complexes in the human lung epithelial cells (BEAS-2B) using trapped in agarose DNA immunostaining (TARDIS) assay, which utilizes antibody specific for Hu-TopoIIα. Furthermore, the increase in γ-H2A.X levels quantitated by flow cytometry and visualized by immunofluorescence microscopy illustrated that accumulation of DNA double-strand breaks inside the cells can be attributed to the inhibition of Hu-TopoIIα. These findings collectively suggest that 1,4-BQ, 1,2-NQ, 1,4-NQ, and 9,10-PQ inhibit the ATPase domain and potentially result in Hu-TopoIIα-mediated clastogenic and leukemogenic events.

Photosensitizing mechanism and identification of levofloxacin photoproducts at ambient UV radiation.

[Dwivedi A, Mujtaba SF, Kushwaha HN, Ali D, Yadav N, Singh SK, Ray RS. Photochem Photobiol. 2012 Mar-Apr;88(2):344-55.]

Levofloxacin (LVFX) is a broad spectrum third generation fluoroquinolone antibiotic, used in the treatment of severe

or life-threatening bacterial infections. Photosensitizing mechanism of LVFX was investigated under the ambient environmental intensities of UV-A, UV-B and sunlight exposure. Phototoxic effects of LVFX were assessed on NIH-3T3 and HaCaT cell lines. Results identified first time three photoproducts of LVFX at ambient levels of UV-R by LC-MS/MS. The generation of reactive oxygen species (ROS) was investigated photochemically as well as intracellularly in HaCaT cell line. ROS were significantly quenched by specific quenchers like DABCO, NaN_3, D-mannitol and NAC. Photosensitized LVFX caused lipid peroxidation at different concentrations. Quenching study with superoxide dismutase confirms the LVFX-induced lipid photoperoxidation. Further, photocytotoxicity of LVFX showed significant reduction in cell viability by MTT and neutral red uptake assays. LVFX caused cell arrest in G2/M phases as well as induced apoptosis through ROS-dependent pathway. In addition, photosensitized LVFX also induced upregulation of p21 and Bax/Bcl-2 genes ratio. India is a tropical country and most of the human activities such as agriculture, commerce, sports, etc. take place in bright sunlight; therefore, photosensitive LVFX may lead to skin/ocular disorders and immune suppression. Information is needed regarding the phototoxicity of LVFX for human safety.

Induction of oxidative stress, DNA damage and apoptosis in mouse liver after sub-acute oral exposure to zinc oxide nanoparticles.

[Sharma V, Singh P, Pandey AK, Dhawan A. Mutat Res. 2012 Jun 14;745(1-2):84-91.]

Zinc oxide (ZnO) nanoparticles are finding applications in a wide range of products including cosmetics, food packaging, imaging, etc. This increases the likelihood of human exposure to these nanoparticles through dermal, inhalation and oral routes. Presently, the majority of the studies concerning ZnO nanoparticle toxicity have been conducted using *in vitro* systems which lack the complex cell-cell, cell-matrix interactions and hormonal effects found in the *in vivo* scenario. The present *in vivo* study in mice was aimed at investigating the oral toxicity of ZnO nanoparticles. Results showed a significant accumulation of nanoparticles in the liver leading to cellular injury after sub-acute oral exposure of ZnO nanoparticles (300 mg/kg) for 14 consecutive days. This was evident by the elevated alanine aminotransferase (ALT) and alkaline phosphatase (ALP) serum levels and pathological lesions in the liver. ZnO nanoparticles were also found to induce oxidative stress indicated by an increase in lipid peroxidation. The DNA damage in the liver and kidney cells of mice was evaluated by the Fpg-modified Comet assay which revealed a significant ($p<0.05$) increase in the Fpg-specific DNA lesions in liver indicating oxidative stress as the cause of DNA damage. The TUNEL assay revealed an induction of apoptosis in the liver of mice exposed to ZnO nanoparticles compared to the control. These results conclusively demonstrate that sub-acute oral exposure to ZnO nanoparticles in mice leads to an accumulation of nanoparticles in the liver causing oxidative stress mediated DNA damage and apoptosis. These results also suggest the need for a complete risk assessment of any new engineered nanoparticle before its arrival into the consumer market.

In vitro studies on immunotoxic potential of Orange II in splenocytes.

[Yadav A, Kumar A, Dwivedi PD, Tripathi A, Das M. Toxicol Lett. 2012 Feb 5;208(3):239-45.]

Orange II, an azo dye, is not permitted in food preparations, but high levels of the dye have been detected in different food commodities. Though there are reports on the toxicity of Orange II but knowledge based on the immunomodulatory properties of Orange II is scanty. The present investigation was undertaken to study the *in vitro* immunotoxic potential of Orange II in splenocytes. Splenocytes were isolated, cultured and subjected to immunophenotypic analysis, mixed lymphocyte reaction (MLR) assay or stimulated with lipopolysaccharide (LPS) or concanavalin A (Con A) for 72 h. The supernatant was collected for cytokine assays. Orange II showed cytotoxic effects at 100-1000 µg/ml concentrations and 50 µg/ml was determined as the highest non-cytotoxic dose. Orange II at the non-cytotoxic dose (50 µg/ml) significantly altered the relative distribution of T and B-cells, MLR response and the mitogen induced proliferative response of T-cells and B-cells. Consistent with the hypo-responsiveness of the T and B-lymphocytes, Orange II induced a concomitant decline in the secretion of cytokines IL-2, IL-4, IL-6, IFN-γ, TNF-α and IL-17. On the contrary, there was an increase in the production of IL-10, an anti-inflammatory regulatory cytokine, which may be one of the causative factors for immunosuppressive property of Orange II. These results suggest that non-cytotoxic dose of Orange II may have immunomodulatory effects.

Optimization and validation of an extraction method for the analysis of polycyclic aromatic hydrocarbons in chocolate candies.

[Kumari R, Chaturvedi P, Ansari NG, Murthy RC, Patel DK. J Food Sci. 2012 Jan;77(1):T34-40.]

Chocolate is a key ingredient in many foods such as milk shakes, candies, bars, cookies, and cereals. Chocolate candies are often consumed by mankind of all age groups.

The presence of polycyclic aromatic hydrocarbons (PAHs) in chocolate candies may result in health risk to people. A rapid, precise, and economic extraction method was optimized and validated for the simultaneous determination of polycyclic aromatic hydrocarbons in chocolate candy by high-performance liquid chromatography (HPLC) and gas chromatography-mass spectrometry (GS-MS) as a confirmatory technique. The method was optimized by using different solvents for liquid-liquid extraction, varying volume of de-emulsifying agent, and quantity of silica gel used for purification. The HPLC separation of 16 PAHs was carried out by C-18 column with mobile phase composed of acetonitrile: water (70: 30) in isocratic mode with run time of 20 min. Limit of detection, limit of quantification (LOQ), and correlation coefficients were found in the range of 0.3 to 4 ng/g, 0.9 to 12 ng/g, and 0.9109 to 0.9952, respectively. The exploration of 25 local chocolate candy samples for the presence of PAHs showed the mean content of benzo[a]pyrene as 1.62 ng/g, which representing the need to evaluate effective measures to prevent more severe PAHs contamination in chocolate candies in future. Chocolate is one of the most favorite food items among people, especially children. Chocolate candies are often consumed by mankind of all age groups. Chocolate candies are often consumed by children in large quantities. The presence PAHs in chocolate candies may result in health risk to people. In the present study, a precise and cost effective rapid method was employed for the determination of PAHs, which can be employed for daily routine analysis of PAHs in chocolate products.

Evaluation of cytotoxic, genotoxic and inflammatory responses of micro- and nano-particles of granite on human lung fibroblast cell IMR-90.

[Ahmad I, Khan MI, Patil G, Chauhan LK. Toxicol Lett. 2012 Feb 5;208(3):300-7.]

Occupational exposure of granite workers is well known to cause lung impairment and silicosis. Toxicological profiles of different size particles of granite dust, however, are not yet understood. Present evaluation of micro- and nano-particles of granite dust as on human lung fibroblast cells IMR-90, revealed that their toxic effects were dose-dependent, and nanoparticles in general were more toxic. In this study authors first demonstrated that nanoparticles caused oxidative stress, inflammatory response and genotoxicity, as seen by nearly 2 fold induction of ROS and LPO, mRNA levels of TNF-α and IL-1β, and induction in micronuclei formation. All these were significantly higher when compared with the effect of micro particles. Thus, the study suggests that separate health safety standards would be required for granite particles of different sizes.

Induction of ROS, mitochondrial damage and autophagy in lung epithelial cancer cells by iron oxide nanoparticles.

[Khan MI, Mohammad A, Patil G, Naqvi SA, Chauhan LK, Ahmad I. Biomaterials. 2012 Feb;33(5):1477-88.]

Autophagy has attracted a great deal of research interest in tumor therapy in recent years. An attempt was made in this direction and now authors report that iron oxide NPs synthesized by authors selectively induce autophagy in cancer cells (A549) and not in normal cells (IMR-90). It was also noteworthy that autophagy correlated with ROS production as well as mitochondrial damage. Protection of NAC against ROS clearly suggested the implication of ROS in hyper-activation of autophagy and cell death. Pre-treatment of cancer cells with 3-MA also exhibited protection against autophagy and promote cellular viability. Results also showed involvement of classical mTOR pathway in autophagy induction by iron oxide NPs in A549 cells. Results had shown that bare iron oxide NPs are significantly cytotoxic to human cancer cells (A549) but not to the normal human lung fibroblast cells (IMR-90). In other words these nanoparticles selectively kill cancerous cells. It is encouraging to conclude that iron oxide NPs bear the potential of its applications in biomedicine, such as tumor therapy specifically by inducing autophagy mediated cell death of cancer cells.

Reduced expression of DNA repair genes (XRCC1, XPD, and OGG1) in squamous cell carcinoma of head and neck in North India.

