Centro Internazionale di Studi Avanzati su Ambiente, ecosistema e Salute umana

International Open Conference
Linking environmental and epidemiological data in contaminated areas

Tuesday 21 November 2017
NRC Area, via Via Ugo la Malfa, 153, Palermo

Conference Report

This report is a summary of the presentations done during the Conference, revised by the authors, to constitute a knowledge basis, to inform the members of the ERA-ENVHEALTH network, and to build competence for further research implementation.

We thank Francesca Gorini and Paolo Lauriola for drafting the report

Institute of Clinical Physiology, National Research Council, Pisa, Italy
January 2018

International Open Conference

Tuesday 21 November 2017

CNR Palermo, via Via Ugo la Malfa, 153

Linking environmental and epidemiological data in contaminated areas

9:00-9:30 *Welcome of participants.* Liliana Cori, IFC-CNR

9:30-10:00 Institutional welcome: Salvatore Scondotto, D.A.S.O.E.

10:00-11:00 Chairs and rapporteurs: Paolo Lauriola and Francesca Gorini

Lilian Corra, ISDE Senior Expert on Health and Environment
Health issues under the Minamata Convention: "to Protect Health and the Environment"

11,00-12,30 *Coffee break*

Mario Sprovieri, IAMC-CNR
CISAS, International Centre of advanced study in environment, ecosystem and human health

Angela Cuttitta, IAMC-CNR
Research on marine environment

Fabio Cibella, IBIM-CNR
Planned environmental health research in three sites in Italy – birth cohort study

Fabrizio Bianchi, IFC-CNR

Planned environmental health research in three sites in Italy – association between pollutants and selected health conditions

12:30-13:30

Ric Van Pol, RIVM
Human Biomonitoring: PFOA case in the Netherlands

Amalia Gastaldelli, IFC-CNR
Human Biomonitoring in the CISAS project

13,30 – 14,30 lunch

14,30 – 17:00

Ariana Zeka, Institute of Environment, Health and Societies, Brunel University, London
Environmental Public Health Tracking

Joana Ferreira, University of Aveiro, Portugal
From atmospheric emissions to health: an integrated assessment approach

Francesco Forastiere, IBIM-CNR, Associate Researcher; WHO Geneva, Consultant
Health Impact Assessment of Air Pollution at national and global level

Fabrizio Bianchi, IFC-CNR
Environmental epidemiology in contaminated sites: from ecological to etiological studies

17.00-17:30 conclusions

Introduction Liliana Cori

Welcome dear colleagues to the Palermo Open Conference, "Linking environmental and epidemiological data in contaminated areas".

One year after the launch of the International Centre for advanced study in environment, ecosystem and human health, **CISAS Project**, the coordinators decided to host the General Assembly meeting of the **ERA ENVHEALTH** network. **ERA ENVHEALTH** is a network of Institutions operating in Europe since 2008 with a Seventh Framework Programme grant (ER-NET, CSA Coordination Action). The network directly funded three research projects in the environment and health domain, produced a database of projects and a tool to support the dialogue between researchers and policy makers. After the official conclusion of the project, most of the participants decided to go on promoting exchange and collaboration and fostering new ideas to enhance the uptake of environmental and health issues in Europe. Yesterday, we hold at the NRC headquarters in Palermo the annual GA meeting, with Anses (*Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail*) and the *Ministère de la Transition écologique et solidaire* from France, the University of Aveiro, Portugal, the RIVM, National Institute for Public Health and the Environment from the Netherlands, and the Italian CNR, National Research Council, in representation of the whole network that is presently composed by 13 members.

This is particularly significant, as the network is representing the ongoing work developed by the Italian National Research Council during the last ten years in the environment and health domain.

The Department of Earth System Sciences and Environmental Technologies, DTA, promoted in 2007 the Environment and Health Interdepartmental Project, PIAS, and participated in the ERA ENVHEALTH network activities. DTA invited in Rome the 2013 meeting of the network, the first convened on a voluntary basis.

DTA and DBS, the Department of Biomedical Sciences, are joining now their efforts to develop multidisciplinary studies focusing on hot-spot areas, three Italian Contaminated Sites of National Interest (CS) under the CISAS project umbrella.

In this framework, the experience of the ERA ENVHEALTH network members is crucial, to compare and promote competence and expertise, and to open the perspective to the European landscape.

As we all know, the international dimension (or, better, the lack of boundaries) is an integral characteristic of environmental determinants. One of the pollutants ubiquitously detected in the environment, the mercury, is the main pollutant in one of the CISAS areas, Priolo, and it is the subject of a series of international agreement, recently culminated with the entry into force of the Minamata Convention in 2017. For this reason, we were delighted to have **Lilian Corra**, who participated to several Conventions on chemicals and international working groups. She is directly responsible for the inclusion of the Article 16, Health aspects, in the Minamata Convention, being representative of the International Society Doctors for the Environment, ISDE, at the discussion tables where the text was

elaborated. The experience of dr. Corra and her international vision will help us to widen the perspective of our research.

Together with the National Research Council experts involved in the CISAS project (**Mario Sprovieri**, **Angela Cuttitta, Fabrizio Bianchi and Fabio Cibella**), two members of the ERA ENVHEALTH network presented the activities of their respective Institutions during the Open Conference.

Human Biomonitoring, HBM, is a research tool that will be used in CISAS: **Ric van Pol**, from RIVM, the Netherlands, presented the case of PFOA pollution, widely detected in water, that has been recently faced in North Eastern Italy too. **Amalia Gastaldelli**, IFC-CNR, presented a specific HBM used to identify alteration in metabolism that can promote liver disease.

Joana Ferreira, from the University of Aveiro, Portugal, presented developments in the integrated assessment from atmospheric emissions to health that is a theme of crucial relevance.

