

ANNUAL REPORT 2011

Milano - Bergamo



DEPARTMENT OF ENVIRONMENTAL HEALTH SCIENCES

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Head Marco LODI, Chemist

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Head Enrico DAVOLI, Anim.Sci.D.

Laboratory of Molecular Toxicology

Head Luisa AIROLDI, Pharm.D.

Protein and Gene Biomarkers Unit

Head Roberta PASTORELLI, Biol.Sci.D

Department's Units

Environmental Pollutants Risk Assessment Unit

Head Elena FATTORE, Biol.Sci.D

Analytical Instrumentation Unit

Head Renzo BAGNATI, Chem.D.

CURRICULA VITAE

Roberto Fanelli, Head of the Environmental Health Sciences Department since 1997, Laboratory Head 1978-97, Researcher 1975-78, Research fellow 1969-74 at the Mario Negri Institute.

Doctoral Degree in Biological Sciences (University of Milan, 1973), Assistant Professor in Biochemistry at Baylor College of Medicine (Houston, Texas). Member of the Commissione Consultiva Prodotti Fitosanitari (Ministero Salute), Member of the Scientific Panel on Contaminants in the Food Chain (European Food Safety Authority, 2003-2006), Certified Italian Toxicologist. Member of the Comitato Scientifico Ente Risi.

Research areas: Sources, diffusion, toxicology, human exposure and risk assessment of persistent environmental pollutants. Environmental risk of plant protection products. Development of analytical methods for identification and measurement of biomarkers in toxicology. Mechanisms of toxic action by proteomic techniques.

Selected publications:

1. Castiglioni S, Bagnati R, Melis M, Panawennage D, Chiarelli M P, Fanelli R, Zuccato E, Identification of cocaine and its metabolites in urban wastewater and comparison with the human excretion profile in urine, *Water Res* 45: 5141-5150 (2011)
2. Macconi D, Chiabrando C, Schiarea S, Aiello S, Cassis L, Gagliardini E, Noris M, Buelli S, Zoja C, Corna D, Mele C, Fanelli R, Remuzzi G, Benigni A. Proteasomal processing of albumin by renal dendritic cells generates antigenic peptides. *J Am Soc Nephrol* 2009 ; 20 : 123-130.
3. Castiglioni S, Zuccato E, Chiabrando C, Fanelli R, Bagnati R. Mass spectrometric analysis of illicit drugs in wastewater and surface water. *Mass Spectrom Rev* 2008 ; 27 : 378-394
4. Zuccato E, Chiabrando C, Castiglioni S, Bagnati R, Fanelli R. Estimating community drug abuse by wastewater analysis. *Environ Health Perspect* 2008 ; 116 : 1027-1032
5. Hodgson S, Thomas Laura, Fattore E, Lind P M, Alfvén T, Hellstrom L, Hakansson H, Carubelli G, Fanelli R, Jarup L. Bone mineral density changes in relation to environmental PCB exposure. *Environ Health Perspect* 2008 ; 116 : 1162-1166
6. Pastorelli R, Carpi D, Campagna R, Airoidi L, Pohjanvirta R, Viluksela M, Hakansson H, Boutros P C, Moffat I D, Okey A B, Fanelli R. Differential expression profiling of the hepatic proteome in a rat model of dioxin resistance: correlation with genomic and transcriptomic analyses. *Mol Cell Proteomics* 2006; 5: 882-894

Luisa Airoidi, Head of the Molecular Toxicology Laboratory since 1994, Unit Head 1987-94, Researcher 1978-87, Technician 1967-75 at the Mario Negri Institute.

Doctoral Degree in Pharmacy (University of Milan, 1975), Postdoctoral fellow at the Massachusetts Institute of Technology (Cambridge, MA, 1976) and at the Northwestern University Medical School (Chicago, IL, 1977), Researcher at the Yale University Medical School (New Haven, CT, 1980-81).

Research areas: Proteomics in toxicology with particular interest on the study of proteome changes in tissues and biological fluids from animals and humans after exposure to toxic compounds; clinical proteomics aimed at the identification of protein biomarkers as diagnostic tools; molecular epidemiology focused on the identification and measurement of biomarkers of exposure to environmental carcinogens and disease susceptibility.

Selected publications:

1. Campagna R, Brunelli L, Airoidi L, Fanelli R, Hakansson H, Heimeier R. A, De Boever P, Boix J, Llansola M, Felipe V and Pastorelli R. Cerebellum proteomics addressing the cognitive deficit of rats perinatally exposed to the food-relevant non-dioxin like polychlorinated biphenyl PCB138. *Toxicol Sci* 2011; 123: 170-9
2. Brunelli L, Campagna R, Airoidi L, Cauli O, Llansola M, Boix J, Felipe V and Pastorelli R. Exploratory investigation on nitro and phospho proteome cerebellum changes in hyperammonia and hepatic encephalopathy rat models. *Metab Brain Dis* 2011
3. Gallo V, Neasham D, Airoidi L, Ferrari P, Jenab M, Boffetta P, Overvad K, Tjonneland A, Clavel-Chapelon F, Boeing H, Pala V, Palli D, Panico S, Tumino R, Arriola L, Lund E, Bueno-De-Mesquita H B, Peeters P H, Melander O, Hallmans G, Riboli E, Saracci R, Vineis P. Second-hand smoke, cotinine levels, and risk of circulatory mortality in a large cohort study of never-smokers. *Epidemiology* 2010 ; 21 : 207-214.
4. Airoidi L, Magagnotti C, Iannuzzi AR, Marelli C, Bagnati R, Pastorelli R, Colombi A, Santaguida S, Chiabrando C, Schiarea S, Fanelli R. Effects of cigarette smoking on the human urinary proteome. *Biochem Biophys Res Commun*. 2009 381: 397-402.
5. Carpi D, Korkalainen M, Airoidi L, Fanelli R, Hakansson H, Muhonen V, Tuukkanen J, Viluksela M, Pastorelli R. Dioxin-sensitive proteins in differentiating osteoblasts: effects on bone formation in vitro. *Toxicol Sci*. 2009 108: 330-43.
6. Peluso M, Airoidi L, Colombi A, Munnia A, Veglia F, Autrup H, Dunning A, Garte S, Gormally E, Malaveille C, Matullo G, Overvad K, Raaschou-Nielsen O, Clavel-Chapelon F, Linseisen J, Boeing H, Trichopoulou A, Palli D, Krogh V, Tumino R, Panico S, Bueno-De-Mesquita H B, Peeters P H, Kumle M, Gonzalez C A, Martinez C, Dorronsoro M, Barricarte A, Tormo M J, Quiros J R, Berglund G, Janzon L, Jarvholm B, Day N E, Key T J, Saracci R, Kaaks R, Riboli E, Bingham S, Vineis P. Bulky DNA adducts, 4-aminobiphenyl hemoglobin adducts, diet and air pollution in a healthy European population. *Br J Nutr* 2008 100: 489-495.

Emilio Benfenati, Head of the Laboratory of Environmental Chemistry and Toxicology since 1997, Unit Head 1987-97, Researcher 1986-87, Research fellow 1981-86 at the Mario Negri Institute. Researcher at Istituto Biochimico Italiano 1979-1981.

Doctoral Degree in Chemistry (University of Milan, 1979).

Member of Commissione Consultiva Prodotti Fitosanitari (Ministero Salute 1997-99), Certified Italian Chemist.

Research areas: Computer-based models for chemistry and toxicology; Molecular descriptors; QSAR; Toxicity prediction; Metabolism studies; Characterization and assessment of wastes, industrial effluents, emissions from landfill and incinerator; Integration of chemical analysis and eco-toxicological data; Chemical analysis of organic compounds by mass spectrometry.

Selected publications:

1. Benfenati E, Gonella Diaza R, Cassano Antonio, Pardoe S, Gini G, Mays C, Knauf R, Benighaus L, The acceptance of in silico models for REACH: Requirements, barriers, and perspectives, *Chem Cent J* 2011 5 : 58
2. Colombo A, Benfenati E, Bugatti S G, Celeste G, Lodi M, Rotella G, Senese V, Fanelli R, Concentrations of PCDD/PCDF in soil close to a secondary aluminum smelte, *Chemosphere* 2011 85 : 1719-1724
3. Toropov A A, Toropova A P, Benfenati E, Gini G, Leszczynska D, Leszczynski J, SMILES-based QSAR approaches for carcinogenicity and anticancer activity: Comparison of correlation weights for identical SMILES attributes, *Anti-Cancer Agents in Medicinal Chemistry* 2011 11 : 974-982
4. Boriani E, Mariani A, Baderna D, Moretti C, Benfenati E, ERICA: a multiparametric toxicological risk index for the assessment of environmental healthiness, *Environmental International*, 2010 36 : 665–674
5. Benfenati E, Benigni R, DeMarini D M, Helma C, Kirkland D, Martin T M, Mazzatorta P, Ouédraogo-Arras G, Richard A, Schilter B, Schoonen W G E J, Snyder R D, Yang C. Predictive models for carcinogenicity and mutagenicity: frameworks, state-of-the-art, and perspectives. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 2009 ; 27 : 57-90.
6. Roncagliani A, Benfenati E, In silico-aided prediction of biological properties of chemicals: oestrogen receptor-mediated effects, *Chem Soc Rev* 2008 37: 441-450

Chiara Chiabrando, Head of the Analytical Biochemistry Laboratory since 1997, Unit Head 1987-97, Researcher 1978-87, Research fellow 1975-78 at the Mario Negri Institute.

