Advancing the use of transcriptomic points of departure for regulatory decision-making

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Society for Risk Analysis, Dose-response Specialty Group
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Collaborators

Health Canada

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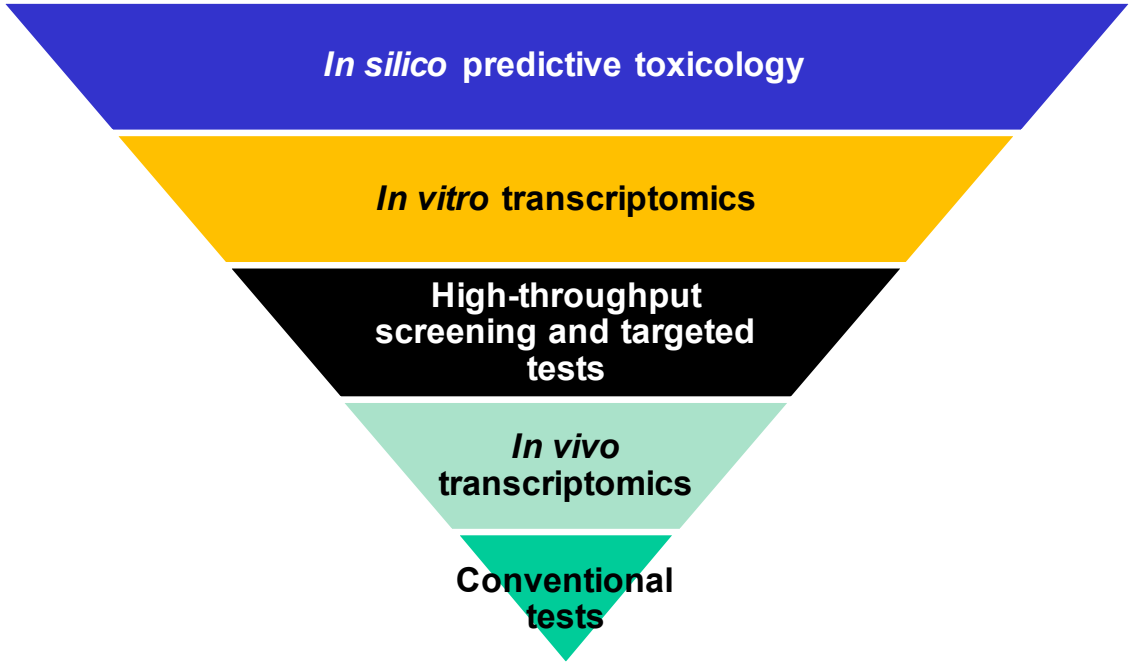
- Matthew Meier, Geronimo Parodi-Matteo
- Tara Barton-Maclaren, Francina Webster, Marc Beal, Matthew Gagné
- Ivy Moffat, Julie Bourdon-Lacombe, Luigi Lorruso, Christine Levicki
- Reza Farmahin, Marjory Moreau, Anne Gannon, Ivan Curran, Andy Nong

US NIEHS: Scott Auerbach, Steve Ferguson

US EPA: Rusty Thomas

Toxicity testing is changing!

Toxicological Testing Paradigms



All chemicals

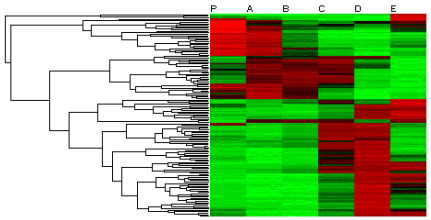
Few chemicals

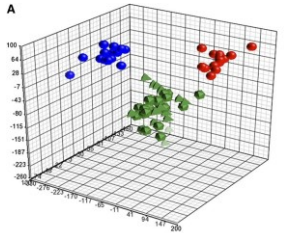
Challenge: How to efficiently analyze and interpret toxicogenomic (TGx) data?

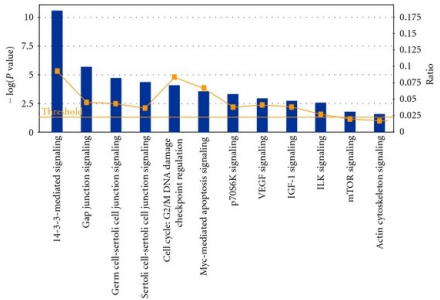
Large gene lists

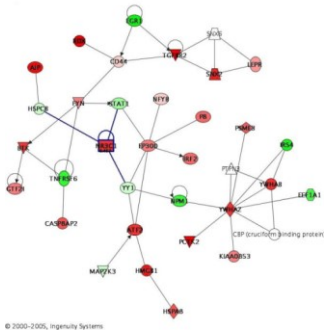
Agilent Probe	Accession Number	Gene Symbol	25mg/kg/day FDR p-value	25mg/kg/day Fold change	50mg/kg/day FDR p-value	50mg/kg/day Fold change	75mg/kg/day FDR p-value	75mg/kg/day Fold change
_55_P1963017	NM_001082543	Stfa1	0.89	2	0	9.9	0	78.5
_66_P133397	NM_145126	Chi3l4	0.97	1.3	0	5.2	0	36.6
_55_P2114187	XM_884904	LOC620515	0.95	1.4	0.05	3.7	0	29.2
_51_P464703	NM_021443	Ccl8	0	6.6	0	13.8	0	16.7
_66_P139618	NM_001082545	Stfa2	0.59	2.2	0	4.4	0	15.5
_55_P2007756	NM_008470	Krt16	0.43	2.3	0	7.3	0	13.3
_52_P398925	NM_173869	Stfa2l1	0.91	1.6	0.02	2.8	0	11.4
_55_P2028949	NR_002880	Defb4l-ps	0.98	1.2	0.07	2.5	0	9
_55_P1998943	NM_145211	Oas1a	0.19	2.4	0	5.1	0	8.9
_55_P2103698	NM_015783	Isg15	0.53	2.1	0	4.6	0	8.8
_55_P2174143	NM_009265	Sprr1b	0.84	1.8	0	3.7	0	8.5
_51_P386870	NM_011472	Sprr2f	0.94	1.5	0.04	3	0	7.2
_51_P113906	NM_025467	Glrx2	0.53	4.3	0.5	3	0.01	6.8
_51_P167292	NM_009892	Chi3l3	0.98	-1.2	0.84	1.4	0	6.4
_66_P116206	NM_013756	Defb3	0.96	1.2	0.3	1.7	0	5.7
_55_P2062246	NM_001145164	Tgm2	0.64	2.2	0	4.4	0	5.6
_66_P128537	NM_015783	Isg15	0.84	1.5	0	2.7	0	5.4
_55_P1998471	NM_009114	S100a9	0.57	2.1	0	4.1	0	5.2
_55_P1978465	NM_023124	H2-Q8	0.92	1.6	0.03	3	0	5.1
_66_P138462	NM_011474	Sprr2b	0.97	1.2	0.15	2.3	0	5
_51_P504170	NM_023386	Rtp4	0.75	1.6	0	3	0	5
_55_P2135064	NM_008204	H2-M2	0.76	1.7	0.01	2.3	0	5
_55_P1979828	NR_003548	Sprr2g	0.9	1.5	0	2.7	0	4.6
_55_P2112005	NM_009362	Tff1	0.55	3.1	0.04	4.3	0	4.6
_51_P504815	NM_025288	Stfa3	1	1	0.41	1.9	0	4.6
_51_P1955372	NM_011477	Sprr2k	0.66	1.7	0	2.3	0	4.5
_52_P104658	NM_008476	Krt6a	0.94	1.4	0.02	3.2	0	4.5
_66_P101935	NM_010669	Krt6b	0.92	1.5	0.01	2.7	0	4.5
_51_P303160	NM_007482	Arg1	0.81	1.7	0	3.3	0	4.5
_51_P126275	NM_010669	Krt6b	0.92	1.5	0.01	2.9	0	4.5
_51_P112355	NM_018738	Iqtp	0.68	2	0	4.1	0	4.4
_55_P2021585	NM_009362	Tff1	0.5	3.2	0.01	4.5	0.01	4.3
_55_P2016462	NM_021274	Cxcl10	0.89	1.6	0	3	0	4.3
_51_P100997	NM_201363	Serpinb3c	0.06	2	0	3.1	0	4.3
_55_P1970144	AK049846	Slc16a14	0.97	1.2	0.17	1.9	0	4.3
_52_P68883	NM_183026	Defb14	0.26	2.1	0	3.6	0	4
_55_P1965303	NM_013505	Dsc2	0.9	1.3	0.04	1.8	0	4
_55_P2016034	NM_001033207	Nlrc5	0	2.2	0	2.7	0	3.8
_30_P0101937			0.93	1.3	0	2.1	0	3.8
_66_P114244	XM_001478461	Gm3914	0.96	1.3	0.05	2.5	0	3.8
_51_P198434	NM_001001892	H2-K1	0.73	1.6	0.01	2.4	0	3.7
_55_P2003746	NM_009126	Serpinb3a	0.74	1.5	0	2.3	0	3.6
_55_P2410304	NM_001146275	Iigp1	0.59	1.8	0	3.1	0	3.6
_55_P2472435	NM_018734	Gbp3	0.87	1.5	0	2.9	0	3.6

Complex analyses and interpretations





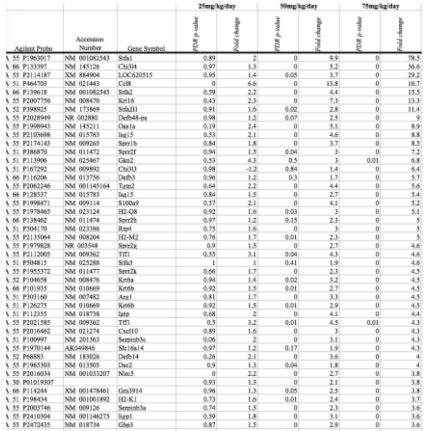




Use in risk assessment?

