HEALS Newsletter

Health and Environment-wide Associations based on Large population Surveys

Project No 603946 of the European Union's Seventh Framework Programme

Contents

Editorial Note

Welcome to the 7th issue of the HEALS Newsletter!

In this issue we are starting with an article that reveals the risks of prenatal exposures to bisphenol A and the dynamics of metabolic reactivation, using a PBPK modeling at pregnancy. In this article, the team from Universitat Rovira i Virgili (URV) in Tarragona (Catalonia) reports the development of tools for measuring the exposome within the HEALS framework. The Newsletter also describes the functioning of an open platform elaborated by HEALS. In another article, Nadine Steckling and Stephan Böse-O'Reilly, from the University Hospital Munich (LMU) in Munich (Germany) show the numerous documents and data files currently available in this online platform that are designed for external training, with focus on an academic audience. Finally, the Newsletter ends with a research issue developed within HEALS: Mercè Garí and Joan O. Grimalt, from the Institute of Environmental Assessment and Water Research (IDAEA–CSIC) in Barcelona (Catalonia), summarize a recently submitted paper on the human exposure to organophosphate and pyrethroid pesticides, specifically in occupationally-exposed and general populations living in rural and urban areas.

The Who is Who section outlines the professional profiles of several researchers who are actively involved in the project and participates in different work packages: Alberto Gotti from the Aristotle University of Thessaloniki (AUTH, Greece), Martine Aggerbeck from the Université Paris Descartes (UPD, France), Michael Jerret from the University of California (UC, USA) and John Bartzis from the University of Western Macedonia (UOWM, Greece).

As usual, the issue ends with a list of the scientific publications, public presentations, workshops, conferences and other knowledge-dissemination activities generated by the HEALS researchers in the period between January and June 2017.

We take this opportunity to inform that the next Annual Meeting of the HEALS project will take place in the Island of San Servolo in Venice (Italy), between 22nd and 25th October 2017.

HEALS annual meeting

How relevant is HEALS

Venice, Italy 22nd – 25th of October 2017

To take place at

Isola di San Servolo – Venice International University (VIU)

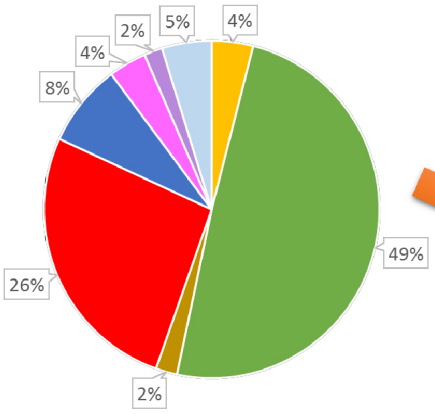
Unravelling the risk concerning prenatal BPA and metabolic reactivation dynamics through a pregnancy-PBPK application

by Vikas Kumar, Raju Prasad Sharma, M. Ángeles Martínez, Joaquim Rovira and Marta Schuhmacher

Universitat Rovira i Virgili (URV)
Tarragona, Catalonia

A crucial topic of the HEALS project is to develop tools for measuring the exposome. Ingestion of Endocrine Disruptors (EDs), such as Bisphenol A (BPA) has been associated with obesity and diabetes in childhood, as well as reproductive, behavioral and neurodevelopment problems.

Around 3 billion kilograms of BPA are produced annually worldwide and over 100,000 kilograms of this compound are released annually into the atmosphere. It can be found in food and beverage processing, and in many other commercial products such as epoxy resin cans, dental sealants, personal care products, baby bottles, and flame retardant materials. Although the ingestion of BPA from food or water is the predominant route of exposure, there are other nonfood routes, such as inhalation of free BPA (concentrations in indoor and outdoor air), indirect ingestion (dust, soil, and toys), and dermal route (contact with thermal papers and application of dental treatment), which contributes to the total BPA exposure.