Doctoral degree in Biological Sciences (University of Milan, 1974), Postdoctoral fellow at the Baylor College of Medicine (Houston, Texas, 1974-75). Postgraduate degree in Pharmacological Research, Mario Negri Institute (1977).

Research areas: Development and application of bio-analytical methods based on mass spectrometry in the fields of biochemistry, metabolism, clinical chemistry and pharmacology. Identification and characterization of proteins and peptides of biomedical interest by proteomic approaches and mass spectrometry. Structural characterization of proteins by mass spectrometry. Proteomics in oncology. Comparative characterization of cancer cell lines secretomes by a global proteomic approach and systems biology tools.

Selected publications

1. Schiarea S, Solinas G, Allavena P, Scigliuolo GM, Bagnati R, Fanelli R, Chiabrando C. Secretome analysis of multiple pancreatic cancer cell lines reveals perturbations of key functional networks. *J Proteome Res.* 2010;9:4376-92.
2. Solinas G, Schiarea S, Liguori M, Fabbri M, Pesce S, Zammataro L, Pasqualini F, Nebuloni M, Chiabrando C, Mantovani A, Allavena P. Tumor-conditioned macrophages secrete migration-stimulating factor: a new marker for M2-polarization, influencing tumor cell motility. *J Immunol.* 2010;185:642-52.
3. Airoidi L, Magagnotti C, Iannuzzi AR, Marelli C, Bagnati R, Pastorelli R, Colombi A, Santaguida S, Chiabrando C, Schiarea S, Fanelli R. Effects of cigarette smoking on the human urinary proteome. *Biochem Biophys Res Commun.* 2009; 381:397-402.
4. Macconi D, Chiabrando C, Schiarea S, Aiello S, Cassis L, Gagliardini E, Noris M, Buelli S, Zoja C, Corna D, Mele C, Fanelli R, Remuzzi G, Benigni A. Proteasomal processing of albumin by renal dendritic cells generates antigenic peptides. *J Am Soc Nephrol* 2009 ; 20 : 123-130.
5. Zuccato E, Chiabrando C, Castiglioni S, Bagnati R, Fanelli R. Estimating community drug abuse by wastewater analysis. *Environ Health Perspect* 2008; 116: 1027-1032.
6. Castiglioni S, Zuccato E, Chiabrando C, Fanelli R, Bagnati R. Mass spectrometric analysis of illicit drugs in wastewater and surface water. *Mass Spectrom Rev* 2008; 27: 378-394.

Enrico Davoli, Head of the Mass Spectrometry Laboratory since 1997, Unit Head 1994-97, Researcher 1989-94, Research Fellow 1985-87 at the Mario Negri Institute. Fellow at USDA, Beltsville, MD 1977-78.

Doctoral Degree in Animal Sciences (University of Milan, 1983), Postdoctoral fellow at the University of Nebraska (Lincoln, NE, 1987) and at the University of Colorado Health Sciences Center (Denver, CO, 1988). Postgraduate degree in Pharmacological Research, Mario Negri Institute (1988). Member of the American Association for Mass Spectrometry (ASMS) of the Environment and Safety Commission of IGQ and of the ETS (Emission Trading System) commission. Member of the National Biomass Research Center Scientific Committee. Environmental Applications Interest Group Coordinator (ASMS).

Research areas: Development of methodology, instrumentation and software for environmental research. Studies of urban air pollution and characterization of environmental odor annoyance.

Selected Publications

1. Scaglia B, Orzi V, Artola A, Font X, Davoli E, Sanchez A, Adani F. Odours and volatile organic compounds emitted from municipal solid waste at different stage of decomposition and relationship with biological stability. *Bioresour Technol* 2011 ; 102 : 4638-4645
2. Martinez Bueno M J, Ucles S, Hernando M D, Davoli E, Fernandez-Alba . Evaluation of selected ubiquitous contaminants in the aquatic environment and their transformation products. A pilot study of their removal from a sewage treatment plant. *Water Res* 2011 ; 45 : 2331-2341
3. Ulaszewska M M, Zuccato E, Davoli E. PCDD/Fs and dioxin-like PCBs in human milk and estimation of infants' daily intake: A review. *Chemosphere* 2011 ; 83 : 774-782
4. Bagnati R, Davoli E. Analytical methods for the detection of illicit drugs in wastewaters and surface waters. In: *Illicit drugs in the environment: Occurrence, analysis, and fate using mass spectrometry* Wiley, Hoboken, 2011; 55-67
5. Orzi V, Cadena E, D'Imporzano G, Artola A, Davoli E, Crivelli, M, Adani F. Potential odour emission measurement in organic fraction of municipal solid waste during anaerobic digestion: relationship with process and biological stability parameters. *Bioresour Technol* 2010 101 : 7330-7337.
6. Davoli E, Fattore E, Paiano V, Colombo A, Palmiotto M, Fanelli R, Rossi A N, Il Grande M. Waste management health risk assessment: A case study of a solid waste landfill in South Italy. *Waste Manag* 2009, DOI 10.1016/j.wasman.2009.10.013.

Ettore Zuccato, Head of the Food Toxicology Laboratory since 2005, Unit Head 1997-2005, Researcher 1986-97, Technician 1975-86 at the Mario Negri Institute.

Doctoral degree in Medicine (University of Milan, 1986), Postdoctoral degree in Human Nutrition (1999), Postdoctoral fellow at the King's College School of Medicine (London, UK, 1988-89).

Member of the ANSISA, EMEA expert, member of the Commissione Consultiva per i Prodotti Fitosanitari, and expert for the evaluation of plant protection products for registration within the EU. Research areas: Food safety, including the study of dietary chemical contaminants, safety assessment of GMO in human nutrition, food allergens and toxicants, emerging issues in food toxicology, risk perception and risk communication to the consumers, and evaluation of plant protection products for registration within the European Union. Environmental pollution by pharmaceuticals, and monitoring of illicit drugs in surface waters to estimate community drug abuse.

Selected publications

1. Zuccato E, Castiglioni S, Tettamanti M, Olandese R, Bagnati R, Melis M, Fanelli R. Changes in illicit drug consumption patterns in 2009 detected by wastewater analysis. *Drug and Alcohol Dependence* 2011, 118: 464-469
2. Ulaszewska M M, Zuccato E, Capri E, Iovine R, Colombo A, Rotella G, Generoso C, Grassi P, Melis M, Fanelli R. The effect of waste combustion on the occurrence of polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) in breast milk in Italy. *Chemosphere* 2011 ; 82 : 1-8
3. Ulaszewska M M, Zuccato E, Davoli E. PCDD/Fs and dioxin-like PCBs in human milk and estimation of infants' daily intake: A review. *Chemosphere* 2011 ; 83 : 774-782
4. Zuccato E, Castiglioni S, Bagnati R, Melis M, Fanelli R. Source, occurrence and fate of antibiotics in the Italian aquatic environment. *J Hazard Mater* 2010 ; 179 : 1042-1048
5. Zuccato E, Chiabrando C, Castiglioni S, Bagnati R, Fanelli R. Estimating community drug abuse by wastewater analysis. *Environ Health Perspect* 2008, 116: 1027-1032.
6. Castiglioni S, Zuccato E, Chiabrando C, Fanelli R, Bagnati R. Mass spectrometry analysis of illicit drugs in wastewater and surface water. *Mass Spectrom Rev*, 2008, 27: 378-394.

Renzo Bagnati, Head of the Analytical Instrumentation Unit since 2005, Researcher 1992-2005, Research fellow 1986-92 at the Mario Negri Institute.

Doctoral degree in Chemistry (University of Turin, 1985), Postgraduate degree in Pharmacological Research, Mario Negri Institute (1989).

Research areas: Mass spectrometry applied to the analysis of biological and environmental relevant substances (proteins, peptides, hormones, pharmaceuticals, drugs of abuse, pesticides).