Vision for use of transcriptomics in regulatory decision-making

Large gene lists



Agilent Probe	Accession Number	Gene Symbol	25mg/kg/day		50mg/kg/day		75mg/kg/day	
			FDR p-value	Fold change	FDR p-value	Fold change	FDR p-value	Fold change
A_55_P1963017	NM_001082543	Srfn1	0.89	2	0	9.9	0	78.5
A_66_P133397	NM_145126	Chi3l4	0.97	1.3	0	5.2	0	36.6
A_55_P2114187	XM_884904	LOC620515	0.95	1.4	0.05	3.7	0	29.2
A_51_P464703	NM_021443	Ccl8	0	6.6	0	13.8	0	16.7
A_66_P139618	NM_001082545	Srfn2	0.59	2.2	0	4.4	0	15.5
A_55_P2007756	NM_008470	Krt16	0.43	2.3	0	7.3	0	13.3
A_52_P398925	NM_173869	Srfn2l1	0.91	1.6	0.02	2.8	0	11.4
A_55_P2028949	NR_002880	Def6-48-ps	0.98	1.2	0.07	2.5	0	9
A_55_P1998943	NM_145211	Osa1a	0.19	2.4	0	5.1	0	8.9
A_55_P2103698	NM_015783	Isg15	0.53	2.1	0	4.6	0	8.8
A_55_P2174143	NM_009265	Stmn1b	0.84	1.8	0	3.7	0	8.5
A_51_P386870	NM_011472	Stmn2f	0.94	1.5	0.04	3	0	7.2
A_51_P113906	NM_025467	Gkn2	0.53	4.3	0.5	3	0.01	6.8
A_51_P197292	NM_009892	Chi3l1	0.98	-1.2	0.84	1.4	0	6.4
A_66_P116206	NM_013756	Defb3	0.96	1.2	0.3	1.7	0	5.7
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A_66_P138462	NM_011474	Stmn2b	0.97	1.2	0.15	2.3	0	5
A_51_P104170	NM_023386	Ifrpl	0.75	1.6	0	3	0	5
A_55_P2135064	NM_008204	Il2-M2	0.76	1.7	0.01	2.3	0	5
A_55_P1979828	NR_003548	Stmn2a	0.9	1.5	0	2.7	0	4.6
A_55_P2112005	NM_009892	Tff1	0.55	3.1	0.04	4.3	0	4.6
A_51_P504815	NM_025288	Srfn3	1	1	0.41	1.9	0	4.6
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A_55_P103160	NM_007482	Anxa1	0.81	1.7	0	3.3	0	4.5
A_51_P126273	NM_010669	Krt6b	0.92	1.5	0.01	2.9	0	4.5
A_51_P112353	NM_018738	Iqgap	0.68	2	0	4.1	0	4.4
A_55_P2021585	NM_009362	TFF1	0.5	3.2	0.01	4.5	0.01	4.3
A_55_P2016462	NM_021274	Cxcl10	0.89	1.6	0	3	0	4.3
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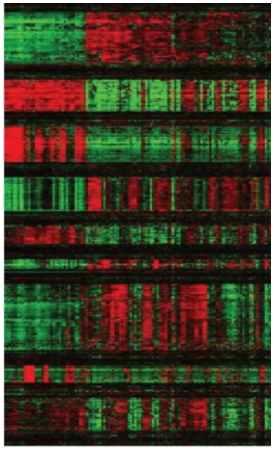
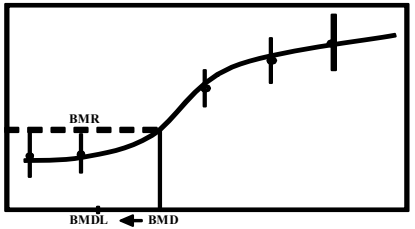
A_55_P2410304	NM_001146275	Ifrpl	0.59	1.8	0	3.1	0	3.6
A_55_P2472435	NM_018734	Ghn3	0.87	1.5	0	2.9	0	3.6

Extract predictive signatures (biomarkers) and pathways



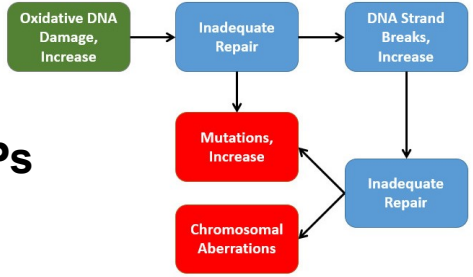
Dose-response modeling



Risk assessment

At what dose do effects occur?
Reverse dosimetry (IVIVE) required?

Human exposure levels?



Align to AOPs

Hazard identification
Mode of action analysis

In the near-term: does a transcriptomic POD (regardless of hazard) provide protection from potential human health effects?

Phenotypes
- Body/organ
- Histopathology
- Blood chemistry

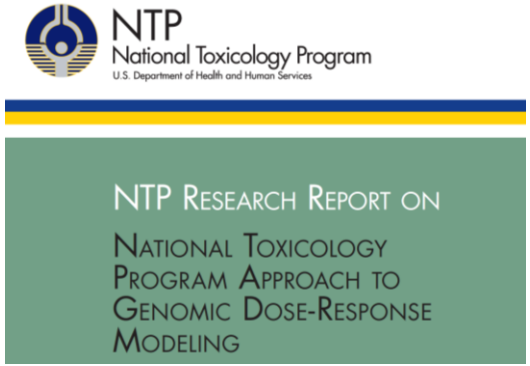
Global gene expression profiling

Lowest gene set BMD
Lowest adverse effect

BMR
BMDL BMD

Point of Departure (POD)

Human exposure?



Context of use: various applications in regulatory decision making

Transcriptomic data set

↓

Extract predictive biomarkers

↓

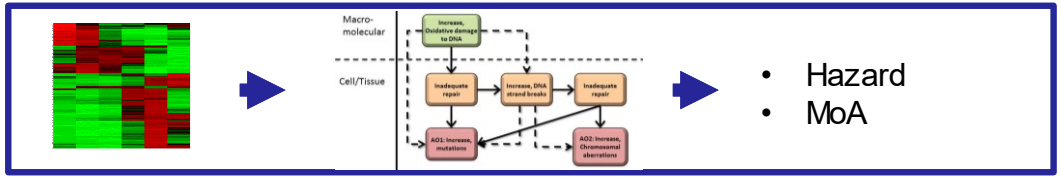
Dose-response modeling

↓ Equivalent dose

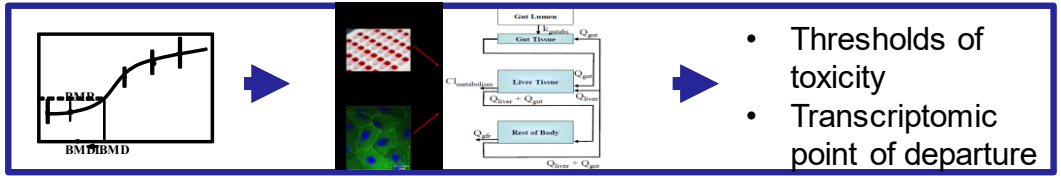
Human exposure levels

↓

Regulatory decision making

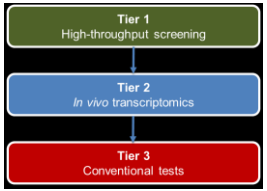


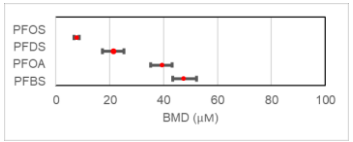
- Hazard
- MoA

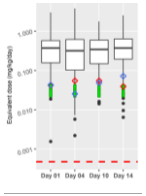


- Thresholds of toxicity
- Transcriptomic point of departure

Context-specific regulatory applications







Reference dose

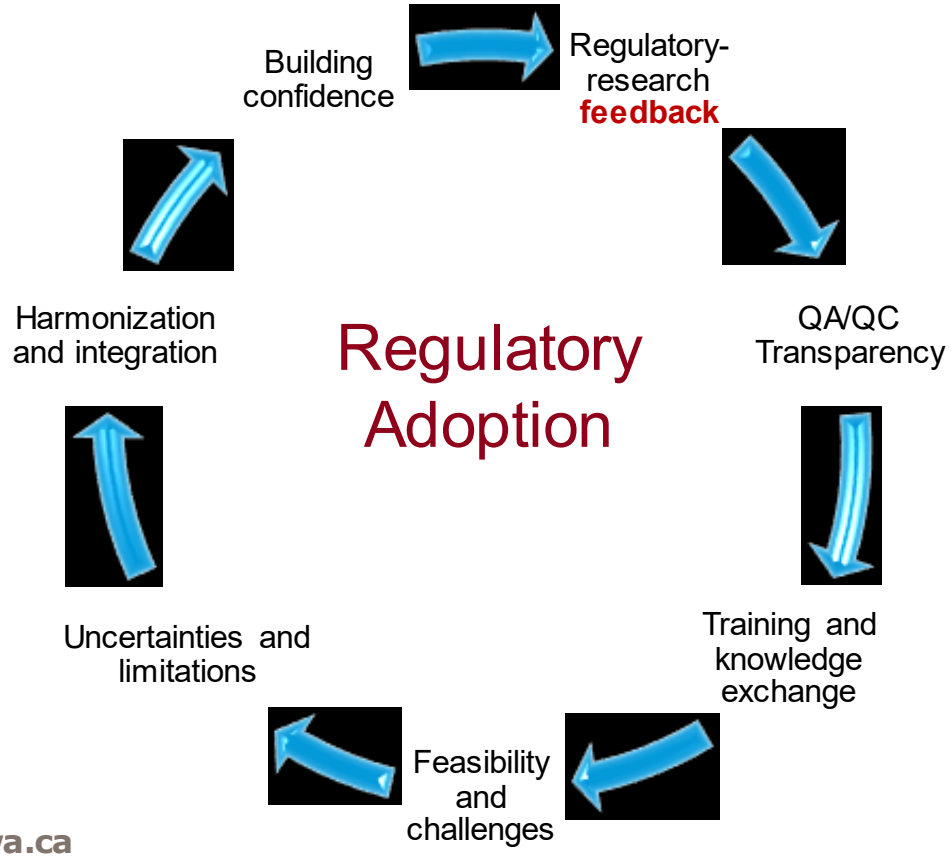
What are the regulatory concerns?