We have been in contact with INPHET, International Network on Public Health and Environment, a group of researchers committed to provide an international clearinghouse for public health practitioners and researchers on how to monitor environmental hazards, exposure and health data (http://www.epiprev.it/INPHET/home). Members of the network are Dr. **Lauriola**, rapporteur of the present conference, and Dr. **Ariana Zeka**, from the Institute of Environment, Health and Societies of the Brunel University in London. She presented the Environmental Public Health Tracking.

The presentation of the state-of-the-art went on with **Francesco Forastiere**, one of the international leading experts in the matter of Health Impact Assessment of Air Pollution.

Fabrizio Bianchi, IFC-CNR, one of the coordinators of the CISAS project and member of the ERA ENVHEALTH network reviewed and completed the themes covered by the Open Conference.

I want to thank all the participants, and especially **Adrienne Pittman**: she was the brilliant coordinator of the ERA ENVHEALTH network, and she is going on strongly contributing to the activities, and **Dominique Thierry**, that were present to contribute to the discussion, together with several researchers involved in CISAS and operating in Sicily on environment and health,

Salvatore Scondotto
Department of Occupational Health and Epidemiological Observatory

The Department of Occupational Health and Epidemiological Observatory (D.A.S.O.E.) has enhanced epidemiological surveillance in environments with high environmental risk to meet the expectations of the local community over the years. Recently, the population has increasingly required the initiation of adequate measures to combat the health problems described by the numerous studies carried out in the area. For this reason, in 2015 the Sicilian Region started a public health program based on the following elements.

Advocacy of Provincial Public Health Authorities:

- to strengthen the role and responsibility of local public health bodies;
- to maintain a strong link with local public health bodies (Provincial Public Health Authorities, Health District, Prevention Department, Health Education Unit, Cancer Registry) to develop participatory forms of prevention policy and offering channels of discussion and orientation to tackle complex social situations early and correctly.

Global approach to health promotion

The attention is not restricted to only one of the possible determinants but to the totality of factors that affect the territory and towards which prevention programs, health education, surveillance of the styles of life and early diagnosis can be effective.

Transparency and correct information

The distortions of perception, often caused by exploitation, lack of information on the actual availability of data and on their transparency, distrust of administrations, and knowledge deficits, require *ad hoc* work that cannot be considered as an optional corollary.

Therefore, the CISAS project should not be limited to describe the critical elements in the study area but must also be accompanied by operational intervention recommendations in line with the started program to respond to the needs of public health protection in the area.

Lilian Corra, ISDE Senior Expert on Health and Environment; ISDE, in official relation with UNEP and WHO; WHO working Group on Children Environmental Health
UNEP Chemicals: participant of SAICM and Minamata Convention negotiation process
Director Master on Communication on Health and Environment, School of Medicine, University of Buenos Aires. Director Medical Specialization on Health and Environment, School of Medicine, University of Buenos Aires

Health issues under the Minamata Convention: "to Protect Health and the Environment"

The exposure to mercury is highly toxic, among others important effects, affects neurodevelopment as present since conception with effects for life on intellectual functions: memory, concentration and learning (IQ) and is associated with autism with sensory, neurological, motor, and behavioural dysfunctions. As well can damage the blood brain barrier and facilitate penetration of the brain by other chemicals, disrupt normal function of the pituitary, thyroid, adrenal glands and pancreas. Hormones that appear to be the most affected by mercury are insulin, estrogen, testosterone, and adrenaline. And last but not least is a very well-known feto-toxic and teratogenic.

May affect animals and people.

The problem is that mercury continues to be widely used and released into the environment, is persistency and bio-accumulates in humans and other living creatures.

The UN Minamata Convention is a global legally binding instrument on mercury to address the risks to human health and the environment. Was agreed in Geneva, Switzerland on 19 January 2013 and adopted on 10 October 2013 at a Diplomatic Conference held in Kumamoto, Japan and reads: "Recognizing that mercury is a chemical of global concern owing to its long-range atmospheric transport, its persistence in the environment once anthropogenically introduced, its ability to bio-accumulate in ecosystems and its significant negative effects on human health and the environment,…" …to initiate international action to manage mercury in an efficient, effective and coherent manner…because of the bio-magnification of mercury and contamination of traditional foods…

As a short abstract of a few the articles may orient researchers and MDs on how this legal framework can help to strength our work to protect health:

Article 1: The objective of this Convention is to protect the human health and the environment from anthropogenic emissions and releases of mercury and mercury compounds.

Article 12: Contaminates sites: Each Party shall identify and assess mercury and mercury compounds contaminated sites. Actions to reduce the risks posed by such sites shall be performed in an environmentally sound manner incorporating an assessment of the risks to human health and the environment from the mercury or mercury compounds they contain.

Article 16: Health aspects: Parties are encouraged to:

- Promote the development and implementation of strategies and programmes to identify and protect populations at risk, particularly vulnerable populations, and which may include adopting science-based health guidelines relating to the exposure to mercury and mercury compounds, setting targets for

mercury exposure reduction, and public education, with the participation of public health and other stakeholders;

- Promote the development and implementation of science-based educational and preventive programmes on occupational exposure to mercury and mercury compounds;
- Promote appropriate health-care services for prevention, treatment and care for populations affected by the exposure to mercury or mercury compounds; and
- Establish and strengthen, as appropriate, the institutional and health professional capacities for the prevention, diagnosis, treatment and monitoring of health risks related to the exposure to mercury and mercury compounds.