Selected Publications

1. Sulaiman G M, Al Sammarrae K W, Ad'hiah A H, Zucchetti M, Frapolli R, Bello E, Erba E, D'Incalci M, Bagnati R, Chemical characterization of Iraqi propolis samples and assessing their antioxidant potentials, *Food Chem Toxicol* 2011 49 : 2415-2421
2. Schiarea S, Solinas G, Allavena P, Scigliuolo G, Bagnati R, Fanelli R, Chiabrando C. Secretome analysis of multiple pancreatic cancer cell lines reveals perturbations of key functional networks. *J Proteome Res* 2010; 9: 4376-4392.
3. Terao M, Kurosaki M, Barzago M M, Fratelli M, Bagnati R, Bastone A, Giudice C, Scanziani E, Mancuso A, Tiveron C, Garattini E. Role of the molybdoflavoenzyme aldehyde oxidase homolog 2 in the biosynthesis of retinoic acid: generation and characterization of a knockout mouse. *Mol Cell Biol* 2009 ; 29 : 357-377.
4. Zuccato E, Castiglioni S, Bagnati R, Chiabrando C, Grassi P, Fanelli R. Illicit drugs, a novel group of environmental contaminants. *Water Res* 2008 ; 42 : 961-968.
5. Bagnati R, Bianchi G, Marangon E, Zuccato E, Fanelli R, Davoli E. Direct analysis of isopropylthioxanthone (ITX) in milk by high-performance liquid chromatography/tandem mass spectrometry. *Rapid Commun Mass Spectrom* 2007 ; 21 : 1998-2002.
6. Castiglioni S, Zuccato E, Crisci E, Chiabrando C, Fanelli R, Bagnati R. Identification and measurement of illicit drugs and their metabolites in urban wastewater by liquid chromatography-tandem mass spectrometry. *Anal Chem* 2006; 78: 8421-8429.

Elena Fattore, Head of the Environmental Pollutants Risk Assessment Unit since 2005, Researcher 2001-2004, Research fellow 1991-1997 at the Mario Negri Institute.

Doctoral Degree in Biological Sciences (University of Milan, 1991), Postgraduate degree in Pharmacological Research, Mario Negri Institute (1994), Postdoctoral fellow at the National Institute of Environmental Medicine, Karolinska Institutet, Stockholm (1998-2000). Member of the Working Group of External Scientific Experts to externally review the quality of the scientific outputs of the European Food Safety Authority (EFSA) in the area of activity of chemical risk assessment and connected fields.

Research areas: Environmental chemistry, toxicology, assessment of human exposure and risk from environmental pollutants with emphasis on dioxins and dioxin-like compounds.

Selected publications

1. Fattore E, Paiano V, Borgini A, Tittarelli A, Bertoldi M, Crosignani P, Fanelli R. Human health risk in relationship to Air Quality in two municipalities in an industrialized area of northern Italy. *Environmental Research* 2011, 111: 1321-1327.
2. Grassi P, Fattore E, Generoso C, Fanelli R, Arvati M, Zuccato E. Polychlorobiphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) in fruit and vegetables from an industrial area in northern Italy. *Chemosphere* 2010; 79: 292-298
3. Davoli E, Fattore E, Paiano V, Colombo A, Palmiotto M, Rossi A N, Il Grande M, Fanelli R. Waste management health risk assessment: A case study of a solid waste landfill in South Italy. *Waste Manag* 2010; 30: 1608-1613.

- Oberg M, Westerholm E, Fattore E, Stern N, Hanberg A, Haglund P, Wiberg K, Bergendorff A, Hakansson H. Toxicity of Bromkal 70-5DE, a technical mixture of polybrominated diphenyl ethers, following 28 d of oral exposure in rats and impact of analysed impurities. *Chemosphere* 2010; 80, 137-143.
- Fattore E, Fanelli R, Dellatte E, Turrini A, Di Domenico A. Assessment of the dietary exposure to non-dioxin-like PCBs of the Italian general population. *Chemosphere* 2008, 73: S278-S283.
- Hodgson S, Thomas L, Fattore E, Lind P M, Alfven T, Hellstrom L, Hakansson H, Carubelli G, Fanelli R, Jarup L Bone mineral density changes in relation to environmental PCB exposure. *Environmental Health Perspective* 2008, 116: 1162-1166.

Marco Lodi, Head of the Industrial and Environmental Unit since 2002, Consultant 1997-2002 at the Mario Negri Institute.

General Certificate of Education in Industrial Chemistry (Milan, 1974).

Member of AIDII (Italian Industrial Hygiene Association), certified by ACGIH (American Conference of Governmental Industrial Hygienist).

Research areas: Emission sources, environmental diffusion, toxicology, human exposure and risk assessment of persistent environmental pollutants. Environmental risk of chemical pollution products. Development of sampling methods for environmental toxic compounds.

Selected publications

- Colombo A, Benfenati E, Bugatti S G, Celeste G, Lodi M, Rotella G, Senese V, Fanelli R. Concentrations of PCDD/PCDF in soil close to a secondary aluminum smelte, *Chemosphere* 2011 85 : 1719-1724
- Baderna D, Maggioni S, Boriani E, Gemma S, Molteni M, Lombardo A, Colombo A, Bordonali S, Rotella G, Lodi M, Benfenati E, A combined approach to investigate the toxicity of an industrial landfill's leachate: chemical analyses, risk assessment and in vitro assays, *Environmental Research* 2011 111 : 603-613
- Colombo A, Benfenati E, Mariani G, Lodi M, Marras R, Rotella G, Senese V, Fattore E, Fanelli R. PCDD/Fs in ambient air in north/east Italy: The role of a MSWI inside an industrial area. *Chemosphere* 2009 ; 77 : 1224-1229.
- Benfenati E, Azimonti G, Auteri D, Lodi M Environmental and ecological toxicology: computational risk assessment. *Computational toxicology. Risk assessment for pharmaceutical and environmental chemicals* John Wiley, Hoboken, NJ, 2007; 625-650
- Grosso M, Cernuschi S, Palini E, Lodi M, Mariani G. PCDD/Fs release during normal and transient operation of a full scale MSWI plant. *Organohalogen Compounds* 2004; 66: 1243-1249
- Benfenati E, Mariani G, Lodi M, Reitano G, Fanelli R. Is bioexsiccation releasing dioxins? *Organohalogen Compounds* 2004; 66: 955-961

Roberta Pastorelli, Head of Protein and Gene Biomarkers Unit since 2004, Researcher 1992-2003, Research fellow 1983-92 at the Mario Negri Institute.

Doctoral Degree in Biological Sciences (University of Milan, 1982), Postgraduate degree in Pharmacological Research, Mario Negri Institute (1986), Postdoctoral fellow at the Massachusetts Institute of Technology, Cambridge, MA (1987-89 and 1991).

Research areas: Proteomics-Metabolomics- System Biology. Investigations of global protein/metabolite expression profiles and their modulation in different biological compartments as a mean for understanding toxicological/pathological response in biological systems.

Selected publications:

- Campagna R, Brunelli L, Airoidi L, Fanelli R, Hakansson H, Heimeier R. A, De Boever P, Boix J, Llansola M, Felipe V, Pastorelli R. Cerebellum proteomics addressing the cognitive deficit of rats perinatally exposed to the food-relevant non-dioxin like polychlorinated biphenyl PCB138. (2011) *Toxicological Sciences* **123**, 170-9.
- Mazzoletti M, Bortolin F, Brunelli L, Pastorelli R, Erba E, Ubezio P, Broggin M. Combination of PI3K/mTOR inhibitors: in vitro and in vivo antitumor activity and molecular correlates. (2011) *Cancer Res.* **71**, 4573-84.
- Brunelli L, Campagna R, Airoidi L, Cauli O, Llansola M, Boix J, Felipe V, Pastorelli R. Exploratory investigation on nitro and phospho proteome cerebellum changes in hyperammonia and hepatic encephalopathy rat models. (2011) *Metab Brain Dis* 2011
- Carpi D, Korkalainen M, Airoidi L, Fanelli R, Hakansson H, Muhonen V, Tuukkanen J, Viluksela M, Pastorelli R. Dioxin-sensitive proteins in differentiating osteoblasts: effects on bone formation in vitro. *Toxicol Sci.* 2009 108: 330-43.
- Pastorelli R, Saletta F, Campagna R, Carpi D, Dell'Osta C, Schiarea S, Vineis P, Airoidi L, Matullo G. Proteome characterization of a human urothelial cell line resistant to the bladder carcinogen 4-aminobiphenyl. *Protome Science* 2007.
- Pastorelli R, Carpi D, Campagna R, Airoidi L, Pohjanvirta R, Viluksela M, Hakansson H, Boutros P C, Moffat I D, Okey A B, Fanelli R. Differential expression profiling of the hepatic proteome in a rat model of dioxin resistance: correlation with genomic and transcriptomic analyses. *Mol Cell Proteomics* 2006; 5: 882-894

ACTIVITIES

The Department 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, and drugs entering the environment after human or veterinary use. The identification –for the first time– of illicit drugs in urban waste and river waters, led to a

new original tool for the evidence-based monitoring of community drug abuse. For all these survey activities sophisticated analytical methods based on advanced mass spectrometric techniques are developed.

The Department is active in the assessment of human exposure to toxic compounds in the atmosphere and the diet, which is the main source of priority pollutants (PCBs, dioxins and other endocrine disruptors).

Assessment of the risk associated to contamination in real-life scenarios has recently gained much importance. In order to respond to the growing demand for information, the Department is more and more involved in toxicological and ecotoxicological risk analysis, based on studies in field and predictive models of toxicity. The activities on predictive models are done in collaboration with the US EPA, and public authorities of some European countries, such as Italy and UK. This produced a platform, VEGA (Virtual models for property Evaluation of chemicals within a Global Architecture), which is open to the public via the internet, for the prediction of toxicological and environmental properties.

The toxic effects of environmental contaminants on neurodevelopmental mechanisms of environmental contaminants are investigated in animal models *in vivo* and *in vitro*.

