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Project title: Integrating Epidemiology and Experimental Biology to Improve Risk Assessment of Exposure to Mixtures of Endocrine Disruptive Compounds

Final Technical Report

Report: Final Technical Report of EDC-MixRisk

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Overview of the results and their exploitation and dissemination

Background and aims

Anthropogenic chemicals with endocrine disrupting properties have been known for long and their health impact on humans and wildlife is of global concern [1]. It is widely acknowledged that a healthy endocrine system is necessary for a healthy development and life. Humans are exposed to endocrine disrupting chemicals (EDCs) throughout their whole life span, from conception, during the foetal period until end of life. However, exposure to these chemicals, even at low doses, is of particular concern during prenatal and early postnatal developmental periods as it can lead to programming and long-lasting effects on the molecular level (e.g. of the proteome, transcriptome and epigenome). Such changes underlie disorders that may manifest later in adult life and contribute to "diseased ageing" with a multitude of chronic diseases. Indeed, EDC exposure has been associated with impaired development of the neurological, metabolic and reproductive systems as well as with disorders such as hormone related cancers. Evidence for EDC related effects is supported by experimental results, observations in wildlife and through epidemiological findings [1].

EDCs are found among the more than 100.000 chemicals registered by e.g. REACH and are used in, and in the production of, consumer products, goods and construction materials. Examples are plasticisers, pesticides and antibiotics. Further, these chemicals are metabolised to potential or actual EDCs and may contain by-products with such properties. Thus, humans and wildlife are exposed to mixtures of EDCs on an everyday basis. Indeed, EDCs and/or their metabolites are routinely detected in e.g. urine, blood and mothers' milk [1]. Yet, although it is clear that real life exposure entails mixtures of chemicals, risk assessment is performed by a compound-by-compound approach. This has raised a concern that the impact of EDCs and other chemicals is underestimated.

The long reaching goal of EDC-MixRisk was to promote risk assessment and management of chemical mixtures to minimize human exposure risks from mixtures of anthropogenic chemicals with endocrine disrupting properties. The objectives were to determine and assess the risk for adverse health outcomes based on molecular mechanisms involved, after early life exposure to complex mixtures of EDCs. The three major aims of EDC-MixRisk were:

i) Identification of EDC mixtures that are associated with adverse health outcomes in epidemiological data for sexual development (S), neurodevelopment (N) and metabolism and growth(G), (called the three health domains, herein);

[1] UNEP/WHO (2013), State of the science of endocrine disrupting chemicals – 2012, Eds. Å. Bergman, J.J. Heindel, S., Jobling, K.A. Kidd and R.T. Zoeller. www.who.int/phe/en/ and www.unep.org/hazardous substances. pp i-xxv, 1-260; Kortenkamp A, Martin O, Faust M, Evans R, McKinlay R, Orton F, Rosivatz E. (2011). State of the Art Assessment of Endocrine Disrupters. Final Report. [Online] Available at: http://ec.europa.eu/environment/endocrine/documents/4_SOTA%20EDC%20Final%20Report%20V3%206%20Feb%2012.pdf.

ii) Identification of molecular mechanisms and pathways underlying the associations between exposure and adverse health outcomes by the use and development of state-of-the-art experimental models;

iii) Development of a transparent and systematic framework in risk assessment for integrating epidemiological and experimental research to facilitate the assessment of risk and societal impact, i.e. to improve risk management of EDCs and their mixtures.

The EDC-MixRisk project, with the goals given above, had the privilege to build on an existing epidemiological study – SELMA, a Swedish mother-child cohort. This cohort study supplied EDC-MixRisk with some baseline exposure data that had already been gathered before the start of the project. Further, EDC-MixRisk attracted scientists with extensive *in vitro* and *in vivo* experimental competences to address numerous toxicological endpoints relevant for endocrine disruption. Finally improving the risk assessment methodology for mixtures of EDCs was built on integration and interdisciplinary cooperation within the project. The outline of the project is visualised in Figure 1. The arrow feeding from the "Experimental methods" back to the "Epidemiology/Biostatistics/Chemistry" module depicts an additional goal of the project, namely to link molecular changes identified by the experimental studies to exposure and health outcomes in humans.

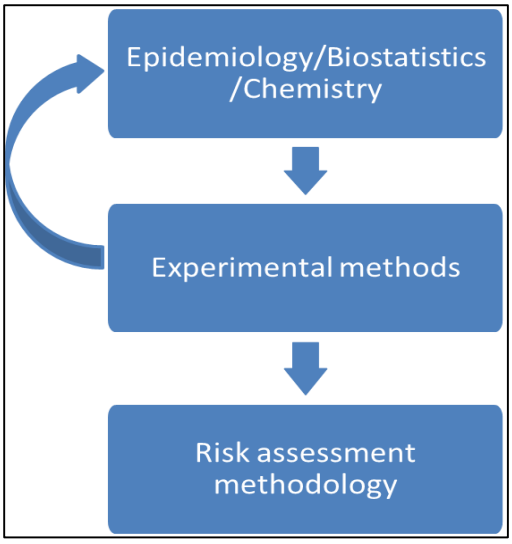

***Figure 1**: EDC-MixRisk project overview*

Main results

As shown in Figure 1, the project integrated advanced expertise in exposure assessment, epidemiology, toxicology and risk assessment to address three inter-linked scientific modules: 1) epidemiology (including WP 2&3), 2) experimental systems (including WP 4&5), and 3) risk assessment and societal impact (including WP 6&7). The scientific key results of the project are thus presented for each module.