[Kumar A, Pant MC, Singh HS, Khandelwal S. Tumour Biol. 2012 Feb;33(1):111-9.]

Squamous cell carcinoma of head and neck (SCCHN) is the sixth most common cancer globally, and in India, it accounts for 30% of all cancer cases. Epidemiological studies have shown a positive association between defective DNA repair capacity and SCCHN. The underlying mechanism of their involvement is not well understood. In the present study, authors have analyzed the relationship between SCCHN and the expression of DNA repair genes namely X-ray repair cross-complementing group 1 (XRCC1), xeroderma pigmentosum group D (XPD), and 8-oxoguanine DNA glycosylase (OGG1) in 75 SCCHN cases and equal number of matched healthy controls. Additionally, levels of DNA adduct [8-hydroxyguanine (8-OHdG)] in 45 SCCHN cases and 45 healthy controls were also determined, to ascertain a link between mRNA expression of these three genes and DNA adducts. The relative expression of XRCC1, XPD, and OGG1 in head and neck cancer patients was found to be significantly low as compared to controls. The

percent difference of mean relative expression between cases and controls demonstrated maximum lowering in OGG1 (47.3%) > XPD (30.7%) > XRCC1 (25.2%). A negative Spearmen correlation between XRCC1 vs. 8-OHdG in cases was observed. In multivariate logistic regression analysis (adjusting for age, gender, smoking status, and alcohol use), low expression of XRCC1, XPD, and OGG1 was associated with a statistically significant increased risk of SCCHN [crude odds ratios (ORs) (95%CI) OR 2.10; (1.06-4.17), OR 2.76; (1.39-5.49), and 5.24 (2.38-11.52), respectively]. In conclusion, this study demonstrated that reduced expression of XRCC1, XPD, and OGG1 is associated with more than two fold increased risk in SCCHN.

Associated risk of XRCC1 and XPD cross talk and life style factors in progression of head and neck cancer in north Indian population.

[Kumar A, Pant MC, Singh HS, Khandelwal S. Mutat Res. 2012 Jan 3;729(1-2):24-34.]

Effective DNA repair machinery ensures maintenance of genomic integrity. Environmental insults, ageing and replication errors necessitate the need for proper DNA repair systems. Any alteration in DNA repair efficacy would play a dominant role in progression of squamous cell carcinoma of head and neck (SCCHN). Genotypes of XRCC1 gene-Arg194Trp, Arg280His, Arg399Gln and XPD Lys751Gln, by PCR-RFLP were studied in 278 SCCHN patients and an equal number of matched healthy controls residing in north India. In XRCC1 polymorphisms, Arg194Trp and Arg399Gln variants showed a reduced risk, whereas, XPD Lys751Gln variants exhibited ~2-fold increase in SCCHN risk. With XRCC1-Arg280His variants, there was no association with SCCHN risk. Arg399Gln of XRCC1 appears to have a protective role in people those consume alcohol, while XPD Lys751Gln variants indicated ~2-fold increased risk of SCCHN in all the co-variate groups. Comparison of gene-gene interaction among XRCC1 Arg280His and XPD Lys751Gln suggested enhanced risk of SCCHN by ~2.3-fold in group one and ~6.1-fold in group two. In dichotomized groups of this combination, the risk was ~2.4 times. Haplotype analysis revealed the frequency of C-G-G-G and C-A-G-G to be significantly associated with an increased risk of SCCHN. On the contrary, T-G-A-A significantly diminished the risk. CART analysis results showed that the terminal node that contains homozygous mutants of XPD Lys751Gln and XRCC1 Arg194Trp, wild type of XRCC1 Arg399Gln and homozygous mutant of XRCC1 Arg280His, represent the highest risk group. Results demonstrate high degree of gene-gene interaction involving DNA repair genes of NER and BER pathways, namely XRCC1 and XPD. This study amply demonstrates positive association of XPD Arg751Gln polymorphism with an increased risk of SCCHN. Further, XRCC1 Arg280His variant though dormant individually, may also contribute to the development of cancer in combination with XPD Arg751Gln.

Optimizing removal of ibuprofen from water by magnetic nanocomposite using Box-Behnken design.

[Singh KP, Singh AK, Singh UV, Verma P. Environ Sci Pollut Res Int. 2012 Mar;19(3):724-38.]

The present research aims to optimize the removal of ibuprofen (IBP), a non-steroidal anti-inflammatory, analgesic, and antipyretic drug from the aqueous solution using a synthesized magnetic carbon-iron nanocomposite, and to investigate the individual and combined effects of the independent process variables. Combining the adsorptive capability of carbon and magnetic property of iron, a carbon-iron nanocomposite was synthesized. A four-factor Box-Behnken experimental design-based optimization modeling was performed for maximizing the removal of IBP from water by the nanocomposite using the batch experimental data. A quadratic model was built to predict the responses. Significance of the process variables and their interactions was tested by the analysis of variance and t test statistics. The experimental maximum removals of IBP from the aqueous solution by carbon and magnetic nanocomposite were 14.74% and 60.39%, respectively. The model predicted maximum removal of 65.81% under the optimum conditions of the independent variables (IBP concentration 80 mg/l; temperature 48°C; pH 2.50; dose 0.6 g/l) was very close to the experimental value (65.12 ± 0.92%). pH of the solution exhibited most significant effect on IBP adsorption. The developed magnetic nanocomposite was found superior than its precursor carbon exhibiting higher removal of IBP from the water and can be easily separated from the aqueous phase under temporary external magnetic field. The developed magnetic nanocomposite may be used for an efficient removal of IBP from the water.

Modeling and optimization of trihalomethanes formation potential of surface water (a drinking water source) using Box-Behnken design.

[Singh KP, Rai P, Pandey P, Sinha S. Environ Sci Pollut Res Int. 2012 Jan;19(1):113-27.]

The present research aims to investigate the individual and interactive effects of chlorine dose/dissolved organic carbon ratio, pH, temperature, bromide concentration, and reaction time on trihalomethanes (THMs) formation in surface water (a drinking water source) during disinfection by chlorination in a prototype laboratory-scale simulation and to develop a model for the prediction and optimization of THMs levels in chlorinated water for their effective control. A five-factor Box-

Behnken experimental design combined with response surface and optimization modeling was used for predicting the THMs levels in chlorinated water. The adequacy of the selected model and statistical significance of the regression coefficients, independent variables, and their interactions were tested by the analysis of variance and t test statistics. The THMs levels predicted by the model were very close to the experimental values ($R(2) = 0.95$). Optimization modeling predicted maximum (192 µg/l) TMHs formation (highest risk) level in water during chlorination was very close to the experimental value (186.8 ± 1.72 µg/l) determined in laboratory experiments. The pH of water followed by reaction time and temperature were the most significant factors that affect the THMs formation during chlorination. The developed model can be used to determine the optimum characteristics of raw water and chlorination conditions for maintaining the THMs levels within the safe limit.

Cypermethrin induces astrocyte apoptosis by the disruption of the autocrine/paracrine mode of epidermal growth factor receptor signaling

[Maurya SK, Rai A, Rai NK, Deshpande S, Jain R, Mudiam MKR, Prabhakar YS, and Bandyopadhyay S. Toxicological Sciences (2012) 125(2), 473–487]

Cypermethrin is reported to affect astrocytes in rat brain; however, its mechanism of action is obscure. Here, authors observed an increase in apoptosis in the cortical astrocytes upon treatment of rats with cypermethrin. Authors then characterized the mechanism governing the apoptosis. Because the epidermal growth factor receptor (EGFR) signaling regulates the survival of astrocytes, authors investigated the effect of cypermethrin on EGFR activation. The astrocytes exhibited an early and irreversible attenuation in the basal EGFR phosphorylation. Supportively, molecular docking studies revealed considerable homology in the docking mode of cypermethrin and the known EGFR inhibitors, erlotinib and AG1478, to the kinase domain of EGFR. Furthermore, treatment with cypermethrin demonstrated a downregulation in the intracellular and secreted levels of heparin-binding epidermal growth factor (HB-EGF), an EGFR ligand. AG1478 reduced the synthesis of HB-EGF, suggesting the dependence of HB-EGF on EGFR activation. In addition, a neutralizing antibody against HB-EGF diminished the basal EGFR levels, indicating ligand-dependent expression of EGFR. Likewise, cypermethrin caused irreversible suppression in the basal EGFR levels, which induced apoptosis in astrocytes. The apoptosis was prevented by exogenous HB-EGF. These data imply an autocrine/paracrine mode of action of HB-EGF-EGFR in astrocyte survival. Consequently, cypermethrin induced a mitochondria-mediated apoptosis, characterized by rise in Bax/Bcl-2 ratio and cleavage of caspase-9, -3, and -7, and the effect was prevented by HB-EGF. HB-EGF activated the extracellular signal-regulated kinases and AKT pathways that protected against apoptosis. Together, these data demonstrate that cypermethrin induces astrocyte apoptosis by disrupting the autocrine/paracrine mode of HB-EGF-EGFR signaling at two levels, irreversible loss of basal EGFR and downregulation of HB-EGF.

HONOUR


This is to certify that
Shruti Singh
was adjudged as the winner of
Young Scientist Award / Poster Award
at
International Symposium
on
Emerging Trends in Free Radicals, Antioxidants and Nutraceuticals on Health
disease and Radiation Biology
January 12th -14th 2012
at
Lake Land Country Club, Kolkata, India

Ms. Shruti Singh, CSIR-SRF, Herbal Research, CSIR-Indian Institue of Toxicology Research has been recently awarded the Young Scientist Award during the International symposium on "Emerging trends in free radicals, antioxidants and nutraceuticals on health, disease and radiation biology", held from January 12th-14th, 2012 at Kolkata.

