

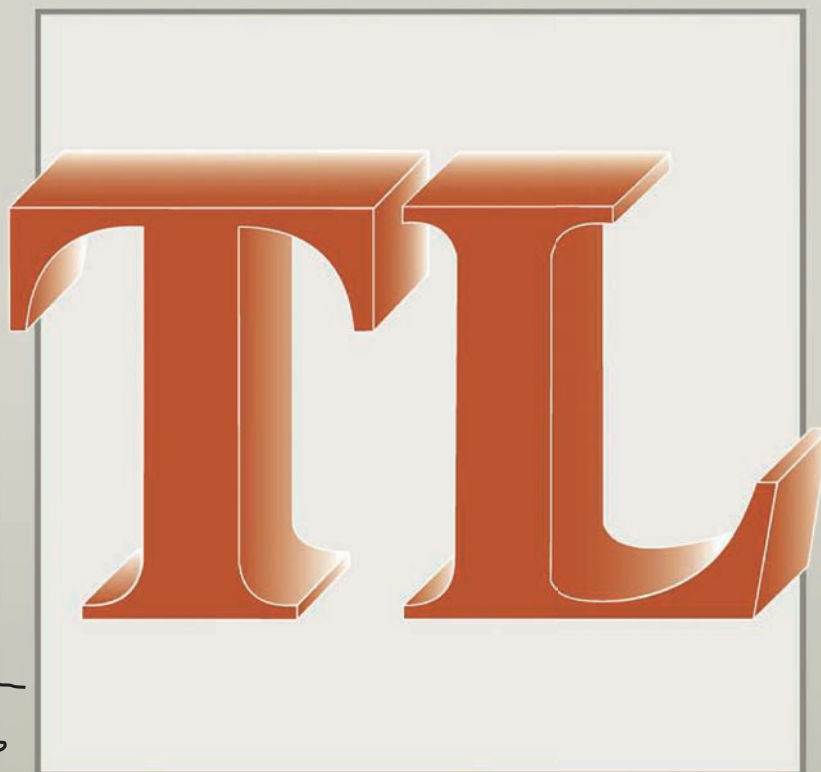
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# Toxicology Letters

Official Journal of EUROTOX



ABSTRACTS of the 55<sup>th</sup> Congress of the European Societies of Toxicology (EUROTOX 2019)  
TOXICOLOGY – SCIENCE PROVIDING SOLUTIONS  
Helsinki, Finland, 8<sup>th</sup>–11<sup>th</sup> of September, 2019

## Aims and Scope

Toxicology Letters serves as a multidisciplinary forum for research in all areas of toxicology. The prime aim is rapid publication of research letters with sufficient importance, novelty and breadth of interest. In addition to research letters, papers presenting hypotheses and commentaries addressing current issues of immediate interest to other investigators are invited. Mini-reviews in various areas of toxicology will also be published. A new feature is the provision of a forum for the discussion and interpretation of data published in the journal. Clinical, occupational and safety evaluation, legal, risk and hazard assessment, impact on man and environment studies of sufficient novelty to warrant rapid publication will be considered.

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# Toxicology Letters

*An International Journal for the Rapid Publication of Short Reports on all Aspects  
of Toxicology Especially Mechanisms of Toxicity*

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Wolfgang Dekant

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Scott Garrett, Yunbo Li and Angela Mally

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# Toxicology Letters

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## Preface

### Continuing Education Courses (CECs)

- CEC01: Development and evaluation of AOPs
- CEC02: Application and integration of increasingly mechanistically driven tools for risk assessment
- CEC03: The pre-specified protocol part of evidence-based assessment in toxicology
- CEC04: Real world safety assessments for data-poor products: How to approach data gaps  
*Supported by ILSI Europe*
- CEC05: Dietary exposure assessment
- CEC06: Determining safe exposure limits in occupational toxicology, application to pharmaceuticals