Article 19: Research, development and monitoring: Parties shall endeavour to cooperate to develop and improve:

- Inventories of use, consumption, and anthropogenic emissions to air and releases to water and land
- Modelling and geographically representative monitoring of levels of mercury and mercury compounds in vulnerable populations and in environmental media, including biotic media such as fish, marine mammals, sea turtles and birds, as well as collaboration in the collection and exchange of relevant and appropriate samples;
- Assessments of the impact of mercury and mercury compounds on human health and the environment, in addition to social, economic and cultural impacts, particularly in respect of vulnerable populations;
- Information on the environmental cycle, transport, transformation and fate in a range of ecosystems,
- Information on commerce and trade in mercury and mercury compounds and mercury-added products; and

Parties should build on existing monitoring networks and research programmes.

Article 22: Effectiveness and Evaluation:

- To facilitate the evaluation the Conference of the Parties shall initiate the establishment of arrangements for providing itself with comparable monitoring data on the presence and movement of mercury and mercury compounds in the environment as well as trends in levels of mercury and mercury compounds observed in biotic media and vulnerable populations.
- The evaluation shall be conducted on the basis of available scientific, environmental, technical, financial and economic information

References:

WHO, UNEP
Environmental Mercury and Its Toxic Effects, Kevin M. Rice, Ernest M. Walker, Jr, Miaozong Wu, Chris Gillette, and Eric R. Blough. Journal of Preventive Medicine and Public Health. 2014 Mar; 47(2): 74–83. Published online 2014 Mar 31. doi: 10.3961/jpmph.2014.47.2.74 PMCID: PMC3988285
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3988285/
Acute Toxic Neuropathy Mimicking Guillain Barre Syndrome, Muhammed Jasim Abdul Jalal, Shirley Joan Fernandez,1 and Murali Krishna Menon, J Family Med Prim Care. 2015 Jan-Mar; 4(1): 137–138. doi: 10.4103/2249-4863.152273. PMCID: PMC4366988
Guillain Barre Syndrome as expression of mercury intoxication. Hospital Garraham Buenos Aires, Argentina. Dr. Marisa Gaioli, personal communication, 2016.

Mario Sprovieri, IAMC-CNR – CISAS WP2 coordinator
CISAS, International Centre of advanced study in environment, ecosystem and human health
Angela Cuttitta, IAMC-CNR - CISAS WP3 coordinator
Research on marine environment

Dr. Mario Sprovieri and Dr. Angela Cuttitta reported the ongoing activities of CISAS WP 2 and WP3.

The main goal of CISAS (International Centre for advanced study in environment, ecosystem and human health) is to study the impact of various species of pollutants, using an integrated analysis of biochemical, molecular and biophysical mechanisms determining and regulating the interactions among pollutants, ecosystem (overall and at different species/population level) and human health. The research program focuses on a significant number of case studies (Contaminated Sites of National Interest - CS of Priolo, Milazzo and Crotone), true natural laboratories suitable for modern multidisciplinary investigation. Milazzo CS area includes the largest petrochemical plant in Europe, whereas Crotone CS is an old industrialized area limited available knowledge. Augusta CS hists the largest petrochemical plant in Europe. CISAS is aimed at understanding processes and mechanisms for the transfer of conventional and emerging contaminants from the environment (as a complex of atmosphere, soil, sediment, inland waters and sea matrices) to ecosystem and to humans. The research will be focusing, in particular, on the selection and use of model systems, toxicological tests and biomarkers closely related to the investigated environment.

Sources, transfer dynamics and mechanisms regulating the "fate" of contaminants in different environmental compartments, with a careful analysis of the interaction processes at the interfaces of the different matrices (atmosphere, water, soil, sea, sediments), will constitute the crucial keys for investigating the biogeochemical cycles of contaminants in the environment. The planned research actions in WP2 are as follows:

- Analysis of sources of contaminants
- Disposal of contaminants
- Contaminants pathways
- "Fate" of contaminants
- Evaluation of atmospheric contaminants toxicity in the particulate phase
- Transfer of contaminants to ecosystem and humans

A general approach to assess the toxicity of chemical compounds in aquatic systems is based on toxicity tests conducted on vertebrates and marine invertebrates, which are widely used in marine ecotoxicology and biochemistry studies. Fish and mollusks are used as a model to highlight the biological hazards of various pollutants such as benzo (a) pyrene (BaP), polycyclic aromatic hydrocarbons (PAHs), heavy metals present in highly contaminated aquatic environments, but also detergents and products derived from human activities. The effects of these compounds in fish seem to be strictly species-specific and have been almost exclusively evaluated in vivo by the expression of the levels of monooxygenase (family of cytochrome P450), of the enzymes involved in phase II of

detoxification (glutathione S- transferases [GST]), UDP-glucuronosyltransferases (UDPGTS) and sulfotransferase (ST) and through oxidative stress markers. The high species-specificity of the main chemical contaminants and the need to necessarily reduce in vivo experiments for ethical, scientific and economic reasons makes it necessary to study processes triggered by exposure to contaminants, effects on cellular systems derived from fish species different from those used so far, such as zebrafish, carp and rainbow trout, in order to be able to effectively assess the risks associated with the presence of xenobiotics in endemic species. In addition, the low availability of data on the effects that many of these compounds determine at the level of the expression of oncogenes and anti-oncogenes can provide the basis for further research aimed at evaluating the molecular mechanisms through which xenobiotics can cause mutagenic events or death for apoptosis in Mediterranean fish species.

In WP3 the effects of contaminants found in the ecosystem in the area of interest will be evaluated using model organisms. In particular pathways leading to differentiation and specification mechanisms will be addressed using in vivo and in vitro approaches. The evolutionary conservation of developmental mechanisms and the overlapping with pathological features, make the use of sea urchin embryo and zebrafish, suitable as models for investigating biological effects of toxicant exposure. Gene expression profiles will be analyzed on stressed organisms to understand the molecular mechanisms induced by exposure to toxicants as individual contaminants and as mixtures. Finally, the results of a molecular modeling survey will allow to verify, on a theoretical basis, the interactions and possible combinations in the interactions between contaminants and biological molecules.