TOPIC OF INTEREST

Indian Scenario of QSAR and QSTR Research

QSTR with extended topochemical atom (ETA) indices. 15. Development of predictive models for toxicity of organic chemicals against fathead minnow using second-generation ETA indices.

[Roy K, Das RN. SAR QSAR Environ Res. 2012 Jan;23(1-2):125-40.]

Modern industrialisation has led to the production of millions of toxic chemicals having hazardous effects on the ecosystem. It is impracticable to determine the toxic potential of a large number of chemicals in animal models, making the use of quantitative structure-toxicity relationship (QSTR) models an alternative strategy for toxicity prediction. Recently authors introduced a set of second-generation extended topochemical atom (ETA) indices for predictive modeling. Here authors have developed predictive toxicity models on a large dataset of 459 diverse chemicals against fathead minnow (*Pimephales promelas*) using the second-generation ETA indices. These descriptors can be easily calculated from two-dimensional molecular representation without the need of time-consuming conformational analysis and alignment, making the developed models easily reproducible. Considering the importance of hydrophobicity for toxicity prediction, AlogP98 was used as an additional predictor in all the models, which were validated rigorously using multiple strategies. The ETA models were comparable in predictability to those involving various non-ETA topological parameters and those previously reported using various descriptors including computationally demanding quantum-chemical ones.

First report on development of quantitative interspecies structure-carcinogenicity relationship models and exploring discriminatory features for rodent carcinogenicity of diverse organic chemicals using OECD guidelines.

[Kar S, Roy K. Chemosphere. 2012 Apr;87(4):339-55.]

Different regulatory agencies in food and drug administration and environmental protection worldwide are employing quantitative structure-activity relationship (QSAR) models to fill the data gaps related with properties of chemicals affecting the environment and human health. Carcinogenicity is a toxicity endpoint of major concern in recent times. Interspecies toxicity correlations may provide a tool for estimating sensitivity toward stoxic chemical exposure with known levels of uncertainty for a diversity of wildlife species. In this background, authors have developed quantitative interspecies structure-carcinogenicity correlation models for rat and mouse [rodent species according to the Organization for Economic Cooperation and Development (OECD) guidelines] based on the carcinogenic potential of 166 organic chemicals with wide diversity of molecular structures, spanning a large number of chemical classes and biological mechanisms. All the developed models have been assessed according to the OECD principles for the validation of QSAR models. Consensus predictions for carcinogenicity of the individual compounds are presented here for any one species when the data for the other species are available. Informative illustrations of the contributing structural fragments of chemicals which are responsible for specific carcinogenicity endpoints are identified by the developed models. The models have also been used to predict mouse carcinogenicities of 247 organic chemicals (for which rat carcinogenicities are present) and rat carcinogenicities of 150 chemicals (for which mouse carcinogenicities are present). Discriminatory features for rat and mouse carcinogenicity values have also been explored.

Identification of novel, less toxic PTP-LAR inhibitors using *in silico* strategies: pharmacophore modeling, SADMET-based virtual screening and docking.

[Ajay D, Sobhia ME. J Mol Model. 2012 Jan;18(1):187-201.]

Human leukocyte antigen-related (PTP-LAR) is a receptor-like trans-membrane phosphatase and a potential target for diabetes, obesity and cancer. In the present study, a sequence of *in silico* strategies (pharmacophore mapping, a 3D database searching, SADMET screening, and docking and toxicity studies) was performed to identify eight novel nontoxic PTP-LAR inhibitors. Twenty different pharmacophore hypotheses were generated using two methods; the best (hypothesis 2) consisted of three hydrogen-bond acceptor (A), one ring aromatic (R), and one hydrophobic aliphatic (Z) features. This hypothesis was used to screen molecules from several databases, such as Specs, IBS, MiniMaybridge, NCI, and an in-house PTP inhibitor database. In order to overcome the general bioavailability problem associated with phosphatases, the hits obtained were filtered by Lipinski's rule of five and SADMET properties and validated by molecular docking studies using the available crystal structure 1LAR. These docking studies suggested the ligand binding pattern and interactions required for LAR inhibition. The docking analysis also revealed that sulfonylurea derivatives with an isoquinoline or naphthalene scaffold represent potential LAR drugs. The screening protocol was further validated

using ligand pharmacophore mapping studies, which showed that the above mentioned interactions are indeed crucial and that the screened molecules can be presumed to possess potent inhibitory activities.

QSTR with extended topochemical atom (ETA) indices. 14. QSAR modeling of toxicity of aromatic aldehydes to *Tetrahymena pyriformis*.

[Roy K, Das RN. J Hazard Mater. 2010 Nov 15;183(1-3):913-22.]

Aldehydes are a toxic class of chemicals causing severe health hazards. In this background, quantitative structure-toxicity relationship (QSTR) models have been developed in the present study using Extended Topochemical Atom (ETA) indices for a large group of 77 aromatic aldehydes for their acute toxicity against the protozoan ciliate *Tetrahymena pyriformis*. The ETA models have been compared with those developed using various non-ETA topological indices. Attempt was also made to include the n-octanol/water partition coefficient (logK(o/w)) as an additional descriptor considering the importance of hydrophobicity in toxicity prediction. Thirty different models were developed using different chemometric tools. All the models have been validated using internal validation and external validation techniques. The statistical quality of the ETA models was found to be comparable to that of the non-ETA models. The ETA models have shown the important effects of steric bulk, lipophilicity, presence of electronegative atom containing substituents and functionality of the aldehydic oxygen to the toxicity of the aldehydes. The best ETA model (without using logK(o/w)) shows encouraging statistical quality (Q(int)(2) = 0.709, Q(ext) (2) = 0.744). It is interesting to note that some of the topological models reported here are better in statistical quality than previously reported models using quantum chemical descriptors.

Toxicity prediction of compounds from turmeric (*Curcuma longa L*).

[Balaji S, Chempakam B. Food Chem Toxicol. 2010 Oct;48(10):2951-9.]

Turmeric belongs to the ginger family Zingiberaceae. Currently, cheminformatics approaches are not employed in any of the spices to study the medicinal properties traditionally attributed to them. The aim of this study is to find the most efficacious molecule which does not have any toxic effects. In the present study, toxicity of 200 chemical compounds from turmeric were predicted (includes bacterial mutagenicity, rodent carcinogenicity and human hepatotoxicity). The study shows out of 200 compounds, 184 compounds were predicted as toxigenic, 136 compounds are mutagenic, 153 compounds are carcinogenic and 64 compounds are hepatotoxic. To cross validate the results, authors have chosen the popular curcumin and found that curcumin and its derivatives may cause dose dependent hepatotoxicity. The results of these studies indicate that, in contrast to curcumin, few other compounds in turmeric which are non-mutagenic, non-carcinogenic, non-hepatotoxic, and do not have any side-effects. Hence, the cost-effective approach presented in this paper could be used to filter toxic compounds from the drug discovery lifecycle.

Strategies for generating less toxic P-selectin inhibitors: pharmacophore modeling, virtual screening and counter pharmacophore screening to remove toxic hits.

[Ananthula RS, Ravikumar M, Pramod AB, Madala KK, Mahmood SK. J Mol Graph Model. 2008 Nov;27(4):546-57.]

This paper describes the generation of ligand-based as well as structure-based models and virtual screening of less toxic P-selectin receptor inhibitors. Ligand-based model, 3D-pharmacophore was generated using 27 quinoline salicylic acid compounds and is used to retrieve the actives of P-selectin. This model contains three hydrogen bond acceptors (HBA), two ring aromatics (RA) and one hydrophobic feature (HY). To remove the toxic hits from the screened molecules, a counter pharmacophore model was generated using inhibitors of dihydrooratate dehydrogenase (DHOD), an important enzyme involved in nucleic acid synthesis, whose inhibition leads to toxic effects. Structure-based models were generated by docking and scoring of inhibitors against P-selectin receptor, to remove the false positives committed by pharmacophore screening. The combination of these ligand-based and structure-based virtual screening models were used to screen a commercial database containing 538,000 compounds.

Computer-assisted methods in chemical toxicity prediction.

[Mohan CG, Gandhi T, Garg D, Shinde R. Mini Rev Med Chem. 2007 May;7(5):499-507.]

In silico predictive ADME/Tox screening of compounds is one of the hottest areas in drug discovery. To provide predictions of compound drug-like characteristics early in modern drug-discovery decision making, computational technologies have been widely accepted to develop rapid high throughput *in silico* ADMET analysis. It is widely perceived that the early screening of chemical entities can significantly reduce the expensive costs associated with late stage failures of drugs due to poor ADME/Tox properties. Drug toxic effects are broadly defined to include

toxicity, mutagenicity, carcinogenicity, teratogenicity, neurotoxicity and immunotoxicity. Toxicity prediction techniques and structure-activity relationships relies on the accurate estimation and representation of physico-chemical and toxicological properties. This review highlights some of the freely and commercially available softwares for toxicity predictions. The information content can be utilized as a guide for the scientists involved in the drug discovery arena.

Utilization of an amphipathic leucine zipper sequence to design antibacterial peptides with simultaneous modulation of toxic activity against human red blood cells.

[Ahmad A, Yadav SP, Asthana N, Mitra K, Srivastava SP, Ghosh JK. J Biol Chem. 2006 Aug 4;281(31):22029-38.]

The toxicity of naturally occurring or designed antimicrobial peptides is a major barrier for converting them into drugs. To synthesize antimicrobial peptides with reduced toxicity, several amphipathic peptides were designed based on the leucine zipper sequence. The first one was a leucine zipper peptide (LZP); in others, leucine residues at the a- and/or d-position were substituted with single or double alanine residues. The results showed that LZP and its analogs exhibited appreciable and similar antibacterial activity against the tested gram-positive and gram-negative bacteria. However, the substitution of alanine progressively lowered the toxicity of LZP against human red blood cells (hRBCs). The substitution of leucine with alanine impaired the binding and localization of LZP to hRBCs, but had little effect on the peptide-induced damage of *Escherichia coli* cells. Although LZP and its analogs exhibited similar permeability, secondary structures, and localization in negatively charged membranes, significant differences were observed among these peptides in zwitterionic membranes. The results suggest a novel approach for designing antibacterial peptides with modulation of toxicity against hRBCs by employing the leucine zipper sequence. Also, to the best of our knowledge, the results demonstrate that this sequence could be utilized to design novel cell-selective molecules for the first time.

