Accepted Manuscript

Title: Toxicology for Real-Life Risk Simulation - Editorial Preface to this Special Issue

Authors: Aristidis Tsatsakis, Marina Goumenou

PII: S0378-4274(18)32065-4
DOI: https://doi.org/10.1016/j.toxlet.2018.12.003
Reference: TOXLET 10379

To appear in: *Toxicology Letters*

Author: Jyrki Liesivuori

PII: S0378-4274(18)32065-4
DOI: https://doi.org/10.1016/j.toxlet.2018.12.003
Reference: TOXLET 10379

To appear in: *Toxicology Letters*

Author: Wolfgang Dekant

PII: S0378-4274(18)32065-4
DOI: https://doi.org/10.1016/j.toxlet.2018.12.003
Reference: TOXLET 10379

To appear in: *Toxicology Letters*

Author: Antonio F. Hernández

PII: S0378-4274(18)32065-4
DOI: https://doi.org/10.1016/j.toxlet.2018.12.003
Reference: TOXLET 10379

To appear in: *Toxicology Letters*

Please cite this article as: Tsatsakis A, Goumenou M, Liesivuori J, Dekant W, Hernández AF, Toxicology for Real-Life Risk Simulation - Editorial Preface to this Special Issue, *Toxicology Letters* (2018), https://doi.org/10.1016/j.toxlet.2018.12.003

Toxicology for Real-Life Risk Simulation - Editorial Preface to this Special Issue

Aristidis Tsatsakis [a], Marina Goumenou [a], Jyrki Liesivuori [b], Wolfgang Dekant [c]

Antonio F. Hernández [d]

[a] Centre of Toxicology Science & Research, Medical School, University of Crete, Heraklion, Crete, Greece

[b] Department of Pharmacology, Drug Development and Therapeutics, University of Turku, Finland

[c] Institute of Toxicology, University of Wuerzburg, Versbacherstrasse 9, 97078 Wuerzburg, Germany

[d] Department of Legal Medicine and Toxicology, University of Granada School of Medicine, Granada, Spain

Abstract

The current approach for the assessment of regulated chemicals does not account for human real-life exposure scenarios. These are featured by exposure to low doses of multiple chemicals through different routes and pathways. For a novel risk assessment paradigm, a number of true exposure scenarios, the co-occurrence of multiple adverse outcomes and possible interactions need to be assessed. This special issue will consider studies specifically designed to simulate real-life conditions of combined exposure to chemicals and to derive respective safe exposure limits.

Abbreviations

AOP	Adverse Outcome Pathways
EFSA	European Food Safety Authority
IPCS	International Programme on Chemical Safety
MoA	Mode of Action
NOAEL	No-observed-adverse-effect-level
RLRS	Real-Life Risk Simulation
PPR	Plant Protection Products and their Residues
WHO	World Health Organisation

Keywords: Risk Assessment, Real-Life Risk Simulation (RLRS), mixtures, low doses, exposure

Introduction

In regulated chemicals, safe exposure limits are set based on a) in vivo studies of single chemicals administered at high doses to experimental animals, b) identification of the no-observed-adverse-effect-level (NOAEL) assuming by default monotonicity and considering only apical effects of adversity, and c) using non-validated uncertainty factors, common for all chemicals. Though this is a practical and globally used approach, the vast majority of human real-life exposure scenarios have two main key components: low doses and many chemicals. The systematic neglection of a) real-life exposure scenarios, b) early signs of adversity at molecular or cellular level, and c) the potential for non-monotonicity (e.g. endocrine disruptors), and d) chemicals' interactions in both toxicokinetic and toxicodynamic (Sarigiannis and Hansen, 2012), challenges the real value of the existing "safety limits" (Dekant and Colnot, 2013). Even newly developed approaches such as grouping of chemicals for cumulative risk assessment are not considering real-life exposure scenarios as they are based on regulatory toxicology studies. Acknowledging the need for a paradigm shift of the current approaches for risk assessment towards a Real-Life Risk Simulation (RLRS) approach, the present special issue is intended to collect key articles and pioneering studies in support of this new area of toxicology.

Problem Formulation

Five hundred years ago, Paracelsus laid the foundations of modern toxicology with the quote "All substances are poisons; it is the dose that makes the poison". His observations showed that while small doses of a chemical might be harmless, or even be used therapeutically, larger doses could be toxic. Since then, monotonicity became the central toxicological assumption (Docea et al., 2018, Tsatsakis et al., 2018). This, together with the study of individual chemicals as single stressors paved the way followed so far for hazard assessment, consisting of studying one chemical at the time at doses high enough to reveal toxicity in the highest level of biological organisation. In addition, though the generally acceptable definition of adversity is "A change in the morphology, physiology, growth, development, reproduction, or life span of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences" (IPCS, 2004), in practice the two latter points have been systematically neglected.