- Can we trust the new tools?
    - Validation – sensitivity, specificity, reproducibility, accuracy
- Will we miss toxicological effects?
    - Have we covered enough biology? Can we predict toxicological effects?
- Gene expression changes ≠ adverse phenotypic changes
    - Are we basing decisions on adaptive versus adverse effects?
- Gene expression changes are the first cellular responses
    - Will the dose at which we see responses be extremely low?
    - i.e., Are we being overly conservative?
        - » Not feasible in terms of risk management
- What is the uncertainty associated with these new approaches?
- How do we do it (experience needed), who will generate the data, and will it give us comparable results?

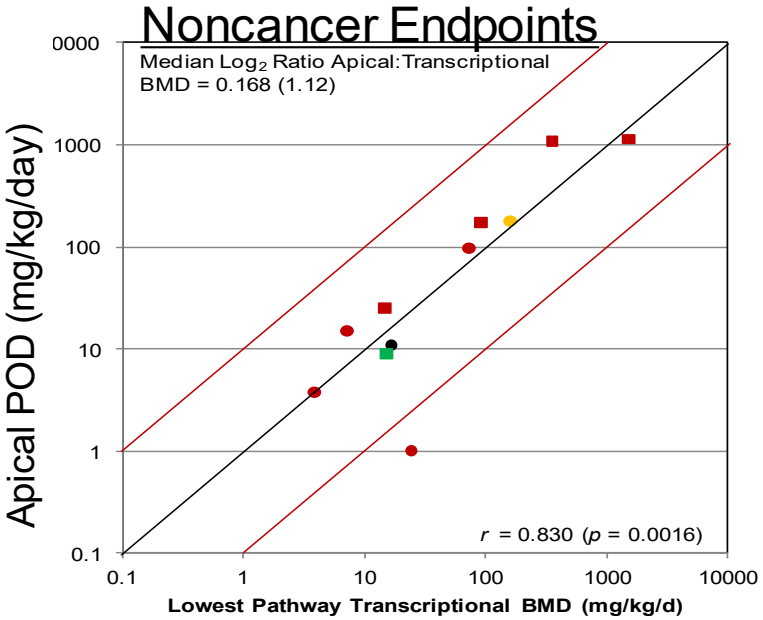
CASE STUDIES

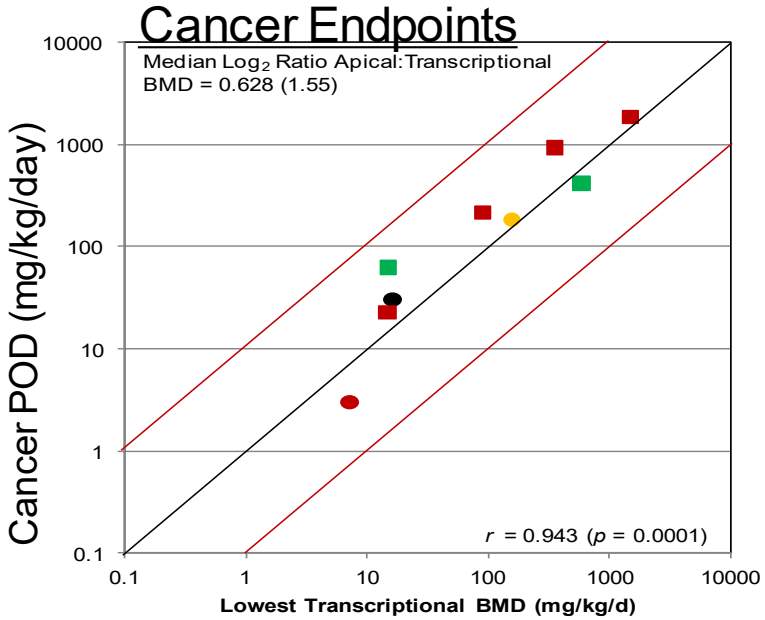
Health Canada Research-Regulatory Collaboration

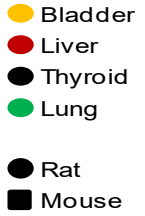
Why case studies?



Foundational studies: Most sensitive (lowest) pathway BMD provides a reasonable estimate of the PoD

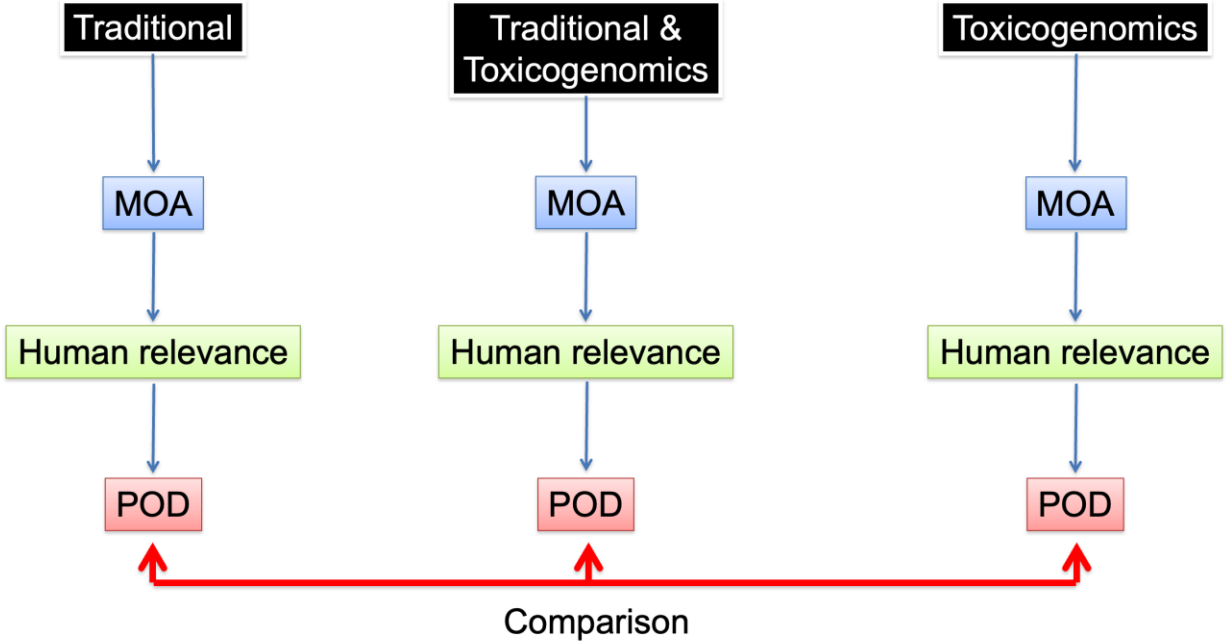






Thomas *et al., Tox Sci.*, 2013

Initial case study focus



Hazard-agnostic tPOD within 10-fold (or less) of regulatory PODs
(early DNA microarray studies)

Toxicant	Relevant Apical (mg/kd/day)	TGx PoD (mg/kg/day)	Apical: TGx	Reference
Benzo[a]pyrene **Liver**	1.2	1.0 (lowest pathway)	**<2-fold**	Moffat et al. *Crit. Rev. Tox.* 2014
Benzo[a]pyrene **Lung**	0.8	3.7 (lowest pathway)	**~5-fold**	Moffat et al. *Crit. Rev. Tox.* 2014
Benzo[a]pyrene **Forestomach**	0.5	7.4 (lowest pathway)	**~10-fold**	Moffat et al. *Crit. Rev. Tox.* 2014
Furan (mouse) **Liver**	2.3	3.6 (median gene BMD)	**<2-fold**	Jackson et al., *Tox Applied Pharm.* 2014
Furan (rat) **Liver**	1.8	1.0 (median gene BMD)	**<2-fold**	Dong et al. *Arch. Tox.*, 2015

Water and Air Quality

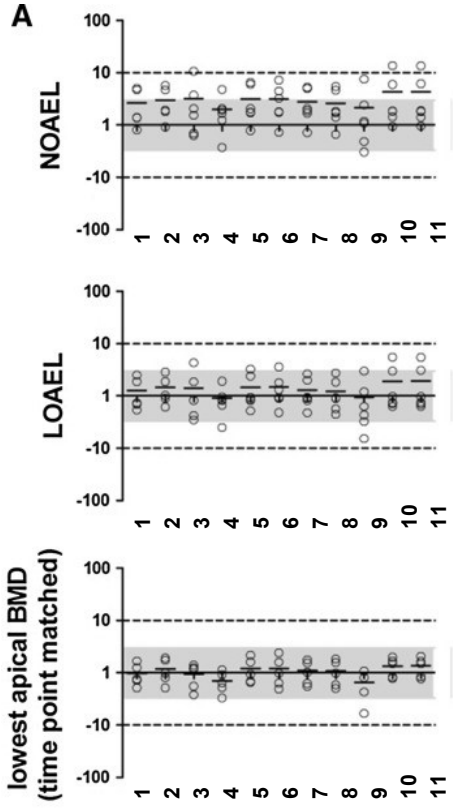
Food

Similar conclusions from case studies on carbon black nanoparticles and acrylamide
Many questions remaining about how to select a POD that represents a tipping point for adverse effects

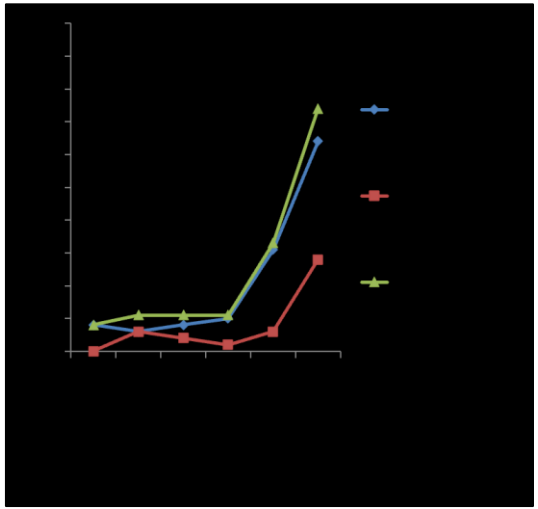
Which tPOD?