Project management (WP1). Efficient management and coordination were established, facilitating the interdisciplinary information and knowledge flow as well as all ensuring smooth progress and reporting. This resulted in the achievement of all the main aims set for the project. The public deliverables of the project are available via Cordis: https://cordis.europa.eu/project/rcn/193310/results/en

Epidemiology (WP 2&3): Epidemiological data from the SELMA study were used to identify EDC mixtures associated with adverse and developmental outcomes in prenatally exposed children in the three health domains, sexual development, neurodevelopment and metabolism and growth.

- Fifty-four potential endocrine disruptors were analysed in blood and urine from pregnant women in the Swedish SELMA pregnancy cohort study. Forty-one of these[2] (75%) were found above the level of detection in the majority of the analysed urine/serum samples from more than 2,300 pregnant women.
- Among the forty-one chemicals, we identified those that were associated with adverse health outcomes in three different health domains in children:
    - Sexual development (measured as a shorter anogenital distance (AGD) in boys at 21 months of age)
    - Neurodevelopment (measured as language delay at 30 months of age, and cognitive functions at 7 years of age), and
    - Metabolism and growth (measured as birth weight and growth during the first 7 years of age).
- The identified chemicals were mixed in ratios corresponding to their geometric mean exposure concentrations in more than 2,300 pregnant women in SELMA. The resulting mixtures (Figure 2, next page) were our "reference mixtures" tested in the experimental models.

[2] The 54 chemicals/metabolites analysed included: 13 phthalate ester metabolites of seven phthalate esters plus a metabolite of DINCH, 2 metabolites of 2 polycyclic aromatic hydrocarbons (PAHs), 5 metabolites of 5 alkyl phenols (4 bisphenols and triclosan), and a metabolite of an organic phosphate esters. Further, 8 perfluoroalkyl substances, 19 polychlorinated persistent aromatics and 3 polybrominated diphenyl ethers.