The transfer of contaminants to the human compartment by ingestion of food will be verified and clearly evaluated.

CISAS is expected to obtain important scientific and technological results:

- development of dispersion models of contaminants in different environmental compartments;
- improvement of knowledge about transfer of contaminants within the marine and terrestrial ecosystems and interactions at biochemical and molecular level of contaminants in model species (terrestrial and marine);
- development of epidemiological knowledge in the studied areas;
- improvement of knowledge about mechanisms of transfer of contaminants from the environment to humans by food, drinking, breathing;
- building of integrated and innovative systems for monitoring in real time the environmental matrices;
- development of conceptual models oriented to the management of landscapes and ecosystems;
- development of decision support tools based on scenario simulations, aimed at supplying decision-makers with forecasts about the consequences of interventions.

Fabio Cibella, IBIM-CNR – CISAS WP5 coordinator
Planned environmental health research in three sites in Italy – birth cohort study

CISAS WP5 will investigate the effects of environmental pollutants on placental physiology and pregnancy outcomes. As the human placenta is posed at the interface between maternal/external environment and embryo, it can be considered as an environmental monitoring system. Following the theory of the "intrauterine origins of health and disease susceptibility" stating adult diseases may have an in utero origin, when suboptimal intrauterine conditions - including exposure to environmental contaminants - induce irreversible changes, the study of this phase is crucial. Specifically, at the time of the delivery, placenta tissue, maternal blood, and umbilical cord blood will be collected to assess contamination (by heavy metals, PCBs, and PBDEs) and to clarify how heavy metals and persistent organic pollutants interact with placental domain. The effects of environmental pollutants on placental transcriptome and their role on the predisposition to late onset diseases will be evaluated in population samples living in highly polluted areas compared to subjects living in control areas. Possible long-term infant outcomes will be evaluated during the first three years of life, using hospitalization databases, through regular clinical evaluations, including diagnosis after hospital access care. Furthermore, WP5 will focus its activities on the effect of environmental pollutants in in vitro and ex vivo assays with human and murine cell lines on the attempt to evaluate the influence of such pollutants on cellular response. Finally, such a data will be matched with those generated by functional studies in a murine system.

Mothers and children are recruited from 2018 in the areas of Priolo, Milazzo and Crotone, included in the list of Italian Contaminated Sites for Remediation (CS).

Fabrizio Bianchi, IFC-CNR - CISAS WP4 coordinator

Planned environmental health research in three sites in Italy – association between pollutants and selected health conditions

In humans, CISAS-WP4 aims to develop knowledge about the association between priority pollutants specific for each area and selected health conditions, identified on the basis of environmental and epidemiological knowledge and relevance for research and innovation. Specifically, the research is designed to study the association:

- between exposure to organic contaminants and risk of liver disease and hepatocellular carcinoma in Priolo CS;
- between exposure to heavy metals and early markers of thyroid disease (thyroid nodules, clinical and subclinical hypothyroidism) in Milazzo CS;
- between exposure to heavy metals and markers of cardiovascular and renal risk and early alterations in Crotone CS.

The study of health risk in population groups at different levels of exposure will support: the selection of reliable markers of exposure and early effect indicators; the construction of targeted environment and health surveillance systems; evidence based indications for primary prevention measure, firstly reclamation.

The site of Priolo (Sicily Region, Southern Italy), identified as a CS in 1998, is characterized by a diffuse environmental contamination due to heavy metals, polychlorinated biphenyls, dioxins, and polycyclic aromatic hydrocarbons. These toxic compounds, persistent and bioaccumulable, mainly derive from the emissions of the petrochemical pole that operated in the area. Increased incidence of all cancers (including of the liver, pancreas and mesothelioma) was reported in the Priolo-CS population in both genders compared to all cancer registries of central-southern Italy (years 1999-2005; SENTIERI, 2014). In addition, increased mortality (years 2003-2010; SENTIERI, 2014) and hospitalization rates, (years 2007-2011, Department of Occupational Health and Epidemiological Observatory of Sicily Region) for chronic liver disease and cirrhosis were found in the population living in the Priolo CS compared with the Sicilian regional and with the neighbouring rates, respectively. Among liver disease, hepatocellular carcinoma (HCC) is the main type of liver cancer and the second leading cause of cancer death in the world. The main risk factors of HCC are:

- viral infections (HBA and HBB);
- alcohol consumption;
- exposure to pollutants that, acting as endocrine disruptors, can induce dysfunctions of lipid metabolism (Rapisarda et al., 2016).

Objectives of the study is to identify whether subjects living in the area of Priolo CS show an increase in risk factors and hepatic biomarkers and HCC and exhibit anomalies in lipid metabolism that may promote the development of liver disease and HCC.

According to a sectional study design, for 250 subjects resident in the exposure area (Municipalities of Augusta, Melilli and Priolo Gargallo) and for 250 subjects resident in the reference area for at least 10 years (Municipalities of Noto and Avola), men and women aged 40-70 years and with no liver disease, the research programme plans:

- an interview through a questionnaire;
- the collection of plasma and urine samples to measure established risk factors (fatty liver index, fibrotic liver index, inflammatory markers, in plasma measure of De Novo Lipogenesis indexes calculated as the ratio palmitic/linoleic ratio and fatty acid composition, in plasma samples lipidomic analysis, in urine sample endocrine disrupting chemicals analysis).

The Milazzo-Valle del Mela (Sicily Region, Southern Italy) high-risk area includes several industrial plants; among them, an oil refinery, a batteries recycling implant, and a fuel powered energy. This area was defined as a CS in 2005. All these plants contribute to the emission of pollutants and heavy metals that represent one of the major threats to human health.