- **Different gene sets identify similar tPODs to each other and to apical endpoint PODs.**

1- 20 lowest pathway BMDs FDR P < 0.05, IPA enriched	5- BMD value between 25th and 75th percentile
2- 20 most significant pathways FDR P < 0.05, IPA	6- Pathways with the highest number of connections to other pathways
3- The lowest 20 pathways ANOVA P <0.05, BMD Data Viewer enriched	7- 20 genes that contribute to the greatest number of pathways
4- 20 biggest fold changes	8- Genes that are regulated by the top 20 most significant upstream regulators
9- Lowest pathway	10- Pathway BMD mean
11- Pathway BMD medians	



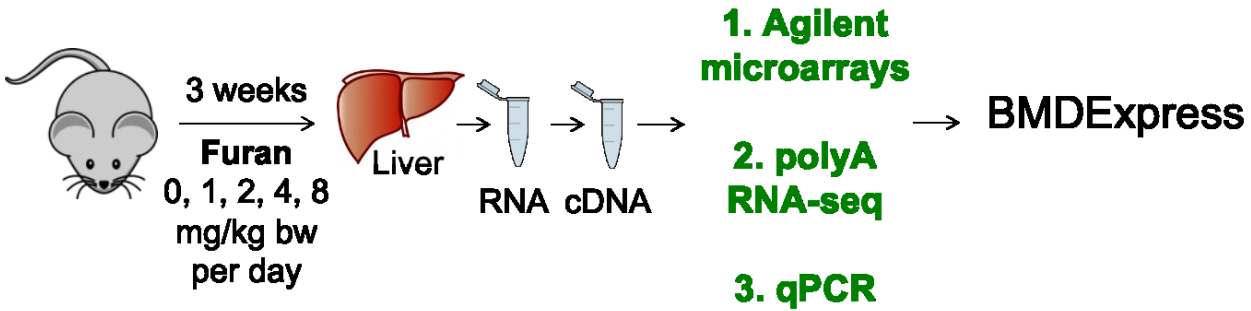
Farmahin et al. Arch. Tox., 2017 (6 chemicals, 4 time points)



What if we use a hazard-based approach?

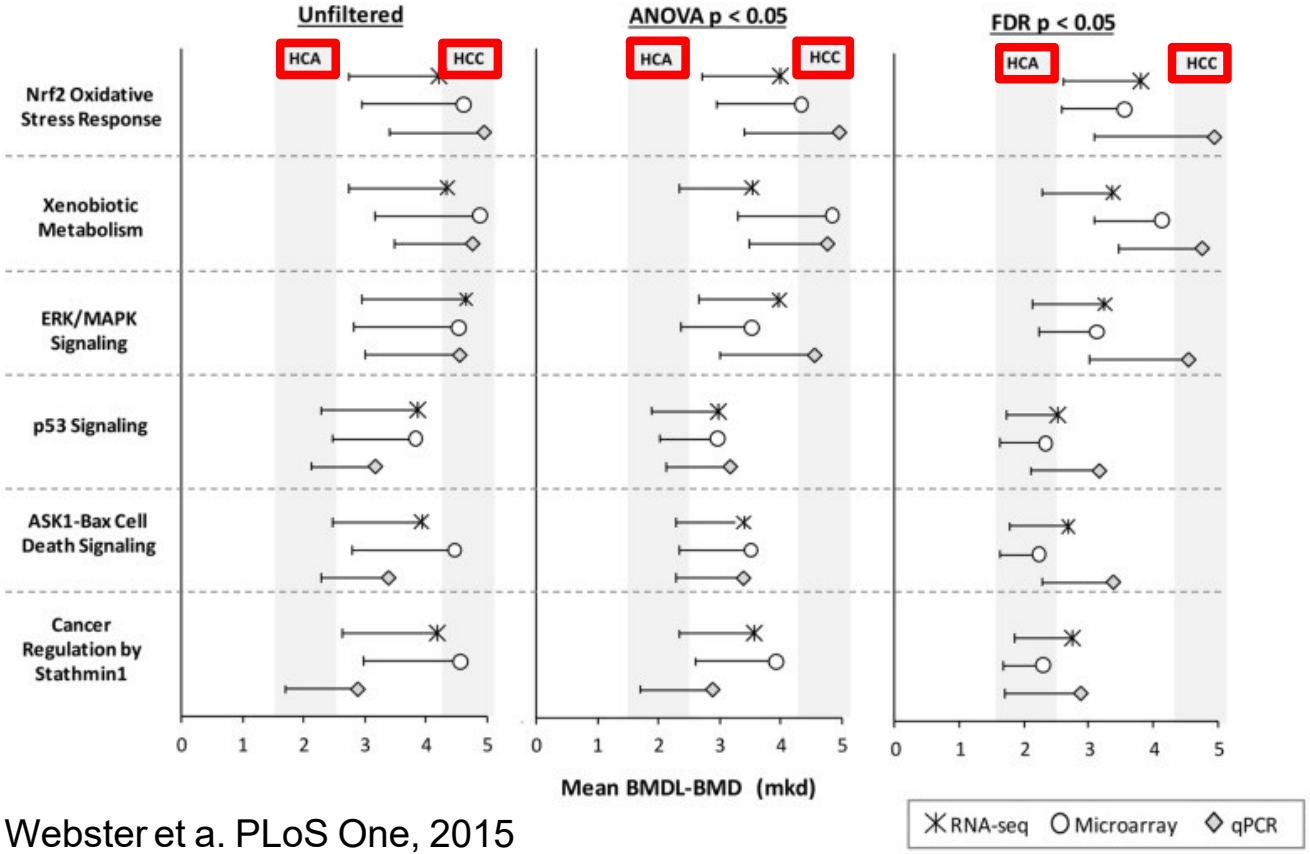
What if we used a different platform?

Impacts of more rigorous filtering?



Webster et a. PLoS One, 2015

MOA-specific pathway BMDs consistent with apical endpoint BMDs



Webster et a. PLoS One, 2015

MoA pathways

- TGx BMD means are consistent across platforms
- TGx BMD means fall within interval between HCA and HCC
- Rigorous filtering had a small impact

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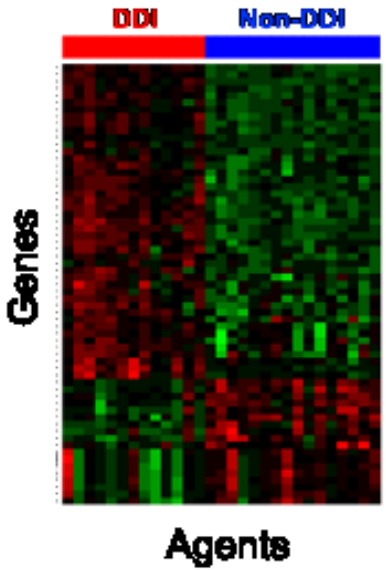
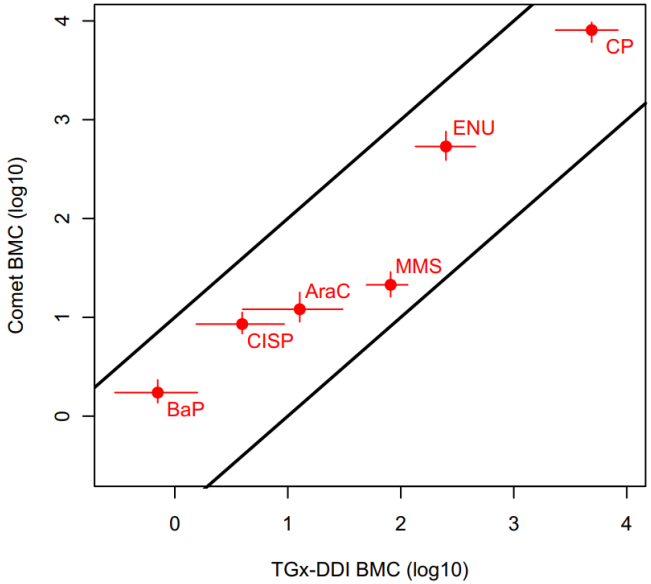
Does this work for TGx biomarker gene sets?
TGx-DDI biomarker BMC predicts the BMC of DNA damage

High-throughput **CometChip®** and **TGx-DDI biomarker** assay measured by TempO-seq in HepaRG cells.



Li, HH et al. *PNAS* (2017)



Buick et al.,
Frontiers in Public Health, 2021

But how do we know we're not modeling noise?