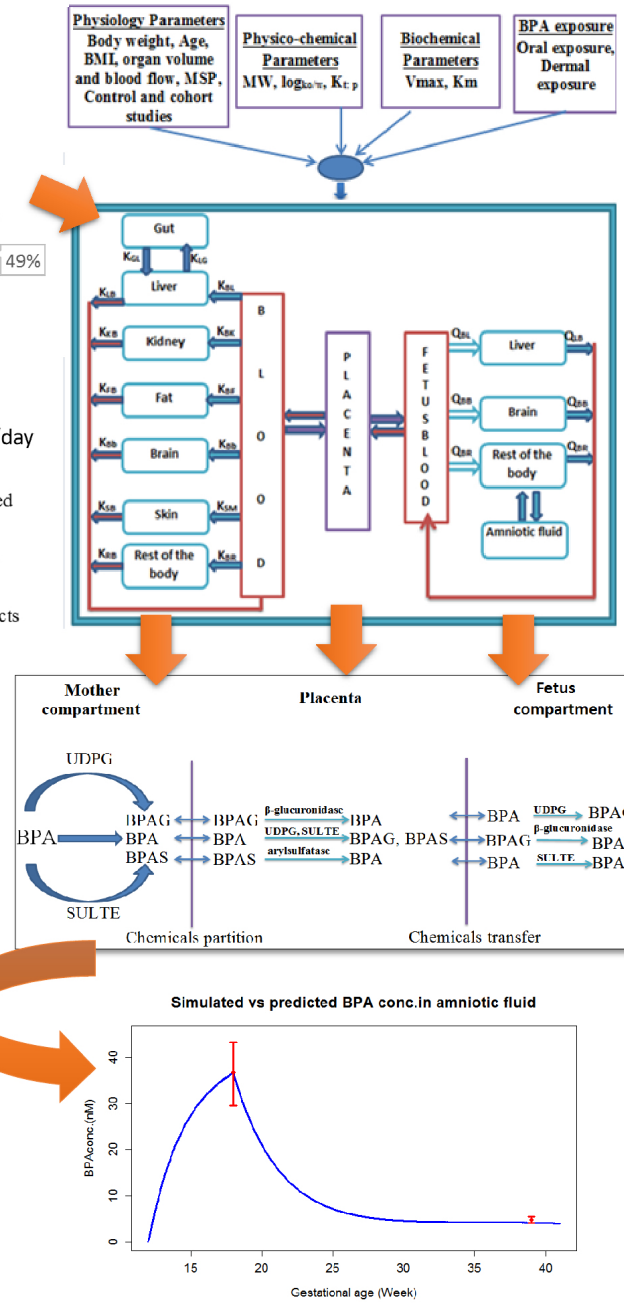
Total dietary intake of BPA = 0.72 µg/kg bw/day (0.28; 1.41)

- Fish and other seafood
- Grains and grain-based products
- Milk and dairy products
- Fruits and vegetables
- Ready to eat (including canned dinners)
- Meat and meat products
- Water

Recent studies suggest that there is an universal fetal exposure of BPA that is associated with the adverse birth outcomes. Fetuses are considered as orphan populations with respect to their safety against BPA exposure. Prediction of fetal blood BPA concentration from maternal blood would be highly useful to predict the risk associated to these compounds for these specific populations.

The study was aimed to estimate the total dietary intake of pregnant women for quantification of the BPA exposure to the growing fetus during pregnancy and to identify the critical fetal windows of exposure. These goals involved the following task:

- External Assessment
  - Recruitment of pregnant women, ongoing birth cohort
  - Estimation of BPA levels in different food categories.
  - Determination of the total exposure of BPA based on their total diet intake
- Internal Assessment
  - Development and validation of a PBPK model with adult human kinetic data.



- Extension of the developed PBPK model to pregnant women by including pregnancy physiology and fetus sub-model (P-PBPK model).
- Assessment of fetal impact conjugation and deconjugation of BPA and its metabolites on fetal PKs.

- Key finding
  - Canned fruits and vegetables followed by canned meat and meat products were the major contributors to the dietary exposure to BPA.
  - Models predicted higher concentration of BPA during the mid-gestational period in amniotic fluid as well in placenta and fetus liver, signifying the critical window of exposure for the fetus.