Though for at least four decades risk assessment in different forms has been a hot topic in most of toxicology congresses and publications all over the world, exposure assessment, one of the crucial elements in risk assessment, has not gained so much interest. This is strange as all toxicologists are taught already at the early phase of their studies that dose is a critical measure and without knowing that proper risk assessment cannot be performed. In pharmacology and animal testing dose is quite clear and in most of the cases known. As to human toxicology the situation is different: the same persons might have been exposed to multitude of chemicals through the diet, environmental sources, use of consumer products or at the workplace (occupational exposure) and many times at the same time or sequentially. This makes exposure assessment even more complicated and hard to identify its linkage with long-term adverse health effects. Since human behavior shows an appreciable degree of variety, exposure will also vary greatly over the heterogeneous population, which differs with the genetically homogenous, inbred strains of experimental animals currently used in regulatory toxicology studies. Single-chemical analysis allows a determination of the individual risk arising from one particular hazard occurring following exposure under

specific conditions. However, it does not provide an integrated assessment of the multiple risks triggered by exposure to different environmental stressors (chemical and non-chemical, be them natural or anthropogenic) and at realistic doses (Saxton 2012; Hernandez and Tsatsakis 2017, EFSA PPR Panel, 2017, Kostoff et al., 2018). In addition, large numbers of chemicals with the same mechanism of toxic action can act jointly at their unique molecular target when present at concentrations not associated with observable effects alone. Their joint effects as well as possible interactions (Sarigiannis and Hansen, 2012) can occur at concentrations of the individual components that, if tested alone, would have produced effects too small to be measurable with the power afforded by the current toxicological methodologies. These observations are of relevance in light of realistic environmental exposure scenarios where multiple chemicals are present at low concentrations (Ray and Richards, 2001, Thrupp et al., 2017). Therefore, a number of true exposure scenarios are needed, and the choice of each one of these scenarios will have a major influence on the results of an exposure assessment (Mäkinen et al., 2002; Colosio et al., 2012, Landberg et al., 2017; Kim et al., 2018,). Furthermore, the novel risk assessment paradigm would benefit by implementing procedures for evaluating the co-occurrence of multiple adverse outcomes, which is more in line with what happens in human settings. Preliminary data should be supported with results from studies specifically designed to simulate real-life conditions of combined exposure to chemicals and to derive respective safe exposure limits (Tsatsakis et al. 2016; Tsatsakis et al. 2017; Docea et al. 2018; Kostoff et al. 2018).

Under this framework a number of questions arise: what is the relation of the current toxicological approaches used for human (and environmental) protection with the real-life exposure scenarios and the actual hazard under such scenarios? Are the current approaches adequate for the derivation of sufficiently protective safe limits (Hernandez et al., 2013; Chen et al., 2015; Maffini and Neltner 2015; Kostoff 2016; Borman et al., 2017, Colnot and Dekant 2017)? What Real-Life Risk Simulation experiments are proving? These are some of the questions foreseen to be addressed in the current special issue.

Particular topics foreseen to be addressed in this Special issue:

The present special issue is envisioned to host key articles in relation to:

- Determination of real-life exposure scenarios
- Assessment of hazards and derivation of safety limits under real-life exposure scenarios
- Development of new methodologies and experimental study protocols (in vivo, in vitro, -omics and in silico) fit-for-purpose of hazard assessment and considering both toxicokinetic and toxicodynamic.
- Put more emphasis on new tools such as Mode of Action (MoA)/Adverse Outcome Pathways (AOP) to move towards a mechanistic-based risk assessment

Acknowledgments

The authors wish to thank the Publisher Jagna Mirska and the special issue manager Nithya Sathishkumar for the technical support and preparation of this special issue and for providing 0A for the preface.

References

Borman, E., Foster, W., de Catanzaro, D., 2017. Concurrent administration of diethylhexyl phthalate reduces the threshold dose at which bisphenol A disrupts blastocyst implantation and cadherins in mice. Environ. Toxicol. Pharmacol. 49, 105-111.

Chen, C., Wang, Y., Qian, Y., Zhao, X., Wang, Q., 2015. The synergistic toxicity of the multiple chemical mixtures: implications for risk assessment in the terrestrial environment. Environ. Int. 77, 95-105.

Colnot T., Dekant W., 2017. Approaches for grouping of pesticides into cumulative assessment groups for risk assessment of pesticide residues in food. Regul Toxicol Pharmacol. 83, 89-99.

Colosio C., Rubino FM., Alegakis A., Ariano E., Brambilla G., Mandic-Rajcevic S., Metruccio F., Minoia C., Moretto A., Somaruga C., Tsatsakis A., Turci R., Vellere F. 2015. Integration of biological monitoring, environmental monitoring and computational modelling into the interpretation of pesticide exposure data: introduction to a proposed approach. Toxicol Lett. 213,49-56.