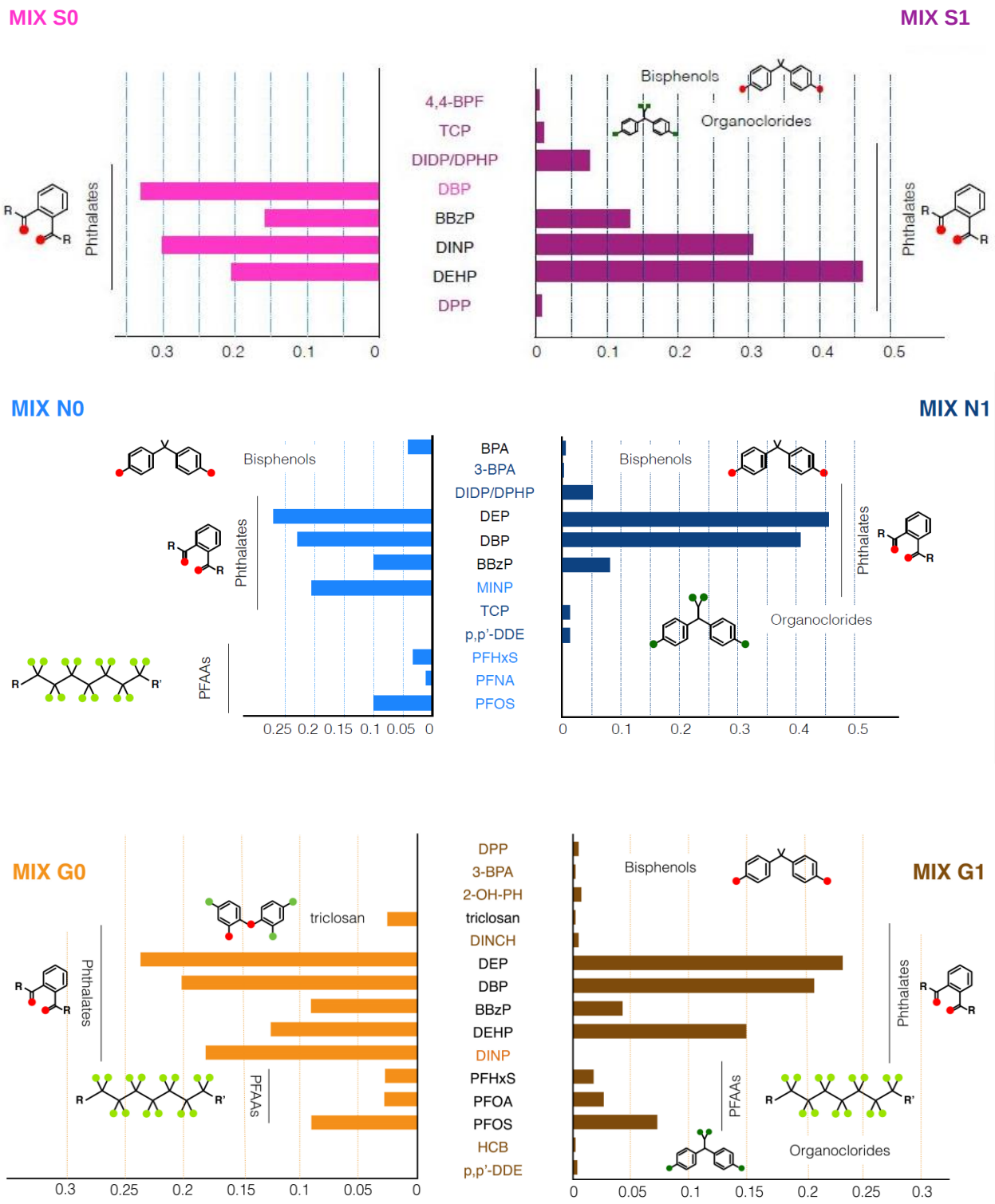

***Figure 2**: Composition and proportion of the reference mixtures identified in the epidemiological data and tested in the experimental systems. S0, N0, and G0 are based on the analyses of 20 chemicals in SELMA mothers' urine and serum, whereas S1, N1, and G1 are based on the analyses of 45 chemicals. S mixtures are associated with shorter AGD (anogenital distance) in SELMA boys, N mixtures with language delay at 30 months, and G mixtures with low birth weight in the SELMA children.*

Experimental *in vivo* and *in vitro* studies (WP4&5): Experimental investigations in animal and cell models were used to uncover molecular mechanisms underlying associations between exposure and effects seen in the epidemiological studies. The cell and animal models included human brain organoids, human cell lines, mice, tadpoles and zebrafish, which were considered relevant for the three health domains.

- Exposing the experimental models to the mixtures caused adverse effects and dysfunctions in animal and cell models.
- The experimental effects were observed at exposure levels similar to those measured in the SELMA cohort.
- The measured effects were also coherent with adverse health outcomes seen in the SELMA children, and further with endocrine disruptive modes of action. For example:
    - The mixture associated with shortened AGD interfered with production of sex hormones and led to morphological changes of the reproductive organs and to a shortened AGD in mice[3].
    - The mixture associated with language delay interfered with thyroid hormone signalling, altered the expression of genes involved in autism spectrum disorder and intellectual disability in human brain organoids, modified neuronal differentiation and function, and induced behavioural changes in tadpoles, zebrafish and mice[4].
    - The mixture associated with low birth weight interfered with thyroid hormone signalling, changed expression of genes involved in fat cell differentiation and obesity, increased differentiation of stem cells into fat cells, and lead to higher fat cell number in developing zebrafish[4]. The mixture also associated with low birth weight in male mice.
- The molecular, cellular, and organismal findings for each health domain, complemented by published findings, were connected in an adverse outcome pathway (AOP)-like manner (Figures 3-5).
- Our results revealed the impact of genetic background diversity on the sensitivity to chemical exposure, demonstrating the unique value of human *in vitro* models and underpinning their potential use for testing chemicals on genetic backgrounds that would be representative for large parts of the (European) population[4].
- Some molecular signatures induced by the mixtures in the experimental models were associated to exposure and health outcomes in the SELMA children. This reinforces human relevance of the experimental finding and pave the way for such molecular signatures as early markers for health risks induced by prenatal chemical exposure.

[3] Repouskou et al., 2019. Gestational exposure to an epidemiologically defined mixture of phthalates leads to gonadal dysfunction in mouse offspring of both sexes. Sci Rep. 2019 Apr 23;9(1):6424. doi: 10.1038/s41598-019-42377-6
[4] Birgersson et al., 2017. From Cohorts to Molecules: Adverse Impacts of Endocrine Disrupting Mixtures. bioRxiv. Doi: 10.1101/206664