The placental-fetal unit assumes a bidirectional transfer process of BPA and BPA-G as consequence of the distribution of BPA and its metabolites in the mother-fetus body. Deconjugation in placenta and fetus body are of major concern at early fetal life where metabolism process is almost null, causing increased level of unconjugated BPA in the fetus. Importantly, free BPA in the fetal compartment are more in steady state (BPA amniotic fluid conc.) and persists even when maternal BPA level declines.

External training materials for public use

by Nadine Steckling and Stephan Böse-O'Reilly

University Hospital Munich (LMU)
Munich, Germany

In October 2017, HEALS will open a data platform with training materials for public use to provide products and knowledge gained through the project activities. The "external training materials" are provided in the "Documents and data files"–folder on the website http://heals.vtt.fi/ (*Box 1*). Access is also possible due to the button "Training materials" on the HEALS website (http://www.heals-eu.eu/).

The external training materials
of the HEALS project
is freely available here:

http://heals.vtt.fi/

↓

Documents & Data Files

↓

External Training Materials (WP18)

Box 1. Access to the training materials.

The materials are useful for an academic audience. The "Welcome"–folder provides basic information about the HEALS project and the data platform. Further folder follow a categorization regarding the topics bioinformatics, environment-wide association studies, exposome, human biomonitoring and –omics, human exposure, and sensor technology what makes a fast and expedient access possible (*Figure 1*). Each abstract, article, poster, presentation, video, or other material is shortly presented in the file description and labeled as basic or special training material. While some material is uploaded elsewhere, the data platform contains links to other sources like the HEALS website (http://www.heals-eu.eu/). The "Further reading"–folder hosts the superior links to the most important HEALS outputs, *i.e.* the deliverables, publications, newsletter, and training schedule. Also, a glossary is included. The content is continuously updated.

The reader should use these materials for self-study, to learn more about the HEALS project, to learn more about the topics included, to cite the materials (if appropriate), to find further literature, to teach students, for inspiration of future research, to contact the author/the HEALS consortium for further questions, and for recommendations to other people interested (*e.g.*, students).

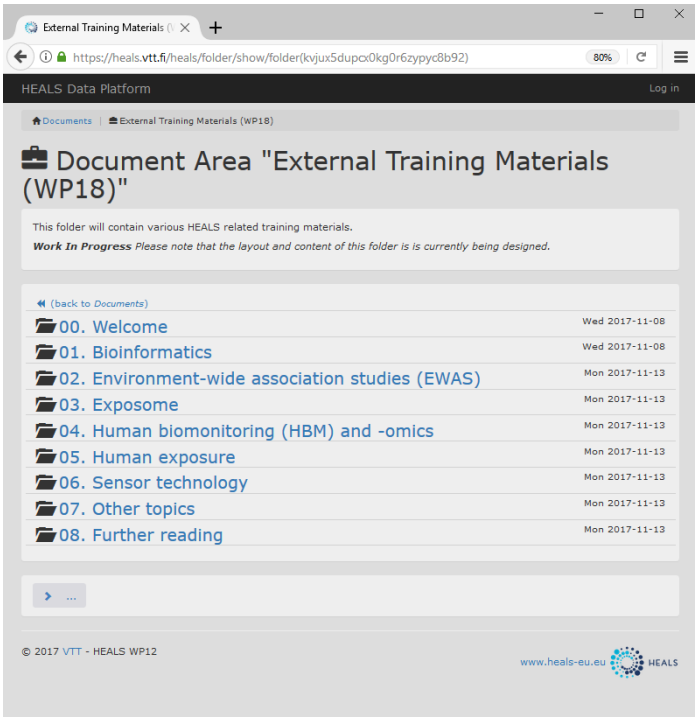


Figure 1. Structure of the file "External Training Materials" on the HEALS data platform (http://heals.vtt.fi/)

How to start? Just have a look in the "Welcome"–folder to become familiar with the HEALS project and the underlying concepts. It is recommendable to watch the HEALS videos, in which HEALS partners explain the exposome, the HEALS project, the expertise of HEALS partners, and the expected influence of HEALS on human health in easy language. In the next step, deepen your knowledge by examining the topic-related contents. Enjoy!

