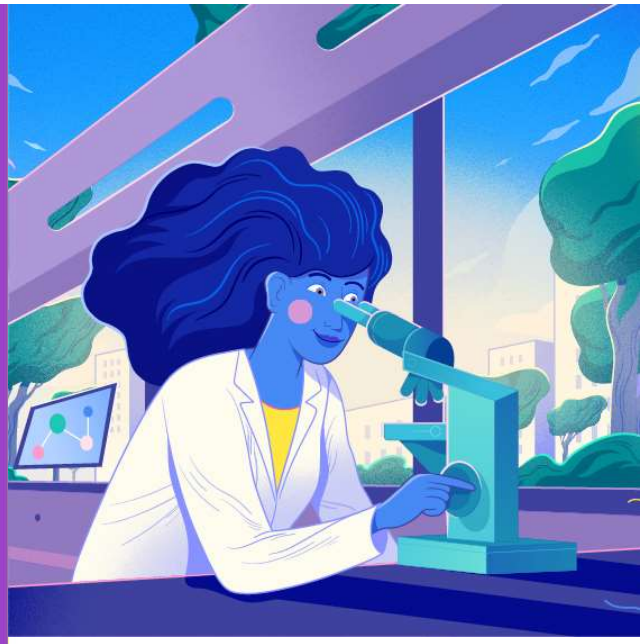
# Beyond AOPs: A Mechanistic Evaluation of NAMs in DART Testing




**Dr Predrag Kukic**
**Science Lead**
**Unilever Safety and Environmental Assurance Centre (SEAC)**


Unilever

ESTIV, 22/11/2022

# Outline

- Unilever's approach: science-based safety
- Overview of  Unilever's NGRA Framework for DART
- Biological coverage of the NGRA Framework for DART
- Next steps, case studies / fit for purpose validation

# Unilever Policy & Approach
## Safe & Sustainable Products without Animal Testing

We say use science.
Not animals.

### What we believe

- **Every Unilever product must be safe for people and our environment**
- **Non-animal testing to assess ingredient & product safety** – there are a wide range of non-animal alternatives grounded in modern science and new technology

### How we do it

40+ years of developing non-animal safety science

70+ collaborations

600+ publications

https://tt21c.org



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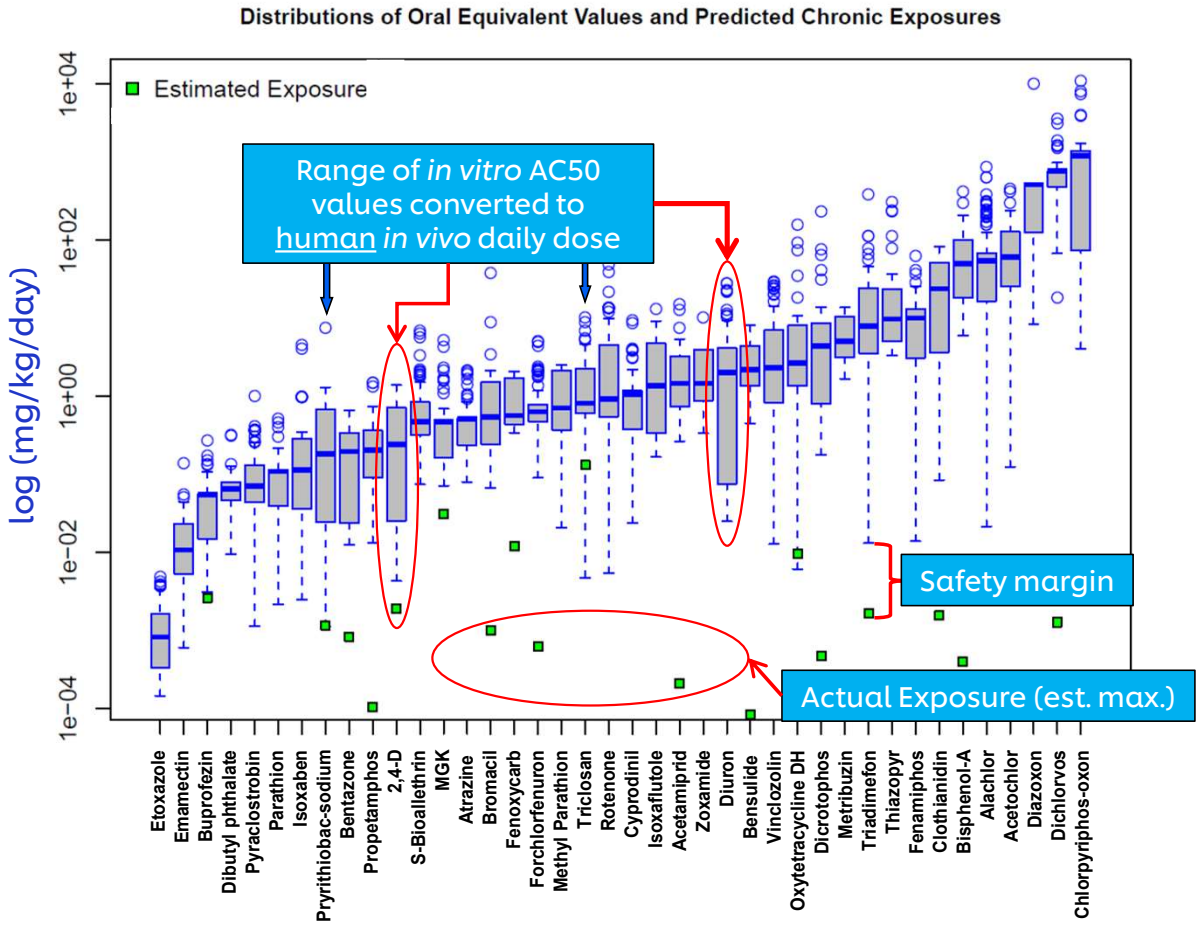
# Using 21st century science to assure safety – NGRA