Molecular epidemiology studies are used to identify genetic and/or environmental factors posing risks to human health. By this approach, we search for new useful "biological markers" to identify susceptible subjects, in view of finding appropriate preventive strategies.

The Department has implemented an advanced technological proteomic platform, in order to identify proteins differentially expressed in biological compartments in various experimental and clinical conditions. This approach is particularly relevant in toxicology, since it can contribute to find new biomarkers of toxicity or pathology, and to identify molecular targets and toxic effect mechanisms of pollutants and drugs. To integrate our proteomic studies, we have now introduced among our activities metabolomics, i.e., the study of small molecules, such as amino acids, carbohydrates, lipids, hormones etc., the final products of protein expression and activity which contribute 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, from GC-MS and LC-MS to MALDI-TOF-MS. These instruments are provided with modern solutions for sample introduction (chip-based nanoLC), sample ionization (ESI, DESI and MALDI), tandem MS (MSn) by triple quadrupole and TOF-TOF instruments, high mass resolution analysis (hybrid ion trap/orbitrap).

FINDINGS/MAIN RESULTS

Untargeted metabolomics reveals perturbations in specific metabolic pathways involved in outcome of cardiopulmonary resuscitation in a rat model of cardiac arrest and thus potential mechanisms accounting for outcome of cardiac arrest.

Importance of NDL-PCBs as a risk factor in developmental neurotoxicity in laboratory rodents. Evidence of brain proteome alterations with detrimental consequences on cognitive functions in the offspring.

Evidence of new molecular players in the effects of TCDD on bone development provided by proteomics coupled to networks analysis.

Resistance to the bladder carcinogen 4-aminobiphenyl in human urothelial cells is mediated by deregulation of apoptosis and membrane trafficking proteins.

Bone protein profile in a murine model of osteoporosis.

Identification of novel protein targets responsive to the effects of estrogens in bone.

TCDD's effect on the liver proteome profile of exposed rats. Determination of a subset of rat hepatic proteins indicative of differences in dioxin susceptibility.

The presence of 4-aminobiphenyl-hemoglobin adducts may help identify nonsmokers at high risk of cancers related to environmental tobacco smoke exposure.

Reference values of allele and genotype frequency of several metabolic genes in 15,000 control subjects.

CYP1A1 polymorphism affects lung tumor risk.

Identification of CYP2C9 genetic polymorphism as a determinant of severe adverse reactions to phenytoin.

On-line *in silico* models to predict ecotoxicity of pesticides for regulatory purposes.

New *in silico* models, freely available on-line, to predict toxicity and ecotoxicity of chemicals for the REACH European legislation. The tools have been used to predict properties of 4 millions chemicals.

A tool to assess if a chemical is bioaccumulative, with a high rate of accuracy, avoiding the use of the experimental fish model.

A new model for identification of endocrine disruptors using molecular docking.

A new index integrating risk assessment for human and ecotoxicity endpoints.
A method aimed at characterizing environmental odors to identify odor sources in complex environments.
Proteomic/bioinformatic workflow for comparative secretome analysis in cancer cell lines. Global proteomic profiles of pancreatic carcinoma cell lines secretomes with identification of perturbed functional networks.
Albumin can become a source of potentially antigenic peptides in proteinuric nephropaties.
Moderate-to-high fish consumption can result in exceeding the daily intake safety levels of PCBs and dioxin-like compounds established by the European Commission.
The same food type may contain significantly different concentrations of PCBs and dioxin-like compounds, depending on the geographic origin (this may help lower the risk for the consumers by understanding and controlling the causes of the differences).
The environmental levels of several drugs exceed the “safety limits” established for them.
Environmental pollution from pharmaceuticals is a general phenomenon that can be described by controllable variables (environmental load and mass balance).
Illicit drug residues and their metabolites were found in urban waste and river waters. Environmental levels can be used as a new tool to estimate illicit drugs consumption in the population.
In Milan, between 2008 and 2009 we observed a significant decrease of heroin and cocaine consumption, and an increase of methamphetamine.
The distribution of dietary intake values of dioxins, dioxin-like PCBs and non dioxin-like PCBs was characterized for the general Italian population.
The higher intake of PCBs due to consumption of farmed fish vs. wild fish is mainly due to the higher fat content in farmed fish.
Development of novel mass spectrometric methods for the selective measurement of therapeutic and illicit drugs in environmental samples.
Development of novel mass spectrometric methods for odour carachterization in environmental samples, for odour pollution and its toxicity.
A cyanobacteria-derived TLR4 antagonist (VB3323) has antiinflammatory and neuroprotective effects in mouse primary spinal cord cultures stimulated by LPS and in a mouse model of spontaneous motor neuron degeneration, the Wobbler mouse.

NATIONAL COLLABORATIONS

AMA Roma
ARPA Emilia Romagna
ARPA Veneto
ASL Bergamo
ASL Brescia
ASL Cagliari
ASL Como
ASL Cremona
ASL Lecco
ASL Lodi
ASL Milano
ASL Milano 1
ASL Milano 2
ASL Monza Brianza
ASL Napoli
ASL Vallecamonica-Sebino
ASL Varese
Centro Reach Srl
CLIR Spa Lomellina
CNR – IRSA
Comune di Peschiera del Garda (BS)

Comune di Rosignano Marittimo (LI)
Comune di Sant'Urbano (PD)
CSRA-Asti
Dipartimento delle Politiche Antidroga, Presidenza del Consiglio dei Ministri
Federchimica
Fondazione 'S. Maugeri'
INRAN-Istituto Nazionale di Ricerca sugli Alimenti e la Nutrizione
ISPO, Firenze
Istituto Clinico Humanitas, Milano
Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano
Istituto Superiore di Sanità
I.Z.S.L.T - Istituto Zooprofilattico Sperimentale del Lazio e Toscana
Metropolitana Milanese
Mineracqua
Ministero dell'Ambiente
Ministero della Salute
Ministero dello Sviluppo Economico
Politecnico di Milano
Politecnico di Torino
Provincia di Vercelli
Provincia Pordenone
Rotary Club Sirmione (BS)
Stazione Sperimentale dei Combustibili, Milano
Università degli Studi del Piemonte Orientale
Università degli Studi di Cagliari
Università degli Studi di Genova
Università degli Studi di Milano
Università degli Studi di Napoli "Federico II"
Università degli Studi di Palermo
Università degli Studi di Pavia
Università degli Studi di Perugia
Università degli Studi di Roma "La Sapienza"
Università degli Studi di Siena
Università degli Studi di Torino
Università dell'Insubria, Varese
Università degli Studi di Verona

INTERNATIONAL COLLABORATIONS

BASF Agricultural Centre, Limburgerhof, Germany
CEFIC, European Chemical Industry Council, Brussels, Belgium
Centre for Environmental Policy, Imperial College, London, UK
Danish Institute of Agricultural Sciences, Research Centre Foulum, Tjele, Denmark
Department of Analytical and Pharmaceutical Chemistry, The Royal Danish School of Pharmacy, Denmark
Department of Computer Science and Engineering, University of Galati, Romania
Department of Electrical and Computer Engineering, University of Patras, Greece
Department of Environmental Health, National Public Health Institute, Kuopio, Finland
Department of Environmental Science, Faculty of Science and Technology, Aarhus University, Aarhus, Finland
Department of Epidemiology & Public Health, Imperial College, London, UK
Department of Inland Fisheries, Institute of Freshwater Ecology and Inland Fisheries, Berlin, Germany
Department of Molecular Biology, University of Bergen, Bergen, Norway
Department of Organic Chemistry, Universidad de Cadiz, Cadiz, Spain
Environmental Chemistry, IIQAB-CSIC, Barcelona, Spain
Environmental Hygiene and Chemistry Department, Institute of Environmental Medicine and Hospital