Human exposure to organophosphate and pyrethroid pesticides

by Mercè Garí and Joan O. Grimalt

Institute of Environmental Assessment and Water Research (IDAEA–CSIC)
Barcelona, Catalonia

Organophosphate and pyrethroid pesticides are chemical compounds with a strong potential to disrupt the brain and nervous system of insects and eliminate them. Unfortunately, this neurotoxic effect is not selective enough as to avoid damage to other non-target species, including humans. These pesticides are commonly used in agriculture, and recent studies performed by the European Food and Safety Authority have encountered some of them in food products from Europe. Farmworkers and operators are directly exposed to these pesticides through inhalation, dermal contact and indirect ingestion. Furthermore, a continuous exposure can occur if they do not undertake additional measures during and after work. These pesticides are also used for domestic and gardening use, hence general populations from both urban and rural environments are also exposed to them through other non-food sources.

The Institute of Environmental Assessment and Water Research (IDAEA–CSIC), in Barcelona, has developed and optimized a methodology for the determination of specific metabolites of organophosphate and pyrethroid pesticides in urine samples. The method, based on an isotope dilution solid phase extraction and using ultra-performance liquid chromatography coupled to a tandem mass spectrometer (UPLC-MS/MS), is able to determine six specific metabolites of the organophosphates parathion, malathion, diazinon, pirimiphos, chlorpyriphos and coumaphos, and two metabolites of the most common pyrethroid pesticides, including permethrin, cypermethrin, deltamethrin, cyfluthrin and esfenvalerate, amongst others. The new methodology has been applied to the analysis of urine samples in non-occupationally exposed individuals from urban and rural areas in Galicia and Catalonia, as well as to a population of farmworkers in Sucs (Catalonia).

The study shows that the most detected compounds in human urine are PNP (metabolite of parathion), TCPY (metabolite of chlorpyriphos), DEAMPY (metabolite of pirimiphos) and 3-PBA (metabolite of several pyrethroid pesticides). Comparison of farmworkers with the general population living in rural and urban areas shows higher concentrations of the aforementioned compounds in the former, which is consistent with occupational activity. However, the results also show that people not occupationally exposed to the use of these pesticides is also incorporating these compounds, probably as consequence of food consumption, as well as other non-food sources, such as the use of those biocidals for domestic purposes, for household pets and gardening, among other applications.

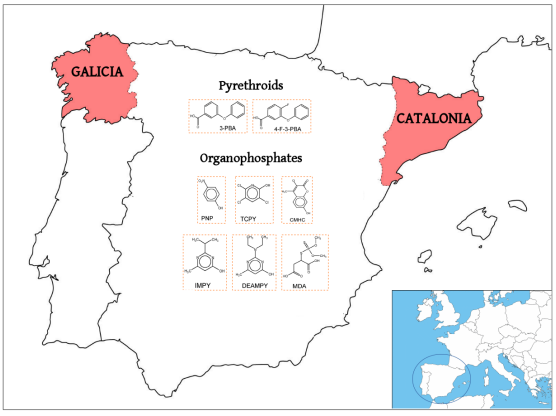


Figure 1. Map showing the location of the studied populations in Galicia (North-West Spain) and Catalonia, and the chemical structures of the analyzed compounds.

In essence, the study shows that metabolites of pyrethroids and organophosphate pesticides are observed in both occupationally and non-occupationally exposed individuals, indicating that these populations are generally exposed to both pesticide groups in their daily life, either by occupational activities, ingestion of contaminated food or other domestic applications. Further studies are required to evaluate the health impacts of pesticide exposures among European populations.