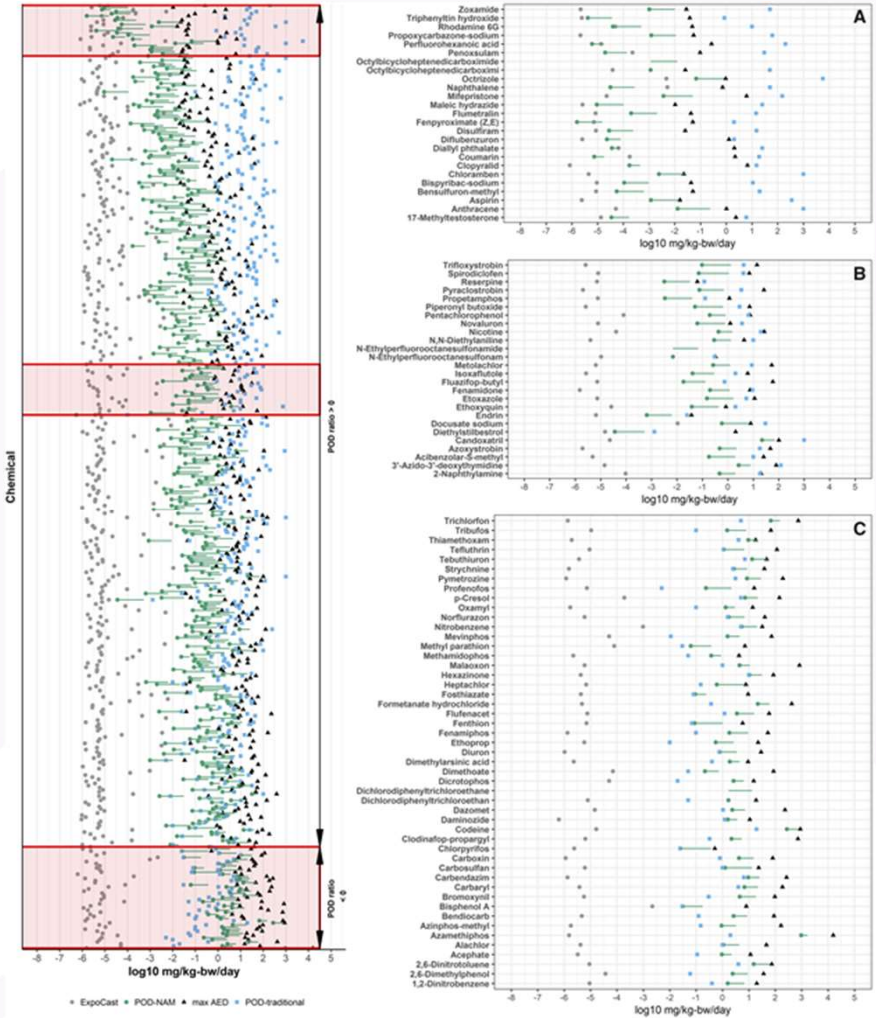

The hypothesis underpinning NGRA is that **if no bioactivity is observed at consumer-relevant concentrations, there can be no adverse health effects.**

At no point does NGRA attempt to predict the results of high dose toxicology studies in animals.

