DEPARTMENT OF ENVIRONMENTAL HEALTH SCIENCE

HEAD OF DEPARTMENT

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Head of the Laboratory of Environmental Pharmacology and Toxicology and then Head of Department of Environmental Health Sciences at the Mario Negri Institute in Milano.
Research interests: environmental factors as determinants of health and disease, experimental methodologies for toxicological risk assessment,
Author of more than 350 publications on peer reviewed scientific journals, has been a member of the Contamination Panel at EFSA , currently member of the National Consulting Board for pesticides (Ministry of Health), is an EUROTOX Registered Toxicologist.
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ACTIVITY OF THE DEPARTMENT
The Department of Environmental Health Science works to investigate environmental factors and their effects on human health. The main research lines focus on the survey of environmental contaminants, the assessment of human exposure with related health risks, and toxicity mechanisms of pollutants. The assessment of environmental contamination is carried out not only for well-known and widespread compounds, like dioxins and PCBs, but also for new classes of “unconventional” pollutants, e.g., endocrine disruptors, potentially toxic “natural” compounds, pharmaceuticals, personal care products and industrial waste products. The identification -for the first time- of illicit drugs in urban wastewaters led to a new original tool for the evidence-based monitoring of community drug abuse, alcohol, nicotine and food contaminants exposure through the analysis of urban wastewaters. Evaluation of risks associated with contamination in real-life scenarios is evaluated by toxicological and ecotoxicological risk analysis, based on studies in field and predictive models of toxicity. Assessment of risk from human exposure to toxic compounds in the atmosphere and the diet is performed by both in vivo, in vitro and in silico studies, utilizing also human staminal cells. Recent studies are devoted to identify adverse effects of neurotoxins on development of the central nervous system. We search also new “biological markers” to identify toxicity or pathology, and to identify molecular targets and toxic effect mechanisms of pollutants and drugs. This is performed through an advanced technological proteomic and metabolomic platform able to identify proteins differentially expressed in biological compartments in various experimental and clinical conditions and to define the biochemical phenotype of a biological system. Mass spectrometry (MS) is a central analytical technique at the Department, where a complete set of state-of-the-art instrumentation is available which covers all the research need of the Institute.

MAIN RESULTS (2016)
Characterization of neurotoxic effects of new generation pesticides (neonicotinoids) on the nervous system development in a murine model. Wastewater amounts of the anti-asthmatic drug salbutamol are directly associated with concentrations of air particulate in Milano. A QSAR model for the estimation of the
olfactory threshold of volatile organic compounds has been developed. A MALDI-Imaging methodology for the 3D visualization of an antitumor drug penetration in xenograft models of human tumors has been developed. Development of nanostructures for the analysis of antitumor drugs by mass spectrometry. By integrating mass spectrometry-based omics, cell biology, and systems-based modeling we discovered that different mutations of oncogenic K-Ras drive metabolism in non-small cell lung cancer (NSCLC) and the response to PI3K inhibition, paving the way for the development of novel combination strategies to increase the killing of cancer cells expressing mutant K-Ras, enhancing the selectivity and improving the therapeutic index. We discovered that lipid homeostasis and tryptophan catabolism might influence mortality in septic shock patients. Such alterations might represent not only risk factors for patients with severe septic shock but important pathophysiologic mechanisms in this clinical setting.

Environmental and toxicological screening and prioritization of all the commercial substances (6 million of substances); integration in ToxRead of read across and the in silico models in a new software (ToxWeight) for the weight of evidence; development of a new software (ToxDelta) to evaluate how structural differences lead to toxicological difference; implementation of a platform (PROMETHEUS) for the PBT (persistence, bioaccumulation and toxicity) properties screening; new in silico models for (eco)toxicological properties of dyes and pesticides; new models for hepatotoxicity, bee toxicity and endocrine disruptors; proposal to evaluate the impact of excavation rocks and conditioning agents for tunnelling; toxic assessment of automotive brakes/wear derived fine particles. Set up of a cookbook to reduce salt and sodium intake in consumers. Set up of an APP interactive model on cell phone to promote healthy nutrition models based on the Mediterranean diet in consumers of workplace dining halls.

Characterization of emerging pollutants in the aquatic environment and description of risks for environment and human health. Description of the illicit drugs consumption in Europe and identification of the substances mostly abused in the different European countries.

Characterization of the exposure to pesticides with the diet in Italy and various European countries. Identification and description of the new psychoactive substances (NPS) mostly used by the consumers in Europe. Meta-analysis of the effect of simple/complex sugars on markers of cardiovascular risk.