Epidemiology, University of Freiburg, Germany
Environmental Protection Agency, US EPA - National Risk Management Research Laboratory (NRMRL), Cincinnati OH, USA
European Chemicals Agency, ECHA, Helsinki, Finland
European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Lisbon, Portugal
Faculté de Médecine et de Pharmacie, Université de Mons-Hainaut, Mons, Belgium
Faculty of Veterinary Medicine, Utrecht University, Utrecht, Netherlands
Food and Environment Research Agency, York, UK
Forschungszentrum Jülich GmbH, Jülich, Germany
Helmholtz-Zentrum für Umweltforschung UFZ, Leipzig, Germany
In Vitro Testing Industrial Platform, Tres Cantos (Madrid), Spain
Institute of Environmental Assessment and Water Research (IDAEA-CSIC) Barcelona, Spain
Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden
Institute of Pharmaceutical Chemistry, University of Pécs, Pécs, Hungary
Institute of Phytomedicine, Biological Control, Horticulture and Nematology, Vienna, Austria
Institute of Soil Science and Plant Cultivation, Pulawy, Poland
Interdisciplinary Nanotoxicity Center, Department of Civil and Environmental Engineering, Jackson State University, Jackson, Mississippi, USA
Interuniversitaeres Forschungsinstitut fuer Agrarbiotechnologie, Tulln, Austria
Istituto di Chimica di São Carlos, Università di São Paulo, Brazil
KnowledgeMiner Software, Berlin, Germany
KWR Water cycle Research Institute (KWR) Utrecht, Netherlands
Laboratory of Chemometrics & Bioinformatics, University of Orléans, Orléans, France
Laboratory of Neurobiology, Centro de Investigación Principe Felipe, Valencia, Spain
Lithuanian Institute of Agriculture, Vilnius, Lithuania
Liverpool John Moores University, Liverpool, UK
National Institute of Chemistry, Kemijski Institut Ljubljana, Ljubljana, Slovenia
Natural Resources Research Institute, University of Minnesota, Duluth, USA
National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands
Norwegian Institute for Water Research (NIVA), Oslo, Norway
Pesticide Safety Directorate, York, UK
Plant Protection Institute, Hungarian Academy of Sciences, Budapest, Hungary
PublicSpace Ltd, Lancaster, UK
Research Institute for Pesticides and Water, University Jaume I Castellón, Spain
Rudjer Boskovic Institute, Zagreb, Croatia
School of Biomedical Sciences, University of Ulster, Coleraine, UK
SETAC Europe, Brussels, Belgium
Symlog, Paris, France
Syngenta Crop Protection AG, Basel, Switzerland
Technische Universität Dresden, Dresden, Germany
TNO, Delft, Netherlands
Toxicological Centre, Department of Pharmaceutical Sciences, University of Antwerp, Antwerp, Belgium
Unit of Environmental Risk and Health, Flemish Institute for Technological Research, Boeretang, Belgium
Universitat Politècnica de Catalunya, Barcelona, Spain
Universitat Rovira i Virgili, Tarragona, Spain
University of Bath, Bath, UK
University of Paris - Sud 11, Paris, France
University of Santiago de Compostela, Santiago de Compostela, Spain
University of Tartu, Tartu, Estonia

EDITORIAL BOARD MEMBERSHIP

Journal of Environmental Science and Health, Part B (Emilio Benfenati), Journal of Environmental Science and Health, Part C (Emilio Benfenati), International Journal of Computational Intelligence (Emilio Benfenati), International Journal of Information Technology (Emilio Benfenati), International Journal of

Signal Processing (Emilio Benfenati), Chemistry Central Journal (Emilio Benfenati), Current Computer Aided Drug Design (Emilio Benfenati), Advances in Chemoinformatics and Computational Methods (Emilio Benfenati), Frontiers (Emilio Benfenati), The Open Toxicology Journal ((Emilio Benfenati), The Open Biomarkers Journal (Luisa Airoidi).

PEER REVIEW ACTIVITIES

Addiction, Analytical Chemistry, Analytical and Bioanalytical Chemistry, Chemical Biology & Drug Design, Chemical Research Toxicology, Chemometrics and Intelligent Laboratory Systems, CHEMOLAB, Chemosphere, Clinical Biochemistry, Drug and Alcohol Dependence, Environment International, Environmental Pollution, Environmental Modelling & Software, Environmental Science & Technology, Journal of Cellular Biochemistry, Journal of Chemical Information and Modeling, Journal of Environmental Monitoring, Journal of Food Composition and Analysis, International Journal of Molecular Science, Journal Computer-Aided Molecular Design, Journal of Environmental Monitoring, Journal of Hazardous Materials, Journal of Neuroscience Research, Molecular Diversity, Royal Society's Philosophical Transactions, Toxicology Letters, Waste Management, Water Research, International Journal of Environmental Analytical Chemistry, Molecular Nutrition and Food Research, Journal of Chromatography A, The Open Biomarkers Journal, The Open Biomarkers Journal, External review of the quality of the scientific outputs of the European Food Safety Authority (EFSA).

NATIONAL AND INTERNATIONAL COMMITTEE MEMBERSHIP

CCPF - Commissione Consultiva Prodotti Fitosanitari (Ministero della Salute, Ministero dell'Ambiente)
ECCO - European Commission Coordination
EFSA - European Food Safety Authority
IGQ - Commissione Ambiente e Commissione Sicurezza

EVENT ORGANIZATION

ORCHESTRA Workshop “REACH & QSAR: What can we learn from case studies?”, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy, April 6, 2011.

ORCHESTRA Course on In Silico Methods, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy, April 5 and 7, 2011.

Organization, as leader of the Local Organizing Committee (Emilio Benfenati), of the 21st SETAC Europe Annual Congress, Milan, Italy, May 15-19, 2011.

59th American Society for Mass Spectrometry Conference, Environmental Interest Group, Denver, CO, USA, June 3, 2011.

Training Workshop on QSAR as a Tool in Chemical Risk Assessment, Lisbon, Portugal, June 20, 2011.

Meeting of the Italian “Gruppo di lavoro sui metodi QSAR per il REACH”, Ministero della Salute, Rome, Italy, September 19, 2011.

Workshop "REACH & QSAR Models for Environment: Discussion based on Case Studies to improve Documentation and Acceptance", Umweltbundesamt, Dessau-Roßlau, Germany, November 22, 2011.

CONFERENCE AND WORKSHOP CONTRIBUTIONS

EMCDDA meeting on Wastewater Analysis (a potential tool for monitoring illicit drugs), Lisbon, Portugal, January 28, 2011.

6° Conferenza Sicurezza Prodotti: REACH, Milan, Italy, February 3, 2011.

Risk assessment. Metodi di valutazione per l'ambiente e per l'uomo. Settimana Ambiente 2011, Milan, Italy, February 21-25, 2011.

Annual meeting of the Society of Toxicology, Washington DC, USA, March 6-10, 2011.

I Workshop EU project JUST/2010/DPIP/AG/1410: New methodological tools for policy and programme evaluation,. Roma, Italy, March 7-9, 2011.

OSIRIS ITS Stakeholder Workshop, Leipzig, Germany, March 8-9, 2011.

ORCHESTRA Workshop “REACH & QSAR: What can we learn from case studies?”, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy April 6, 2011.

ORCHESTRA Course on In Silico Methods, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy, April 5 and 7, 2011.

IEEE Symposium Series on Computational Intelligence, Paris, France, April 11-15, 2011.

Conferenza InterMaster “ Caratterizzazione tossicologica delle sostanze chimiche: prepararsi al futuro con l’esperienza maturata nel 2010 per il REACH”, Pavia, Italy, May 7, 2011.

21st SETAC Europe Annual Congress, Milan, Italy, May 15-19, 2011.

14th International Workshop on QSAR in Environmental and Health Sciences, Montreal, Canada, May 24-28, 2011.

59th American Society for Mass Spectrometry Conference, Denver, CO, USA, June 5-9, 2011.

Training Workshop on QSAR as a Tool in Chemical Risk Assessment, Lisbon, Portugal, June 20, 2011.

2° Scuola Nazionale di Chimica dell’Ambiente e dei Beni Culturali. Il presente e il futuro, Feltre (Belluno), Italy, July 4-8, 2011.

RECETO PhD course: Use of QSAR models - practical use of the CAESAR models for legislative purposes (e.g. REACH legislation), Copenhagen, Denmark, August 23, 2011.

EUROTOX 2011 - 47th Congress of the European Societies of Toxicology, Paris, France, August 28-31, 2011.

CMTPI 2011 - 6th International Symposium on Computational Methods in Toxicology and Pharmacology Integrating Internet Resources, Maribor, Slovenia, September 3-7, 2011.

II Workshop EU project JUST/2010/DPIP/AG/1410: New methodological tools for policy and programme evaluation, Rome, Italy, September 19-21, 2011.

Workshop "REACH & QSAR Models for Environment: Discussion based on Case Studies to improve Documentation and Acceptance", Umweltbundesamt, Dessau-Roßlau, Germany, November 22, 2011.

Sardinia 2011 13th International Waste Management and Landfill Symposium, S. Margherita di Pula (CA), Italy, October 3-7, 2011.

4th RISKCYCLE Workshop "Sustainable Waste Management of additives in products: A global challenge", Dehli, India, October 12-13, 2011.

Expert Meeting of EUROECOTOX on the use of alternative methods, Leipzig, Germany, October 17-18, 2011.

Workshop "Incenerimento e qualità dell'aria", Bolzano, Italy, October 24, 2011.

6th Meeting of the OECD QSAR Toolbox Management Group, Berlin, Germany, October 26-27, 2011.

Drugs in the environment. Ecopharmacovigilance for better health. London, UK, October 31, 2011.

American Heart Association, Orlando, Florida, USA, November 12-15, 2011.

GRANTS AND CONTRACTS

A2A Brescia

ACEGAS S.p.A, Trieste

AIDEPI (Associazione delle Industrie del Dolce e della Pasta Italiane)

AIIPA (Associazione Italiana Industrie Prodotti Alimentari)

AMA, Roma

ASL Cagliari

ASL Como

ASL Mantova

ASL Napoli 2

ASSOFOODTEC/UCIMAC (Costruttori Italiani Macchine per Caffè Espresso ed Attrezzature per Bar)

BASF Italia S.r.l.

Bergamo Pulita S.r.l.