- Need sufficient perturbations and rigorous filtering
- Gene sets to eliminate noise, or robust baseline required

Methods:

- HepaRG cells
- solvent controls assigned randomly to 'dose groups'
- Run BMD analysis
  - BMR 1SD and default filters in BMDExpress
- Derive PODs
- Determine FDR of PODs

EMPIRICAL FALSE DISCOVERY RATE

		Default Settings			Williams Trend Test			Background Filtering			Fold Change		
Study	Design	Median # BMCs	25th Gene	Lowest Pathway	Median # BMCs	25th Gene	Lowest Pathway	Median # BMCs	25th Gene	Lowest Pathway	Median # BMCs	25th Gene	Lowest Pathway
S1500	4 doses, n = 6	8	0.20	0.14	2	0.05	0.05	4	0.12	0.10	1	0.05	0.05
	6 doses, n = 4	8	0.17	0.17	2	0.02	0.03	4	0.11	0.11	1	0.03	0.03
	8 doses, n = 3	8	0.17	0.16	1	0.00	0.01	5	0.13	0.11	2	0.08	0.10
	12 doses, n = 2	6	0.10	0.10	1	0.01	0.01	3	0.08	0.07	2	0.07	0.06
	4 doses, n = 12	1	0.01	0.02	0	0.00	0.00	0	0.00	0.01	0	0.00	0.00
	6 doses, n = 8	2	0.07	0.06	1	0.02	0.01	1	0.05	0.05	0	0.05	0.05
	8 doses, n = 6	5	0	0	2	0	0	2	0	0	0	0.04	0.03
	12 doses, n = 4	8	0.14	0.14	1	0.04	0.04	4	0.10	0.09	2	0.07	0.06
Whole Transcriptome	4 doses, n = 6	2	0.05	0.06	1	0.00	0.00	1	0.00	0.00	1	0.00	0.00
	6 doses, n = 4	15	0.12	0.07	2	0.00	0.00	7	0.02	0.01	3	0.00	0.00
	8 doses, n = 3	13	0.11	0.06	2	0.00	0.00	7	0.02	0.02	3	0.00	0.01
	12 doses, n = 2	10	0.07	0.06	1	0.01	0.01	5	0.04	0.03	4	0.04	0.03
	4 doses, n = 12	2	0.00	0.00	1	0.00	0.00	1	0.00	0.00	1	0.00	0.00
	6 doses, n = 8	5	0.01	0.01	2	0.00	0.00	3	0.00	0.00	0	0.00	0.00
	8 doses, n = 6	9	0.02	0.03	2	0.02	0.01	5	0.02	0.01	1	0.00	0.00
	12 doses, n = 4	14	0.13	0.07	3	0.01	0.00	7	0.03	0.03	2	0.00	0.00

Work done by Andrew Williams, Health Canada (channeling previous work by Scott Auerbach)

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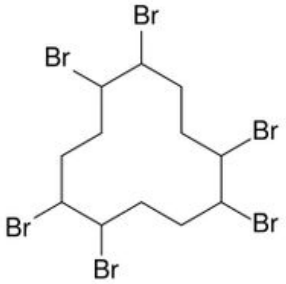
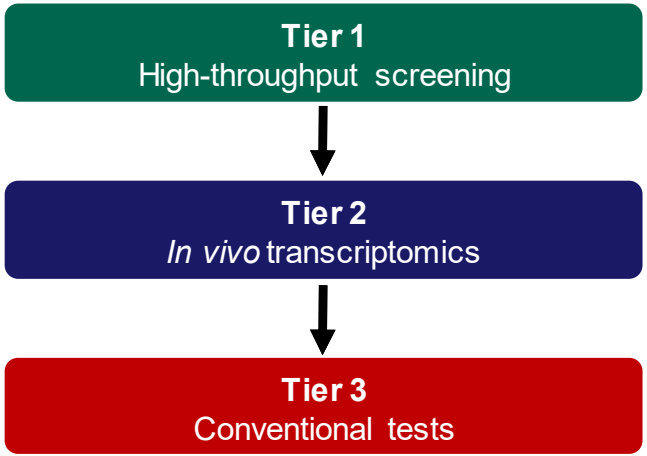
Recent Research-Regulatory case studies to advance our vision

#1. Tiered testing for human health risk assessment Hexabromocyclododecane (HBCD)

Objectives

- Gain experience in applying a tiered testing paradigm;
- Explore consistency across tiers;
- Evaluate use in risk assessment.

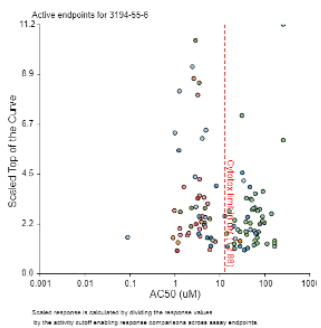


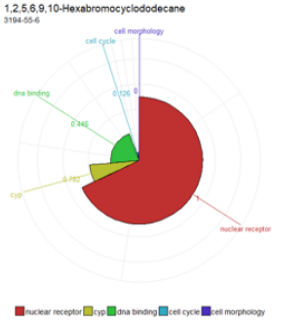


Gannon et al. *Food and Chemical Toxicology*, 2019.

Methods

Tier 1: ToxCast and Tox21 data





Tier 2: Rat liver RNA-sequencing

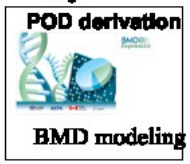
Male and Female Fischer F344 N = 10

Diet, 28 days

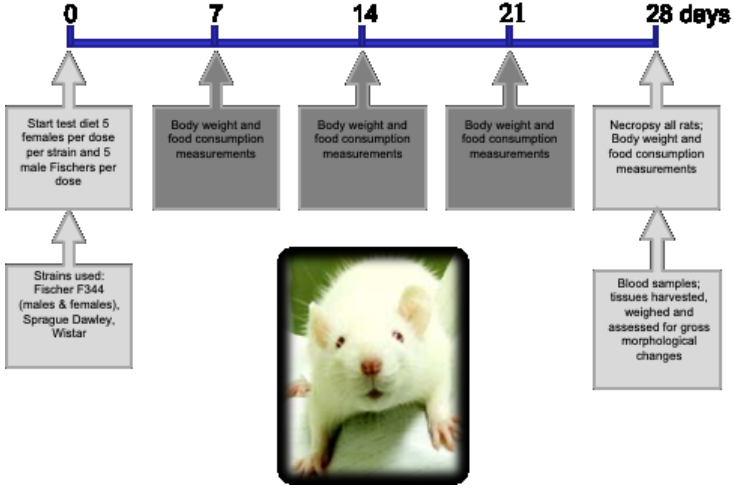
Extract RNA

- Dietary concentrations of 250, 1250, and 5000 mg HBCD/kg diet.

- Altered pathways, upstream regulators
- Signatures of toxicity



Tier 3: Rat sub-chronic studies



Gannon, Moreau, Farmahin et al. *Food and Chemical Toxicology*, 2019.

Transcriptomics is highly consistent with the other tiers for hazard ID

Confirmed effects observed *in vivo*

- Hundreds of differentially expressed genes

Identified sex-specific effects

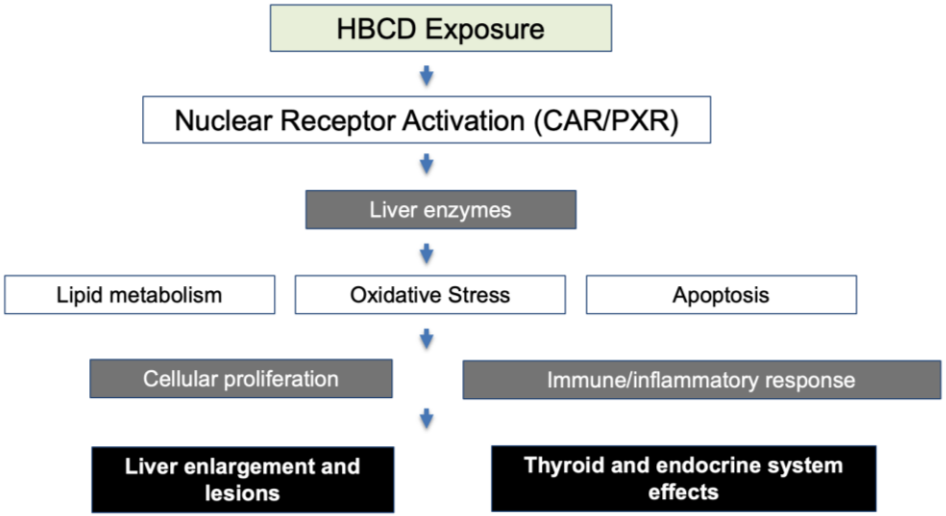
- More changes in males than females

Genes were associated with pathways suggesting:

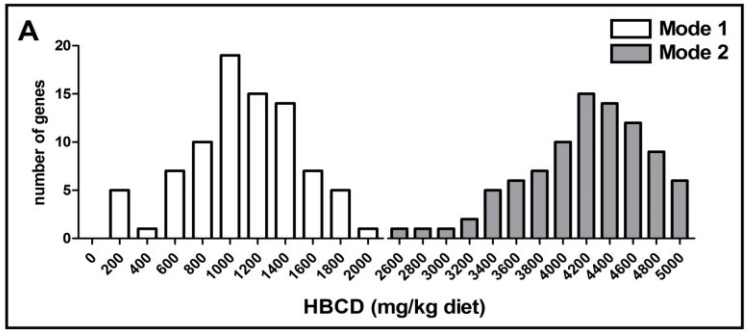
- Alterations in metabolism of xenobiotics and nuclear receptor activity, oxidative stress, cell proliferation and apoptosis, metabolism of glucose and lipid, immune response, fibrotic activity, and hormonal balance

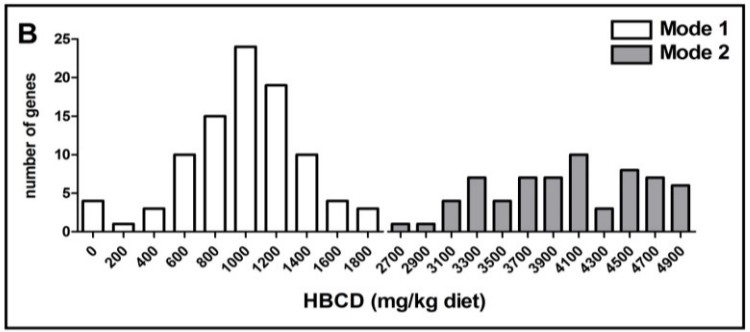
Transcriptomic biomarker analysis revealed

