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# COMMITTEE ON MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COM)

# TOXICOGENOMICS AND RISK ASSESSMENT: A PRELIMINARY LITERATURE-SCOPING DOCUMENT

## Background

1. The Organisation for Economic Co-operation and Development (OECD)[1] describes toxicogenomics as "a study of the response of a genome to hazardous substances, using "omics" technologies such as genomic-scale mRNA expression (transcriptomics), cell and tissue-wide protein expression (proteomics), and metabolite profiling (metabolomics), in combination with bioinformatic methods and conventional toxicology."

2. During revision of the COM overarching guidance document, it became apparent that the area of toxicogenomics should be recognised as an increasingly used tool in genotoxicity risk assessment. It was decided that COM would produce standalone guidance for this area, which would allow for frequent updates to reflect changes, as needed.

3. Toxicogenomics was also discussed during a recent horizon-scanning activity at the joint meeting of the COC and COM in November 2020, and the potential application of toxicogenomics to risk assessment was raised as an area of interest across all three Expert Committees. It was agreed that COM was best placed to lead the development of this document, which could be adopted by the COT and COC or amended to their specific requirements, as needed.

4. To facilitate initial Committee discussions of this topic, this document gathers some relevant literature, based on preliminary searches of COC, COM, and COT publications, the 'PubMed' database, and 'grey' literature.

5. Some of the broad areas that may be of interest to address in a subsequent discussion paper on this topic include: What is toxicogenomics? How is toxicogenomics used in risk assessment? What are the current barriers to the use of toxicogenomics in risk assessment?

[1] See https://www.oecd.org/env/ehs/testing/toxicogenomics.htm (accessed 25-01-2021)

## Previous Committee evaluations, statements and guidance documents that have included commentary on toxicogenomics

6. The COM guidance document, 'Guidance on a Strategy for Genotoxicity Testing of Chemical Substances' (COM 2011) notes, in relation to potential future developments, that "Developments within the field of toxicogenomics are also likely to provide new methods for investigating genotoxic mechanisms and informing on MoGA [mode of genotoxic action]. The COM have reviewed data generated in this field several times during 2008 and 2009 but conclude that the evidence did not support the routine use of toxicogenomic approaches as an adjunct to genotoxicity testing."

7. The revised GD states that the COM is aware that new assays and toxicogenomic approaches are under development which might be of value within genotoxicity testing. The ToxTracker assay uses a series of reporter cell lines expressing biomarker genes selected to detect chemically induced DNA damage and oxidative stress (Hendriks et al., 2012; Hendriks et al., 2011; Brandsma et al., 2020). Whilst the assay presents an interesting approach to identifying MoA, it is not currently considered to be a reliable genotoxicity test and is more suitable as a biomarker assay or in MoA investigations.

8. Other potential tests include investigation of instability in expanded simple tandem repeats in male gametes and offspring to evaluate heritable mutations (Singer et al., 2006). The development of new high throughput assays for the assessment of germ line mutations and the quantification of risk from such data may provide opportunities to protect future generations from mutated DNA sequences. Developments within the field of toxicogenomics are also likely to provide new methods for investigating genotoxic mechanisms and informing on MoA. The COM have reviewed data generated in this field several times up to the drafting of this guidance statement but currently conclude that the evidence does not support the routine use of toxicogenomic approaches as an adjunct to genotoxicity testing.

9. The COM noted that an ILSI-HESI workshop had reviewed 16 assays/technologies which were at various stages of development and had highlighted emerging approaches to genotoxicity testing such as Enzyme-DNA films and DNA adductome studies (*ref cited*: Lynch et al 2011).

10. The potential for the use of toxicogenomics data in risk assessment was considered jointly by COT/COM/COC in 2002 and 2004. COT also considered the area in 2009, with the most recent statement being published in 2012 (COT 2012). This statement defined the term toxicogenomics, noted applications for toxicogenomics in risk assessment and factors to be taken into consideration when

interpreting toxicogenomic studies in risk assessment, and provided some worked examples where toxicogenomics data have been used in an approach relevant to risk assessment. In conclusion the document noted that:

– "TGX data may aid risk assessment in a number of ways, including aiding the assessment of toxicological MOA, informing on inter-species differences, aiding the development of in vitro predictive models, modelling effects at sub-pathological doses, aiding extrapolations between similar substances and identification of biomarkers. Ideally, experiments should be designed to address specific questions in the risk assessment and use a range of doses to support dose-response modelling."