Bluegreen Biotech

Bracco Imaging Spa

Cambrex, Paullo (MI)

Catanzaro Costruzioni S.r.l.

Chemservice S.r.l.

CLIR S.p.A.

COGEIDE S.p.A.

COOP Italia

CSRA

Comune di Gorla Maggiore (VA)

Comune di Lomello (PV)

Comune di Mazzano e Rezzato (BS)

Comune di Rosignano Marittimo (LI)

Comune di Sant'Urbano (PD)

Consorzio Quadrifoglio S.p.A.

Dipartimento delle Politiche Antidroga, Presidenza del Consiglio dei Ministri
ECODECO S.r.l.
EnergyGreen S.r.l.
European Commission (ANTARES, ORCHESTRA, OSIRIS, RISKCYCLE, ToxBank)
Federchimica, Milano
FIAT Auto S.p.A.
Fondazione CARIPLO, Milano
Fondazione Italo Monzino, Milano
Gruppo CSA, S.p.a. Rimini (RN)
HERA S.p.A. (Holding Energia Risorse Ambiente)
INDENA S.p.A.
Istituto Superiore di Sanità, Roma
I.Z.S.L.T - Istituto Zooprofilattico Sperimentale del Lazio e Toscana
Lachifarma, Zollino (LE)
Ministero dell'Ambiente, Italia
Ministero della Salute, Italia
Nufarm S.A.S., Francia
Oxon Italia S.p.A., Pero (MI)
Politecnico di Milano
Provincia di Pordenone
Provincia di Vercelli
Regione Lombardia
SO.GE.NU.S. S.p.A
Tenacta Group
T.M.E. S.p.A.
Università degli Studi di Milano
Veolia Servizi Ambientali S.p.A.

SCIENTIFIC PUBLICATIONS (2011)

Brunelli L, Campagna R, Airoidi L, Cauli O, Llansola M, Boix J, Felipo V, Pastorelli R
Exploratory investigation on nitro- and phospho-proteome cerebellum changes in hyperammonemia and hepatic encephalopathy rat models.
Metab Brain Dis 2011 E-pub

Campagna R, Brunelli L, Airoidi L, Fanelli R, Hakansson H, Heimeier R A, De Boever P, Boix J, Llansola M, Felipo V, Pastorelli R
Cerebellum proteomics addressing the cognitive deficit of rats perinatally exposed to the food-relevant polychlorinated biphenyl 138
Toxicol Sci 2011 123 : 170-179

Mazzoletti M, Bortolin F, Brunelli L, Pastorelli R, Di Giandomenico S, Erba E, Ubezio P, Brogginini M
Combination of PI3K/mTOR inhibitors: antitumor activity and molecular correlates
Cancer Res 2011 E-pub

Fjodorova N, Novich M, Roncaglioni A, Benfenati E
Evaluating the applicability domain in the case of classification predictive models for carcinogenicity based on the counter propagation artificial neural network
J Comput Aid Mol Des 2011 25 : 1147-1158

Gonella Diaza R, Roncaglioni A, Benfenati E
In silico approaches to screening dietary endocrine disruptors
in: Pongratz I, Vikstrom Bergander L (Eds.), Hormone-disruptive chemical contaminants in food, Royal Society of Chemistry, Cambridge (2011), 170-183

Milan C, Schifanella O, Roncaglioni A, Benfenati E
Comparison and possible use of in silico tools for carcinogenicity within REACH legislation
J Environ Sci Health C 2011 29 : 300-323

Benfenati E, Gonella Diaza R, Cassano Antonio, Pardoe S, Gini G, Mays C, Knauf R, Benighaus L
The acceptance of in silico models for REACH: Requirements, barriers, and perspectives

Chem Cent J 2011 5 : 58

Toropov A A, Toropova A P, Benfenati E, Gini G, Leszczynska D, Leszczynski J
SMILES-based QSAR approaches for carcinogenicity and anticancer activity: Comparison of correlation weights for identical SMILES attributes
Anti-Cancer Agents in Medicinal Chemistry 2011 11 : 974-982

Toropov A A, Toropova A P, Martyanov S E, Benfenati E, Gini G, Leszczynska D, Leszczynski J
Comparison of SMILES and molecular graphs as the representation of the molecular structure for QSAR analysis for mutagenic potential of polyaromatic amines
Chemometrics Intelligent Laboratory System 2011 109 : 94-100

Colombo A, Benfenati E, Bugatti S G, Celeste G, Lodi M, Rotella G, Senese V, Fanelli R
Concentrations of PCDD/PCDF in soil close to a secondary aluminum smelte
Chemosphere 2011 85 : 1719-1724

Casalegno M, Benfenati E, Sello G
Identification of toxifying and detoxifying moieties for mutagenicity prediction by priority assessment
J Chem Inf Model 2011 51 : 1564-1574

Toropova A P, Toropov A A, Benfenati E, Gini G, Leszczynska D, Leszczynski J
CORAL: Quantitative Structure-Activity Relationship models for estimating toxicity of organic compounds in rats
J Comput Chem 2011 42 : 2727-2733

Toropova A P, Toropov A A, Benfenati E, Gini G, Leszczynska D, Leszczynski J
QSAR modeling of anxiolytic activity taking into account the presence of keto- and enol-tautomers by balance of correlations with ideal slopes
Cent Eur J Chem 2011 9 : 846-854

Adler S, Basketter D, Creton S, Pelkonen O, Van Benthem J, Zuang V, Andersen K E, Angers-Loustau A, Aptula A O, Bal-Price A, Benfenati E, Bernauer U, Bessems J, Bois F Y, Boobis A, Brandon E, Bremer S, Broschard T, Casati S, Coecke S, Corvi R, Cronin M T D, Daston G, Dekant W, Felner S, Grignard E, Gundert-Remy U, Heinonen T, Kimber I, Kleinjans J, Komulainen H, Kreiling R, Kreysa J, Leite S B, Loizou G, Maxwell G, Mazzatorta P, Munn S, Pfuhler S, Phrakonkham P, Piersma A, Poth A, Prieto P, Repetto G, Rogiers V, Schoeters G, Schwarz M, Serafimova R, Tahti H, Testai E, Van Delft J, van Loveren H, Vinken M, Worth A, Zaldivar J
Alternative (non-animal) methods for cosmetics testing: current status and future prospects-2010
Arch Toxicol 2011 85 : 367-485

Toropova A P, Toropov A A, Benfenati E, Gini G
Simplified Molecular Input-Line Entry System and International Chemical Identifier in the QSAR Analysis of Styrylquinoline Derivatives as HIV-1 Integrase Inhibitors
Chem Biol Drug Des 2011 77 : 343-360

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CORAL: Quantitative Structure-Activity Relationship models for estimating toxicity of organic compounds in rats
J Comput Chem 2011 42 : 2727-2733

Baderna D, Maggioni S, Boriani E, Gemma S, Molteni M, Lombardo A, Colombo A, Bordonali S, Rotella G, Lodi M, Benfenati E
A combined approach to investigate the toxicity of an industrial landfill's leachate: chemical analyses, risk assessment and in vitro assays
Environmental Research 2011 111 : 603-613

Toropova A P, Toropov A A, Benfenati E, Gini G, Leszczynska D, Leszczynski J
CORAL: QSPR models for solubility of [C60] and [C70] fullerene derivatives
Mol Divers 2011 15 : 249-256

Benfenati E, Toropov A A, Toropova A P, Manganaro A, Gonella Diaza R
CORAL Software: QSAR for Anticancer Agents
Chem Biol Drug Des 2011 77 : 471-476

Toropov A A, Toropova A P, Lombardo A, Roncaglioni A, Benfenati E, Gini G
CORAL: Building up the model for bioconcentration factor and defining its applicability domain
Eur J Med Chem 2011 46 : 1400-1403

Toropova A P, Toropov A A, Benfenati E, Gini G
Co-evolutions of correlations for QSAR of toxicity of organometallic and inorganic substances: An unexpected good prediction based on a model that seems untrustworthy
Chemometrics Intelligent Laboratory System 2011 105 : 215-219

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Analysis of the co-evolutions of correlations as a tool for QSAR-modeling of carcinogenicity: an unexpected good prediction based on a model that seems untrustworthy
Cent Eur J Chem 2011 9 : 166-174

Toropova A P, Toropov A A, Benfenati E, Gini G
QSAR for modelling toxicity of inorganic substances to rats by means of CORAL
Cent Eur J Chem 2011 9 : 75-85

Ferrari T, Gini G, Golbamaki Bakhtyari N, Benfenati E
Mining toxicity structural alerts from SMILES: A new way to derive structure activity relationships
in: Proc. 2011 IEEE Symposium on Artificial Life (IEEE Symposium Series on Computational Intelligence - SSCI 2011), April 11-15, 2011, Paris, France, IEEE 2011, ISBN: 978-1-4577-0470-3

Canta A, Chiorazzi A, Carozzi V, Meregalli C, Oggioni N, Sala B, Crippa L, Avezza F, Forestieri D, Rotella G, Zucchetti M, Cavaletti G
In vivo comparative study of the cytotoxicity of a liposomal formulation of cisplatin (lipoplatin?)
Cancer Chemother Pharmacol 2011 68 : 1001-1008