Quantitative structure-activity relationships based on functional and structural characteristics of organic compounds.

[Kulkarni SA, Raje DV, Chakrabarti T. SAR QSAR Environ Res. 2001;12(6):565-91.]

In the present quantitative structure-activity relationship (QSAR) modeling, organic compounds, including priority pollutants, have been considered and classified based on their functional and structural characteristics. Five physico-chemical characteristics have been used to develop a QSAR model for *Pimephales promelas*, by means of multiple regression analysis. Collinearity diagnostics was carried out using two different approaches based on condition index and K correlation index. The outlier analysis was carried out using the variable subsets obtained through both the approaches. An attempt has been made to justify the deletion of outliers in each group referring to their physico-chemical characteristics. The expressions obtained by using both approaches provide almost the same prediction accuracy, however, the latter approach resulted in expressions with reduced number of molecular descriptors. The QSARs obtained through this exercise would certainly assist in designing environment-friendly molecules with lower toxicity.

Prooxidant and antioxidant activities of bilirubin and its metabolic precursor biliverdin: a structure-activity study.

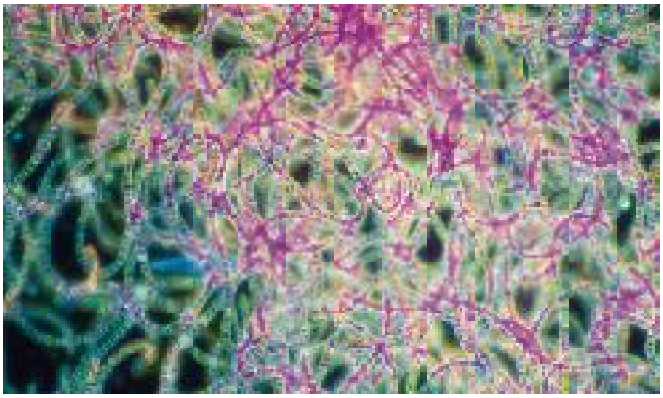
[Asad SF, Singh S, Ahmad A, Khan NU, Hadi SM. Chem Biol Interact. 2001 Jul 31;137(1):59-74.]

Bilirubin, which is derived from its metabolic precursor biliverdin, is the end product of heme catabolism. It has been proposed as a physiological antioxidant present in human extracellular fluids. Authors have earlier shown that bilirubin in the presence of the transition metal ion Cu(II) causes strand cleavage in DNA through generation of reactive oxygen species, particularly the hydroxyl radical. Thus bilirubin possesses both antioxidant and prooxidant properties. In order to understand the chemical basis of various biological properties of bilirubin, authors have studied the structure-activity relationship between bilirubin and its precursor biliverdin. The latter has also been reported to possess both antioxidant and toxic properties. In the present studies bilirubin was found to be more effective in the DNA cleavage reaction and a more efficient reducer of Cu(II). The rate of formation of hydrogen peroxide and hydroxyl radicals by the compounds also showed a similar pattern. The relative antioxidant activity was also examined by studying the effect of these compounds on DNA cleavage by a hydroxyl radical generating system and their quenching effect on hydroxyl radicals. The results indicate that bilirubin is more active both as an antioxidant as well as an oxidative DNA cleaving agent. A model for binding of copper to bilirubin has been proposed where two copper ions are bound to two molecules of bilirubin through their terminal pyrrole nitrogens. In order to account for the enhanced copper reducing capacity of bilirubin authors have further proposed that an additional copper binding site is provided for in the case of bilirubin due to the absence of a double bond between pyrrole rings II and III. Further it would appear that the structural features of the bilirubin molecule which are important for its prooxidant action are also the ones that render it a more effective antioxidant.

RESEARCH DIGEST

Do cyanobacteria contribute to neurodegenerative disease?

Environ Health Perspect 120:a110-a116



In the late 1990s ethnobotanist Paul Alan Cox visited the indigenous Chamorro people of Guam, sleuthing for cancer cures in the lush rainforest. He soon stumbled upon troubling facts that would change the trajectory of his career, leading to major clues in understanding Lou Gehrig's disease (amyotrophic lateral sclerosis, or ALS) and possibly other neurodegenerative diseases. Since that time, major breakthroughs in the fields of neurobiology, epidemiology, and ecology have led to an increased interest in an unlikely hypothesis: that β-methylamino-L-alanine (BMAA)—a cyanobacterial neurotoxin found in contaminated seafood and shellfish, drinking water supplies, and recreational waters—may be a major factor in these diseases.

CT scans: balancing health risks and medical benefits.

Environ Health Perspect 120:a118-a121

Computed tomography (CT) has been a boon for medical care. By generating detailed anatomical pictures, the technology can improve diagnoses, limit unneeded medical procedures, and enhance treatment. However, CT scans also dose patients with ionizing radiation, a known human carcinogen, posing a potential downside for public health. Mounting health worries over radiation risks are now driving efforts to limit avoidable CT scans and to reduce radiation doses where possible. "There's a national focus on this issue right now," says Marilyn Goske, a professor of radiology at Cincinnati Children's Hospital Medical Center and chairwoman of the Image Gently campaign, a pediatric

education and awareness campaign from the Alliance for Radiation Safety in Pediatric Imaging. In December 2011 the Institute of Medicine (IOM) published a report concluding that ionizing radiation contributes more to the development of breast cancer than any other type of routine environmental exposure. About half the U.S. annual exposure to ionizing radiation comes from natural sources, including cosmic rays, but most of the rest comes from medical imaging and from CT scans in particular. The IOM cited research by Amy Berrington de González, a senior investigator in the Radiation Epidemiology Branch of the National Cancer Institute (NCI), whose calculations suggest that the CT scans performed in the United States in 2007 might produce up to 29,000 cancers in the future, about 6% of them in the breast and the remainder in the lungs, brain, and other organs. But the spotlight on CT safety has also drawn a backlash from those who say the risks are overblown. On 13 December 2011 the American Association of Physicists in Medicine (AAPM) issued a statement claiming that risks from CT imaging are "too low to be detectible and may be non-existent." The AAPM added that "speculative predictions about cancer incidence and death" should be discouraged because they generate sensationalist media coverage that deters some patients who need CT scans from having them. Donald Miller, acting chief of the Diagnostic Devices Branch of the U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health, cites 2 basic principles for decreasing CT radiation risks. One is justification, which refers to prescribing a CT exam only when it is medically necessary. The other is optimization, which refers to adjusting and operating a CT scanner so that images adequate for diagnosis are obtained at the lowest possible dose. Justification is more difficult to address, Miller says, because it involves case-by-case decisions made by

individual clinicians. More attention has been paid to optimization, he says, but both principles are equally important.

Air pollution exposure intervention and cardiovascular health

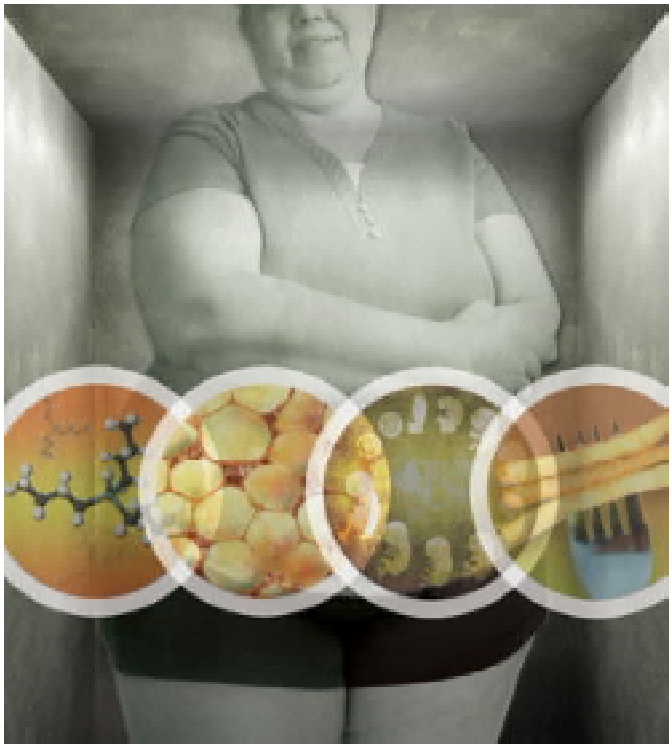
Environ Health Perspect 120:367-372.

Exposure to air pollution is associated with increased cardio-vascular morbidity and mortality. However, few studies have examined the potential benefits of reducing personal exposure to urban air pollution in patients with coronary heart disease. Langrish et al. conducted an open randomized crossover trial study of 98 patients with coronary heart disease. The participants walked a predefined route in central Beijing, China, on two occasions, once while wearing a face mask and once without the mask. Symptoms, movement, personal air pollution exposure, blood pressure, heart rate, and 12-lead electro-cardiography were monitored throughout the 24-hr study period. Fine particulate matter [0.18–2.5 µm in aero-dynamic diameter (PM2.5)] and ultrafine PM [< 0.18 µm] were present at high levels (74 µg/m^3 for PM2.5). Consistent with traffic-derived sources, this PM contained organic carbon and polycyclic aromatic hydrocarbons and was highly oxidizing. Using the face mask was associated with decreased self-reported symptoms and reduced maximal ST segment depression during the 24-hr period. In addition, mean arterial pressure was lower and heart rate variability increased during the prescribed walk. The mask did not appear to influence heart rate or energy expenditure. The authors conclude that reducing personal exposure to air pollution using a face mask may reduce symptoms and improve a range of cardio-vascular health measures in patients with coronary heart disease.