– "Where TGX changes are consistent with an established MOA, it would be important not to ignore other changes; the observation of a TGX effect does not inevitably mean that an adverse effect was occurring or would follow in time or at higher exposure. In order for TGX changes to be useful in risk assessment, it is essential for them to be clearly associated to specific pathways relevant to toxicological effects. TGX outcome measures used also need to be sufficiently reproducible within and between laboratories, and an appropriate level of sensitivity and specificity is required."

– "If, in the future, transcriptional changes were to form the basis for establishing a health-based guidance value, there should be clear understanding that the specific gene was critical to the MOA. Where relevant TGX studies were available, they could be used in risk assessment as part of a weight of evidence approach alongside the results of other experimental approaches."

11. The COC guidance statement G07 ('Alternatives to the 2-year bioassay') includes discussion of 'Omics, high-throughput screening technologies, and bioinformatics' (part C) (COC 2019). The guidance states that the term 'omics' refers to genomic (DNA sequence analysis) and post-genomic (e.g. transcriptomics, proteomics, metabolomics, epigenomics) technologies that are used for the characterisation and quantitation of pools of biological molecules (e.g. DNA, mRNAs, proteins, metabolites) and the exploration of their roles, relationships and actions within an organism. It is noted that the term 'toxicogenomics' can be used to describe the application of omics technologies to the study of adverse effects of toxicants or environmental stressors (*ref cited*: Waters 2016). However, the COC chose to use the term 'omics', to avoid the suggestion of being focussed on genomic techniques.

12. G07 part c) discusses the aims of predictive omics in carcinogenicity evaluation, summarises areas of study that have used omics technologies to predict outcomes of 2-year rodent bioassays by applying methods to short-term studies *in vivo* (which had mostly focussed on mRNA profiling in rat liver), and the identification of gene signatures to discriminate between direct- and indirect-acting genotoxic carcinogens, non-genotoxic carcinogens, and non-carcinogens. Other concepts that are introduced include: 'shared cancer biology'; 'profiling to the phenotype'; the application of 'omics' technologies *in vitro* and current obstacles to this approach (noting that such methods are useful in characterising toxicity pathways to elucidate modes of action (MOA)); the 'comparison approach'; the availability of a large catalogue of (*in vivo* and *in vitro*) datasets, based on a large set of compounds, consistent study designs and standardised experimental protocols; the 'parallelogram approach' and 'concordance model'; progress in integrating omics data into quantitative cancer risk assessments (derivation of PoDs, usually BMDs, which can be compared with PoDs from conventional/apical endpoints); a framework for applying transcriptomic data to (non-cancer and cancer) risk assessment (*cited ref:* Thomas et al 2013); and mentions concepts of managing and evaluating large datasets (artificial intelligence, deep learning, data mining..).

13. The COC guidance document highlights that [at the time of writing] although individual omics-based assays can provide information about multiple changes in response to chemical exposure, these methods currently have limited applicability for use in high-throughput screening (HTS). The document concludes that "these newer methods [omics and HTS] show promise for the future but are not yet sufficiently developed of validated to be used in the formal assessment of carcinogenic risk to humans from chemicals in the environment.".

**Evaluations and publications by other expert bodies**

14. Searches of 'grey' literature and of PubMed identified narrative of relevance to the topic published by other expert organisations.

15. Health Canada (HC) have published a number of articles on the application of toxicogenomics in risk assessment; among the most recent of these are: 'Toxicogenomic applications in risk assessment at Health Canada' (Yauk et al. 2019); and 'Evaluation of the Use of Toxicogenomics in Risk Assessment at Health Canada An Exploratory Document on Current Health Canada Practices for the Use of Toxicogenomics in Risk Assessment' (Health-Canada 2018). Topics covered include the 'International context', and 'An overview of area-specific applications for toxicogenomics within HC' (existing substances; drinking water; nanomaterials; radiation; food; pesticides).

16. In synthesis, HC noted that a role for toxicogenomics data in risk assessment could be foreseen. Most toxicogenomics data are of an exploratory or research nature and are not currently well established scientifically for decision-making in isolation, but data contribute to the WoE approach. Overall, HC would accept submissions of toxicogenomics data when available in support of risk assessment. Some challenges were noted: lack of international harmonised guidelines (experimental protocols, quality standards, references and analytical frameworks); lack of accepted international strategies or frameworks for applying toxicogenomics to specific risk assessment needs; lack of expertise and training in toxicogenomics within the regulatory community; underdeveloped regulatory capacity to accept and interpret submitted data; incomplete validation of pathway perturbations causative of specific diseases or linked to specific MOAs, or incomplete validation that measured changes are proportional to the severity of the observed effect; lack of toxicogenomics biomarkers that can be applied to predict toxicological effects, including validation; acknowledgement that changing paradigms within the regulatory community requires time and willingness; lack of high-quality toxicogenomics data from which to acquire experience, including submissions from industry.