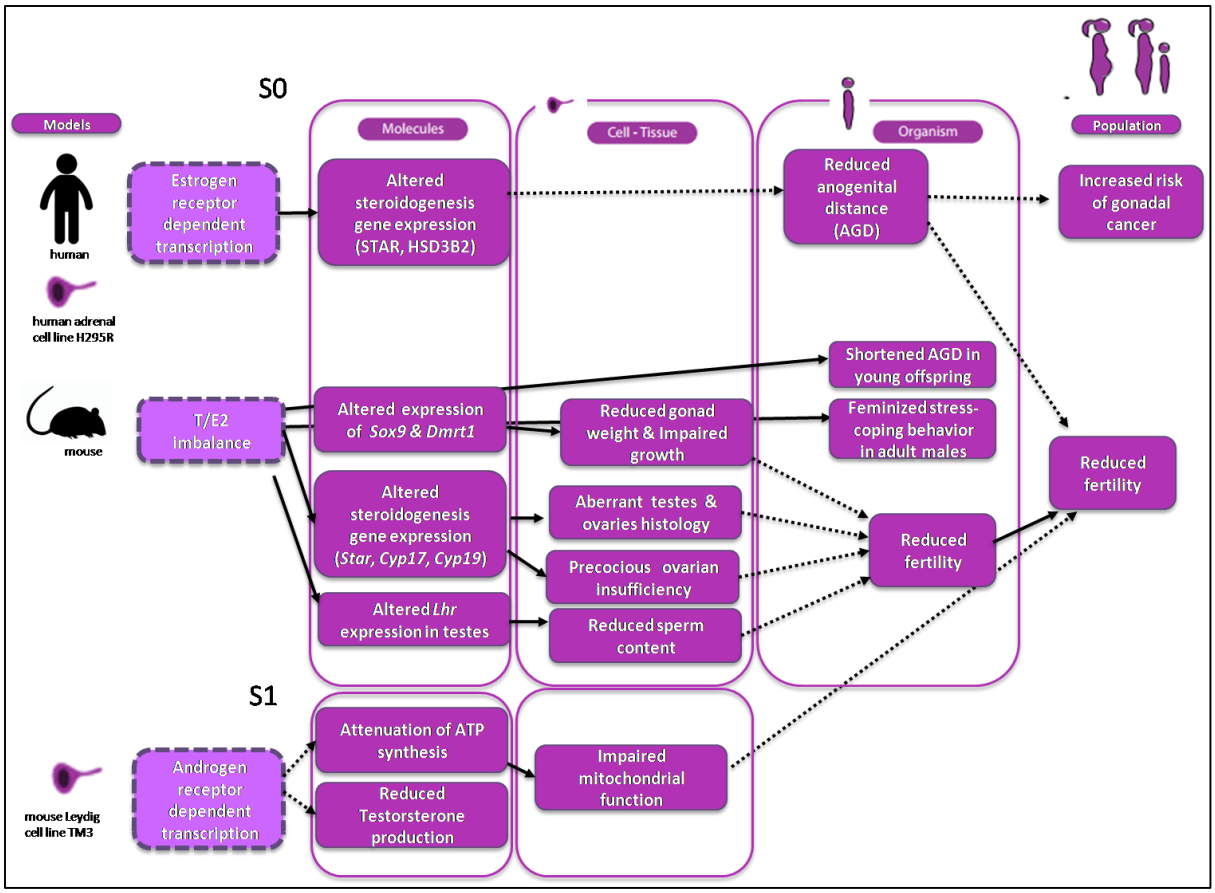

***Figure 3**: Summary of the results obtained with mixtures S in different experimental systems, arranged in an adverse outcome pathway (AOP)-like representation. Note that the boxes with dashed lines are hypothetical events based on scientific literature while solid line boxes represent events shown in the EDC-MixRisk project.*

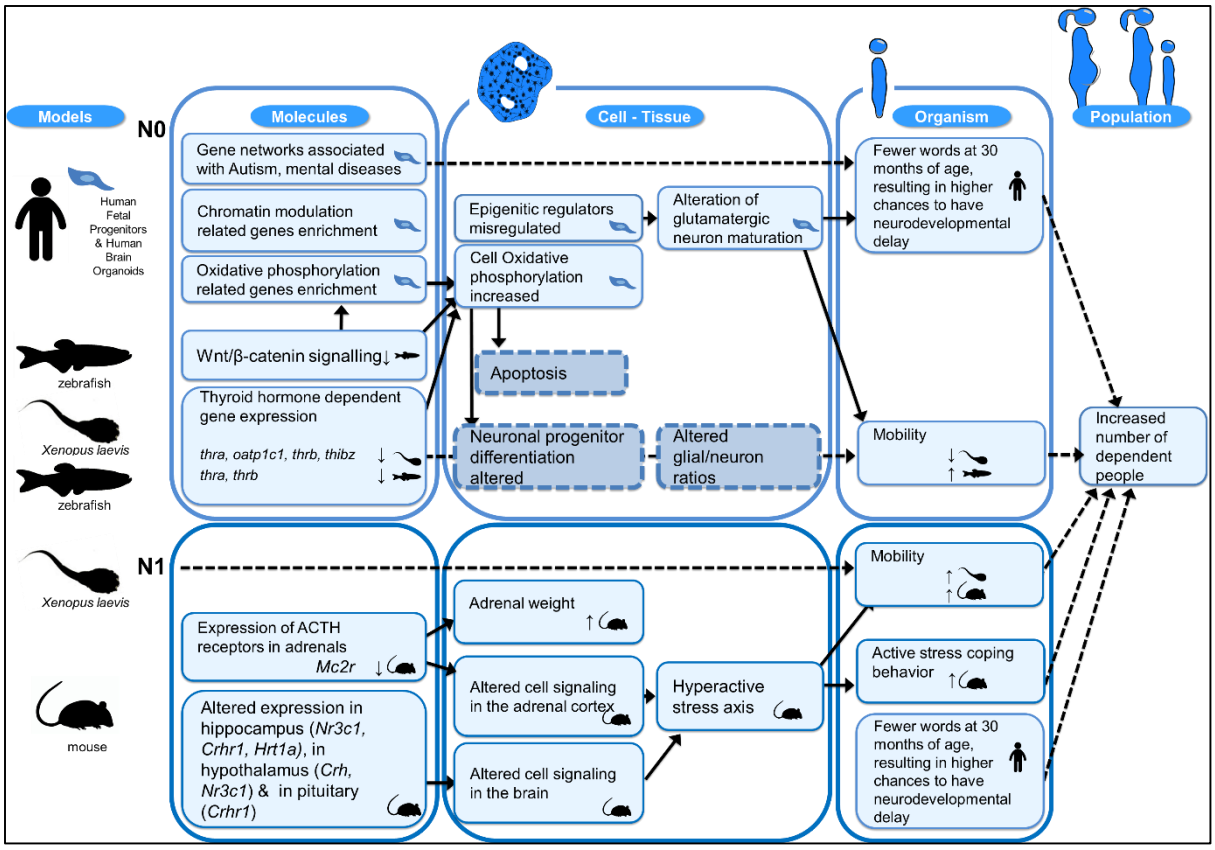

***Figure 4**: Summary of the results obtained with mixtures N in different experimental systems, arranged in an adverse outcome pathway (AOP)-like representation. Note that the boxes with dashed lines are hypothetical events based on scientific literature while solid line boxes represent events shown in the EDC-MixRisk project.*