NGRA **uses new exposure science and understanding of human biology.**

Graph from Rusty Thomas EPA, with thanks. Rotroff *et al* (2010) Toxicological Sciences , **117**, 348-358

# How PODs from NAMs compare to PODs coming from animal studies
## -including chronic, developmental/reproductive studies




**448 chemicals**

APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

**"The primary conclusion of our work is that for 89% of the chemicals in this case study, the HTS approach to derivation of a $POD_{NAM,\ 95}$ for screening and prioritization purposes produced a value less than or equal to the $POD_{traditional}$ from *in vivo* toxicology studies."**

*Toxicol Sci*, Volume 173, Issue 1, January 2020, Pages 202–225, https://doi.org/10.1093/toxsci/kfz201

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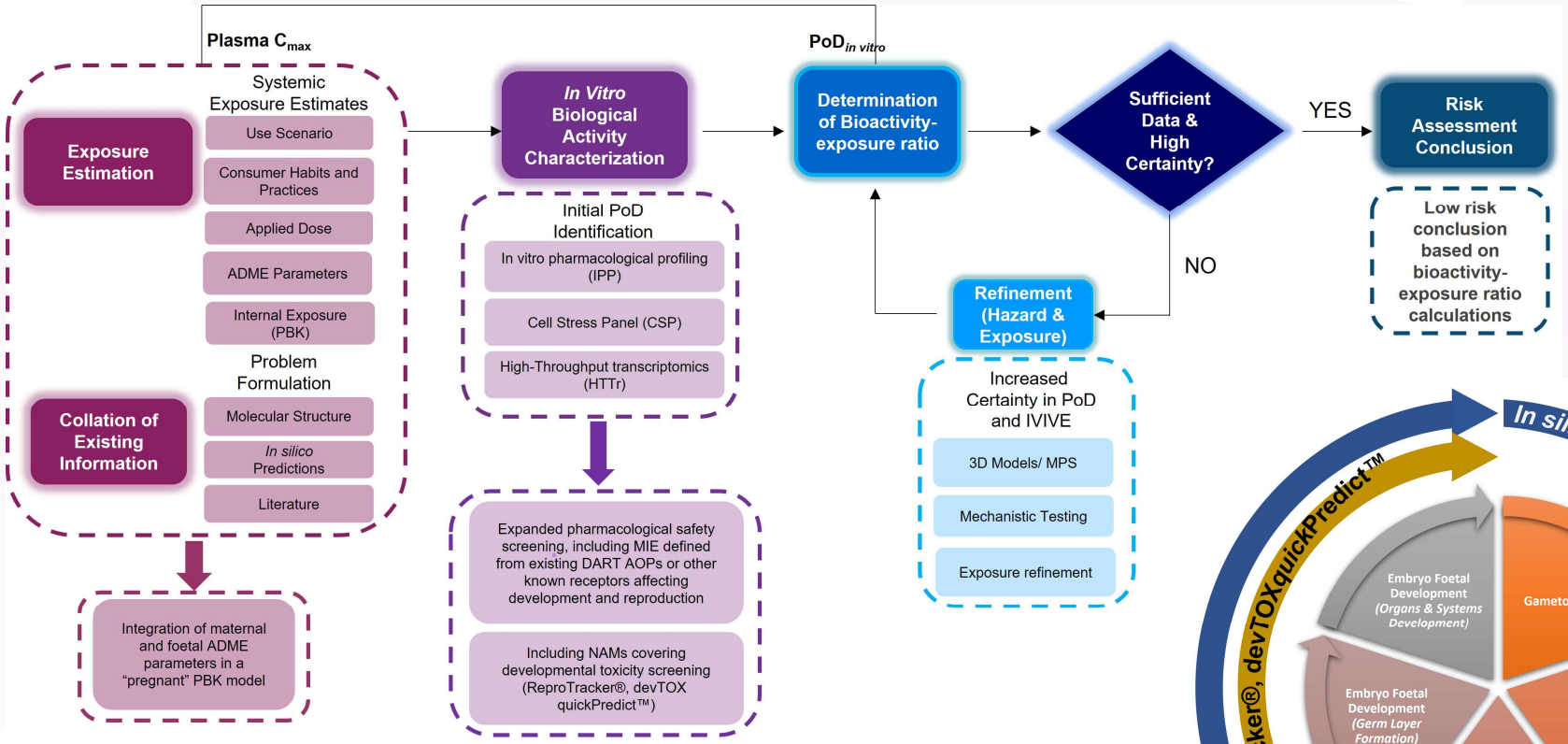
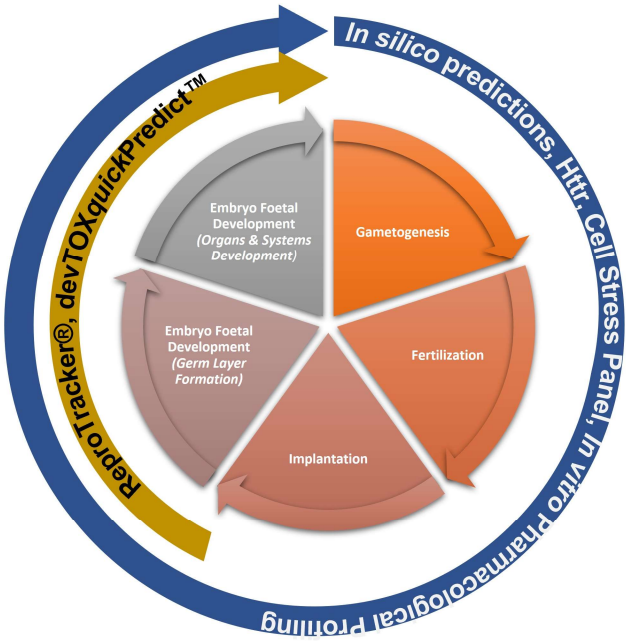
# Unilever's Framework for NGRA DART