17. The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) held a workshop on 'Applying 'omics technologies in chemicals risk assessment' in October 2016. The key objective of the workshop was to establish approaches to connect 'omics perturbations to phenotypic alterations. Ahead of the workshop, expert teams drafted background narrative and frameworks for best practices:

– The challenge of the application of 'omics technologies in chemicals risk assessment: Background and outlook. (Sauer et al. 2017).

– A generic Transcriptomics Reporting Framework (TRF) for 'omics data processing and analysis (Gant et al. 2017).

– Framework for the quantitative weight-of-evidence analysis of 'omics data for regulatory purposes (Bridges et al. 2017).

– Framework for the quality assurance of 'omics technologies considering GLP requirements (Kauffmann et al. 2017).

18. Workshop participants considered that is would be promising to aim to link gene expression changes and pathway perturbations to phenotype by mapping them to specific adverse outcome pathways (AOPs). Further work would be necessary

before gene expression changes could be used to establish safe levels of substance exposure. An overall report of the workshop was published:

Applying 'omics technologies in chemicals risk assessment: Report of an ECETOC workshop (Bridges et al. 2017).

**Recently published scientific literature**

*Review articles*

19. Preliminary searches of PubMed and grey literature using a combination of the terms 'toxicogenomic(s)' AND 'risk assessment' identified approximately 70 articles of clear relevance to this topic. Of these, focussing on the period from 2015 to date, approximately 35 review articles relating to the application of toxicogenomics to risk assessment were noted. Formal searches on this topic, with specified search strings and inclusion/exclusion criteria, have not yet been conducted. A brief summary or the abstract from the review articles that were considered to be of particular interest in relation to introductory discussions on this topic are highlighted below.

20. ***Transcriptomics in Toxicogenomics****:* A three-part publication on the application of toxicogenomics to risk assessment. Summarises recent developments in design and analysis of DNA microarray, RNA seq, and single-cell RNA-seq. Describes guidelines on exposure time, dose, complex endpoint selection, sample quality considerations, and sample randomisation. Summarises publicly available data resources, highlights applications of toxicogenomics data to understanding and predicting chemical toxicity potential. Discusses progress in implementing toxicogenomics in regulatory decision making to promote alternative methods for risk assessment and to support 3Rs. Includes the following three parts:

– *Part I: Experimental design, technologies, publicly available data, and regulatory aspects*. (Kinaret et al. 2020). Replicates and reference samples; time and dose selection; transcriptomic technologies in toxicogenomics; publicly available datasets for toxicogenomics; regulatory aspects.

– *Part II: Preprocessing and differential expression analysis for high quality data*. (Federico et al. 2020). Data preprocessing; RNA sequencing; single cell RNA-seq; differential expression analysis; gene functional annotation and pathway analysis.

– *Part III: Data modelling for risk assessment*: (Serra et al. 2020). Use of toxicogenomics data for predictive toxicology; BMD analysis; read across and AOP

modelling methodologies; MOA or specific biomarkers of exposure; description of main AI technologies applied to toxicogenomics data to create predictive classification and regression models; deep learning (DL) and data integration methodologies.

21. Toxicogenomics – what added value do these approaches provide for carcinogen risk assessment? (Schmitz-Spanke 2019). *Abstract:* "It is still a major challenge to protect humans at workplaces and in the environment. To cope with this task, it is a prerequisite to obtain detailed information on the extent of chemical perturbations of biological pathways, in particular, adaptive vs. adverse effects and the dose-response relationships. This knowledge serves as the basis for the classification of non-carcinogens and carcinogens and for further distinguishing carcinogens in genotoxic (DNA damaging) or non-genotoxic compounds. Basing on quantitative dose-response relationships, points of departures can be derived for chemical risk assessment. In recent years, new methods have shown their capability to support the established rodent models of carcinogenicity testing. In vitro high throughput screening assays assess more comprehensively cell response. In addition, omics technologies were applied to study the mode of action of chemicals whereby the term "toxicogenomics" comprises various technologies such as transcriptomics, epigenomics, or metabolomics. This review aims to summarize the current state of toxicogenomic approaches in risk science and to compare them with established ones. For example, measurement of global transcriptional changes generates meaningful information for toxicological risk assessment such as accurate classification of genotoxic/non-genotoxic carcinogens. Alteration in mRNA expression offers previously unknown insights in the mode of action and enables the definition of key events. Based on these, benchmark doses can be calculated for the transition from an adaptive to an adverse state. In short, this review assesses the potential and challenges of transcriptomics and addresses the impact of other omics technologies on risk assessment in terms of hazard identification and dose-response assessment."