Obesogens: an environmental link to obesity

Environ Health Perspect 120:a62-a68.

Obesity has risen steadily in the United States over the past 150 years, with a marked uptick in recent decades. In the United States today more than 35% of adults and nearly 17% of children aged 2–19 years are obese. Obesity plagues people not just in the United States but worldwide, including, increasingly, developing countries. Even animals—pets, laboratory animals, and urban rats—have experienced increases in average body weight over the past several decades, trends not necessarily explained by diet and exercise. In the words of Robert H. Lustig, a professor of clinical pediatrics at the University of California, San Francisco, "Even those at the lower end of the BMI [body mass index] curve are gaining weight. Whatever is



happening is happening to everyone, suggesting an environmental trigger." Many in the medical and exercise physiology communities remain wedded to poor diet and lack of exercise as the sole causes of obesity. However, researchers are gathering convincing evidence of chemical "obesogens"—dietary, pharmaceutical, and industrial compounds that may alter metabolic processes and predispose some people to gain weight.

Extra heat waves could kill 150,000 Americans by 2099

http://www.newscientist.com/article/dn21862-extra-heatwaves-could-kill-150000-americans-by-2099.html

The US could end up as full of hot air as the politicians skeptical of climate change. By the end of the century, heat waves caused by global warming could kill 150,000 people who would otherwise live. A report by the US Natural Resources Defense Council (NRDC) estimates how many extreme heat events will hit the US this century, assuming greenhouse gas emissions continue on their current path. Climate models suggest that by 2099 the 40 most populous cities will have approximately eight times as many days of extreme heat per year as today. About 1330 Americans die each year from extreme heat events. That figure will rise to about 4600 by 2099, giving a total of more than 150,000 extra deaths by the end of the century. The figure may actually be an underestimate, because the US

population is ageing and older people are more vulnerable to heat. Louisville in Kentucky will be the worst affected city, with an extra 19,000 deaths by 2099. The European heat wave of 2003 killed 35,000 people, so the report's estimate is "not unrealistic", says Andreas Sterl of the Royal Netherlands Meteorological Institute in De Bilt. Cities can use forecasting systems to warn people of imminent heat waves and protect at-risk residents, says the NRDC's climate and clean air campaign director Peter Altman. "But no preventive measures can keep up with the added risk due to rising temperatures, so the other solution is to reduce the pollution driving climate change." This March was the warmest on record for the lower 48 states, and temperatures continue to be high, according to the National Oceanic and Atmospheric Administration's National Climatic Data Center.

Earthquake triggering and large-scale geologic storage of carbon dioxide

PNAS June 26, 2012 vol. 109 no. 26 10164-10168

Despite its enormous cost, large-scale carbon capture and storage (CCS) is considered a viable strategy for significantly reducing CO_2 emissions associated with coal-based electrical power generation and other industrial sources of CO_2 [Intergovernmental Panel on Climate Change (2005) IPCC Special Report on Carbon Dioxide Capture and Storage. Prepared by Working Group III of the Intergovernmental Panel on Climate Change, eds Metz B, et al. (Cambridge Univ Press, Cambridge, UK); Szulczewski ML, et al. (2012) Proc Natl Acad Sci USA 109:5185–5189]. Authors argue here that there is a high probability that earthquakes will be triggered by injection of large volumes of CO_2 into the brittle rocks commonly found in continental interiors. Because even small- to moderate-sized earthquakes threaten the seal integrity of CO_2 repositories, in this context, large-scale CCS is a risky and likely unsuccessful, strategy for significantly reducing greenhouse gas emissions.

Arsenic-transformed malignant prostate epithelia can convert noncontiguous normal stem cells into an oncogenic phenotype

Environ Health Perspect 120:865-871.

Cancer stem cells (CSCs) are likely critical to carcinogenesis, and, like normal stem cells (NSCs), are affected by micro environmental factors. Malignant cells release extracellular factors, modifying tumor behavior. Inorganic arsenic, a human carcinogen, is associated with an overproduction of CSCs in various model systems of carcinogenesis. Authors aimed to determine if NSCs are influenced by nearby arsenic-transformed malignant epithelial cells (MECs) as a possible factor in arsenic-associated CSC overabundance. Transwell noncontact co-culture allowed the study of the effects of non-contiguous, arsenic-transformed prostate MECs on the isogenic human prostate NSC line, WPE-stem. Cancer phenotype was assessed by evaluating secreted matrix metalloproteinases (MMPs), invasiveness, colony formation, and spheroid formation. Gene expression was assessed at the protein (Western blot) or mRNA (real-time reverse transcription–polymerase chain reaction) levels. Noncontact co-culture of MECs and NSCs rapidly (= 3 weeks) caused hypersecretion of MMPs and marked suppression of the tumor suppressor gene PTEN in NSCs. NSCs co-cultured with MECs also showed increased invasiveness and clonogenicity and formed more free-floating spheroids and highly branched ductal-like structures in Matrigel, all typical for CSCs. MEC co-culture caused dysregulated self-renewal and differentiation-related gene expression patterns and epithelial-to-mesenchymal transition in NSCs consistent with an acquired cancer phenotype. Interleukin-6 (IL-6), a cytokine involved in tumor microenvironment control, was hypersecreted by MECs, and IL-6 exposure of NSCs resulted in the duplication of several responses in NSCs of conversion to CSCs via MEC co-culture (e.g., MMP hypersecretion, decreased PTEN). Thus it can be concluded that arsenic-transformed MECs recruit nearby NSCs into a cancer phenotype, thereby potentially increasing CSC number. This may be a factor in arsenic-induced CSC overabundance seen in multiple model systems.

Potential for inhalation exposure to engineered nanoparticles from nanotechnology-based cosmetic powders

Environ Health Perspect 120:885–892 (2012).

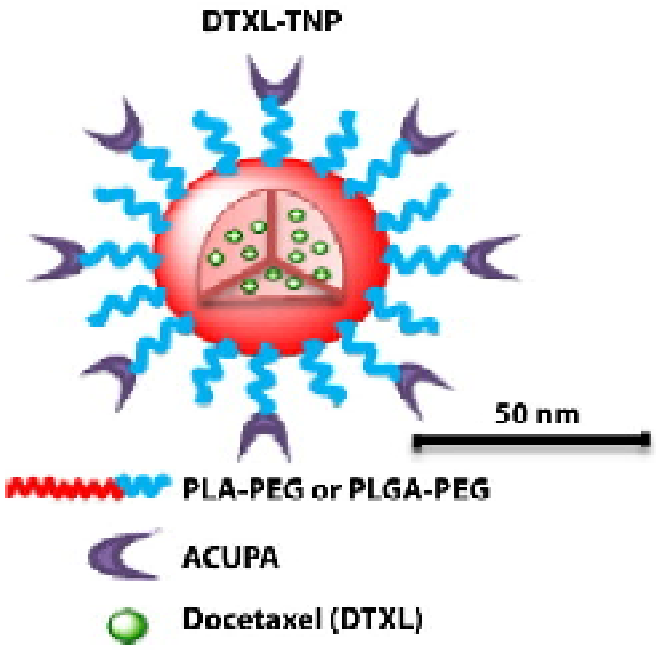
The market of nanotechnology-based consumer products is rapidly expanding, and the lack of scientific evidence describing the accompanying exposure and health risks stalls the discussion regarding its guidance and regulation. Authors investigated the potential for human contact and inhalation exposure to nanomaterials when using nanotechnology-based cosmetic powders and compare them with analogous products not marketed as nanotechnology based. Authors characterized the products using transmission electron microscopy (TEM) and laser diffraction spectroscopy and found nanoparticles in five of six tested products. TEM photomicrographs showed highly agglomerated states of nanoparticles in the products. Authors realistically simulated the use of cosmetic powders by applying them to the face of a human mannequin head while simultaneously sampling the released airborne

particles through the ports installed in the mannequin's nostrils. Authors found that a user would be exposed to nanomaterial predominantly through nanoparticle-containing agglomerates larger than the 1–100-nm aerosol fraction. Predominant deposition of nanomaterial(s) will occur in the tracheobronchial and head airways—not in the alveolar region as would be expected based on the size of primary nanoparticles. This could potentially lead to different health effects than expected based on the current understanding of nanoparticle behavior and toxicology studies for the alveolar region.