Dekant W, Colnot T. 2013. Endocrine effects of chemicals: aspects of hazard identification and human health risk assessment. Toxicol Lett. 223, 280-286

Docea, A., E. Gofita, E., Goumenou, M., Calina, D., Rogoveanu, O., Varut, M., Olaru, C., Kerasioti, E., Fountoucidou, P., Taitzoglou, I., Zlatian, O., Rakitskii, V., Hernandez, A.F., Kouretas, D., Tsatsakis, A., 2018. Six months exposure to a real-life mixture of 13 chemicals' below individual NOAELs induced non monotonic sex-dependent biochemical and redox status changes in rats. Food Chem. Toxicol. 115, 470-481.

EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), Scientific Opinion of the PPR Panel on the follow-up of the findings of the External Scientific Report 'Literature review of epidemiological studies linking exposure to pesticides and health effects'. EFSA J 2017;15(10):5007, 101 pp

Hernandez, AF., Parron, T., Tsatsakis, AM., Requena, M., Alarcon, R., Lopez-Guarnido, O., 2013. Toxic effects of pesticide mixtures at a molecular level: their relevance to human health. Toxicology 307, 136-145.

Hernandez, AF., Tsatsakis, AM., 2017. Human exposure to chemical mixtures: challenges for the integration of toxicology with epidemiology data in risk assessment. Food Chem. Toxicol., 103, 188-193.

IPCS/WHO 2004. IPCS harmonization project - IPCS Risk Assessment Terminology World Health Organization 2004, Geneve, p. 10, ISBN 92 4 156267 6. Available online at: http://www.inchem.org/documents/harmproj/harmproj/harmproj1.pdf (accessed on 2 December 2018).

Kim DH, Lee JH, Oh JE. 2018. Assessment of individual-based perfluoroalkly substances exposure by multiple human exposure sources. J Hazard Mater. 365, 26-33.

Kostoff, RN., 2016. Under-reporting of adverse events in the biomedical literature. J. Data Inform. Sci. 1, 10-32.

Kostoff RN., Goumenou M., Tsatsakis A., 2018. The role of toxic stimuli combinations in determining safe exposure limits, Editorial in Toxicology Reports, Published online 7 November 2018 https://doi.org/10.1016/j.toxrep.2018.10.010, In press.

Landberg HE, Axmon A, Westberg H, Tinnerberg H., 2017. A Study of the Validity of Two Exposure Assessment Tools: Stoffenmanager and the Advanced REACH Tool. Ann Work Expo Health. 61, 575-588.

Maffini, M., Neltner, T. 2015. Brain drain: the cost of neglected responsibilities in evaluating cumulative effects of environmental chemicals, J. Epidemiol. Community Health, 69 (5) (2015), pp. 496-499

Mäkinen M, Hämäläinen M, Forsman K, Liesivuori J, 2002. Chemical Exposure and Risk Assessment at Workplaces - Modelling Approach. Appl Occup Environ Hyg 17 (2002) 744-749.

Ray DE., Richards PG. 2001. The potential for toxic effects of chronic, low-dose exposure to organophosphates. Toxicol Lett, Volume 120, Issues 1–3, 31 March 2001, Pages 343-351

Sarigiannis DA., Hansen U., 2012. Considering the cumulative risk of mixtures of chemicals – A challenge for policy makers, Environ Health. 2012; 11(Suppl 1): S18.

Sexton, K. 2012. Cumulative risk assessment: an overview of methodological approaches for evaluating combined health effects from exposure to multiple environmental stressors. Int. J. Environ. Res. Public Health, 9, 370-390.

Thrupp TJ., Runnalls TJ., Martin S., Kugathas S., Kortenkamp A., Sumpter GP., 2018. The consequences of exposure to mixtures of chemicals: Something from 'nothing' and 'a lot from a little' when fish are exposed to steroid hormones. Science of The Total Environment, Volumes 619–620, 1 April 2018, Pages 1482-1492

Tsatsakis A.M., Docea A.O., Tsitsimpikou C., 2016. New challenges in risk assessment of chemicals when simulating real exposure scenarios; simultaneous multi-chemicals' low dose exposure, Food Chem. Toxicol. 96 (2016) 174–176.

Tsatsakis A.M., Kouretas D., Tzatzarakis M.N., Stivaktakis P., Tsarouhas K., Golokhvast K.S., Rakitskii V.N., Tutelyan V.A., Hernandez A.F., Rezaee R., Chung G., Fenga C., Engin A.B., Neagu M., Arsene A.L., Docea A.O., Gofita E., Calina D., Taitzoglou I., Liesivuori J., Hayes A.W., Gutnikov S., Tsitsimpikou C., 2017. Simulating real-life exposures to uncover possible risks to human health: a proposed consensus for a novel methodological approach, Hum. Exp. Toxicol. 36 (6) (2017) 554–564.

Tsatsakis A.M., Vassilopoulou L., Kovatsi L., Tsitsimpikou C., Karamanou M., Leon G., Liesivuori J., Hayes A.W., Spandidos D.A., 2018. The dose response principle from philosophy to modern toxicology: The impact of ancient philosophy and medicine in modern toxicology science- Toxicol Rep. 2018; 5: 1107–1113.