SELECTED PUBLICATIONS (2016)


RESEARCH ACTIVITIES

Identification and characterization of proteins by mass spectrometry. Our laboratory is developing and employing different analytical and instrumental techniques based on mass spectrometry (LC-ESI-MS/MS and MALDI-TOF-MS) for the identification and structural characterization of proteins and peptides in biological samples. This activity is mainly aimed at 1) global proteomic characterization and comparison of secretomes from human cancer cell lines; 2) profiling proteins in biological fluids for discovery and identification of biomarkers of physiopathological and toxicological relevance, 3) identifying and characterizing endogenous degradation products of proteins, 4) identifying proteins produced by cells in vitro in response to given stimuli, 5) identifying and characterizing biologically relevant proteins isolated from biological samples by immunoaffinity-based techniques. The complex alterations observed in the global protein expression are rationalized and interpreted by using “systems biology” tools that are able to highlight the functional networks most significantly perturbed in the biological systems under analysis.

Neurotoxicity induced by environmental pollutants on the developing Central Nervous System: we have preliminarily characterized the alterations induced by a class of neuro-active insecticides chemically similar to nicotine (Neonicotinoids) on neuronal cell primary cultures and in a mouse model of prenatal exposure to the contaminants. The most important proteins and molecules regulating the nervous system development were studied by biochemical and immunochromatographic methods in vitro, and by histological and immunoblotting analysis in vivo. We have developed and characterized a new in vitro model for neurotoxicological studies of environmental contaminants consisting of human inducible pluripotent stem cells (iPSC)-derived neural cell lines.

MAIN RESULTS (2016)

We have accomplished and published a study aimed at determining the protective effects of synthetic and natural Toll-like Receptor 4 antagonists in in vitro models of spinal cord neurodegeneration. We have also preliminarily characterized the alterations induced by Neonicotinoids on neuronal cell primary cultures and in a mouse model of prenatal exposure to the contaminants.
Set up of a mass spectrometry-based workflow aimed at the simultaneous identification of the active and inactive form of SDF-1, a chemokine that plays a pivotal role in angiogenesis.

Evidence about the capability of some aspartyl proteases to generate p17, a viral protein, able to deregulate the function of different cells involved in AIDS pathogenesis.

Ongoing project focus on secretome of cancer cell lines aimed at characterizing their protein expression profiles and identifying the main alterations in the protein secretion in relation to their normal counterpart. In particular, we are investigating the alterations in the secretome of pancreatic ductal epithelial cells become tumorigenic after transfection with mutant K-RAS.

SELECTED PUBLICATIONS (2016)


LABORATORY OF ENVIRONMENTAL CHEMISTRY AND TOXICOLOGY

Emilio Benfenati, Chem.D.

Graduated in chemistry summa cum laude. Researcher at Stanford. He participates / participated in 43 EC-funded projects, of which 16 as coordinator.

Research areas: (eco)toxicity, environmental modeling, risk assessment, in silico models, QSAR, read across, endocrine disrupters, pesticides, biocides, pollutant analysis.

He is the leading developer of software platforms for (eco) toxicity such as VEGA and ToxRead. Author of 340 articles in scientific journals.

HEAD OF LABORATORY

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RESEARCH ACTIVITIES

Studies on environmental and (eco)toxicological properties of chemicals.

Methods are developed for assessing properties (eco)toxicological and environmental conditions of the substances, by in silico models, and laboratory methods. This assessment is combined with analytical measures, in a risk assessment framework.

Models are implemented in VEGA (www.vegahub.eu) and allow screening millions of substances. ToxRead (www.toxread.eu) evaluates in detail the properties of a substance, with the display of possible associated reasons for the effects and of the similar substances, from a read across perspective. The models start from the chemical formula only, and can be used for pesticides, cosmetics, biocides, natural and industrial substances and nanomaterials.

Industrial and Environmental Hygiene Units, Risk Analysis Related to Pollutants

The research deals with risk analysis for the population and the environment, associated with exposure to contaminants. Modeling studies are performed for transport and dissemination, to reach a planned concentration. That is combined with chemical analysis of pollutants and characterization of (eco)toxicity.

We use test batteries, applied to different situations, such as land from excavation, air pollution, emissions, and landfills. Pollutants analysis are carried out in mass spectrometry, on dioxins, PCBs, PAHs, polybromobiphenyls, pesticides, endocrine compounds, industrial pollutants, etc.

MAIN RESULTS (2016)

SELECTED PUBLICATIONS (2016)

CERAPP: Collaborative Estrogen Receptor Activity Prediction Project
Environ Health Perspect, 2016; 124: 1023-1033. DOI: 10.1289/ehp.1510267

Pizzo F, Lombardo A, Brandt M, Manganaro A, Benfenati E
A new integrated in silico strategy for the assessment and prioritization of persistence of chemicals under REACH Environment International, 2016, 88, 250-260


LABORATORY OF
MASS SPECTROMETRY

Enrico Davoli, Anim.Sci.D
Laurea in Animal Science (Milano, Università Statale), USDA Fellow, Beltsville, MD 1977-78.
Post doctorate fellow at University of Nebraska-Lincoln (Lincoln, NE 1987-88).
Fellow at the University of Colorado Medical Centre (1988). Member of ISO 14000 (Environmental Management System) and ISO 18000 (Occupational Health and Safety) Commission (IGQ, Italy).
Environmental Interest Group Coordinator, American Society for Mass Spectrometry), President, Italian Mass Spectrometry Society.
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RESEARCH ACTIVITIES

Analytical technologies for mass spectrometry-based research in environmental, biochemistry and toxicology. Environmental studies on air quality and odour pollution aspects. Development of technologies for mass spectrometry imaging (MSI) of drug and metabolites imaging in tissues, in 2 and 3D. Development of bioinformatics approaches to analyse MSI data.
Mass-spectrometry-based metabolomics and proteomics as tools for the discovery of novel diagnostic-prognostic markers and/or therapeutic targets in human diseases with particular attention to those with potential in early diagnosis, prognosis, or innovative therapies.