- CAR and PXR biomarker activation at all doses in both sexes (no other biomarkers)



BMD analysis reveals bi-modal distributions and consistency between males (A) and females (B)

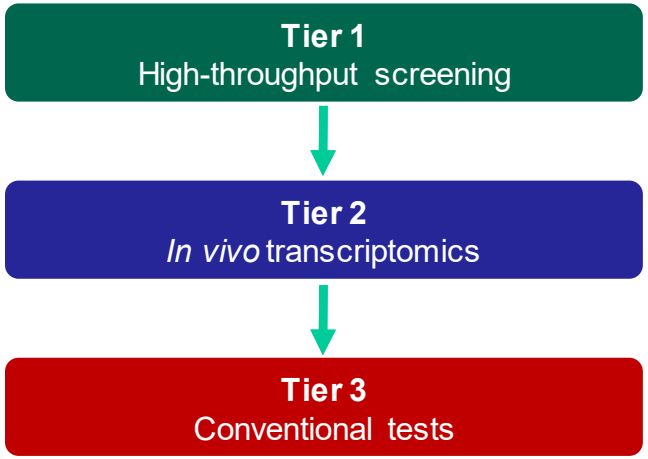


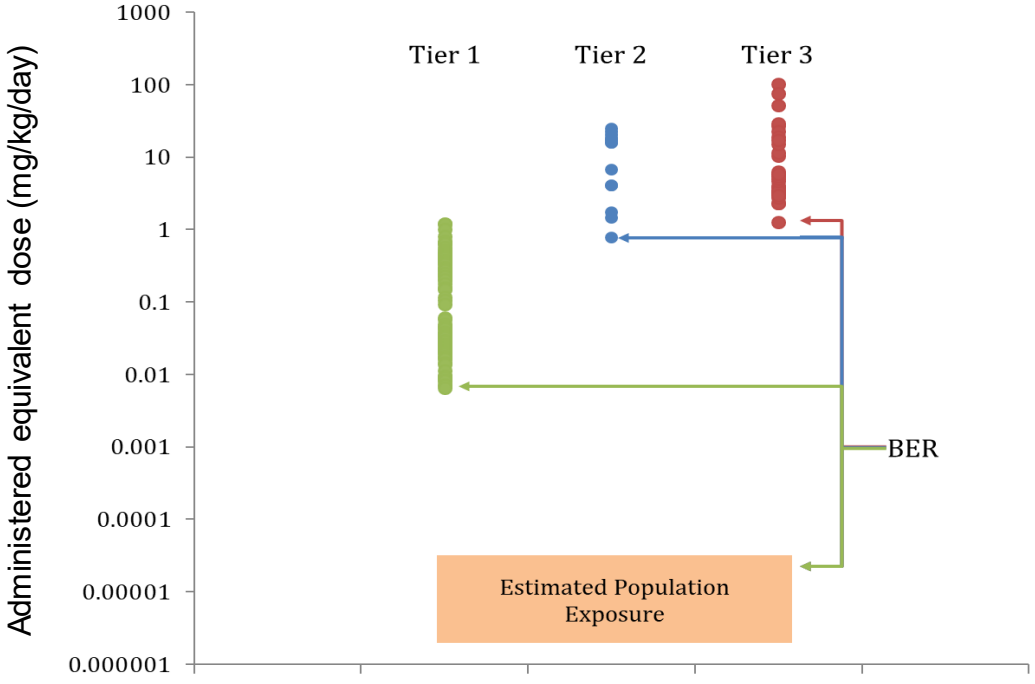


Approach used to derive BMD	Male BMD (mg/kg.day)	Female BMD (mg/kg.day)
Median of significantly enriched pathway BMDs	77	73
20 genes with the largest fold changes	84	65
Lowest statistically significant pathway	66	71
Lowest overall pathways (5% and min 3 genes)	7.2	3.2

Tier 2 is highly overlapping with Tier 3

- human oral equivalent doses for ToxCast AC50s & rat liver transcriptomic BMDs, compared to apical endpoint BMDs in rats and relative to human exposure (Canadian Health Measures survey)



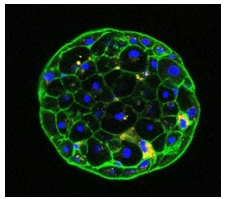


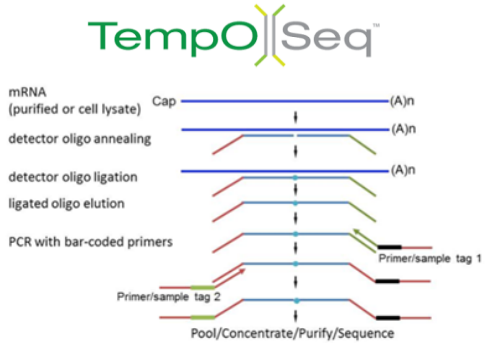
Gannon et al. *Food and Chemical Toxicology*, 2019.

#2. PFAS regulatory needs

- Understand potential toxicity and potencies of emerging PFAS
- Acceptable concentrations of PFAS in drinking water and for cleanup of contaminated sites
- **Prototypes for comparison – PFOA and PFOS**

Methods





Perfluorooctanoic acid
PFOA (C8)

Perfluorodecane Sulfonic Acid
PFDS (C10)

- 10 concentrations, 4 time points (1, 4, 10 and 14 days)
- Media changed every three days and cytotoxicity monitored

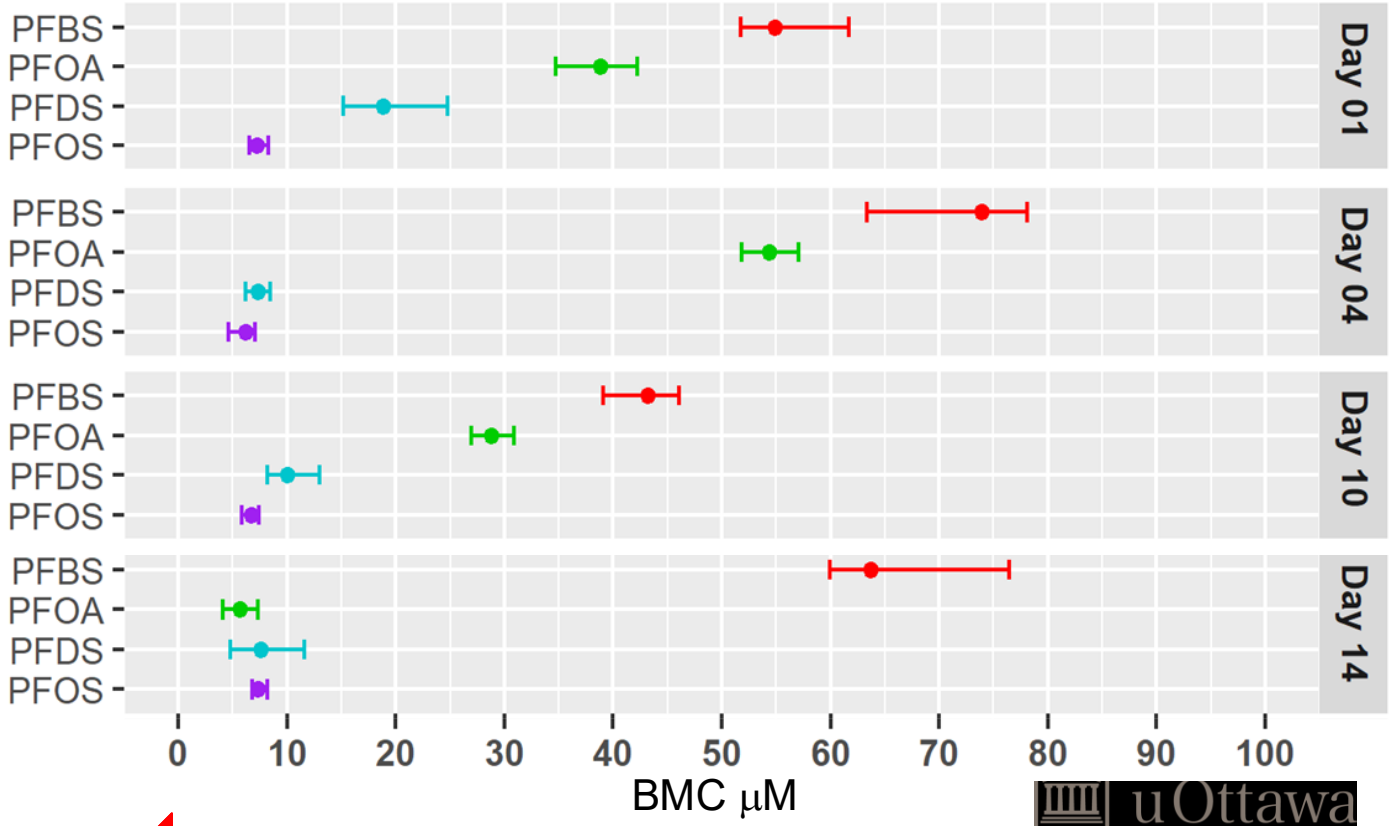
Rowan-Carroll et al., Tox Sci 2021

Median gene BMC (central measure of activity)
Potency comparison of prototypes: PFOS > PFDS > PFOA > PFBS