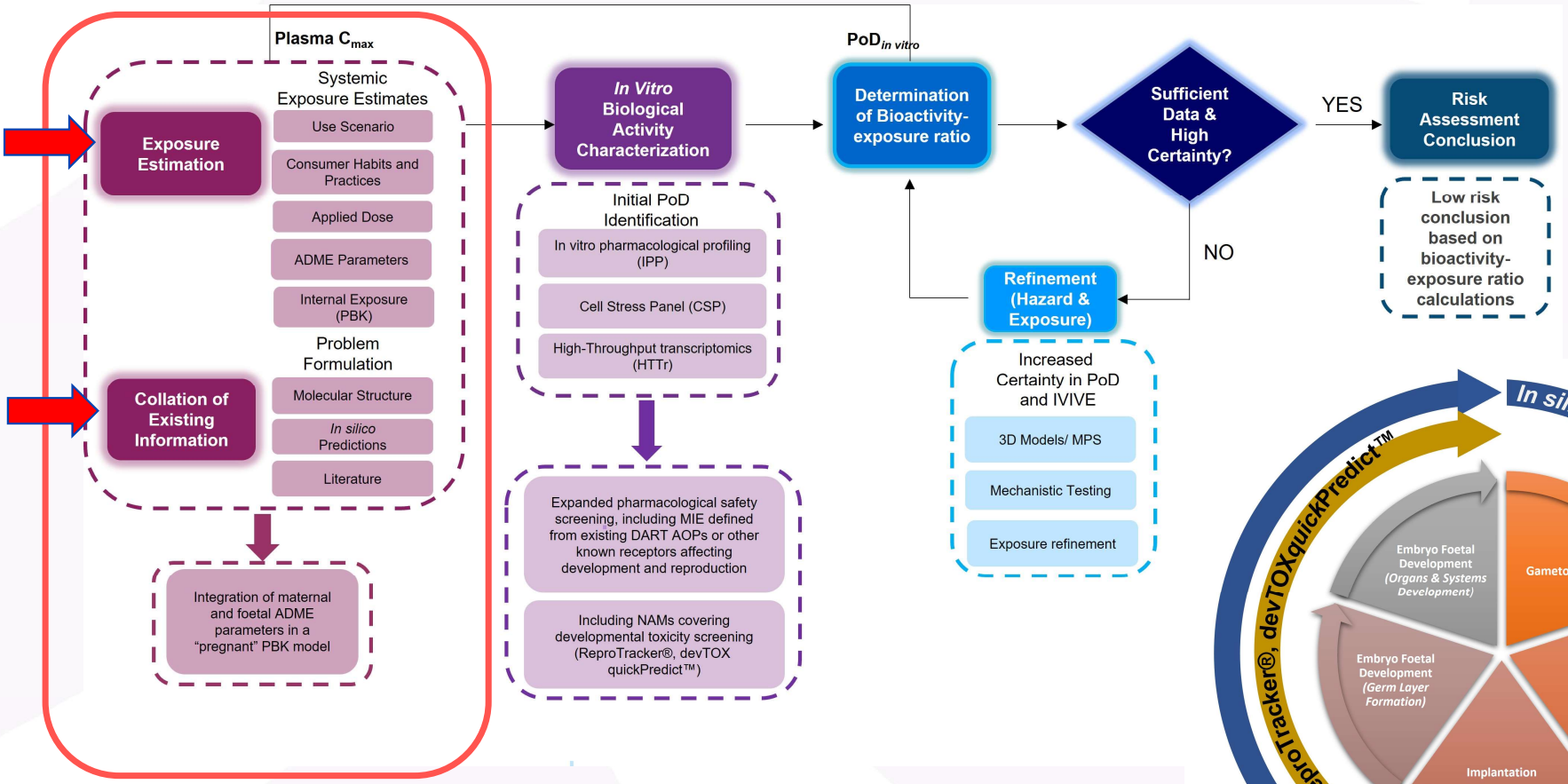
# Unilever's NGRA Framework for DART – tiered approach