De Paola M, Visconti L, Vianello E, Mattana F, Banfi G, Corsi M M, Beghi E, Mennini T
Circulating cytokines and growth factors in professional soccer players: correlation with in vitro-induced motor neuron death
Eur J Neurol 2011 18 : 85-92

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Bioresour Technol 2011 102 : 4638-4645

Martinez Bueno M J, Ucles S, Hernando M D, Davoli E, Fernandez-Alba A
Evaluation of selected ubiquitous contaminants in the aquatic environment and their transformation products. A pilot study of their removal from a sewage treatment plant
Water Res 2011 45 : 2331-2341

Vannini C, Domingo G, Marsoni M, De Mattia F, Labra M, Castiglioni S, Bracale M
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Aquat Toxicol 2011 101 : 459-465

Ulaszewska M M, Zuccato E, Capri E, Iovine R, Colombo A, Rotella G, Generoso C, Grassi P, Melis M, Fanelli R
The effect of waste combustion on the occurrence of polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) in breast milk in Italy
Chemosphere 2011 82 : 1-8

Castiglioni S, Bagnati R, Melis M, Panawennage D, Chiarelli M P, Fanelli R, Zuccato E
Identification of cocaine and its metabolites in urban wastewater and comparison with the human excretion profile in urine
Water Res 2011 45 : 5141-5150

Zuccato E, Castiglioni S, Tettamanti M, Olandese R, Bagnati R, Melis M, Fanelli R
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Drug Alcohol Depend 2011 118 : 464-469

Van Nuijs A L N, Castiglioni S, Tarcomnicu I, Postigo C, Lopez de Alda M J, Neels H, Zuccato E, Barcelo D, Covaci A
Illicit drug consumption estimations derived from wastewater analysis: A critical review
Sci Total Environ 2011 409 : 3564-3577

Ulaszewska M M, Zuccato E, Davoli E
PCDD/Fs and dioxin-like PCBs in human milk and estimation of infants daily intake: A review
Chemosphere 2011 83 : 774-782

Melis M, Castiglioni S, Zuccato E
Metabolism and excretion of illicit drugs in humans.
In: Castiglioni S, Zuccato E, Fanelli R (Eds), *Illicit drugs in the environment: Occurrence, analysis, and fate using mass spectrometry*, Wiley, Hoboken, 31-52 (2011)

Bagnati R, Davoli E
Analytical methods for the detection of illicit drugs in wastewaters and surface waters.
In: Castiglioni S, Zuccato E, Fanelli R (Eds), *Illicit drugs in the environment: Occurrence, analysis, and fate using mass spectrometry*, Wiley, Hoboken, 55-67 (2011)

Castiglioni S, Zuccato E

Occurrence of illicit drugs in wastewater and surface water in Italy.

In: Castiglioni S, Zuccato E, Fanelli R (Eds), *Illicit drugs in the environment: Occurrence, analysis, and fate using mass spectrometry*, Wiley, Hoboken, 137-151 (2011)

Zuccato E, Castiglioni S

Assessing illicit drug consumption by wastewater analysis: History, potential, and limitation of a novel approach.

In: Castiglioni S, Zuccato E, Fanelli R (Eds), *Illicit drugs in the environment: Occurrence, analysis, and fate using mass spectrometry*, Wiley, Hoboken, 291-304 (2011)

Panawennage D, Castiglioni S, Zuccato E, Davoli E, Chiarelli M P

Measurement of illicit drug consumption in small populations: Prognosis for noninvasive drug testing of student populations.

In: Castiglioni S, Zuccato E, Fanelli R (Eds), *Illicit drugs in the environment: Occurrence, analysis, and fate using mass spectrometry*, Wiley, Hoboken, 321-331 (2011)

Fanelli R

Conclusions and future perspectives.

In: Castiglioni S, Zuccato E, Fanelli R (Eds), *Illicit drugs in the environment: Occurrence, analysis, and fate using mass spectrometry*, Wiley, Hoboken, 335-338 (2011)

Melis M, Zuccato E

Analysis of PCBs in food.

In: Nollet L M L (Ed.), *Analysis of endocrine disrupting compounds in food*, Wiley, Chichester, 19-48 (2011)

Sala F, Livi V, Cereda R, Bagnati R, D'Incalci M, Zucchetti M

Development and validation of a high-performance liquid chromatography-tandem mass spectrometry method for the determination of the novel proteasome inhibitor CEP-18770 in human plasma and its application in a clinical pharmacokinetic study

J Mass Spectrom 2011 46 : 1039-1045

Cod: 13269

Bonati M, Severino F, Bagnati R, Carrà A, Fanelli R

Millet-porridge with *Artemisia annua* as first aid for African children with malaria?

Journal Alternative Complementary Medicine 2011 17 : 371-373

Sulaiman G M, Al Sammarrae K W, Ad'hiah A H, Zucchetti M, Frapolli R, Bello E, Erba E, D'Incalci M, Bagnati R

Chemical characterization of Iraqi propolis samples and assessing their antioxidant potentials

Food Chem Toxicol 2011 49 : 2415-2421

Fattore E, Paiano V, Borgini A, Tittarelli A, Bertoldi M, Crosignani P G, Fanelli R

Human health risk in relation to air quality in two municipalities in an industrialized area of Northern Italy

Environ Res 2011 111 : 1321-1327

LAY PRESS SELECTION (2011)

Capelli L, Sironi S, Davoli E, Valutazione di impatto olfattivo e tossicologico delle emissioni di odore: il caso di Terni

In: M.C. Aprea, R. Demi, S. Luzzi, A. Peretti, G. Sciarra (Eds.), *Atti del 28° Congresso Nazionale AIDII, 22-24 giugno 2011, Ravenna, Italia*. Tipografia PI-ME Editrice, Pavia, 2011, 287-293

Capelli L, Sironi S, Davoli E, Risultati della valutazione di tossicità delle emissioni odorigene nella Conca Ternana

In: *Atti della giornata di studio "Impatto odorigeno: lo stato dell'arte in Italia. Aspetti tecnici e nuovi sviluppi normativi"*, Rapporti G.S.I.S.R. N. 253 05/11, 05 maggio 2011, Milano, Italy, 2011, 102-116

OTHER PUBLICATIONS (2011)

Castiglioni S, Zuccato E, Fanelli R (Eds), *Illicit drugs in the environment: Occurrence, analysis, and fate using mass spectrometry*, Wiley, Hoboken, 2011

Bilitewski B, Barcelo D, Darbra R M, v.d. Voet E, Belhaj M, Benfenati E, Grundmann V, Report on the 1st workshop of the RISKCYCLE coordination action. Hanoi, Vietnam, 4–5 May 2010, *Environ Sci Pollut Res* 2011 18 : 827-828

RESEARCH ACTIVITIES

Laboratory of Molecular Toxicology

Proteome Analysis

Proteome analysis includes protein separation by one- and two-dimensional gel electrophoresis, protein excision from the gel, their digestion with proteolytic enzymes and their identification by mass spectrometry (MALDI-TOF-MS, LC-ESI-MS/MS) coupled to the use of existing databases. Alternatively, peptides resulting from the digestion of protein mixtures with specific proteases are separated by two-dimensional liquid chromatography.

Toxicoproteomics

Studies are ongoing on the characterization of changes in the proteome profile induced by environmental toxic compounds, with the aim of obtaining protein biomarkers with the ability to differentiate two or more biological states. Proteome changes in tissues and target organs of animals, and cells treated with endocrine disruptors, estrogens, or environmental carcinogens, are related to functional changes during toxicological processes.

Clinical Proteomics

Qualitative and quantitative proteome changes resulting from the exposure to environmental toxic compounds or in pathological conditions are monitored in human biological plasma and urine. Ongoing studies aim at the characterization of protein biomarkers for early diagnosis of diseases and for the identification of therapeutic targets.

Pathways analysis

An integrated data-mining platform such as MetaCore (GeneGo Inc., USA) is used in order to map the differentially expressed proteins into biological networks and for functional interpretation of the protein data.

Metabolomics

Metabolites are the biological endpoints of gene expression and enzyme activity and include small molecules such as amino acids, carbohydrates, fatty acids, hormones, etc., that provide the metabolic phenotype of individuals. Metabolomic research focuses on the quantitative analysis of metabolites in biological fluids to link human metabolic profile variations to endogenous or exogenous pathophysiological stimuli and to genetic modifications.

Selected metabolites are extracted from plasma or urine by solid phase extraction and analyzed by HPLC coupled to high-resolution mass spectrometry.

The integration of proteomic and metabolomic studies will provide information that can help to better understand disease development and to identify preventive interventions.

Molecular Epidemiology

The laboratory works mainly on the measurement of biological markers used to assess human exposure to environmental toxic compounds. Our studies include DNA- and blood protein-adduct formation by several environmental carcinogens. In addition, we study whether the polymorphism of genes coding for enzymes involved in the activation and detoxification of carcinogens are determinants of adduct formation. Genotypes are detected by restriction fragment length polymorphism analysis, after the amplification by polymerase chain reaction of specific nucleotide sequences of the genes under study.