- PFBS – Least potent
- PFOS – Most Potent
- PFOA
- PFDS

↑ potency with time

Equipotent to PFOS by Day 14

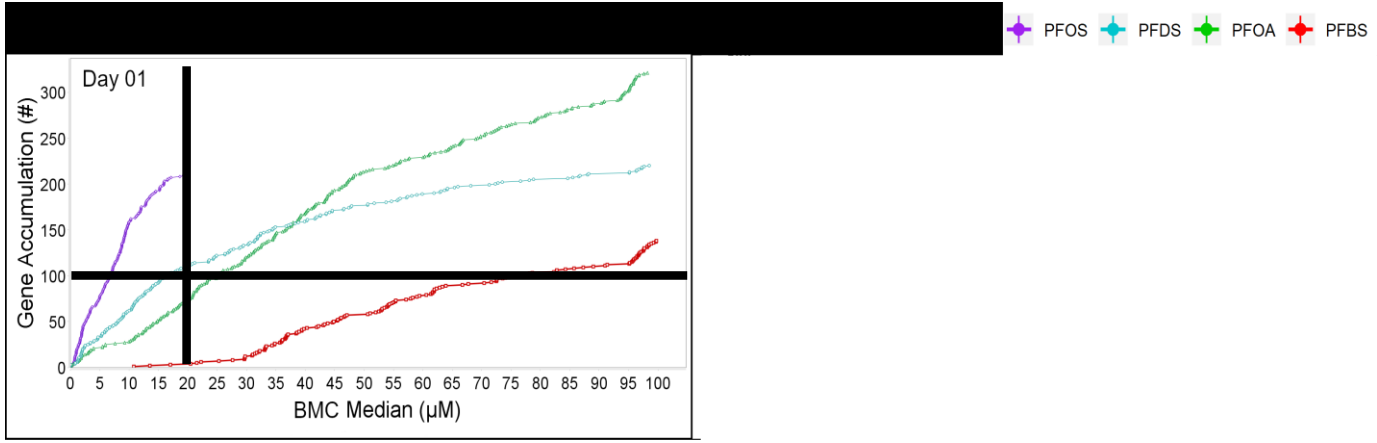


Rowan-Carroll et al.
Tox Sci, 2021

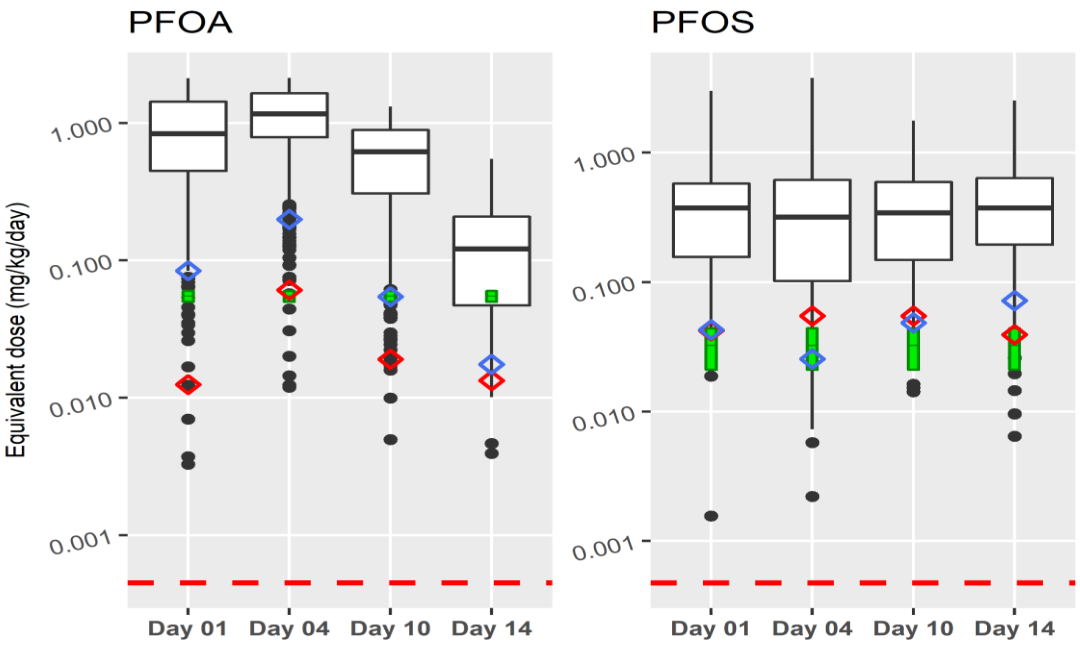
Increasing Potency

Similar potency rankings in overall BMC distribution
Potency: PFOS > PFDS > PFOA > PFBS

- Lowest effects occur at similar concentrations for PFOS, PFOA, PFDS (similar potencies)
- Transcriptional activity initiated: 1 – 15 µM
- PFOS has more genes fitting BMC models below 20 (biological activity)
- Potential use of liver toxicity thresholds (Ramaiahgari SC et al. *Tox Sci* 2019)



tPODs for PFOA and PFOS consistent with apical PODs and potential for human health risk

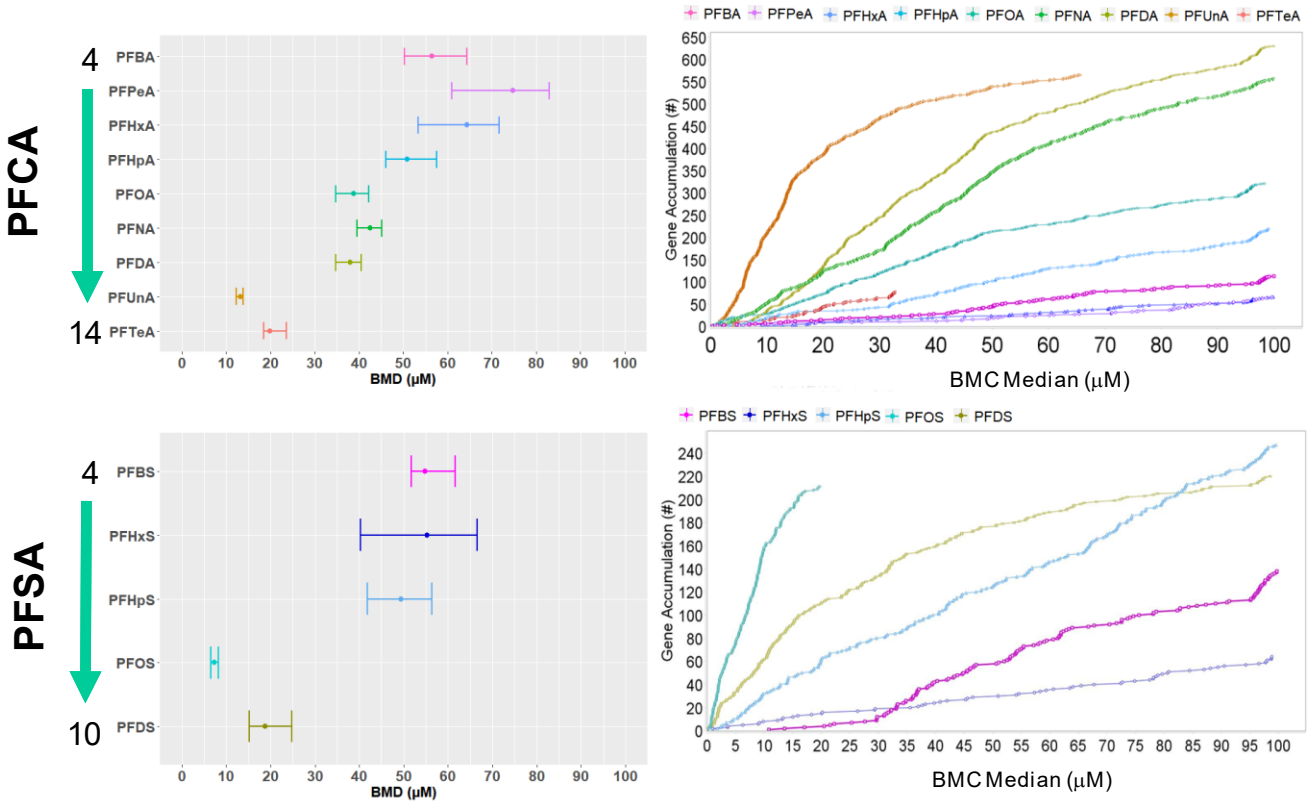


Lowest pathway

5th percentile gene

Conventional tests

Decreasing BMC with increasing PFAS chain length



- Analysis separated by functional groups
- Relationship between chain length and potency
- Use of information for read-across to inform data-poor and untested PFAS