Programmable nanoparticles improve chemotherapy's aim

Science Now 4 April 2012

Chemotherapy drugs are like a shotgun. Even though doctors are just aiming for tumors, the compounds hit a variety of other places in the body, leading to side effects like bone marrow damage and hair loss. To improve their aim, researchers have tried to package these drugs inside tiny hollow nano-sized containers that can be directed toward tumors and bypass healthy tissues. But the size, shape, and makeup of these "nanoparticles" can drastically affect where and when they are taken up. Now, scientists have surveyed the landscape of some 100 different nanoparticle formulations and shown that when a conventional chemotherapeutic drug is packaged inside the best of these nanoparticles, it proves considerably more effective at fighting prostate cancer in animals than the drug alone. The new results aren't the first to show the promise of nanoparticle therapeutics against cancer. Nearly a dozen of these tiny drug carriers are already in clinical trials. But researchers are still struggling to sort out the size and makeup of nanoparticles that work best for ferrying drugs to tumors. So for their current study, a team of 30 researchers led by chemical engineer Robert Langer at the Massachusetts Institute of Technology in Cambridge, physician-scientist Omid Farokhzad of Harvard Medical School, and biochemical engineer Stephen Zale of BIND Biosciences in Cambridge, Massachusetts, decided to take a more systematic approach. Rather than looking at all types of biomaterials from which to make their particles, the researchers started with six different materials already approved for use by the U.S. Food and Drug Administration, as well as an already-approved anticancer cargo compound called docetaxel. They then varied 10 different factors, including the size of the particles in which they trapped docetaxel, the density of chemical groups used to shroud the particles from the immune system, additional surface compounds used to target the particles to tumor cells of interest, the amount of docetaxel they carried, and how fast the particles decomposed and released their cargo. After a preliminary evaluation of more than 100 different nanoparticle drug formulations, Langer and his colleagues settled on a design containing 100-nanometer particles made from a combination of a biodegradable polymer known as PLA and a coating of PEG, another polymer that readily binds water molecules and helps hide the particles from the immune system. Some of the PEG chains were also capped with copies of a small molecule called ACUPA that binds to receptor molecules over expressed on the surface of prostate cancer cells. Tests on mice, rats, and monkeys showed that delivering docetaxel in nanoparticles produced plasma concentrations of the drug over a 24-hour period 100 times as high as standard docetaxel injections did; 10 times as much of the drug accumulated in tumors, as well. And in an early clinical safety trial on 17 people, the researchers found drug accumulation in tumors and clinical effects at doses as low as 20% of the normally prescribed docetaxel dose, as they report in *Science Translational Medicine*. Additional clinical trials are now testing increased doses, and no new toxicities have been observed to date. "It's an important result, and a terrific direction to go in," says Joseph DeSimone, a chemist and nanoparticle drug expert at the University of North Carolina, Chapel Hill. The study shows that delivering drugs inside nanoparticles has the potential to improve the effectiveness of many conventional cancer drugs and other therapeutics that are limited by their side effects, he says: "When you change where drugs deposit, you fundamentally change the outcome."



Climate combat could turn sky white

Science NOw 1 June 2012

Talk about a vanilla sky. A scheme that would add light-colored, highly reflective particles to the atmosphere to reflect sunlight and cool the planet would significantly whiten the heavens, a new study suggests. Researchers analyzed the effect of adding enough aerosols to block 2% of the sun's light from reaching the ground, the amount needed to offset a carbon dioxide concentration twice that found in the air before the Industrial Revolution. (The approach is one of a series of so-called geoengineering efforts to tinker with the planet to mitigate the effects of climate change.) Depending on the size of the particles injected into the atmosphere, which would likely range between 0.7 and 0.9 micrometers in diameter, the aerosols' light-scattering effect would render the sky between three and five times brighter than it is now, the researchers report in *Geophysical Research Letters*. Most infrared wavelengths outbound from Earth wouldn't be strongly scattered by aerosols this size, so the particles wouldn't effectively trap heat in the atmosphere. But in visible wavelengths, the particles would tend to scatter more red light than blue,

rendering the heavens whiter—in essence, giving the deep-blue sky now seen in remote areas such as Utah's Arches National Park (shown) the same hazy appearance often found in urban areas. Other side effects would include redder sunsets and brighter glows in the sky just after sunset—the same sort of phenomena seen after large volcanic eruptions, which spew large amounts of geological aerosols high into the atmosphere until natural processes clear the air.

Is cadmium the new lead? Link reported between the ubiquitous metal and kids with learning disabilities.

Environmental Health News
February 10, 2012

It's a heavy metal. It's linked to learning problems in school children. And every child is exposed. Sounds like lead? It's cadmium. Signs are emerging that cadmium – a widespread contaminant that gets little attention from health experts and regulators – could be the new lead. Children with higher cadmium levels are three times more likely to have learning disabilities and participate in special education, according to a new study led by Harvard University researchers. Absorbed from the soil, cadmium is found in certain foods, particularly potatoes, grains, sunflower seeds and leafy greens, as well as tobacco. It also has been discovered in some inexpensive children's jewelry, prompting new voluntary industry standards last fall. Dr. Robert Wright, the study's senior author, emphasized that the links to learning disabilities and special education were found at commonplace levels previously thought to be benign. "One of the important points of the study is that we didn't study a population of kids who had very high exposures. We studied a population representative of the U.S. That we found any [effect] suggests this is occurring at relatively low levels," said Wright, an associate professor of pediatrics and environmental health at Harvard. Scientists said the new findings are a sign that cadmium could have dangerous properties similar to lead that alter the way children's brains develop. More research is necessary, though, to confirm and refine the potential effects on kids. "It does certainly point to the fact that we need more attention paid to the neurotoxic effects of cadmium in children," Wright said. Until now, the nervous system has not received much attention as a target for cadmium. Some studies of adult workers, however, have shown that high exposures can trigger neurological problems, and small, earlier studies of children found links to mental retardation and decreased IQs. The new study is the largest to look at connections between cadmium in urine and neurological effects, and the only one that has used a national group of children.

"Collectively, the studies are very consistent. They provide fairly substantial support that cadmium is a neurotoxin," said Dr. Bruce Lanphear, a pediatrician and epidemiologist at Simon Fraser University who was a co-author of the study. Lanphear, one of the world's leading experts on the effects of lead in children, added that "the pattern we're seeing here with cadmium is very consistent with what we see with other toxicants," including lead and mercury. The two scientists recommended that government re-examine its standards and guidelines for cadmium in food, soil, workplaces and consumer products to consider the effects on children's brains. Current regulations for cadmium are based on threats to adults, and the kidneys have been considered the most sensitive organ to its toxic effects. Classified as a known human carcinogen, it is linked to lung, kidney and prostate cancer in workers. "We've got a large new national study showing a threefold increase [in children's learning disabilities and special education]. But I wouldn't go so far to say we definitely need to lower regulatory levels. It deserves to be re-evaluated, though," said Lanphear.

Of the 2,199 children between the ages of 6 and 15 included in the new study, 12.6 percent had a learning disability and 10.5 percent were enrolled in special education classes, according to the study, published online in Environmental Health Perspectives last month. The children were not tested for disabilities; instead it was reported by their parents on a questionnaire that is part of the National Health and Nutrition Examination Study. For those with the highest cadmium levels, the odds of having a learning disability were 3.21 times higher than for the children with the lowest exposures. For special education, the odds were 3 times higher. No association was found with attention deficit hyperactivity disorders. "The three times higher risk is high for such low cadmium levels," said Aimin Chen, an assistant professor of environmental health at University of Cincinnati's College of Medicine. He was not associated with the study. But Chen said the link at this point is preliminary because researchers have not yet looked for any specific, more definitive neurological effects, such as reduced IQs, memories or vocabularies — outcomes already linked to two other toxic metals, lead and mercury. The connection to both learning disabilities and special education could indicate cadmium has an array of effects on a child's brain just like lead does. Those two outcomes "are actually a mixture of different brain function problems," Chen said.

Lead has been studied and regulated for many decades, leading to evidence that it reduces children's IQs at low concentrations and contributes to attention disorders and even violent behaviors. Since cadmium is also a heavy metal, it might have similar effects on the brain, say scientists. One big difference turned up in the new study: No link was found between cadmium and attention deficit disorders. "It stands out because one thing we've found fairly consistently with lead, tobacco and others is that it seems that some of these contaminants might increase the risk for ADHD," Lanphear said. That could be a sign that cadmium is working on a different part of the brain, not the prefrontal cortex. Another big mystery is the source of the cadmium in the kids. Cadmium stays in the body for long periods, so the tests measured amounts the children were exposed to over years. Cadmium is in tobacco smoke, but surprisingly, concentrations in the kids were similar whether they lived with smokers or not. That 'might mean for most kids [secondhand] smoking was not a major source," Wright said. An abundant element in the Earth's crust, cadmium is found naturally in soil in some parts of the country. But it also is released by battery manufacturers, smelters, electroplating plants and other industries. It is one of the top chemicals reported in Superfund sites, found in virtually all of them, according to a Centers for Disease Control and Prevention document. Some crops, including tobacco plants and leafy greens, easily absorb cadmium from the soil. A map by the U.S. Geological Survey shows cadmium hot spots in ground water in California's Central Valley, where most of the nation's lettuce and spinach is grown.

Leafy greens are among crops that easily absorb cadmium.

Renee Gardner, a postdoctoral fellow at Sweden's Karolinska Institutet who studies heavy metals, said "the most important source of exposure is food. Green leafy vegetables and grains are the biggest sources, though most plant foods have some cadmium in them." Since these foods are important nutritionally, they shouldn't be avoided. But Gardner said that iron helps prevent absorption of cadmium, so parents worried about exposure should ensure their kids have adequate iron in their foods. Some children may have been exposed through inexpensive jewelry. In 2010, the Associated Press tested children's jewelry manufactured in China and found cadmium, prompting recalls by stores. Cadmium was being used to replace lead. Last fall, the Consumer Product Safety Commission considered standards, but backed off when the industry set its own voluntary testing procedures and limits for cadmium in children's jewelry. California set its own standards. Lanphear said for most children, jewelry probably isn't responsible for the cadmium in their bodies. "But for some kids, those kids that swallow it, it's an extraordinarily important source," he said. It also can enter the body by mouthing the jewelry.

Saying the voluntary standards don't go far enough, Wright recommended that cadmium be removed from all jewelry and other children's products. "It's very concerning to me that cadmium can be found in a children's product," Wright said. "Even if one child in a million is exposed that's one child too many." The jewelry is an example of how one dangerous substance often replaces another, Lanphear said.

"Perhaps the biggest failure is to fail to learn the lesson of the lead pandemic, that environmental chemicals and metals have the potential to be toxic, so in the end they shouldn't be treated any differently than drugs. They shouldn't be used unless proven safe," he said.

FORTHCOMING EVENTS

The **XXXII Annual Meeting of Society of Toxicology (STOX), India** will be held under the Chairmanship of Dr. K.C. Gupta, Director, CSIR-Indian Institute of Toxicology Research, Lucknow during December 5-7, 2012. The Theme of the conference is **New Paradigms in Toxicology**.

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International Symposium on Advances in Free Radicals, Redox Signalling and Translational Antioxidant Research will be held under the Chairmanship of Dr. K.C. Gupta, Director, CSIR-Indian Institute of Toxicology Research, Lucknow during January 30-February 01, 2013.