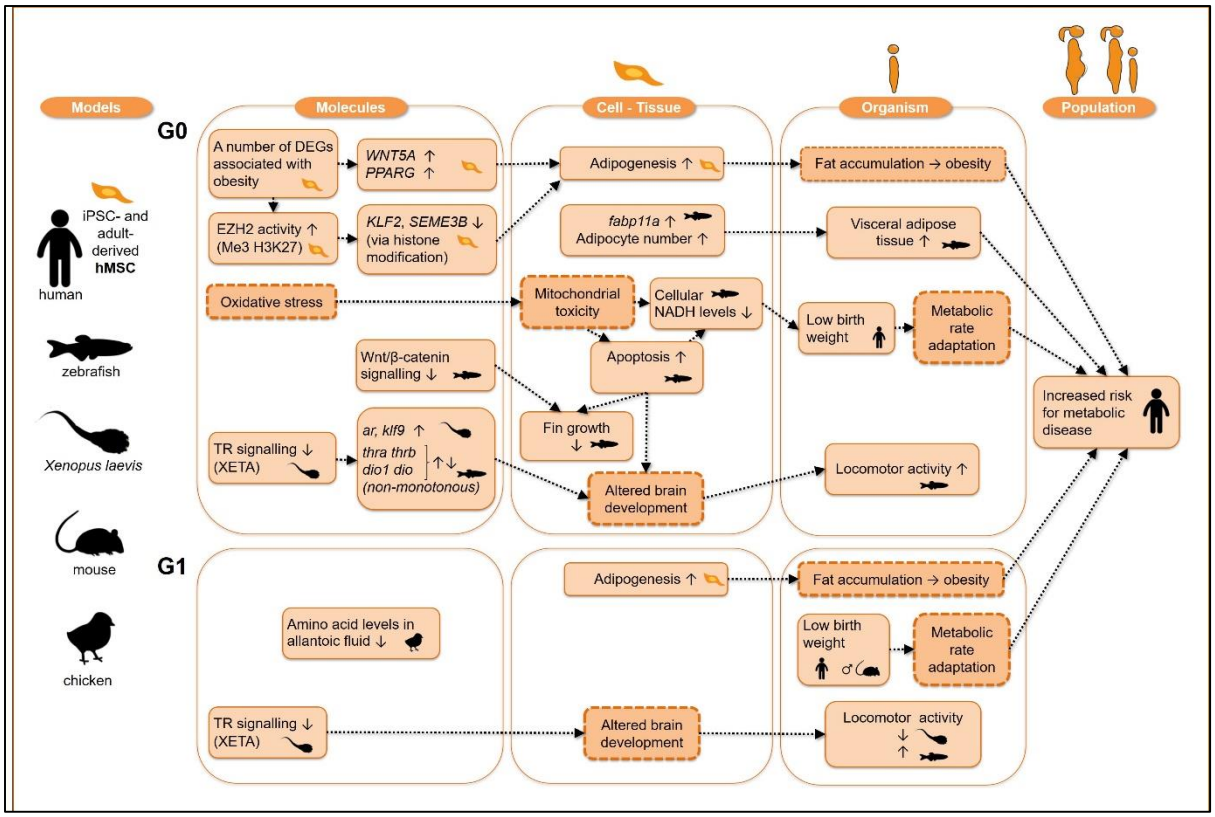

Figure 5*: Summary of the results obtained with mixtures G in different experimental systems, arranged in an adverse outcome pathway (AOP)-like representation. Note that the boxes with dashed lines are hypothetical events based on scientific literature while solid line boxes represent events shown in the EDC-MixRisk project.*

Risk assessment and societal impact (WP6 and WP7): Epidemiological and experimental data from the project have been used to develop new mixture risk assessment methods and approaches that complement current strategies.

- By defining and experimentally testing a reference mixture, i.e., a whole mixture approach (Figure 6), we could assess how many mothers in the SELMA study are at risk for effects in their children. This was performed by applying advanced biostatistical methods[5]:
    - This novel approach indicates that a large proportion of the SELMA women had mixtures in their blood that were considered sufficiently similar to the tested reference mixtures. If generalized, this means that it is possible to identify and test a rather small number of chemical mixtures that are relevant for a large proportion of the population. This is a significant step forward as it is not feasible to test all possible combinations of different mixtures.

[5] Marshall et al., 2013. An empirical approach to sufficient similarity: Combining exposure data and mixtures toxicology data. *Risk Analysis.* Volume 33(9), pages 1582-1595.

- When applied in the three health domains we observed:
  - When assessing sexual development, i.e., AGD, a higher rate (13%) of pregnant women were assessed as being at increased risk of giving birth to baby boys with shortened AGD, when compared with traditional risk assessment strategies based on the assumption of additivity(<5%), or the most used single compound approach (<2%)[6].
  - When assessing neurodevelopment, i.e., language delay at 30 months of age, 0.2% of the pregnant women were at increased risk for having a child with language delay.
  - When assessing metabolism and growth, i.e., birth weight, 23% of the pregnant women were at increased risk for having a child with lower birth weight.