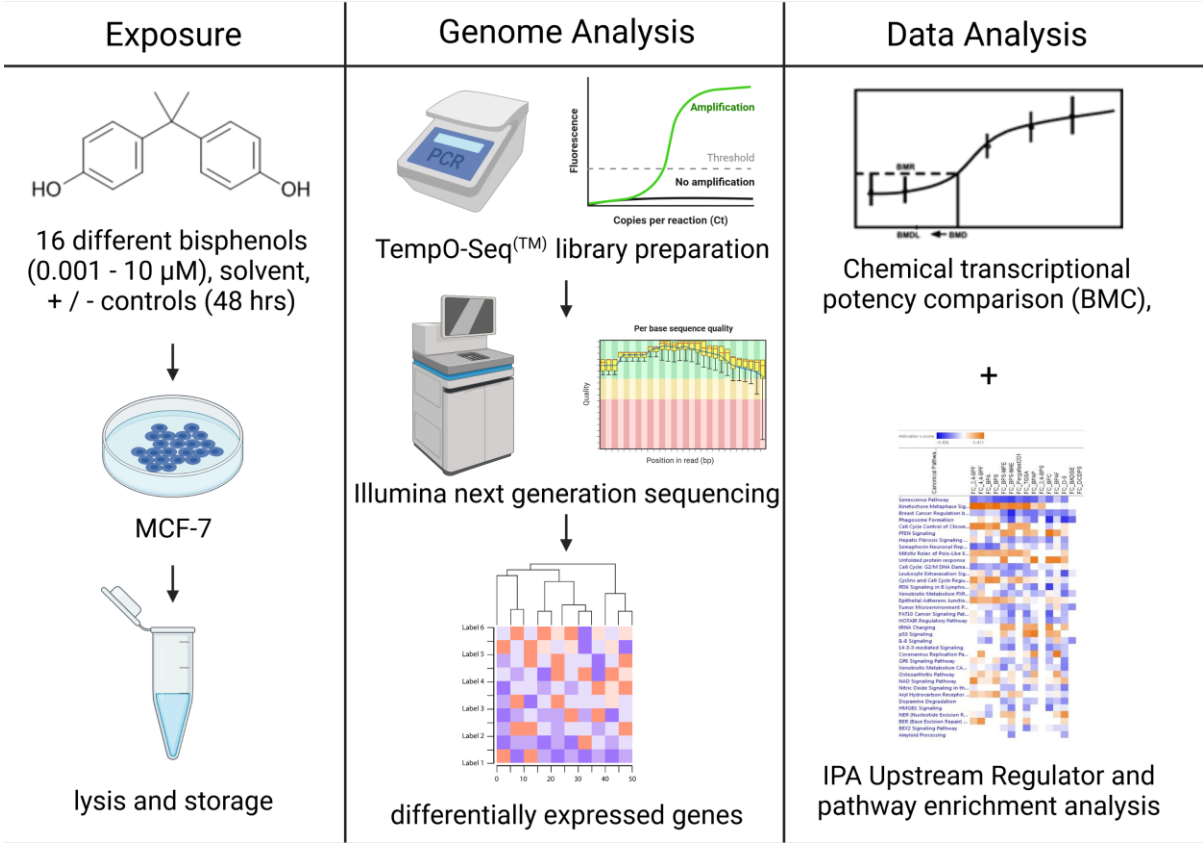
Reardon et al. Tox Sci, 2021

Accelerating the Pace of Chemical Risk Assessment
APCRA

#3. Bisphenol and bisphenol replacements: tPODs to compare potencies and identify active/inactive chemicals

- Estrogenic activity and potency analysis of BPA alternatives
- MCF7 cells, 9 concentrations, 48 hr exposures

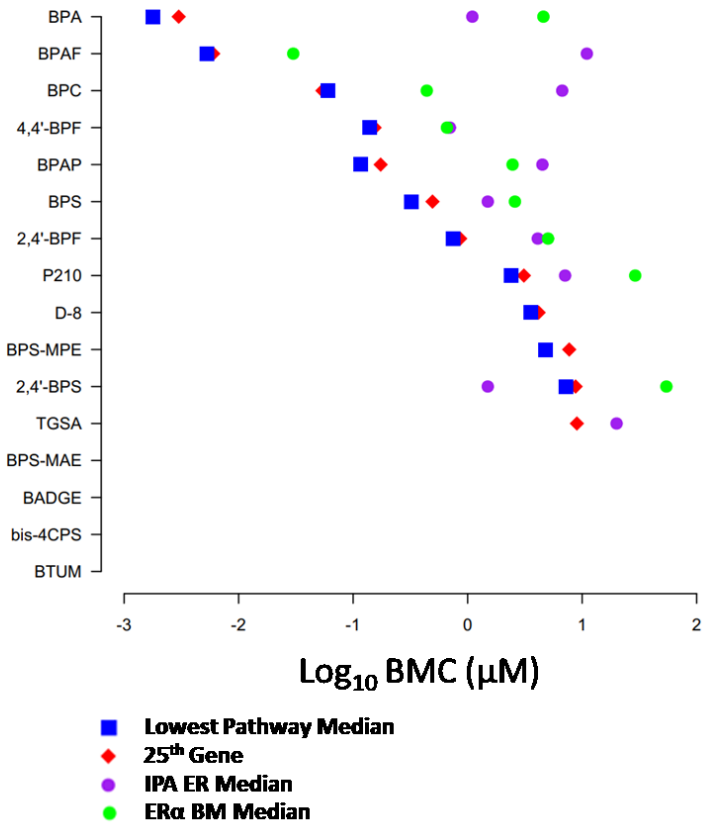
Parodi-Matteo *in preparation*



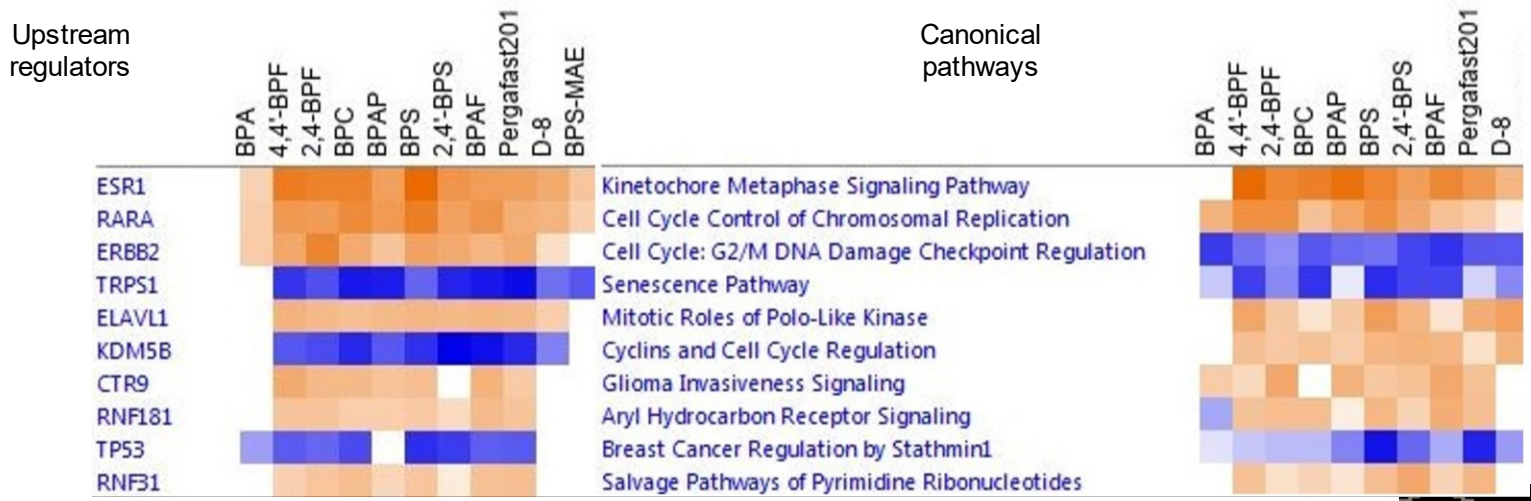
#3. Bisphenol and bisphenol replacements: tPOD approach identifies active/inactive chemicals and enable potency ranking

	ERα Prediction	25th gene	Lowest Pathway Median	IPA ER Median	ERα BM Median
BPA	Agonist	0.003	0.0018	1.1	4.59
BPAF	Agonist	0.006	0.0053	11	0.03
BPC	Agonist	0.054	0.0604	6.7	0.44
4,4'-BPF	Agonist	0.154	0.1406	0.7	0.66
BPAP	Agonist	0.174	0.1170	4.5	2.47
BPS	Agonist	0.494	0.3252	1.5	2.59
2,4'-BPF	Agonist	0.861	0.7511	4.1	5.04
P210	Agonist	3.102	2.3989	7.1	29.08
D-8	Inactive	4.172	3.5581		
BPS-MPE	Inactive	7.715	4.8011		
2,4'-BPS	Agonist	8.774	7.2158	1.5	54.45
TGSA	Agonist	8.999		20	
BPS-MAE	Inactive				
BADGE	Antagonist				
bis-4CPS	Inactive				
BTUM	Inactive				

Rooney et al. *Chem Res Toxicol*. 2021



Gene set enrichment analysis of genes fitting BMC models (concentration-responsive genes) reveals high similarity across the chemicals



What does this mean?

- Dose at which we see transcriptional perturbations (i.e., tPOD) in short-term studies predicts the dose at which adverse effects occur following longer-term exposures
- tPODs are generally conservative, but not overly conservative
- A variety of approaches work, both hazard-based and agnostic
  - When the transcriptome is robustly perturbed, prolonged exposed at this dose is likely to lead to adverse health consequences
- Approach taken should be context specific
  - Selecting the lowest tPOD is protective of adverse health effects
- Case studies useful for informing regulatory applications and building confidence

Major needs

- Socialize this idea
    - Paradigm-changes are challenging
- Establish best practices for deriving tPODs for different contexts of use
    - OECD Transcriptomic Reporting Framework has a BMD module, which ensures transparency in regulatory submissions and may facilitate developing acceptable practices
- Identify model-specific baseline filtering requirements
- Studies to establish confidence that hazard-agnostic tPOD can be protective of human health effects
- Demonstrate applicability across broad chemical and biological space
    - Critical to mainstream integration for decision making
- Determine how to address uncertainty

Program	Potential uses for toxicogenomics in risk assessment			
	Weight of evidence	Mode of Action analysis	Prioritization	Chemical Grouping to support Read across
Existing substances	✔	✔	✔	✔
New substances and nanomaterials	✔	✔	✔	✔
Water	✔	✔	✔	✔
Air	✔	✔	✔	✔
Controlled substances	✔	✔	✔	✔
Radiation	✔	✔		
Consumer products, cosmetics and workplace chemicals	✔	✔	✔	✔
Food	✔	✔	✔	✔
Biologics and genetic therapies	✔	✔		
Marketed health products	✔	✔		
Therapeutic products	✔	✔		
Pesticides	✔	✔	✔	✔

Toxicogenomic applications in risk assessment at Health Canada. *Current Opinions in Toxicology*. Volume 18, December 2019, Pg 34-45.

Conclusions

These case studies build confidence in the application of tPODs in regulatory evaluations and help to define suitable contexts of use

- Much to learn from focused collaborative studies on individual chemicals or small chemical groupings
- Demonstrating applicability across broad chemical and biological space will be critical to mainstream integration for decision making
- Growing interest in use across regulatory bureaus

HESI eSTAR POD Working Group

Funding Provided by:

- Genomics Research & Development Initiative
- Chemicals Management Plan
- NSERC CREATE-REACT
- Canada Research Chairs Program