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हिंदी भाषा खंड

मामूली ब्लड टेस्ट से स्तन कैंसर का पता लगाना संभव

ब्लड टेस्ट से यह भी जाना जा सकता है कि मरीज को इलाज के बाद क्या यह बीमारी दोबारा हो सकती है या उसकी मौत हो सकती है। यूनिवर्सिटी ऑफ टैक्सास के एमडी एंडर्सन कैंसर सेंट के अनुसंधानकर्ताओं की ओर से किया गया यह अध्ययन उस पुराने काम पर आधारित है जिसमें स्तन कैंसर मेटास्टैटिक के मरीजों के खून में प्रवाहित हो रही ट्यूमर कोशिकाओं की पहचान की गई थी। वैज्ञानिकों के अनुसार, आमतौर पर अब तक माना जाता रहा है कि कैंसर के ट्यूमर रक्त प्रवाह से नहीं बल्कि लिम्फैटिक सिस्टम के जरिये फैलते हैं। इस प्रकार पूर्व का अनुसंधान कैंसर का पता लगाने के तरीकों से हट कर था। ''द लैन्सेट ओन्कोलॉजी'' जर्नल में यह

अध्ययन प्रकाशित हुआ है। अनुसंधानकर्ताओं के अनुसार रक्त में एक या अधिक 'सरकुलेटिग ट्युमर सेल' (सीटीसीएस) की मौजूदगी बता सकती है कि क्या बीमारी की जल्द ही पुनरावृत्ति होगी और मरीज के बचने की उम्मीद कितनी कम है। सर्जिकल ओकोलॉजी विभाग के प्रो एंथनी ल्यूसी की अगुवाई में टैक्सास के दल ने यह जांच की कि क्या सीटीसीएस स्तन कैंसर की शुरूआती अवस्था में मरीज के रक्त में पाई जाती हैं जब कैंसर अपने मूल स्थान (नॉन मेटास्टैटिक) से अलग न फैला हो। अध्ययन दल ने यह परीक्षण उन 302 मरीजों पर किया जिनका इस सेंटर में फरवरी 2005 से दिसंबर 2010 तक इलाज चला था। अनुसंधानकर्ताओं ने 24 फीसदी मरीजों के खून में सीटीसीएस की पहचानकी। उन्होंने यह भी पाया कि सीटीसीएस की मौजूदगी ने साफ-साफ बताया कि क्या बीमारी की जल्द ही पुनरावृत्ति होगी और मरीज के बचने की उम्मीद कितनी कम है। कुल 15 फीसीद मरीज सीटीएस'एस की पुनरावृत्ति के लिए पॉजिटिव पाए गए और दस फीसदी की फरवरी 2005 से दिसंबर 2010 के बीच हुए अध्ययन के दौरान मौत हो गई। जिन मरीजों में सीटीसी'एस नहीं पाया गया उनमें से तीन फीसदी मरीजों को दोबारा बीमारी हुई और दो फीसदी की मौती हो गई। अनुसंधानकर्ताओं के अनुसार, जिन मरीजों के खून में सीटीएस'एस अधिक पाई गई उनमें से 31 फीसदी की अध्ययन के दौरान या तो मौत हो गई या उन्हें फिर से यह बीमारी हो गई। इस खोज से यह उम्मीद जगी है कि भविष्य में ब्लड टेस्ट की मदद से स्तन कैंसर और इसके इलाज का शुरूआती अवस्था में पता लगाया जा सकता है।

दी लांसेट ओंकोलोगी, वोलूम 13, इसु 7, पेज 688-695, जुलाई 2012
doi:10.1016/S1470-2045(12)70209-7

हल्दी बचा सकती है दिल के दौरे से

थाईलैंड में हुए एक अध्ययन से संकेत मिले हैं कि बायपास सर्जरी कराने वाले हृदय रोगियों के लिए हल्दी बहुत फायदेमंद साबित हो सकती है और दिल के दौरे से बचा सकती है। बायपास सर्जरी के दौरान रक्त प्रवाह की कमी के चलते हृदय की मांसपेशियों को नुकसान हो सकता है, जिससे मरीज को दिल का दौरा पड़ने की आशंका बढ़ जाती है। हल्दी में कई ऐसे तत्व पाए जाते हैं जो इन खतरों का मुकाबला करने में मददगार साबित होते हैं। समाचार एजेंसी रॉयटर्स के अनुसार अमरीका के ह्यूस्टन में स्थित एंडरसन कैंसर रिसर्च सेंटर के भरत अग्रवाल ने इसे बहुत ही उत्साहजनक शोध बताया है। यह शोध थाईलैंड के चियांग माई विश्वविद्यालय में

हुआ जिसमें 2009 से 2011 के बीच बाइपास सर्जरी कराने वाले 121 लोगों ने हिस्सा लिया। इनमें से आधे लोगों को दिन मे ंचार बार एक ग्राम हल्दी के तत्व से बने कैप्सूल दिए गए जबकि बाकी लोगों को दूसरे कैप्सूल दिए गए। ये कैप्सूल सर्जरी होने से तीन दिन पहले और सर्जरी होने के पांच दिन बाद तक दिए गए। 'अमेरिकन जनरल ऑफ कार्डियोलॉजी' में छपे इस शोध के नतीजों के मुताबिक ऑपरेशन के बाद अस्पताल में रहने के दौरान हल्दी का कैप्सूल लेने वालों में दिल का दौरान पड़ने की आशंका 13 प्रतिशत थी जबकि दूसरे कैप्सूल लेने वालों में यह आशंका 30 प्रतिशत के आसपास पाई गई। यह शोध करने वाले टीम के प्रमुख डॉक्टर वारवारंग वांगचेरोन का कहना है कि हल्दी से बने कैप्सूल लेने वालों में दिल के दौरे का खतरा 65 फीसदी कम पाया गया। हालांकि यह शोध हृदय रोगियों के छोटे से समूह पर किया गया और जानकारों का मानना है कि अभी और व्यापक शोध करने होंगे।

अमेरिकन जौर्नल ऑफ कार्दिओलोगी वोलूम 110, इसु 1, पेज 40-44, जुलाई 2012
doi:10.1016/j.amjcard.2012.02.043

कैल्शियम की दवा से पड़ सकता है दिल का दौरा

जर्मनी में कुछ शोधकर्ताओं का कहना है कि जो लोग कैल्शियम के लिए अलग से दवा लेते हैं उन्हें दिल का दौरा पड़ने का ज्यादा खतरा होता है। हार्ट नाम की पत्रिका में निकले शोध में कहा है कि कैल्शियम सप्लीमेंट सावधानी से लेने चाहिए। विशेषज्ञों का मानना है

कि इसके बजाए संतुलित आहार खाना बेहतर तरीका होगा खासकर जिसमें कैल्शियम शामिल हो। जर्मन कैंसर रिसर्च सेंटर के शोध कर्ताओं ने एक दशक से भी जयादा समय तक 23980 लोगों का अध्ययन किया है। उन्होंने अतिरिक्त कैल्शियम दवा लेने वाले ऐसे लोगों में दिल का दौरा पड़ने की घटनाओं की तुलना उन लोगों से की है जो ये दवाएँ नहीं लेते।

जिन लोगों ने कोई सप्लीमेंट नहीं लिया उन 15959 लोगों में से 851 को हार्ट अटैक हुआ। लेकिन अध्ययन के दौरान पाया गया कि कैल्शियम के लिए दवा लेने वाले लोगों में दिल का दौरा पड़ने के आसार 86 फीसदी ज्यादा हैं। वहीं द हेल्थ सप्लीमेंट इनफोरमेशन सर्विस के डॉक्टर केरी रक्सटन कहते हैं, ''महिलाओं में ऑस्टियोपोरोसिस बड़ी समस्या है। ये गैर जिम्मेदारना है कि एक सर्वे के आधार पर डॉक्टर महिलाओं से कहें कि वे अतिरिक्त कैल्शियम न लें। खासकर तब जब कैल्शियम, विटामिन डी और हड्डियों के बीच संबंध को यूरोपीय खाद्य सुरक्षा अथॉरिटी भी मानती है। ब्रिटिश हार्ट फाउंडेशन में वरिष्ठ नर्स नताशा स्टीवर्ट कहती हैं कि नया शोध ये संकेत देता है कि कैल्शियम सप्लीमेंट लेने वालों में दिल का दौरा पड़ने के आसार ज्यादा हो सकते हैं लेकिन इस मतलब ये नहीं है कि इन्हीं के कारण दिल का दौरा पड़ता है। वे मानती हैं कि इस बारे में और शोध करने की जरूरत है। वहीं ब्रिटेन के स्वास्थ्य विभाग के प्रवक्ता ने कहा कि ज्यादातर लोगों को कैल्शियम की दवा लेने की जरूरत नहीं होती अगर वे संतुलित भोजन खाएं जिसमें दूध, डेयरी उत्पाद शामिल हैं।

हार्ट, वोलूम 98, पेज 920-925, जुलाई 2012
doi: 10.1136/ heartjnl-2011-30 1345

डीजल के धुएं से होता है कैंसरः डब्ल्यूएचओ

खदानों और रेलवे में काम करने वालों व ट्रक ड्राइवरों पर शोध के आधार पर इन विशेषज्ञों ने पाया कि यह धुंआ यकीनी तौर पर फेफड़े को कैंसर देता है। विशेषज्ञों के इस पैनल ने आम आदमी को डीजल के धुएं से बचने की सलाह दी है। हालांकि इससे पहले संस्था ने डीजल के धुएं को महज कैंसरकारी तत्व बताया था। लेकिन आईएआरसी का अब मानना है कि इस धुएं से यकीनी तौर पर कैंसर होता है। हालांकि आईएआरसी ने यह नहीं बताया कि इससे कैंसर के खतरे का लेबल क्या है। ऐसा माना जाता है कि जोखिम भरे उद्योगों में काम करने वाले लोगों में फेफड़े का कैंसर विकसित