- New statistical models developed in the project deliver "guideline values" for risk based on epidemiological data to inform risk assessment of mixtures. The *acceptable concentration range model*[7] provides estimates of acceptable exposures to mixtures using human biomonitoring data from cohort studies.
  - When assessing language delay and birth weight endpoints, we found that the current single compound approaches underestimated risk by a factor that ranged from 1 to 100 for different chemicals.
  - Our study shows that it is possible to derive health based guideline values from epidemiology data. Such estimates may provide empirical support for determining assessment factors for mixtures.
- The Systematic Review and Integrated Assessment (SYRINA) methodology[8] was applied with the aim to contribute to a development where the identification of endocrine disrupting chemicals and mixtures becomes systematic and transparent. We found that:
  - The SYRINA framework is suitable for assessment under the WHO definition for endocrine disrupting chemicals.
  - The assessment of mechanistic (*in vitro*) data is time consuming and should be modified in order to find a balance between a comprehensive and a practically feasible process.
  - The use of structured reporting of data, and data repositories designed for risk assessment purposes have the potential to make the evaluation process more efficient.

[6] Bornehag et al., 2019. A novel approach to chemical mixture risk assessment - Linking data from population based epidemiology and experimental animal tests. *Risk Analysis, in press.*
[7]Gennings et al., 2018. Incorporating regulatory guideline values in analysis of epidemiology data. *Environment International*. Volume 120, Pages 535-543. doi: 10.1016/j.envint.2018.08.039
[8] Vandenberg et al. 2016. A proposed framework for the systematic review and integrated assessment (SYRINA) of endocrine disrupting chemicals. *Environmental Health* 15:74. https://doi.org/10.1186/s12940-016-0156-6

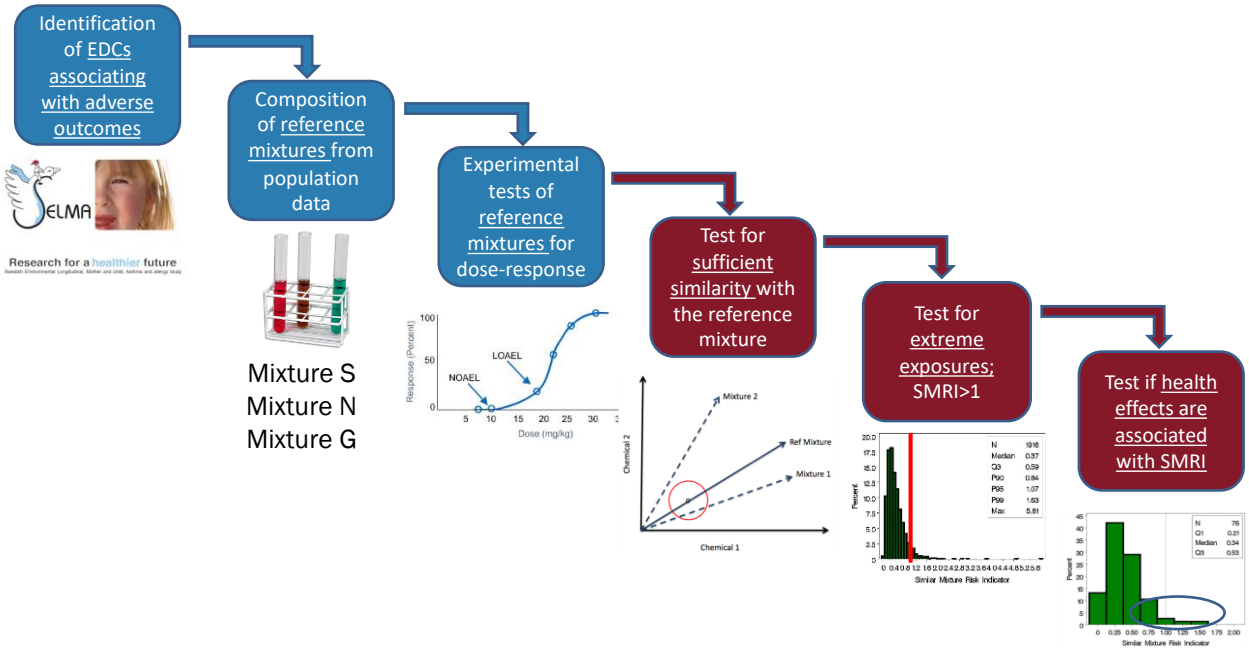

***Figure 6**: Whole mixture approach developed in the EDC-MixRisk project called similar mixture approach (SMACH), integrating epidemiological and experimental data to assess the risk of chemicals in mixtures. SMACH is based on 4 steps: (1) identification of EDCs that are associated with negative outcomes in epidemiological data; (2) composition of a reference mixture consisting of the chemicals identified in step 1; (3) experimentally testing this mixture to establish a dose response relationship and determine a point-of-departure (i.e., reference dose) where adversity is observed; and (4) using a statistical measure of "sufficient similarity" to compare the experimental reference dose (from step 3) to the exposure measured in the human population and generate a "similar mixture risk indicator" (SMRI).*

Summary: Based on the scientific work described above, the overarching results were summarised in the EDC-MixRisk Policy Brief[9] as follows:

- Chemicals identified in pregnant women within the general population originated from different sources and application areas which are currently regulated by different pieces of European Union legislations.
- Epidemiological analysis showed that prenatal exposure to mixtures of EDCs was associated with various effects in children's health and development. Some effects were sex specific.
- The tested mixtures affected hormone-regulated and disease-relevant outcomes in a variety of experimental models at similar concentrations found in the pregnant women.
- Applying our novel whole mixture approach indicates a higher risk for children compared to risk estimated by current methods based on a single compound assessment.