The incidence of thyroid cancer is increasing in many countries, including the United States, France and Italy (Pellegriti et al., 2013). Increased incidence (years 2003-2005; SENTIERI, 2014) and hospitalization (years 2007-2011, SENTIERI, 2014) of thyroid cancer was observed in the population living in the Milazzo-CS compared with the regional rate. Palpable thyroid nodules are present in about 5% of the population. Most are benign, commonly colloid nodules, cysts, nodular thyroiditis or benign neoplasm, whereas about 5% are malignant (Walsh, 2016).

Metals can behave both as endocrine disruptors, perturbing the hormonal system. In adult subjects, a positive association between Cd and thyroid hormones was found (Chen et al., 2013, NHANES data 2008-2008). Other studies suggest the role of Cd and lead (Pb) as endocrine disruptors (Christensen, 2013, NHANES data 2007-2008; Luo & Hendryx, 2014, NHANES data 2007-2010). Cd blood concentration positively correlates with its accumulation in the thyroid gland (Jancic & Stosic, 2014), whereas thyroid cancer incidence is markedly increased in the Mt Etna volcanic area (Catania province, Sicily) where a non-anthropogenic pollution with heavy metals has been documented (Pellegriti et al., 2009; Vigneri et al., 2017). In addition, Cd levels were significantly higher in adolescents living in the Milazzo-Valle del Mela area, compared to both age-matched subjects living far from the industrial plants and the reference values (Interdonato et al. 2014).

Objectives of the study is to evaluate the relationship between exposure to index pollutants and increased risk of both subclinical and clinical hypothyroidism and early indicators of thyroid cancer.

According to a sectional study design, for 240 subjects resident in the exposure area (Municipalities of Milazzo, San Filippo del Mela and Pace del Mela) and for 240 subjects resident in the reference area

for at least 10 years (Municipalities of Barcellona Pozzo di Gotto, Terme Vigliatore, Villafranca Tirrena and Spadafora), men and women aged 18-44 years with no thyroid disease or drug therapy for thyroid disease, the research programme allows:

- an interview through specific standardized questionnaire;
- a blood sampling for the measure of thyroid function (FT3, FT4, TSH, thiroglobulin, anti-thyroglobulin Abs), Cd and Pb, and expression of thyroid hormone receptors (THRalpha and THRbeta) and retinoid receptors (RARalpha, RARgamma and RXRalpha) in peripheral mononuclear cells;
- the collection of a sample of urine for measuring the Cd and Pb exposure;
- the thyroid sonographic measurements (glandular volume).

Crotone, with the municipalities of Cassano and Cerchiara, was identified in 2001 as a CS due to the environment and health risk given the past presence of chemical plants and a widespread contamination by heavy metals. In the municipalities of Crotone and Cassano-Cerchiara (years 2006-2012) an excess of mortality was reported for kidney cancer in males and females, and for urinary tract infections and kidney failure in women, whilst increased hospitalization rate in men and women for ischemic heart disease ischemic disease, nephritis, nephrotic syndrome in both genders, and for renal tumors emerged among males was observed (Rapporti Istisan 16/9, 2016). Both high levels of Pb in the blood and bones (Navas-Acien et al., 2004) and high levels of Cd in urine (Tellez-Plaza et al., 2013) are associated with increased cardiovascular mortality. In addition, a significant negative correlation between Cd levels and endothelial function was found among patients in hemodialysis, who are at high risk due to exposure to toxic trace elements (Kaya et al., 2012).
Objectives of this study is to assess the effects of exposure to heavy metals on cardiovascular risk as early phase of the primary prevention strategy.
According to a sectional study design, for 150 subjects in CV primary prevention and resident in the exposure area (Municipalities of Crotone) and for 150 subjects resident in the reference area for at least 5 years (Municipalities of Cutro and Isola di Capo Rizzuto), men and women aged 40-70 years, the research programme allows:

- an interview through a questionnaire;
- a blood sampling for measurements of inflammatory and oxidative stress markers, markers of cardiac damage, fibrosis, blood vulnerability to thrombosis, bone health, Cd and Pb;
- the characterization of carotid atherosclerotic plaques;
- the measurement of the endothelial function;
- the electrocardiogram examination.

Furthermore, a pilot study on the impact of exposure to heavy metals on glomerular and tubular damage has been planned. Chronic kidney disease (CKD) is a progressive and irreversible

deterioration in the renal function, which can lead to chronic dialysis treatment or a kidney transplantation. The main risk factors of CKD are diabetes mellitus, hypertension, and obesity. Pb, Hg and Cd are established nephrotoxins at high exposure levels (Evans & Elinder, 2011; Zhang et al., 2010; Muntner et al., 2003). Environmental low Cd and Pb exposure may be also contribute to the risk of CKD (Navas-acien et al., 2009), especially in adults with hypertension or diabetes (Kim et al., 2015; Muntner et al., 2003).

Thus, on 75 subjects resident in the exposure area and on 75 subjects resident in the reference area recruited for the study on the cardiovascular risk, with no history of renal disease secondary to hypertension, diabetes and other parenchymal renal diseases, will be performed:

- the collection of a daily urine sample for measure of tubular damage;
- the collection of a 24h urine sample for measure of Cd and Pb;
- a serum sampling to estimate glomerular filtration rate.

Following the approval by the Ethical Committees, the three studies are now in progress.