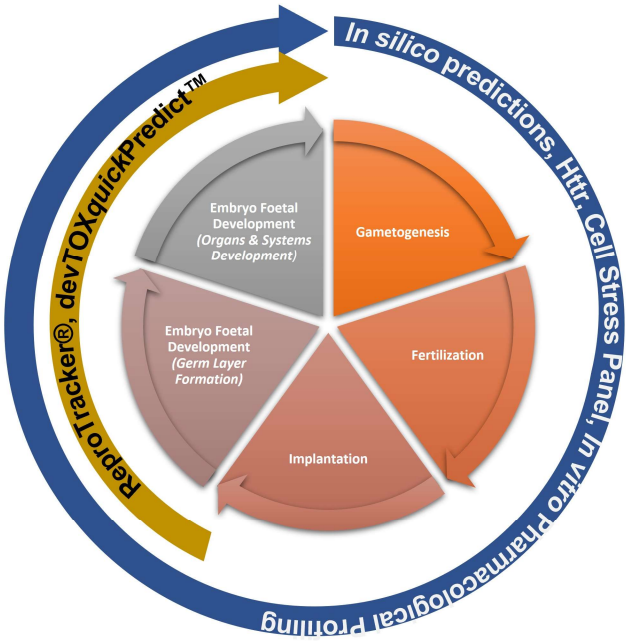



Rajagopal et al., Front. Toxicol., 07 March 2022
https://doi.org/10.3389/ftox.2022.838466

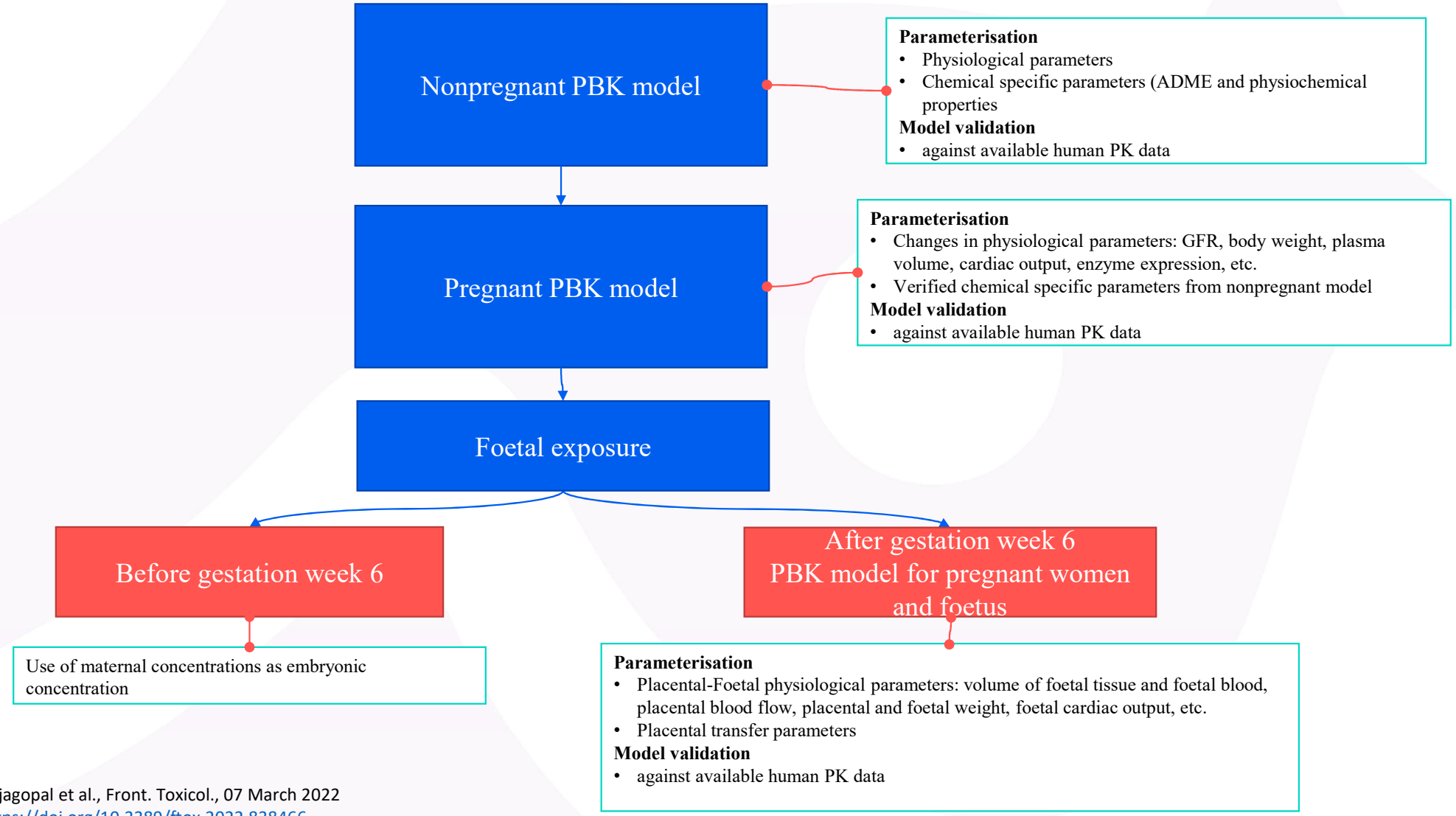
# Unilever's NGRA Framework for DART – exposure