This contribution is a synopsis of the publication entitled **Analysis of metabolites of organophosphate and pyrethroid pesticides in human urine from urban and agricultural populations (Catalonia and Galicia)**, by **M. Garí**, **Y. González-Quinteiro**, **N. Bravo** and **J.O. Grimalt**, to be published in 2018 at *Science of the Total Environment 622–623: 526–533*.

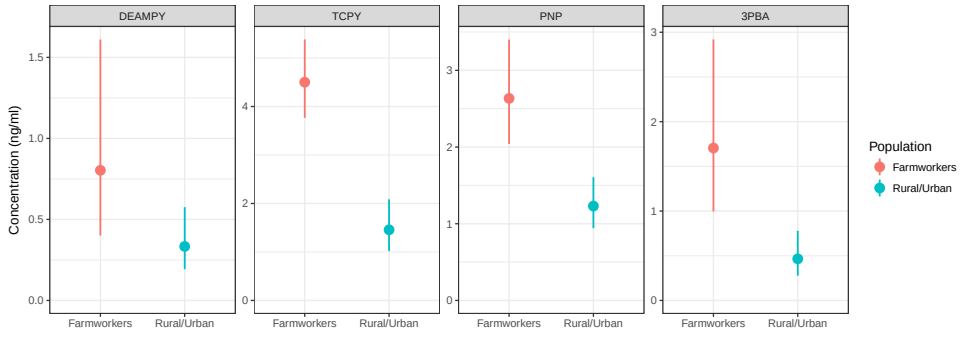


Figure 2. Median concentrations (and 95% CI) of organophosphate and pyrethroid metabolites found in urine of occupational and general populations in Galicia (Spain) and Catalonia.

WHO is WHO

Dr. **Alberto Gotti** is a physicist of the University of Milan with over 23 years of experience in environment and health impact assessment, data assimilation and exposure modelling. In the last fifteen years, he has worked for the European Commission's Joint Research Centre (EC-DG-JRC), for the Centre for Research and Technology Hellas (CERTH), for the European Centre for Training and Research in Earthquake Engineering (EUCENTRE) and for Aristotle Univeristy of Thessaloniki (AUTH). Dr. Gotti has an extensive experience on environment and health impact assessment, exposure modelling including biologically-based toxicokinetics/dynamic models (PBTK/PD), development of dose-response relationships based on both mechanistic Biology-Based Dose Response (BBDR) modelling and epidemiological approach through statistical modeling, climate change processes and policies, advanced use of GIS for environment and health impact assessment, data fusion comprising the assimilation and integration of data from different information sources, advanced statistical data analysis and techniques (Markov Chain Monte Carlo) to assess and reduce uncertainty in human health risk assessment and air quality assessment. He is also an active scientist on using satellite data. He was involved in the EU-funded projects ICAROS-NET, SMAQ, HEIMTSA, 2-FUN, HEREPLUS, TAGS, INTERA, URGENCHE, INTEGRA, CROME-LIFE, CHERRIE and in the ongoing ones HEALS, ICARUS, PEC, GRIN, BLUEHEALTH and HBM4EU. He participated and chaired several dissemination activities at National and International level through both classical channels (*i.e.* scientific workshops, conferences) and online systems (*i.e.* video conferences) targeting both expert and non-expert audiences. Dr. Gotti is Vice-President of the Mediterranean Scientific Association of Environmental Protection (MESAEP).

Dr. **Martine Aggerbeck** was born in Paris in 1953 and she received her PhD in Molecular and Cellular Pharmacology in 1983 from the Pierre and Marie Curie University (Paris). Since 1980, she has been a CNRS (Centre National de la Recherche Scientifique) scientist (Chargée de Recherches). Between 1980 and 2006, she worked in several INSERM (National Institute of Health and Medical Research) laboratories, mainly on adrenergic receptors in rat liver and on the cloning of the promoters of the aspartate and alanine aminotransferases and their regulation by hormones and drugs in human and rat liver. Since 2006, she has worked (in INSERM 1124, formerly INSERM 747) on the regulation of the expression of genes by pollutants (dioxin and organochlorine pesticides alone or as mixtures) in human liver cell lines and in the mouse. She has co-authored about 50 articles in international peer-reviewed journals. She has been involved in several national projects. She is also involved in teaching, particularly in a "Predictive Toxicology" module at the Master's level in the Paris Descartes University. Within HEALS, Dr. Aggerbeck is involved in WPs 3, 5, 7 and 16.