Ric Van Pol, RIVM

Human Biomonitoring: PFOA case in the Netherlands

Long-term exposure to perfluorooctanoic acid (PFOA) in the past may have affected the health of people living nearby the DuPont/Chemours factory. This is partly because it is likely that the concentrations of PFOA in the blood were substantially higher in the past than have now been measured. The outcomes of the blood tests confirm previous model calculations. Residents who have lived in the vicinity of the factory for a long period of time have higher concentrations of PFOA in their blood than residents who live further away or who have lived in the vicinity for shorter periods of time.

These results were in line with an earlier risk assessment carried out by RIVM in 2016. The calculations revealed that it was probable that the health-based threshold value for PFOA was exceeded for a long period of time.

An analysis of various epidemiological studies showed that there were links between undesirable changes in the body and the PFOA concentration in the blood. Changes were noticeable even at relatively low PFOA blood concentrations, as occur in the general population. A link is most probable for changes in cholesterol, liver enzymes and birth weight.

Scientists are still unsure about the exact blood concentrations at which these undesirable changes occur in the body. On the basis of the available epidemiological information it is not possible to demonstrate a causal relationship between the undesirable changes and PFOA exposure.

RIVM expects that an (individual) health study among local residents will produce little to no health benefits for the people in question. In some cases the undesirable changes in the body which may occur as a consequence of exposure to PFOA can already be detected by standard controls and can therefore be treated. The possible serious health effects (such as kidney cancer, testicular cancer and ulcerative colitis) occur only on a very limited scale. As a result, the chance is small that a screening for these conditions will lead to the detection of any new cases. A number of the possible undesirable changes cause health effects that will be discussed in good time with GPs. People who are concerned about their health are advised to contact their GP.

Amalia Gastaldelli, IFC-CNR – CISAS WP4

Human Biomonitoring in the CISAS project

The emerging field of omics — large-scale data-rich biological measurements of the genome — provides new opportunities to advance and strengthen research into endocrine-disrupting chemicals (EDCs). Evolving omics technologies have the potential to generate data that enhance exposure assessment to include the exposome - the totality of the lifetime exposure burden - and provide biology-based estimates of individual risks. EDCs and potential EDCs are mostly man-made, found in various materials such as pesticides, metals, additives or contaminants in food, and personal care products. Human exposure to EDCs occurs via ingestion of food, dust and water, via inhalation of gases and particles in the air, and through the skin.

Recent studies have associated the exposure to di(2-ethylhexyl phthalate) (DEHP) and BPA to development of endocrine related diseases in both adults and children, in particular for altered timing of puberty and obesity, thus posing the subjects at increased risk for type 2 diabetes and cardiovascular diseases.

Precocious puberty and childhood obesity are multi-factorial diseases and growing attention has been paid to EDCs exposure. In Italy, 10% of children aged 6-10 years are obese; changes in the timing of puberty markers currently affects 1/5000 children, being more common in girls.

No national data exist up to now on levels of DEHP, and its metabolites (MEHP and secondary metabolites) and BPA in toddlers, children and adolescents nor on associations between exposure and such diseases

PERSUADED is a cross-sectional study that will involve children and adolescents (males and females), aged 4-6, 7-10, 11-14 years, and their mothers. Family pediatricians from each Italian geographic macro-area (4 urban, 4 rural) will select pairs mother child. A total of 2023 pairs mother-child were enrolled from urban and rural areas defined according to population density (> or < 150 inhabitants/Kmsq) in North, Centre and South Italy. DEHP metabolites levels measured in children urine are higher in the South of Italy than North and Centre, for both rural and urban areas. BPA levels are higher in the North than in the Centre. MEHP levels are higher in male aged 4-6 years; BPA levels are higher in males aged 4-6 and 7-10 years than females.

The territory around the industrial Sicilian area of Priolo, Italy, has been defined as a contaminated site (CS) of national priority for remediation because of diffuse environmental contamination caused by large industrial settlements, especially in the petrochemical field. In this area, persistent and bioaccumulable toxic compounds such as heavy metals, polychlorinated biphenyls (PCBs), dioxins, polycyclic aromatic hydrocarbons (PAHs) and volatile organic compounds (VOCs) were detected. In this context, there was an increase in the incidence of different types of tumors in the population living in the area of Priolo in the pool of tumor registers in Central and Southern Italy; in particular, an increase of mesothelioma and liver and pancreatic neoplasia have been observed.

Increased chemical production has been associated with increased prevalence of diabetes, cardiovascular diseases (CVD), fatty liver, cancer.

In the overview of liver disease, hepatocellular carcinoma (HCC) is the primary type of liver cancer and the second leading cause of cancer deaths in the world. Among the risk factors for HCC, in addition to viral infections (HCV and HBV) and excess alcohol, there is also the exposure to pollutants that can act as endocrine disrupters and induce metabolic alterations, particularly in lipid metabolism. Oxidative stress and lipotoxicity have been suggested to be likely involved HCC development due to alterations in lipid metabolism. Most pollutants are liposoluble and when absorbed they accumulate in fat and liver tissue where they can promote cellular lipotoxicity, increase de novo lipogenesis (DNL) and synthesis of saturated fatty acids, in particular palmitic acid (PALM) and other lipid classes such as ceramides, di- and tri-acylglycerols (DAG and TAG).

There are multiple potential causal pathways through which an environmental exposure may lead to epigenetic modifications, which may, in turn, impact clinical outcomes. Additional human studies that extend over the entire causal pathway are needed to establish cause-and-effect relationships between exposures and outcomes. Exposures that occur preconceptionally, in utero, in early life and in adult life may result in epigenetic dysregulation.

EDCs can alter an individual's susceptibility to the development of nonalcoholic fatty liver disease (NAFLD) both via early-life effects that increase susceptibility to obesity and alter hepatic 'set points' to favor the development of steatosis and via later-life effects that contribute to the development of liver disease alone or in combination with other NAFLD risk factors such as diet, diabetes mellitus and/or obesity.