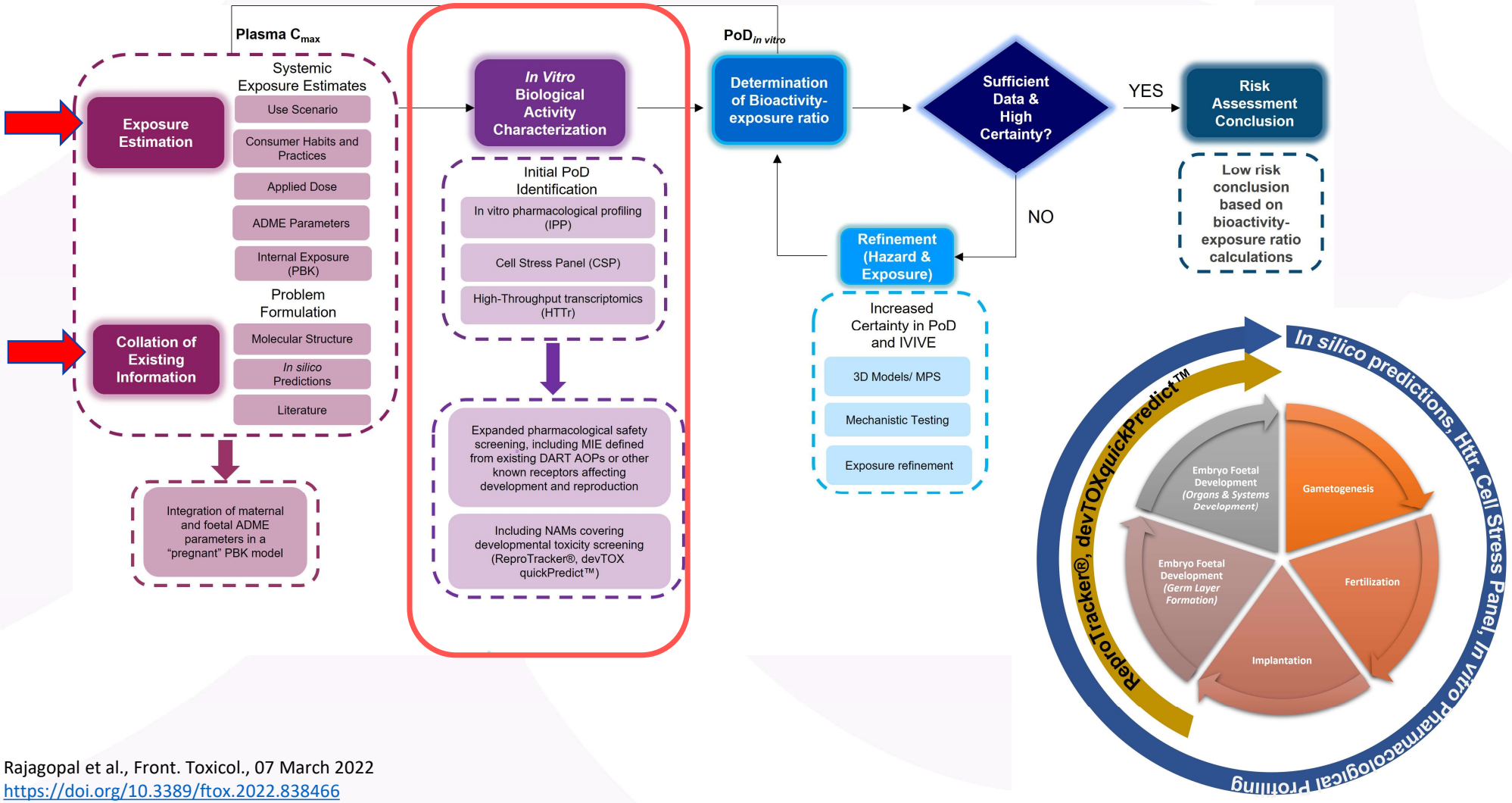

Rajagopal et al., Front. Toxicol., 07 March 2022
https://doi.org/10.3389/ftox.2022.838466

# Systemic exposure estimates– pregnant PBK modelling




Rajagopal et al., Front. Toxicol., 07 March 2022
https://doi.org/10.3389/ftox.2022.838466

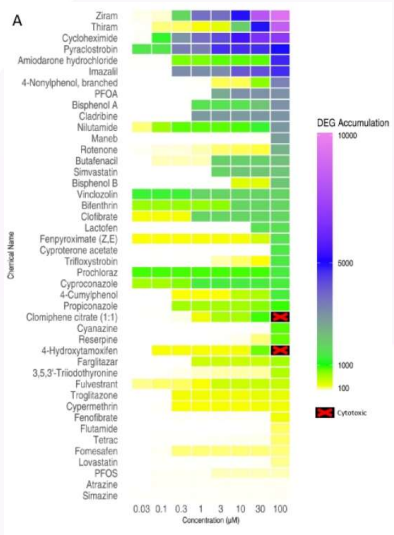
# Unilever's NGRA Framework for DART – exposure