[9] http://www.diva-portal.org/smash/record.jsf?pid=diva2%3A1318468&dswid=1272

Exploitation and dissemination of the results

The knowledge generated within EDC-MixRisk aimed at contributing to "development of chemicals control" for hazardous substances and mixtures and ultimately, to lead to reduced health risks especially for vulnerable groups. Throughout the project we used a strategic communication plan that identified stakeholders, their needs, and preferred channels/fora. This was linked to an impact evaluation and monitoring system to work in a timely manner, considering also ongoing policy and regulatory processes. The project has used various channels and fora for dissemination of results, such as the EDC-MixRisk website, Policy Brief, news articles, press releases, radio and TV interviews, conferences, workshops, video etc. Information generated within EDC-MixRisk has been visible in various EU member states, as well as in countries outside the EU. The scientific community has been reached via numerous conferences and peer-reviewed publications, whereas an extensive media outreach and a project video are examples of how we have reached the general public and civil society.

EDC-MixRisk has focused on relevant dissemination and communication activities in order to raise awareness and increase knowledge exchange, but also to achieve the expected impacts of the project, including wider societal impact and added value at the European level. There has been a strong strive for better science-to-policy interaction with relevant regulatory and policy actors and cross-project collaboration to reach towards a more holistic and coordinated mixture risk governance approach that has a solid scientific basis, but also addresses wider societal needs for sufficient protection of health.

Main dissemination activities have included:

- Position paper entitled "Preventing risks for people and environment from hazardous chemical mixtures" proposes 12 key actions and recommendations to help better address combined effects and overcome remaining gaps in chemical mixture research and policy making. To express concern and raise awareness on hazardous chemical mixtures and combined exposure, the Coordinators and representatives of several EU-funded research projects, EDC-MixRisk, EuroMix, EU-ToxRisk, HBM4EU, SOLUTIONS, sent a position paper (17 April 2018) to Director-Generals of DG Environment, DG Research and Innovation and DG Health and Food Safety. The paper is available via the Nordic Diva portal: http://www.diva-portal.org/smash/record.jsf?pid=diva2%3A1318469&dswid=8634
- A joint workshop 'Advancing the Assessment of Chemical Mixtures and their Risks for Human Health and the Environment' was held 29-30 May 2018 at the Joint Research Centre in Ispra, Italy. Five EU-funded H2020 and FP7 research projects i.e. EDC-MixRisk, EuroMix, EU-ToxRisk, HBM4EU and SOLUTIONS, were working together to address different aspects of the impacts of mixtures on human health and the environment, including also exchange with EFSA, JRC, EEA, ECHA, DG ENV and DG RTD. Through this collaboration, synergies, knowledge exchange and identification of research and policy gaps and needs were promoted. It resulted in a joint publication

"Current EU research activities on combined exposure to multiple chemicals" (Bopp et al. 2018) [10] and a workshop outcome paper that will be published later this year (2019).

- Chemical Cocktail Challenge – Joint EDC-MixRisk and EuroMix Stakeholder workshop was organised in Brussels 26 March 2019. The workshop was attended by around 120 participants. The aim of the workshop was to highlight the main results and conclusions from the two projects, and their implications for future needs for chemical mixture risk assessment. Both projects presented key results and demonstrated new tools and approaches for risk assessment of combined exposure to multiple chemicals (mixtures) and how these could benefit future European food and chemical safety policy.
- The EDC-MixRisk Policy Brief was launched in the context of the Joint EDC-MixRisk and EuroMix Stakeholder workshop. The Policy brief and the project have been extensively reported in various media and websites at European level, including e.g. ENDS Europe, Chemical Watch, CHeMyCAl, EurekAlert!, Cordis, H2020 Magazine, ChemTrust blog, HEAL website, Food Packaking Forum. The policy brief is available at Diva portal: http://www.diva-portal.org/smash/record.jsf?pid=diva2%3A1318468&dswid=1272
- The EDC-MixRisk Scientific Conference presented the project's whole mixture approach and key results. It took place 27 March 2019 in Brussels, Belgium (DG RTD). This conference brought together researchers and experts working in the field of endocrine disruptors and chemical mixtures to discuss the scientific results generated within the project and to reflect on the project's lessons learned and future implications. The final conference gathered around 50 participants representing mostly academia and civil society organisations.
- A short video film that was produced to present the project and its main outcome related to the exposure to multiple man-made chemicals from various sources. The video has been disseminated via YouTube and other social media to reach general public and a variety of stakeholders. It is available at: https://www.youtube.com/watch?v=XumDwTEDcl0

The web link to the EDC-MixRisk web page is https://edcmixrisk.ki.se

Socio-economic impact of the project

Endocrine disrupting chemicals (EDCs) have been linked to serious health problems, and have thus raised concerns world-wide. This has prompted the EU to take steps towards regulating EDCs in several legislations. However, testing and risk assessment methods for EDCs are still limited. Additionally, humans and wildlife are exposed to complex mixtures of such chemicals,

[10] Bopp SK, Barouki R, Brack W, Dalla Costa S, Dorne JCM, Drakvik PE, Faust M, Karjalainen TK, Kephalopoulos S, van Klaveren J, Kolossa-Gehring M, Kortenkamp A, Lebret E, Lettieri T, Nørager S, Rüegg J, Tarazona JV, Trier X, van de Water B, van Gils J, Bergman Å (2018) Current EU research activities on combined exposure to multiple chemicals. Environment International 120, 544-562. doi: 10.1016/j.envint.2018.07.037

yet, chemical risk assessment is still mainly conducted one substance at a time. EDC-MixRisk has focused especially on societal impact from policy and regulatory perspective. This is natural as one of the main goals has been better incorporation of mixture aspects in risk assessment in order to reduce harm to human health. EDC-MixRisk has significantly advanced knowledge on how prenatal exposure to mixtures of EDCs affect children's health and development, and has developed novel tools for risk assessment of chemical mixtures.