In CISAS, the main objective is to discover if subjects living in the exposed area display alteration in metabolism that can promote liver disease and HCC. Thus the experimental design of the study plans to recruit two groups of subjects (exposed vs non-exposed) and to measure:

- clinical and biochemical routine parameters
- fatty liver index (FLI)
- fibrotic liver indexes
- inflammatory markers
- adipocyte hormone leptin and the pancreatic hormone insulin
- lipidomic profile (e.g. ceramides, di- and tri-acylglycerols) that will be measured in plasma samples by liquid chromatography mass spectrometry LC-MS Q-TOF
- DNL indexes calculated as the ratio palmitic/linoleic acid (16:0/18:2)
- free fatty acid (FFA) concentration and composition measured by gas chromatography mass spectrometry GCMS

Expected results in CISAS are: - to check if noninvasive non expensive scores of liver diseases are altered in the Priolo area vs non exposed area; - to identify potential biomarkers involved in specific metabolic pathways that could be associated to alteration in metabolism related to exposure to EDCs;

- to start a policy of prevention for metabolic disease that can develop because of EDCs

Ariana Zeka, Institute of Environment, Health and Societies, Brunel University, London

Environmental Public Health Tracking

Today environmental health problems need a systems approach to account for the broader spatial, socio-economic and cultural context, beyond the individual toxic or infectious exposures. Monitoring environmental hazards is critical for the prevention of disease. Environmental Public Health Tracking (EPHT) aims to merge, integrate, analyze and interpret environmental hazards, exposure and health data. EPHT can provide timely, accurate and systematic environmental data to public health decision makers on how to reduce the environmental health burden. By effectively linking environmental health data and translating it into meaningful information, EPHT can help protect the health of the public. Thus, EPHT represents the essence of proactive public health practice, since the ultimate goal of such a system is to guide public health action.

Tracking activities have been conducted across the world. The international EPHT network (INPHET) aims to support the development, implementation and evaluation of national EPHT initiatives, raising awareness of the on-going surveillance activities related to environmental threats and the impact on health and facilitating collaboration and exchange experiences and good practices. Specifically, INPHET activities include how:

- Monitor environmental precursors of disease
- Merge, integrate, analyze and interpret environmental hazards, exposure and health data
- Examine relationships between environmental hazards and diseases
- Identify populations at risk from environmental hazards
- Implement and evaluate intervention and prevention strategies
- Inform public health policy makers.

An international EPHT network provides a number of benefits to (public) health professionals, policy makers, local, national and international stakeholders, through evidence-based information that can be used to guide public health actions in different settings, such as regional and national health departments. In fact, different policies influence significant differences in drop mortality for cardiovascular disease, respiratory diseases and stroke, as shown in Republic of Ireland and Northern Ireland.

EPHT may be a useful tool in the development of a resilient society. INPHET has the potential to enhance understanding of environmental public health issues and provide direct access to health and exposure data among citizens, institutions and the private sector.

Joana Ferreira, University of Aveiro, Portugal

From atmospheric emissions to health: an integrated assessment approach

Nowadays, poor air quality is recognized as one of the most pressing problems in urban areas with very harmful impacts on health and the environment. Anthropogenic emissions are identified as the greatest contributors to air pollutant concentrations, but atmospheric phenomena occurring at different spatial scales also contribute to the increase in environmental damages.

To reduce air pollution effects, particularly in cities where most the European population lives, it is important to define effective plans for air quality improvement. Notwithstanding the achievements in emission reductions and air quality improvement, additional efforts need to be undertaken to improve air quality in a sustainable way, i.e. through a cost-efficiency approach.

Integrated assessment (IA) jointly addresses the environmental and health impacts of the mitigation measures, as well as their implementation costs and the economic quantification of damages/benefits. A large variety of modelling systems and options exist but it is possible to identify two main conceptual approaches: scenario analysis and optimization approach.

The scenario analysis starts with the identification of control strategic measures as a result of air quality exceedances. These measures have to be translated to emission reductions and their impacts on the air quality, quantified using modelling tools. Policy implications, technical feasibility, resulting costs and environmental and health impacts are also evaluated. In case of an optimization approach, costs and benefits are integrated towards the optimization of the measures considering a cost-effectiveness approach. In the IA optimization approach, the emission reduction measures are selected by an optimization algorithm assessing their impact on air quality, health exposure and implementation costs. Among the IA optimization approaches, the Regional Integrated Assessment Tool (RIAT) has been applied in different European regions to local/urban areas.

This work focuses on a cost-benefit analysis of abatement measures to improve the air quality in an urban area in Portugal, by means of two different IAM tools: i) the MAPLIA system developed in the scope of the concluded MAPLIA national research project “Moving from Air Pollution to Local Integrated Assessment”, ii) the RIAT+ model. The MAPLIA system was applied to the Grande Porto urban area (Portugal), addressing PM10 and NOx as the most important pollutants in the region. Four different measures to reduce PM10 and NOx emissions were defined and characterized, in terms of emissions and implementation costs, and combined into 15 emission scenarios, simulated by the TAPM air quality model. Air pollutant concentration fields were then used to estimate health benefits in terms of avoided costs (external costs), using dose-response health impact functions. Results revealed that, among the 15 scenarios analyzed, the scenario including all 4 measures lead to a total net benefit of 0.3 M €·y−1. The largest net benefit is obtained for the scenario considering the conversion of 50% of open fireplaces into heat recovery wood stoves. Although the implementation costs of this measure are high, the benefits outweigh the costs. RIAT+, on its optimized mode, has

indicated domestic and industrial combustion and traffic as the main sectors to consider. It is a versatile model permitting the quick analysis of different investment options and their associated benefits.