MAIN RESULTS (2016)

Analysis of salbutamol in wastewater: development of approaches to measure population consumption, to identify industrial contaminations and to assess correlations between air pollution and salbutamol use.

Development of a QSAR model to predict olfactory thresholds of chemicals and odorants. Development of a 3D platform to visualize anticancer drugs penetration and distribution in xenografts models. Development of nano-structured approaches to analyse drug residues in tissues by MSI.

Cancer metabolism reprogramming. By integrating mass spectrometry-based omics, cell biology, and systems-based modeling we discovered that different mutations of oncogenic K-Ras drive metabolism in non-small cell lung cancer (NSCLC) and the response to PI3K inhibition, paving the way for the development of novel combination strategies to increase the killing of cancer cells expressing mutant K-Ras, enhancing the selectivity and improving the therapeutic index.

Biomarkers.
We discovered that lipid homeostasis and tryptophan catabolism might influence mortality in septic shock patients. Such alterations might represent not only risk factors for patients with severe septic shock but important pathophysiologic mechanisms in this clinical setting.
SELECTED PUBLICATIONS (2016)


Caioia E, Brunelli L, Marabese M, Broggi M, Lupi M, Pastorelli R. Different metabolic response to PI3K inhibition in NSCLC cells harboring wild-type and G12C mutant KRAS. Oncotarget 2016; E-pub


Wastewater based epidemiology to evaluate environmental air pollution effects on asthma

Methods: wastewater analysis with mass spectrometry and calculation of the daily dose excreted by the population of Milan

Results: direct and significant correlation between the number of salbutamol doses used and PM_{10} and PM_{2.5} levels

RR = 1.06 (95% CI: 1.02-1.10) for an increase of 10 mg/m³ of PM_{10}
RESEARCH ACTIVITIES

Human nutrition: studies on food and nutrition education, to contribute to the improvement of the health status of the population. A first study, directed to users of workplace dining halls, has investigated the possibility to reduce the sodium intake by administration of low salt meals (“Sale in zucca” Project); a second study will evaluate the use of cell phone applications to promote the use of the Mediterranean diet in this population (“Buon APP... etito” Project).

Environmental pollution: presence and risk assessment of the pharmaceuticals, illicit drugs, and other emerging pollutants in the aquatic environment. We measure these novel pollutants in rivers, lakes, ground and drinking water by using advanced mass spectrometry techniques, and assess the risk for the environment and the human health related to the exposure to these substances (“Sant’Anna” and “Nissan” Project).

3. Wastewater-based epidemiology (Environmental Biomarkers Unit): study of the population lifestyle by using the wastewater analysis technique. We study the consumption of illicit drugs (Watch and NPS-Euronet Project), alcohol and tobacco (Cost Project), and the dietary exposure of the population to pesticides and mycotoxins (Sewprof Project). Exposure to these substances is assessed by measuring their urinary metabolites excreted in urban wastewater.

MAIN RESULTS (2016)

Set up of a cookbook to reduce salt and sodium intake in consumers. Set up of an APP interactive model on cell phone to promote healthy nutrition models based on the Mediterranean diet in consumers of workplace dining halls.

Characterization of emerging pollutants in the aquatic environment and description of risks for environment and human health.

Description of the illicit drugs consumption in Europe and identification of the substances mostly abused in the different European countries.

Characterization of the exposure to pesticides with the diet in Italy and various European countries.

Identification and description of the new psychoactive substances (NPS) mostly used by the consumers in Europe.
SELECTED PUBLICATIONS (2016)


Gonzalez-Marino I, Gracia-Lor E, Rousis N, Castignanò E, Thomas K V, Quintana J B, Kasprzyk-Hordern B, Zuccato E, Castiglioni S

Increased levels of the oxidative stress biomarker 8-iso-prostaglandin F2α in wastewater associated with tobacco use. Sci Rep 6: 30055 (2016)


THC, cocaine, heroin, methamphetamine, and MDMA consumption (grams of pure substance/day/1000 inhabitants) measured by wastewater analysis in the seven large cities (>350,000 inhabitants) in May 2010, October 2011 and 2012, November 2013 and May 2014 (grams of pure substance/day/1000 inhabitants; means ±SD). **p<0.01, 2010 vs. 2011-13 (heroin); ****p<0.0001, 2010 vs. all years (methamphetamine).