This is important also from a socio-economic point of view. EDC-associated health costs are significant, and implications of EDC-induced health effects include both monetary costs in terms of health care and medical costs as well as unnecessary human suffering. EDC-MixRisk has expressed concern about the underestimation of mixture risks as a result of the current regulatory and policy frameworks and practices that are limited to sectors or to a source of exposure. The project's impact (as identified by UK's 2014 Research Excellence Framework[11]) may link to but is not limited to, an effect on, change or benefit to:

- the activity, attitude, awareness, behaviour, capacity, opportunity, performance, policy, practice, process or understanding of an audience, beneficiary, community, constituency, organization or individuals in any geographic location whether locally, regionally, nationally, or internationally.
- impact also includes the reduction or prevention of harm, risk, cost or other negative effects.

EDC-MixRisk has continuously informed stakeholders about the progress in the mixture research area, e.g. MEPs, Commission and national authorities in Europe, Japan and the USA as well as national stakeholders. This will enable authorities to consider future risk assessment and management measures for hazardous substances and mixtures that have a wide range of uses in industries as diverse as agriculture, construction, pharmaceuticals, cosmetics and consumer products. To ensure that the results and policy recommendations from EDC-MixRisk will continue to evolve further in the following years, we have strongly promoted the creation of platforms for collaborations between other research projects, regulatory agencies, industry, civil society and academia. The uptake of EDC-MixRisk results and the new approaches will be facilitated by the extensive network between researchers and societal actors that are firmly based on the contacts established within EDC-MixRisk and build on the recommendations clearly stated in publicly available consensus reports and recommendations.

Further, EDC-MixRisk has involved a larger scientific community in the form of collaborative efforts to a create joint statement and position papers stemming from various needs and activities. The joint activity manifested in the Mixture Workshop in Ispra, co-organised by JRC, is one such activity. The joint stakeholder conference was another important societal activity reaching out for decision makers, industry and civil society in the EU.

[11] Source: http://www.ref.ac.uk/pubs/2011-02/

Last but not least, EDC-MixRisk has created opportunities for fostering next generation researchers and experts by involving them to the project as PhD students and post-docs and by offering training and dissemination opportunities that have been relevant for both the project but also to the individuals themselves to enable networking and promotion of their work and ultimately, their careers.

Conclusions

Based on the project results the following overarching conclusions have been drawn:

- Current regulations of man-made chemicals systematically underestimate health risks associated with combined exposures to EDCs or potential EDCs.
- Interdisciplinary collaborations and the integration of multiple methods have proven successful for developing novel approaches for testing and risk assessing EDC mixtures.
- EDCs and mixtures need to be tested in complementary models covering several molecular, cellular and organismal effects.
- The feasibility of identifying and testing a small number of chemical mixtures that are broadly relevant for the exposed population can pave a way to similar efforts at the European and global-scale.
- Our new approaches can be used to define “acceptable” levels of exposure based on epidemiological data or the integration of human and experimental data.
- These new approaches may also provide empirical support for estimating the size of a potential additional mixture assessment factor that could take mixtures into account in chemical risk assessment.
- Our whole mixture approaches can only be used retrospectively for chemicals for which epidemiological data are available. For “new chemicals” a prospective risk assessment is required.

The results and conclusions of EDC-MixRisk have led to identification of several needs for the future. These are:

- Current, single substance risk assessment paradigm assumes that substances are released into a pristine environment. However, they enter into the environment or a human body where other chemicals are already present. Calculating risk ratios for single chemicals underestimates the risk, and hence, if we add up the risk quotients we could exceed acceptable levels of risk. Therefore, regulatory requirements should take mixtures and combined exposures into account in all relevant EU chemicals and environment legislations.
- Legislative measures should be taken to assure full insight to which chemicals are used in all products, materials and goods on the market. This would enable allocating research efforts to chemicals and mixtures of concern, increase diversity of chemicals under scrutiny and to promote consumers’ informed choices of products and goods.

- Our research results add to the increasing scientific evidence that health risks associated with EDC mixtures are underestimated. There is an urgent need to assess the magnitude of this problem. Our novel whole mixture approach could supplement the current regulatory system to improve risk assessment of mixtures. To achieve this, we need access to appropriate data. Therefore, we propose that future and ongoing biomonitoring efforts should include (a) analyses on complex mixtures, (b) assessment of adverse health outcomes in the same cohorts, (c) good quality toxicity data to identify hazardous chemicals, (d) long-term resources to follow time trends and evaluate risk management measures.
- Interdisciplinary research initiatives are critical to bridge the current data and knowledge gaps. We see that development and validation of sensitive and fit-for-purpose test methods with inclusion of new approach methodologies (NAM) as well as increased efforts on exposure assessment and modelling are essential.
- Given the large amounts of money invested in the implementation of chemicals legislation, it is important to ensure that regulatory processes and practices are efficient and up to date with current scientific knowledge. Therefore, innovations at the cross section of science and policymaking should be facilitated by creating platforms for collaborations between regulatory agencies, industry and academia.