### Invited sessions

- Keynotes – EUROTOX/SOT Debate – SOT Merit Award – HESI CITE Lecture
- K01 Keynote lecture: Atmospheric aerosols: from molecular clustering to regional air quality and global climate
- K02 Keynote lecture: Systems toxicology: a key towards reliable hazard prediction
- D EUROTOX-SOT Debate: Classification of substances as endocrine disruptors has a public health benefit
- B Bo Holmstedt Memorial Fund Lecture: Understanding fundamental quantitative principles is a prerequisite for improving toxicological science and risk assessment
- SOT SOT Merit Award Lecture: Bis-Indoles as receptor ligands and novel anticancer agents
- H HESI CITE Lecture: Toxicology in the era of the exposome

## Sessions

- Session 01: Metabolic capacity and functionality of the gut microbiome
- Session 02: Fetus – the most sensitive individual
- Session 03: The Exposome – understanding the role of environmental exposure in human health and disease
- Session 04: How innate immune cells recognize toxicants
- Session 05: New tools and application in reg. risk assessment – moving toward mechanistic risk assessment
- Session 06: Developments in the use of systematic review in chemical risk assessment
- Session 07: Speeding up hazard assessment of nanomaterials
- Session 08: Human adaptation to environmental pollution: dose-response relationship revisited
- Session 09: Application of new approach methods and development of integrated approaches to testing and assessment – moving toward mechanistic risk assessment
- Session 10: The process of ageing and its modulation: telomeres as biomarkers in *in vitro* and *in vivo* studies
- Session 11: Challenges of non-animal approaches for food safety: from inception to application
- Session 12: Implications of biodistribution of inhaled nanoparticles: effects in organs other than the lung
- Session 13: Knowledge-based computational approaches in predictive toxicology
- Session 14: Understanding the interindividual variability in toxicity involving the psychotropic drugs
- Session 15: Investigative Toxicology Leaders Forum (ITLF): Scientific advancements and case studies for the optimization of drug discovery. Trends in investigative toxicology
- Session 16: Chemical risk assessment using human *in vitro*, *ex vivo*, *in silico* and biomonitoring data
- Session 17: Experimental comprehensive toxicological studies simulating real-life exposures: Long-term combined exposures on multi endpoints

sis, reticulocyte micronuclei may become an individual biomarker of the effects of genotoxic carcinogens and cancer risk.

### P01-029 Updating strategies for nonnegative matrix factorization to integrate cross omics layers

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**Introduction:** The ongoing development of high-throughput technologies has generated large and complex data sets of different omics layers, such as mRNA, methylation and protein expression. It is believed that the integration of these different layers should lead to a more complete understanding of cellular events. However, this integration step is not trivial, due to the different distributions and dimensions in each layer, and therefore an appropriate computational method has to be selected. Previous studies have shown the promising results of detecting clusters and features by applying Nonnegative Matrix Factorization (NMF). Here, we propose a multi-layer NMF with a prior knowledge integration workflow to detect both inter and intra relationships in all layers of omics information.

**Method:** The original NMF method by Lee and Seung decomposes one layer of information into a feature matrix  $W$  and a coefficient matrix  $H$ , by applying an update rule for both  $W$  and  $H$ . First, to take multiple omics layers into account, a new set of update rules has to be defined. Therefore, we introduce an update rule for  $H$  based on the omics layers  $W_i$  ( $i$  equals the number of omics layers). This will result in a clustering coefficient matrix  $H$  built from all omics layers and thus can be used to relate the different biological entities.

Second, the optimization problem for NMF is not necessarily convex and multiple local minima can be identified. Here, we hypothesize that initializing  $H$  with prior knowledge, a local minimum can be found associated with the features and clusters representing the different phenotypic endpoints or experimental conditions. This prior knowledge can contain information about exposure concentrations, compound information but also sample characteristics or disease development.