Dr. **Michael Jerret** is an internationally recognized expert in Geographic Information Science (GIS) for Exposure Assessment, Environmental Epidemiology, and Health Geography. He is professor and chair of the Department of Environmental Health Sciences in the Fielding School of Public Health, University of California, Los Angeles, and a professor in-residence in the Division of Environmental Health Sciences, University of California, Berkeley. For the past 22 years, Dr. Jerrett has researched how to characterize population exposures to air pollution and built environment variables, the social distribution of these exposures among different groups (*e.g.*, poor vs. wealthy), and how to assess the health effects from environmental exposures. Over the past 15 years, Dr. Jerrett has also studied how built and natural environments affect health, particularly physical activity and obesity. He has published some of the most widely-cited papers in the fields of Exposure Assessment and Environmental Epidemiology in leading journals, including *The New England Journal of Medicine*, *The Lancet*, *Nature*, and *Proceedings of the National Academy of Science of the United States of America*. In 2009, the US National Academy of Science (NAS) appointed him to the Committee on "Future of Human and Environmental Exposure Science in the 21st Century". The Committee published a report entitled *Exposure Science in the 21st Century: A Vision and a Strategy*. Dr. Jerrett led the chapter covering scientific and technological advances, with a focus on sensors, GIS, and satellite remote sensing. In 2014, 2015, and 2016, Dr. Jerrett was named to the Thomson Reuters List of Highly-Cited Researchers, indicating he is in the top 1% of all authors in the fields of Environment/Ecology in terms of citation by other researchers. Dr. Jerrett earned a B.Sc. in Environmental and Resource Science from Trent University, and an M.A. in Political Science with accredited specialization in Environmental Studies and a Ph.D. in Geography, both from the University of Toronto.

Prof. **John Bartzis** is Emeritus Professor in the School of Engineering of the University of Western Macedonia. He is currently Director of Research in the Environmental Technical Laboratory in the Department of the University Mechanical Engineering Department. He obtained his Diploma in Mechanical and Electrical Engineering from the National Technical University of Athens, Greece (1970), his M.S. in Nuclear Engineering from the MIT, USA (1975), and his Ph.D. in Nuclear Engineering from the MIT, USA (1977). He has worked as Research Assistant at the MIT, USA (1974–1977), Quality Engineer at the Public Power Corporation, Athens (1977–1978), Visiting Assistant Professor, at the Nuclear Engineering Department, Purdue University, USA (1979), Assistant Professor of Mechanical Engineering, at the Midwest College of Engineering (Chicago, USA) (1979–1980), Research Engineer, at the

Argonne National Laboratory, USA (1979–1980) and Researcher in NCSR "Demokritos" (1980–2001). He has participated in or coordinated numerous European Research Projects in the field of Environment and Health as well as Radiation Protection. He participates/has participated in several international scientific committees. He has authored or coauthored over 300 publications in journals, conference proceedings, books and reports. In HEALS Project, Prof. Bartzis is the leader of Stream 3 and WP8, and he is involved in WPs 1, 2, 9, 10, 11, 12, 18 and 19.

Publications

The scientific contributions of the HEALS Project are hosted on ZENODO, an open digital repository that enables researchers, scientists, EU projects and institutions to share and showcase multidisciplinary research results (data and publications).