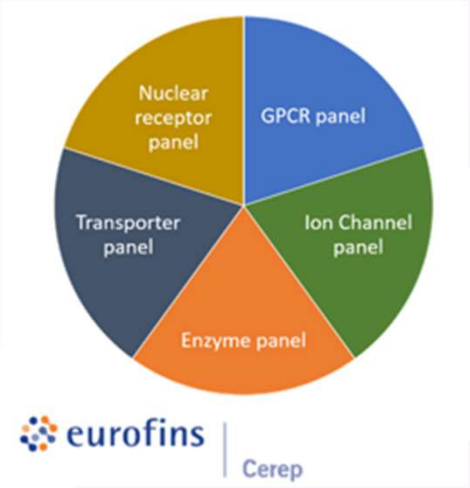

Rajagopal et al., Front. Toxicol., 07 March 2022
https://doi.org/10.3389/ftox.2022.838466

# Unilever's NGRA Framework for DART – biological activity

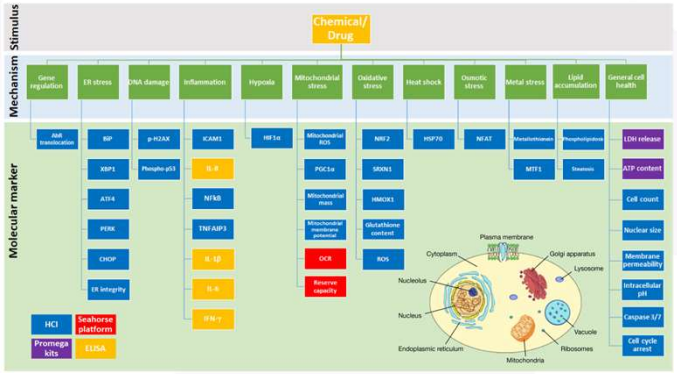
**HTTr**



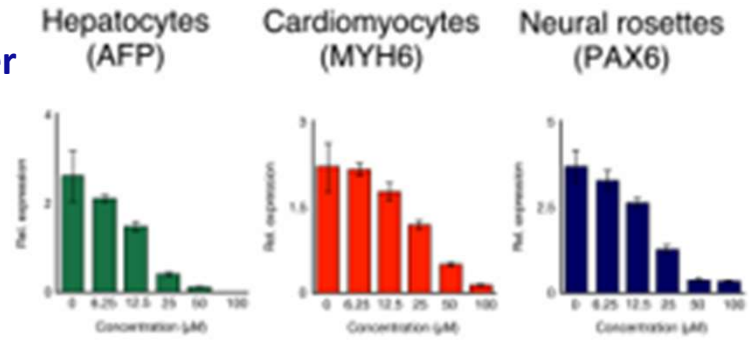

**IPP+**



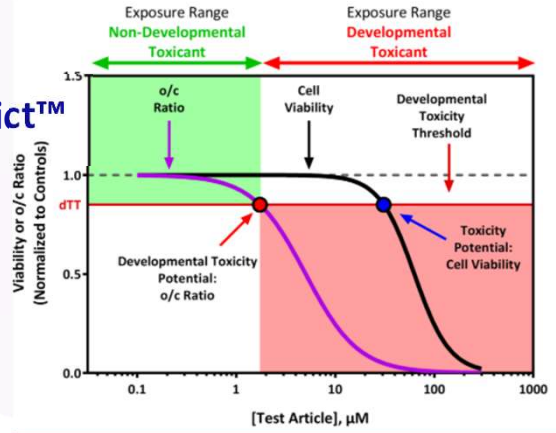

**CSP**




**Repro Tracker**




**devTox quickPredict™**



# Scientific and Technical Challenges associated with NGRA

- Metabolic capacity of the framework (cell models, MPS, alginate technology, etc.)
- Short duration exposures and extrapolation to chronic effects
- Complex data interpretation and uncertainty analysis
- Spatio-temporal complexity of developmental and reproductive processes
- Coverage of important cellular and intercellular processes
- Chemical domain of applicability / case studies – need for a flexible and fit for purpose validation