22. Toxicogenomics: A 2020 Vision (Liu et al. 2019). Emphasises: reproducibility; role of machine learning in developing predictive models; facilitation of AOP development and read-across; development of toxicogenomics for risk assessment.

23. The state-of-the art of environmental toxicogenomics: challenges and perspectives of 'omics' approaches directed to toxicant mixtures (Martins, Dreij and Costa 2019). Focus on application of toxicogenomics to mixtures: What are "omics"?; genomics and epigenomics; transcriptomics; proteomics; metabolomics and lipidomics; multi-omics.

24. Recommended approaches in the application of toxicogenomics to derive points of departure for chemical risk assessment (Farmahin et al. 2017). *Abstract*: "There is increasing interest in the use of quantitative transcriptomic data to determine benchmark dose (BMD) and estimate a point of departure (POD) for human health risk assessment. Although studies have shown that transcriptional PODs correlate with those derived from apical endpoint changes, there is no consensus on the process used to derive a transcriptional POD. Specifically, the subsets of informative genes that produce BMDs that best approximate the doses at which adverse apical effects occur have not been defined. To determine the best way to select predictive groups of genes, we used published microarray data from dose–response studies on six chemicals in rats exposed orally for 5, 14, 28, and 90 days. We evaluated eight approaches for selecting genes for POD derivation and three previously proposed approaches (the lowest pathway BMD, and the mean and median BMD of all genes). The relationship between transcriptional BMDs derived using these 11 approaches and PODs derived from apical data that might be used in chemical risk assessment was examined. Transcriptional BMD values for all 11 approaches were remarkably aligned with corresponding apical PODs, with the vast majority of toxicogenomics PODs being within tenfold of those derived from apical endpoints. We identified at least four approaches that produce BMDs that are effective estimates of apical PODs across multiple sampling time points. Our results support that a variety of approaches can be used to derive reproducible transcriptional PODs that are consistent with PODs produced from traditional methods for chemical risk assessment."

25. Editor's highlight: application of gene set enrichment analysis for identification of chemically induced, biologically relevant transcriptomic networks and potential utilization in human health risk assessment (Dean et al. 2017). *Abstract*: "The rate of new chemical development in commerce combined with a paucity of toxicity data for legacy chemicals presents a unique challenge for human health risk assessment. There is a clear need to develop new technologies and incorporate novel data streams to more efficiently inform derivation of toxicity values. One avenue of exploitation lies in the field of transcriptomics and the application of gene expression analysis to characterize biological responses to chemical exposures. In this context, gene set enrichment analysis (GSEA) was employed to evaluate tissue-specific, dose-response gene expression data generated following exposure to multiple chemicals for various durations. Patterns of transcriptional enrichment were evident across time and with increasing dose, and coordinated enrichment plausibly linked to the etiology of the biological responses was observed. GSEA was able to capture both transient and sustained transcriptional enrichment events facilitating differentiation between adaptive versus longer term molecular responses. When

combined with benchmark dose (BMD) modeling of gene expression data from key drivers of biological enrichment, GSEA facilitated characterization of dose ranges required for enrichment of biologically relevant molecular signaling pathways, and promoted comparison of the activation dose ranges required for individual pathways. Median transcriptional BMD values were calculated for the most sensitive enriched pathway as well as the overall median BMD value for key gene members of significantly enriched pathways, and both were observed to be good estimates of the most sensitive apical endpoint BMD value. Together, these efforts support the application of GSEA to qualitative and quantitative human health risk assessment."