The collection of HEALS scientific papers on ZENODO can be found in the following website:

https://zenodo.org/collection/user-heals

Papers published since January 2017 include:

- I. Prpić, A. Milardović, I. Vlašić-Cicvarić *et al.* (2017) Prenatal exposure to low-level methylmercury alters the child's fine motor skills at the age of 18 months. Environmental Research 152: 369–374.
- N. Steckling, M. Tobollik, D. Plass *et al.* (2017) Global Burden of Disease of Mercury used in Artisanal Small-Scale Gold Mining. Annals of Global Health.
- E. Junqué, M. Garí, A. Arce *et al.* (2017) Integrated assessment of infant exposure to persistent organic pollutants and mercury via dietary intake in a central western Mediterranean site (Menorca Island) Environmental Research 156: 714–724.
- L.J.M. Cluitmans (2018) Managing heterogeneous data in the HEALS project. In: Eskola H., Väisänen O., Viik J., Hyttinen J. (eds) EMBEC & NBC 2017. EMBEC 2017, NBC 2017. IFMBE Proceedings, vol 65. Springer, Singapore.
- R.P. Sharma, M. Schuhmacher, V. Kumar (2017) Review on crosstalk and common mechanisms of endocrine disruptors: Scaffolding to improve PBPK/PD model of EDC mixture. Environment International 99: 1–14.
- R.M. Llull, M. Garí, M. Canals *et al.* (2017) Mercury concentrations in lean fish from the Western Mediterranean Sea: Dietary exposure and risk assessment in the population of the Balearic Islands. Environmental Research 158: 16–23.
- N. Bravo, S. Hansen, I. Okland *et al.* (2017) Influence of maternal and sociodemographic characteristics on the accumulation of organohalogen compounds in Argentinian women. The EMASAR study. Environmental Research 158: 759–767.
- K. Polanska, W. Hanke, A. Krol *et al.* (2017) Micronutrients during pregnancy and child psychomotor development: Opposite effects of Zinc and Selenium. Environ Res 158: 583–589.
- E.A. Attignon, E. Distel, B. Le-Grand *et al.* (2017) Down-regulation of the expression of alcohol dehydrogenase 4 and CYP2E1 by the combination of α-endosulfan and dioxin in HepaRG human cells. Toxicology in vitro S0887-2333(17):30185-6.
- K. Polanska, A. Krol, D. Merecz-Kot *et al.* (2017) Environmental Tobacco Smoke Exposure during Pregnancy and Child Neurodevelopment. Int J Environ Res Public Health 14(7): E796.

Presentations at International Meetings

Dissemination and networking activities since January 2017 included the participation of several HEALS members at international workshops, conferences and scientific events hereinafter summarised:

- **Joan O. Grimalt (CSIC)** (lecture). 4th International Conference on Global Warming: Ecosystem Productivity. Dubai, United Arab Emirates. 3–5th April 2017.
- **Mercè Garí (CSIC)** *Exposure to persistent organic pollutants and risk of metabolic syndrome in the population of Catalonia* (lecture). 27th SETAC-Europe Annual Meeting. Brussels, Belgium. 8–11th May 2017.
- **Joan O. Grimalt (CSIC)** (poster). 27th SETAC-Europe Annual Meeting. Brussels, Belgium. 8–11th May 2017.
- **Joan O. Grimalt (CSIC)** (Chair platform session) Effects of Endocrine Disruptors in the environment and human health. 27th SETAC-Europe Annual Meeting. Brussels, Belgium. 8–11th May 2017.
- **Joan O. Grimalt (CSIC)** (lecture). Past Global Changes (PAGES). Zaragoza, Spain. 9–13th May 2017.
- **John G. Bartzis *et al.* (UOWM & NCSR)** Short Time Individual Exposure from Airborne Hazardous Releases in Urban Environments. The effect of time size. 14th International Conference on Atmospheric Sciences and Applications. Strasbourg, France. 29–31st May 2017.
- **Luc JM Cluitmans (VTT)** *Managing heterogeneous data in the HEALS project* (lecture). EMBEC & NBC 2017. Tampere, Finland. 11–15th June 2017.
- **Maria A. Martínez *et al.* (URV)** (lecture) Early prenatal exposure to the environmental endocrine disruptors. XIV Congreso de Salud Ambiental. Sociedad Española de Sanidad Ambiental (SESA). Zaragoza, Spain. 21–23rd June 2017.