**Results:** The proposed multi-layer semi-supervised NMF workflow gives valuable information about sample clustering and features. The workflow has been evaluated with toy data, but also with gene expression and CpG methylation values from the NCI60 tumor cell line database. With the integration of those two platforms by our workflow, it becomes possible to obtain the relationships between CpG and gene data for different biological clusters. Future development of the workflow to handle time series data could allow for dynamic cross omics analysis.

### P01-030 Using human biomonitoring for the risk assessment of polycyclic aromatic hydrocarbons in occupational exposures

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**Background and Purpose:** The Human Biomonitoring Initiative (HBM4EU) is a joint effort of 28 countries, the European Environment Agency and the European Commission, co-funded under Horizon 2020. HBM4EU is generating evidence of the current exposure of Eu-

ropean citizens to chemicals and the possible health effects in order to assess the associated risks and support policy making towards human health protection. Polycyclic aromatic hydrocarbons (PAH) were considered one of the 1<sup>st</sup> priority substance groups to be addressed. In the scope of this project, the present work aimed to evaluate the added value of human biomonitoring (HBM) for the PAH risk assessment process, in the case of occupational exposure.

**Methods:** An extensive literature search was performed to identify scientific papers published between 2008 and 2018 that included air monitoring and HBM data in several occupational settings based in Europe. Among them, those papers presenting urinary 1-hydroxypyrene (1-OHP) quantification – the most common exposure biomarker of pyrene and a surrogate for exposure to PAHs mixtures – were selected. Based on the 1-OHP values the excess lifetime cancer risk (ELCR) for workers, concerning lung cancer, was estimated following the ECHA recent approach (<https://echa.europa.eu/fi/applying-for-authorisation/evaluating-applications>). ELCR values calculated using air and HBM data were compared.

**Results:** Based on the criteria described, only 7 out of 28 papers were considered for ELCR estimation. Overall, high ELCR values were estimated (several values higher than  $10^{-4}$ ). Moreover, for some studies (3 out of 7) the ELCR estimation using HBM data yielded values higher than those estimated from air monitoring data. This might indicate that, for those specific workplaces, transdermal absorption or even hand-mouth exposure can have an important role in the total exposure to PAH and that the HBM data allows a more accurate PAH exposure assessment. Nevertheless, these findings should be interpreted with caution, since ELCR estimates from air monitoring data are based on Benzo[a]pyrene (BaP) concentrations while HBM-based ELCR determination uses urinary 1-OHP concentration that reflects exposure not only to BaP but to all PAHs, irrespectively of sources or routes of exposure.

This work claims attention for two main aspects, namely: i) the exposure levels are still high in some occupational settings and ii) there is a need for developing new occupational studies, applying a set of exposure biomarkers or a more specific biomarker for BaP exposure, which would allow a better ELCR estimation for exposed workers.

The authors are grateful to HBM4EU project. The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 733032.

### References

RAC-Committee for Risk Assessment (2018a). Note on reference dose-response relationship for the carcinogenicity of pitch, coal tar, high temperature and on PBT and vPvB properties. Helsinki Available at: [https://echa.europa.eu/documents/10162/13637/ctph\\_rac\\_note\\_en.pdf/a184ee42-0642-7454-2d18-63324688e13d](https://echa.europa.eu/documents/10162/13637/ctph_rac_note_en.pdf/a184ee42-0642-7454-2d18-63324688e13d) [Accessed February 11, 2019].

### P01-031 Toxicity assessment caused by the insecticide methamidophos in bullfrog's tadpoles

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In Mexico, currently are sold various plagicides prohibited in other countries, thus it is important to determine its toxicity and how it affects to humans and animals. Methamidophos is one of the above mentioned pesticides and belongs to a group of organophosphates that are characterized by causing neurological damage and alterations in various defense mechanisms. The purpose of this study was to assess the acute effects (median lethal concentration, LC50) as well as neurotoxic damage and the evaluation of oxidative stress markers in a non-lethal concentration.