26. Toxicogenomics in predictive carcinogenicity [book] (Waters MD 2016). Addresses: the development and application of toxicogenomics *in vitro* and *in vivo*; toxicogenomics dose-response analysis and mode of action; effects of xenobiotics on the genome and epigenome of stem cells, and use of toxicogenomics data by IARC to evaluate carcinogenic hazards to humans; research on some specific chemicals; use of the parallelogram approach; and the use of bioinformatics of genomics in the assessment of cancer. The book comprises 15 chapters. Chapter 1: Introduction to predictive toxicogenomics for carcinogenicity (Waters, MD). Chapter 2: Genomic biomarkers in cell-based drug screening (Li, H-H). Chapter 3: Toxicogenomics *in vitro*: gene expression signatures for differentiating genotoxic mechanisms (Buick, JK & Yauk, CL). Chapter 4: *In vivo* signatures of genotoxic and non-genotoxic chemicals (Auerbach, SS). Chapter 5: Transcriptomic dose-response analysis for mode of action and risk assessment (Thomas, RS & Waters, MD). Chapter 6: Using transcriptomics to evaluate thresholds in genotoxicity dose-response (McMullen, PD et al). Chapter 7: Dissecting modes of action of non-genotoxic carcinogens (Schaap, MM et al). Chapter 8: Human embryonic stem cells as biological models to examine the impact of xenobiotics on the genome and epigenome (Recio, L). Chapter 9: Novel data streams in the assessment of mutagenicity and carcinogenicity: implications for cancer hazard assessment (Guyton, KZ & Water, MD). Chapter 10: Conazoles and cancer: a review (Newnow, S). Chapter 11: Application of trascriptomics in exposed human populations: benzene as an example (McHale, CM et al). Chapter 12: Toxicogenomics case study: furan (Webster, AF et al). Chapter 13: The parallelogram approach to assess human relevance of toxicogenomics-derived toxicity pathways in human health risk assessment (Kienhuis et al). Chapter 14: Bioinformatics of genomics in the assessment of cancer (Bushel, PR).

27. SEURAT: safety evaluation ultimately replacing animal testing—recommendations for future research in the field of predictive toxicology (Daston et al. 2015). *Abstract*: "The development of non-animal methodology to evaluate the potential for a chemical to cause systemic toxicity is one of the grand challenges of

modern science. The European research programme SEURAT is active in this field and will conclude its first phase, SEURAT-1, in December 2015. Drawing on the experience gained in SEURAT-1 and appreciating international advancement in both basic and regulatory science, we reflect here on how SEURAT should evolve and propose that further research and development should be directed along two complementary and interconnecting work streams. The first work stream would focus on developing new 'paradigm' approaches for regulatory science. The goal here is the identification of 'critical biological targets' relevant for toxicity and to test their suitability to be used as anchors for predicting toxicity. The second work stream would focus on integration and application of new approach methods for hazard (and risk) assessment within the current regulatory 'paradigm', aiming for acceptance of animal-free testing strategies by regulatory authorities (i.e. translating scientific achievements into regulation). Components for both work streams are discussed and may provide a structure for a future research programme in the field of predictive toxicology."

28. Technical guide for applications of gene expression profiling in human health risk assessment of environmental chemicals (Bourdon-Lacombe et al. 2015). *Abstract*: "Toxicogenomics promises to be an important part of future human health risk assessment of environmental chemicals. The application of gene expression profiles (e.g., for hazard identification, chemical prioritization, chemical grouping, mode of action discovery, and quantitative analysis of response) is growing in the literature, but their use in formal risk assessment by regulatory agencies is relatively infrequent. Although additional validations for specific applications are required, gene expression data can be of immediate use for increasing confidence in chemical evaluations. We believe that a primary reason for the current lack of integration is the limited practical guidance available for risk assessment specialists with limited experience in genomics. The present manuscript provides basic information on gene expression profiling, along with guidance on evaluating the quality of genomic experiments and data, and interpretation of results presented in the form of heat maps, pathway analyses and other common approaches. Moreover, potential ways to integrate information from gene expression experiments into current risk assessment are presented using published studies as examples. The primary objective of this work is to facilitate integration of gene expression data into human health risk assessments of environmental chemicals."

**Summary and conclusions**

29. Some preliminary literature is provided as a starting point for consideration of the application of toxicogenomics to risk assessment by the UK COM, COC and COT. At a first-glance, literature to date appears to broadly concur that

toxicogenomic data are currently not well enough established for use alone in decision making but can contribute to a weight-of-evidence approach to support MOA. Validation of methodologies and the implementation of international harmonised guidelines are required.

**Questions for the Committee**

i. Does the preliminary literature base provide useful information for the further development of Committee discussions on the topic of the potential application of toxicogenomics to risk assessment?

ii. What are the main aspects that Members consider of importance to address in developing a guidance statement on the topic of the application of toxicogenomics to risk assessment?

iii. Would Members like to note any further sources of literature or information of relevance to this topic, for example published literature, ongoing research projects or evaluations by other expert bodies?

iv. How would the Committee like to proceed with addressing this topic?

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