The laboratory participates in an international cooperation study aimed at the collection of reference values on allele and genotype frequency of the most common metabolic enzyme polymorphisms in control populations.

Laboratory of Analytical Biochemistry

Identification and characterization of proteins by mass spectrometry

Our laboratory is developing different analytical and instrumental techniques –based on mass spectrometry– for the identification and 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.

Proteomics in oncology

This activity is mainly aimed at discovering –among the proteins we find abnormally secreted by human cancer cell lines– new molecules of oncological interest, and in particular novel candidate therapeutic targets or diagnostic/prognostic biomarkers. Ongoing projects include the characterization of the secretomes of cancer cell lines *in vitro* to identify the most relevant abnormalities. The complex alterations observed in the cancer secretomes are then rationalized and interpreted by using “systems biology” tools that are able to highlight the functional networks most significantly perturbed.

Glycoproteomics

Glycoproteomic characterization (amino acid sequence, glycosylation site(s), and type of bound saccharides) of plant proteins of pharmaceutical/nutraceutical interest by gel electrophoresis, enzymatic degradation and mass spectrometry.

Inflammation and neurodegeneration induced by environmental agents

We are studying the neurotoxic effects of endotoxin (LPS) and other environmental contaminants (PBDE e methylmercury) on neuronal cell primary cultures and in animal models. The mechanisms leading to the activation of the inflammatory reaction are studied by biochemical and immunochemical methods *in vitro*, and by histological and functional analysis *in vivo*. Novel anti-inflammatory drugs of natural origin are tested in this model, with the aim of evaluating their neuroprotective effects.

Laboratory of Environmental Chemistry and Toxicology

Development and use of analytical methods to evaluate contamination in water bodies, soil, biota, human samples in exposed population

Analytical methods are developed to study environmental pollutants in water ecosystems, landfills, contaminated sites. Qualitative and quantitative analyses of organic pollutants are done by mass spectrometry (GC-MS, LC-MS, LC-MS/MS). Typical analyses include PCDD/F, PCB, PAH, polybrominated diphenylethers, pesticides, endocrine disruptor chemicals, and industrial pollutants.

Studies on environmental, toxicological and ecotoxicological properties of chemicals

Research is carried out on pollutant properties, exploring a broad range of toxicological and environmental properties in order to get safer chemicals. The use of computational models allows processing millions of chemicals. This involves searching literature data, comparing and evaluating different sources, and mainly developing predictive models to cope with the lack of experimental data. Thus, we develop models starting merely from the chemical structure. The research addresses the different kinds of chemical descriptors and chemical fragments, obtained with different software. Then, we develop models using algorithms such as neural network, fuzzy logic, genetic algorithms, classifiers, multivariate analysis, etc. Different methods are compared and integrated within a structured ensemble. Standardized methods for pesticides were developed and validated according to OECD guidelines. Innovative tools to evaluate the applicability domain of the models have been developed, to get predictions useful for regulatory purposes, such as REACH, biocide,

pesticides, and other regulations.

Risk assessment of pollutants

Studies are aimed at assessing the risk of pollutants for human population and environment. For this we model transport and diffusion of pollutants, to obtain a predicted concentration on given space and time scales. Such an activity is integrated with those above described on chemical analyses and toxicity prediction, to achieve a continuous transfer of data and research.

Research on pollutants emitted in the atmosphere (Unit of Industrial and Environmental Hygiene)

Studies address different aspects of atmospheric pollution. Research deals with: sampling areas around the pollution source, chemical analyses, transport modeling depending on meteorological conditions and orography, risk assessment for population and environment. Qualitative and quantitative analyses are done by gas chromatography-mass spectrometry using high resolution for PCDDs/PCDFs, and negative ion-chemical ionization for PCBs.

Laboratory of Mass Spectrometry

Particulate air pollution

Epidemiological studies consistently show an association between an increasing number of pathologies, both acute and chronic, and particulate air pollution. This has been shown not only in respiratory, but in cardiovascular diseases as well. Airborne particulate sampling and analysis strategies are developed to characterize both adsorbed compounds and exposition in different activities.

Method development in environmental sciences

Methods, analytical methodologies, instrumentation and software for data acquisition and reduction, are developed for environmental studies. High-sensitivity instrumentation, mainly based on mass spectrometry, is developed for trace and ultra-trace analysis. Also, transportable instrumentation is developed for field studies or continuous monitoring.

Characterization of environmental odor annoyance and its toxicity

Characterization of odors poses several analytical problems because they result from a complex mixture of compounds (odorants) stimulating receptors in the nasal cavity. Most odorants are volatile organic compounds (VOC) generated by bacterial degradation of organic matter. They are often present at trace levels, while numerous sources can contribute to the total odor. Using sampling techniques specifically developed for olfactometry, solid phase microextraction and GC/MS analysis, we can detect traces (low ppb to high ppt) of a wide polarity/volatility range of airborne VOC odorant compounds. With a chemometric approach, we can characterize the sources of emissions, assess odor control methods, and identify emissions that contribute to odors in ambient air.

Laboratory of Food Toxicology

Nutrition studies: Chemical contaminants in food. Nutrition and Health

We are studying human exposure to dietary PCBs and dioxins in Italy. In particular, contaminants were measured in samples of human milk collected from mothers living in highly contaminated areas. Further studies were aimed at measuring PCBs and dioxins in samples of fish caught in Italy and in food items from an Italian area at high risk of contamination.

Further studies will investigate the relationship between dietary sodium intake and health. In particular this activity will set up and apply practical methodologies to reduce sodium content of the daily diet in groups of volunteers.

Therapeutic and illicit drugs in the environment

Pharmaceuticals are a class of emerging environmental pollutants. We have organized a campaign to detect the presence of pharmaceuticals and their metabolites in Italian rivers and sewage treatment plants and in samples of drinking water, with the aim of characterizing the contamination and assessing related risks. Further ongoing studies are aimed at investigating a possible relationship between antibiotic occurrence and resistance in environmental bacteria.

The possible presence of illicit drugs in water samples from sewage treatment plants and rivers was investigated, starting with cocaine and its metabolites. Their levels, used to estimate drug abuse in the local population, revealed that cocaine consumption greatly exceeds official estimates. This approach has been subsequently extended to include other common drugs of abuse such as cannabis, opiates (heroin, morphine), and amphetamines (amphetamine, methamphetamine, ecstasy). Our evidence-based method allows monitoring of patterns and trends of drug abuse in local communities, and is able to detect qualitative and quantitative consumption changes in real time. This tool can therefore complement survey methods in more realistically describing the drug abuse phenomenon. Ongoing studies are focussed to assess consumptions at national scale, in collaboration with the National Agency for Drug Policy, at regional scale in collaboration with Regione Lombardia, and locally, in collaboration with Metropolitana Milanese.

Further ongoing studies, carried out in collaboration with several research groups in Europe and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), are aimed to study illicit drug consumption in Europe. We will simultaneously measure consumptions in 19 cities in 14 different nations and will compare our results with consumptions estimated by traditional epidemiological methods.

Unit of Environmental Pollutants Risk Assessment

Toxicological risk assessment

Starting from real cases of contamination, the unit aims to develop methods for the exposure assessment also employing probabilistic approaches, and more refined statistical models. The activities focus on risk assessment related to specific environmental conditions, or human activities, which pose a risk for human health. These studies include risk assessments related to contamination of water or soil, emissions of toxic pollutants from waste management processes, including transfer of these compounds into the food chain. During 2011, studies focused on health effects due to waste disposal into landfills, soil treatment with sludge and the potential transfer of persistent organic pollutants across the food chain, and health effects due to atmospheric pollution.

Research activities also include measurement of contaminants in environmental samples, and assessment of human exposure. Specific research projects focus on analysis of polychlorinated and polybrominated dioxins and furans (PCDD, PBDD, PCDF and PBDF), polychlorinated biphenyls (PCBs), perfluorooctanoic acid (PFOA), and perfluorooctane sulphonate (PFOS), in aquatic organisms at different levels of the food chain, and farmed fish coming from different areas of the Mediterranean sea. The purpose is to estimate the exposure to these pollutants through fish consumption in the general Italian population.

Another study on-going during 2011 focuses on analysis and exposure assessment of acetaldehyde as contaminant in beverage samples, in order to assess the risk of health effects for general population.

Unit of Analytical Instrumentation

Development and application of analytical methods for compounds of biological and environmental interest.

Biological fluids and environmental samples are analysed mainly using solid phase extraction (SPE) and liquid chromatography - mass spectrometry (LC-ESI-MS/MS). Proteins and peptides are also analysed by laser desorption ionization techniques. Tissue samples are directly analyzed by using MALDI or PALDI Imaging (Matrix or nanoParticle Laser Desorption Ionization).

Available instruments include liquid chromatographs and mass spectrometers equipped with different analyzers: time of flight (TOF), triple quadrupoles, ion traps and high resolution LTQ-Orbitrap, with conventional and nanoElectroSpray sources.

Substances of interest include proteins, peptides, hormones, pharmaceuticals, drugs of abuse, and other environmental contaminants (pesticides, perfluorinated compounds).