In summary, integrated assessment methodologies are privileged approaches to support the policy decision, allowing better management of human, technical and financial resources, public and private, contributing to a greater acceptance and facilitated implementation by the agents involved, and towards an improved air quality and a better life quality and health of citizens.

Francesco Forastiere, IBIM-CNR, Associate Researcher; WHO Geneva, Consultant

Health Impact Assessment of Air Pollution at national and global level

Health Impact Assessment (HIA) is "A combination of procedures, methods and tools by which a policy, programme or project may be judged as to its potential effects on the health of a population, and the distribution of those effects within the population" (WHO, European Centre for Health Policy. Gothenburg Consensus Paper, Health Impact Assessment- main concepts and suggested approach. Bruxelles, 1999).

It is useful to define policy question with respect to risk to health of exposure to the health hazard due to air pollution. Along this line some issues must be explained such as: what is the risk related to the population under investigation? How can exposure best be described according to the spatial resolution and the pollutant of concern? What are the long- and short term health effect? (WHO 2016).

The current HIA applications are:

- Burden of diseases (comparison of different risk factors)
- Scenario comparisons (what if)
- Cost-benefit analysis

After showing some different figures describing the impact ambient air pollution risk factor (4.2 Million deaths attributable to PM2.5 in 2015, The Lancet 2017) also according to the different emissions scenarios (i.e., Current legislation, Max feasible reduction), the main critical steps pertaining air pollution health risk assessment have been scrutinised, in particular those related to:

1) Estimate exposure. Ground-level monitoring data, modelling and satellite data;
2) Decide the counterfactual (or cut-off) value of the specific pollutant above which the estimate of the health impact is actually performed;
3) Assess the health impact: use the appropriate exposure – response functions (ERFs) and the baseline local health statistics.
4) Report numbers of premature deaths, cases of disease, years of life lost, disability-adjusted life years, or change in life expectancy;
5) Critically evaluate the uncertainties involved in all the process.

Some methodological evolutions have been then considered such as:

- Impact based on linear (log-linear) functions
- Global Burden of Disease based on Integrated Exposure Response (IERs) functions,

Anyway a particular emphasis must be given to the underlying assumptions and problems such as:

- Causal relationship
- Populations extrapolation ("external validity")
- Applicability to all the PM components
- Similarity in the distribution of the causes of death
- Short lag time of the effect

All these issues are essential to provide a better understanding of the currently available meta analysis. According to the criteria agreed and stated within the HRAPIE document (WHO-Europe 2013) the meta analysis carried out by Hoek in 2013) and afterwards in Europe, USA, Canada and China have been described.

In conclusion:

- The updates of the exposure-response risk (ERF) for total mortality indicate a significant increase compared to the Hoek's meta-analysis: 10% versus 6%
- There is a suggestion of non-linearity in the range 5-30ug/m3
- As such the currently available impact estimates betweenPM2.5 and all-cause mortality should be revisited.

In the end some data and estimations focusing on Italian regions and in particular some contaminated sites have been presented.

Fabrizio Bianchi, IFC-CNR – CISAS WP4 coordinator

Environmental epidemiology in contaminated sites: from ecological to etiological studies

SENTIERI Project (Mortality study of residents in Italian polluted sites) studies mortality of residents in the 44 sites of national interest for environmental remediation (Italian Contaminated Sites, CSs). IPSs are located in the vicinity of industrial areas, either active or dismissed, near incinerators or dumping sites of industrial or hazardous waste. A characterizing element of SENTIERI Project is the a priori evaluation of the epidemiological evidence of the causal association between cause of death and exposure. Exposures for which epidemiological evidence was assessed are divided into IPSs environmental exposures and other exposures. It developed a framework to examine the epidemiological literature. It identified a hierarchy in the literature sources used to classify each combination of cause of death and exposure in terms of strength of the association. This hierarchy relies on the epidemiological community consensus, on assessments based on the application of standardized criteria, weighting the study design and the occurrence of biased results. Statistical re-analysis, literature review, multi-centric study and single investigation were also considered. According to the above mentioned criteria, the epidemiological evidence of the association between cause of death and exposure was classified in three categories: Sufficient (S), Limited (L) and Inadequate (I).

As a whole at present the evidence on environment and health in Italian Contaminated Sites (CSs) are prevalently from descriptive studies and many results are now available for specific each CS, and consequent messages and recommendations for restoration, biomonitoring surveys, etiological studies on workers and resident communities are now feasible.

In the 1990s it was widely accepted that not all evidence is the same. The main principle of evidence-based medicine stated that a hierarchy of evidence exists. The common version of evidence pyramid claim that weaker study designs are in the bottom (such as ecological studies), followed by case–control and cohort studies in the middle, then randomised controlled trials (RCTs), and at the top systematic reviews and meta-analysis. As such according to the traditional pyramid the process to establish casualty starts from generation of Hypotheses with basic science and case series. Anyway this process must be based on Bradford Hill criteria of causation.

According to a recent paper (M Hassan Murad 2016) “heterogeneity (clinical, methodological or statistical) is an inherent limitation of meta-analyses that can be minimised or explained but never eliminated… One valuation of 163 meta-analyses demonstrated that the estimation of treatment outcomes differed substantially depending on the analytical strategy being used”. Therefore they a revised pyramid to underline two methodological principles (1) lines separating the study designs become wavy (Grading of Recommendations Assessment, Development and Evaluation), (2) systematic reviews are ‘chopped off’ the pyramid. As such systematic reviews are a lens through which evidence is viewed (applied).

Changing how systematic reviews and meta-analyses are perceived by stakeholders (including patients, clinicians and decision-makers) has important implications. In particular, the quality of evidence drives the strength of recommendation which is one of the last translational steps of research, most proximal to patients cure and communities prevention.