Other dissemination activities

URV Doctoral Day of the PhD Programme on *Nanoscience, Materials and Chemical Engineering* of the Universitat Rovira i Virgili (URV). Annually, the Doctoral Programme organises a day in which doctoral students have the opportunity to discuss their work and have it evaluated by a prestigious panel of experts during a poster exhibition session. The TecnATox-URV member M.A. Martínez won the second award of the 1st year Ph.D. students with a work related with HEALS. *Retrieved from:* http://www.tecnatox.cat/noticies

CSIC Prof. Joan Grimalt, director of IDAEA-CSIC, was interviewed by the Menorca Local Press in relation to the studies on mercury levels found in fish and other foodstuff in the Menorca Island. *Retrieved from:* https://menorca.info/menorca/local/2017/605891/

MENORCA
PAÍS: España
PÁGINAS: 5
TARIFA: 838 €
ÁREA: 327 CM² - 34%
FRECUENCIA: Diario
O.J.D.: 5144
E.G.M.: 32000
SECCIÓN: LOCAL
2 Julio, 2017

«La pregunta es por qué hay tanto mercurio en el Mediterráneo»

▶ El director del estudio, Joan Grimalt Obrador, considera que dar con el origen del problema permitiría atajarlo y tomar cartas en el asunto

MERCÈ PONS

El director del estudio, profesor de investigación del Consejo Superior de Investigaciones Científicas, y director del Instituto de Diagnóstico Ambiental y Estudios del Agua (Idaea-CSIC), Joan Grimalt, indica que la existencia de mercurio en las dietas es un problema de todo el Mediterráneo -no solo de Menorca- y también del resto de España, que acumula marcas máximas en relación con otros países europeos.

Esta realidad para nada debe generar alarma entre la población porque «comer pescado es muy saludable, los médicos no nos dicen que debemos dejar de comerlo, pero hay este problema del mercurio. Y el porcentaje de lo que se incumple es alto». Pero indica que

Joan Grimalt, investigador del CSIC.

rentes tipos de pescado blanco. Es ya conocido que el pescado azul tiene concentraciones de mercurio, pero el informe confirma que no es un caso único sino que el blanco, tales como el dentón o mero, altamente consumidos en la Isla, también tienen concentraciones de este metal inorgánico tóxico.

Grimalt explica que el estudio se ha centrado en la Isla porque, por un lado, está en el Mediterráneo, está preservada y con una actividad humana nada explotada y porque Menorca se puede tomar como ecosistema modelo.

A ello, cabe sumar que Menorca fue el segundo enclave donde se puso en marcha una red sobre infancia y medio ambiente. Dirigido por el médico del Servei de Salut, Maties Torrent, esta red sigue

Forthcoming Events

HEALS meetings

- **4th HEALS Annual Meeting**
  22–25th October 2017, Island of San Servolo, Venice (Italy)
  http://www.heals-eu.eu/

Other related meetings

- **European Respiratory Society International Congress (ERS)**
  9–13th September 2017, Milan (Italy)
  https://erscongress.org/
- **53rd Congress of the European Society of Toxicology**
  10–13th September 2017, Bratislava (Slovak Republic)
  http://www.eurotox2017.com/
- **19th Annual Scientific Conference of the ISEE**
  24–28th September 2017, Sydney (Australia)
  http://www.isee2017.com/
- **19th International Symposium on Environmental Pollution and its Impact on Life in the Mediterranean Region**
  4–6th October 2017, Rome (Italy)
  http://www.mesaep.org/
- **International Society of Exposure Science Annual Meeting**
  15–19th October 2017, Durham, North Carolina (USA)
  http://intlexposurescience.org/ISES2017/
- **Biospecimen Research Symposium: Quality matters**
  27–28th February 2018, Luxembourg
  http://www.isber.org/events/EventDetails.aspx?id=1022653

Editorial Board

Prof. Joan O. Grimalt

Dr. Mercè Garí

Editorial Information

If you wish to contribute to the *Newsletter* or share information for publication, please contact Mercè Garí:

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