होने का खतरा 40 फीसदी बढ़ जाता है। आईएआरसी की इस शोध की अगुआई करने वाले डॉक्टर क्रिस्टोफर पोरटियर का कहना था, ''इस बात के वैज्ञानिक दस्तावेज मौजूद हैं और सभी इस राय से सहमत हैं कि डीजल के धुएं से इंसानों के फेफड़ों में कैंसर होता है।'' उन्होंने कहा, ''इंसारी सेहत पर इसके बुरे प्रभाव को देखते हुए पूरी दुनिया में डीजल के धुएं को कम किया जाना चाहिए।'' हालांकि अभी यह साफ नहीं है कि जो लोग थोड़े समय के लिए या कभी कभार डीजल के धुएं के संपर्क में आते हैं, उनमें कैंसर का खतरा कितना होता है। वैसे आईएआरसी के ही एक दूसरे वैज्ञानिक कर्ट स्ट्रायफ ने कहा कि जो धुएं के ज्यादा संपर्क में आते हैं, उनके चपेट में आने का खतरा ज्यादा होता जबकि कम वालों में यह कम होता है।

बी ऐम जे, वोलूम 344, 14 जून 2012
doi: 10.1136/bmj.e4174

लगातार ऐसिडिक हो रहा है समुद्री पानी

विश्व में समुद्रों के भविष्य को लेकर शोधकर्ताओं ने चिंता जताई है। नए शोध के मुताबिक अगर समुद्रों का पानी लगातार ऐसिडिक या अम्लीय होता रहा तो पानी में फल फूलने वाली करीब 30 प्रजातियां सदी के आखिर तक लुप्त हो सकती हैं। ये शोध कनाडा के वैंकूवर में हुए सम्मेलन में पेश किया गया। दरअसल ईंधन के जलने से

वातावरण में जितनी भी कार्बन डाइऑक्साइड उत्सर्जित होती है, उसका ज़्यादातर हिस्सा समुद्र सोख लेते हैं। इस वजह से सागरों का पानी एसिडिक होता जा रहा है, कोरल या मूँगा की परतें इससे छिलती जा रही हैं और अन्य प्रजातियों को भी नुकसान हो रहा है। वैज्ञानिक इस बात पर शोध कर रहे हैं कि भविष्य में हालात और कितने बिगड़ सकते हैं। इसके लिए वे समुदों में ज्वालामुखियों का अध्ययन कर रहें हैं जहाँ कार्बन डाइऑक्साइड प्राकृतिक रूप से पानी में मिली रहती है। इस प्रक्रिया से पैदा होने वाली स्थिति से पता चलता है कि अगर वातावरण में ऐसे ही कार्बन डाइऑक्साइड का उत्सर्जन होता रहा तो समुद्रों का क्या हाल होगा। शोधकर्ताओं ने जो नए आंकड़े इकट्ठा किए हैं उसके मुताबिक वर्ष 2100 तक जैव विविधता पर इसका बुरा असर होगा और पानी में तीस फीसदी प्रजातियाँ खत्म हो सकती है। प्रमुख शोधकर्ता डॉक्टर जेसन हॉल स्पेंसर बताते हैं, ''हमने पाया कि इकोसिस्टम या पारिस्थितिक तंत्र में तेज़ी से बदलाव हुआ है। इस सदी के अंत तक समुद्रों के पानी में एसिड की मात्रा बहुत ऊँचे स्तर पर पहुँच जाएगी। अगले कुछ सालों में एसिड की वजह से जंतुओं के शैल खराब होने लगेंगे और कुछ मूंगे बच नहीं पाएँगे।'' वैज्ञानिकों ने आगाह किया है कि समुद्री पानी में जिस तेज़ी से परिवर्तन आ रहा है वो पृथ्वी के इतिहास में अप्रत्याशित है और इस नुकसान से उभरने में हज़ारों, लाखों साल लग सकते हैं।

साइंस 2 मार्च 2012, वोलूम 335, इसु 6072, पेज जुलाई 2012 1058-1063
doi: 10.1126/science.1208277

सूक्ष्म प्लास्टिक कचरे का खतरा

शोधकर्ताओं को इन सूक्ष्म प्लास्टिक के कणों का पता सिंथेटिक कपड़ों से चला है जो हर धुलाई में कम से कम 1900 सूक्ष्म रेशे पानी में छोड़ते हैं। इसके पहले के शोध में ये पाया गया था कि एक मिली मीटर से भी छोटे प्लास्टिक के रेशों को आमतौर पर जानवर खा लेते हैं जिससे वो उनकी खाद्य श्रृंखला का हिस्सा बन जाता था। ये जानकारी 'इनवायरनमेंटल साइंस और टेक्नॉलॉजी' पत्रिका में प्रकाशित हुई है। इस शोधपत्र के सहलेखक मार्क ब्राउन के अनुसार, ''हमारे पहले के शोधकार्य में ये पाया गया था कि हमारे वातावरण में जितनी भी सूक्ष्म कण पाये जाते हैं उनमें से 80 प्रतिशत प्लास्टिक के छोटे टुकड़े होते हैं'' वे कहते हैं, ''इस खोज ने हमें ये पता लगाने को प्रेरित किया कि आख़िर ये प्लास्टिक के सूक्ष्म कण किस तरह के हैं और कहां से आते हैं'' डॉ ब्राउन के मुताबिक प्लास्टिक के ये सूक्ष्म कण चिंता का एक विषय थे क्योंकि प्रमाणों से पता चल रहा था कि

प्लास्टिक का ये कचरा हमारी फूड चेन खाद्य श्रृंखला में शामिल हो रहा है। ''जब एक बार ये प्लास्टिक का यह कचरा खाने के साथ जानवरों के पेट में पहुंचता है तो वे उनके पूरे शरीर में फैलकर रक्त कोशिकाओं में जमा हो जाता है'' समुद्री तटों पर सूक्ष्म प्लास्टिक का ये कचरा किस हद फैला हुआ है इसका पता लगाने के लिए ब्रिटेन, भारत और सिंगापुर के कई समुद्री तटों से पानी का नमूना लिया गया। उनका कहना है कि पानी के इन नमूनों के अध्ययन के बाद पाया गया कि पूरी दुनिया से इकट्ठा किए गए पानी के इन नमूनों में से एक भी ऐसा नहीं था जिसमें प्लास्टिक का कचरा न हो। इनमें से सबसे ज्यादा नुकसान इन रेशों के सबसे छोटे टुकड़े कर सकते हैं। ब्राउन के अनुसार पाए गए अधिकतर प्लास्टिक रेशेदार थे। पाए गए इन प्लास्टिक के कचरों के अध्ययन के बाद ये पता चला कि ये रेशें ज्यादातर पॉलिस्टिर, एक्रिलिक और नायलॉन के थे।

इन आंकड़ों में ये भी जाहिर हुआ है कि सूक्ष्म प्लास्टिक का ये कचरा शहरी इलाकों में ज्यादा पाया गया है। इन प्लास्टिक के कचरों के स्रोत का पता लगाने के लिए इस टीम ने ऑस्ट्रेलिया के साउथ वेल्स प्रांत में एक प्राधिकरण के साथ मिलकर काम किया और वहां के घरों से निकाले गए गंदे पानी में उन्हें ठीक-ठीक उसी मात्रा में प्लास्टिक का कचरा मिला। जिसके बाद ब्राउन और उनके सहयोगी रिचर्ड थॉम्पसन ये पता लगाने में लग गए कि वॉशिंग मशीन से फेंके गए

पानी में किस तरह का कचरा मिला था। उन्हें पता चला कि धुले हुए कुछ पॉलिस्टर के कपड़ों से कभी-कभी तो 1900 से भी ज़्यादा प्लास्टिक के रेशें छूटते हैं। हो सकता है कि ये सुनने में बहुत डरावना न लगता हो लेकिन ज़रा सोचिए कि अगर एक कपड़ा इतने रेशें छोड़ता है तो जितने कपड़े धुलते हैं उससे किए अनुपात में ये कचरा जमा रहा है।

एन्विरोंमेंटल साइंस एंड टेक्नोलोजी वोलुम 45, पेज 9175-9179, 2012
doi: 10.1021/es201811s

SEVICES OFFERED BY IITR

A. Safety/toxicity evaluation of chemicals/ finished products

- Toxicity evaluation in mice, rat, guinea pig and rabbit
- Neurobehavioral Toxicity
- Neurotoxicity
- Teratogenicity
- Gastrointestinal Toxicity
- Immunotoxicity
- Dermal Toxicity
- Reproductive Toxicity
- Carcinogenicity and Genotoxicity (*In vivo*)
- Carcinogenicity and Genotoxicity (*In vitro*)
- Safety evaluation of plastics
- Cytotoxicity
- Phototoxicity of chemicals/cosmetics
- Food Contamination and Adulteration Monitoring

B. Analytical Services

- Metals in soil, air, water, food, biological samples and other matrices (24 metals)
- Pesticides in water, soil, food and biological samples
- PAHs in water, food and biological samples
- Scanning of spectra and kinetics on spectrophotometer and spectrofluorometer
- Measurement of beta counts on scintillation counter
- Analysis of total organic carbon (TOC) in water/effluents

C. Environmental Monitoring and Impact Assessment

D. Water Quality Assessment and Monitoring

- Drinking water (as per IS10500)
- Raw water (sewage/industrial effluents) as per Pollution Board

E. Epidemiological Studies

F. Environmental Monitoring and Impact Assessment

- Multi species tests for ecotoxicity evaluation
- Seed germination test Environmentally safe reuse of effluents for agriculture and aquaculture
- Safety evaluation and management of industrial solid wastes

Feedback on the publication are always welcome

For information and feedback please write to:

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