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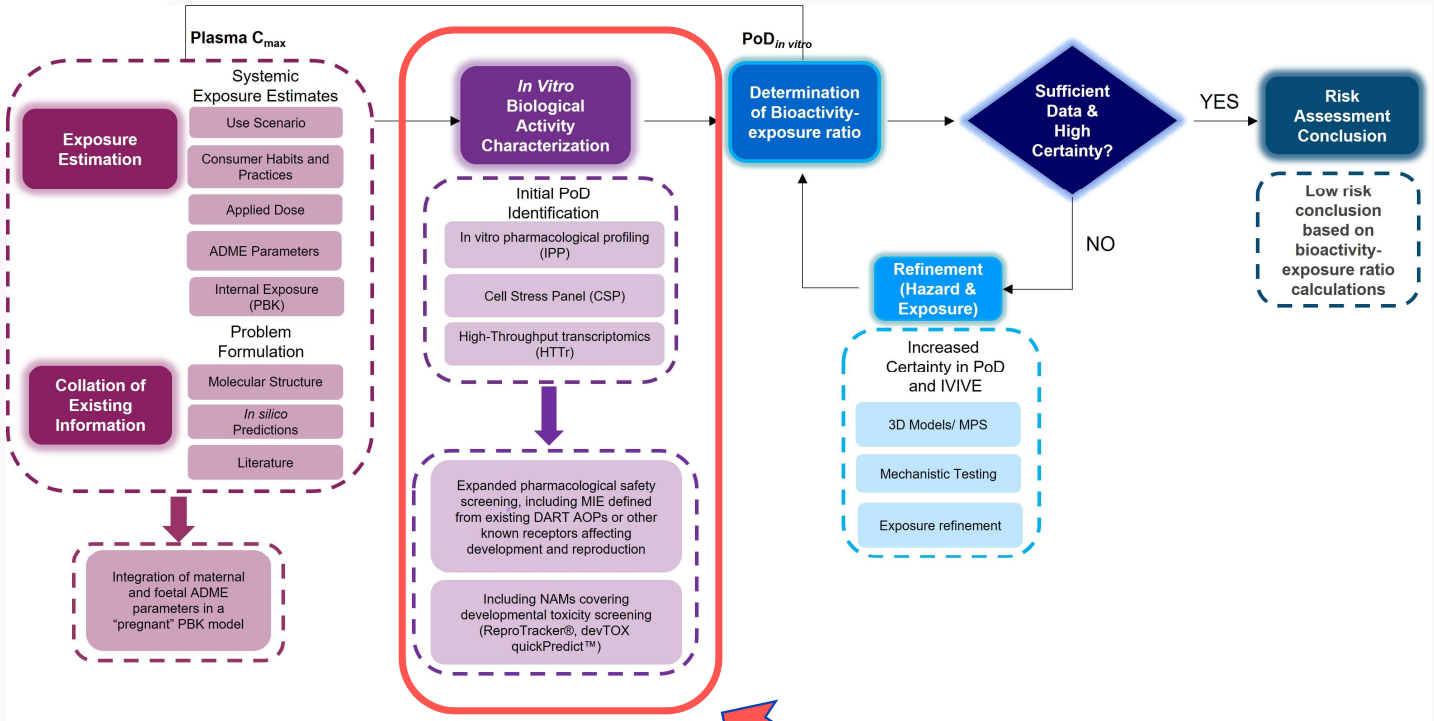
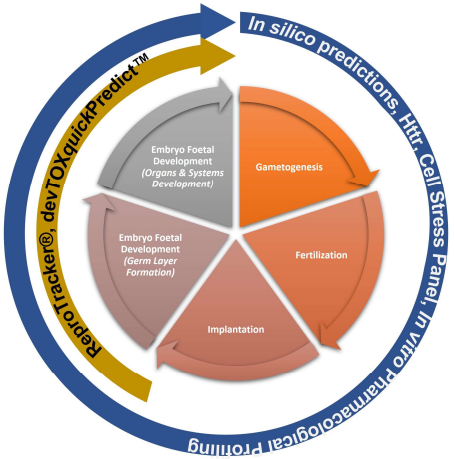
# Biological coverage of the NGRA Framework for DART

# What is the biological coverage of the NGRA DART Framework?



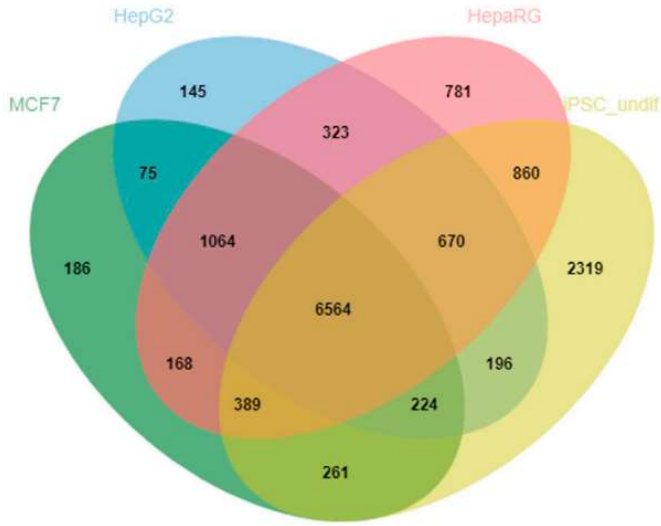



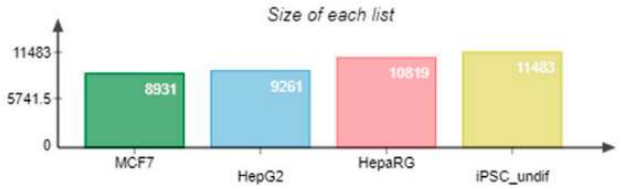

## Does the Bioactivity Characterisation cover for important cellular and intercellular processes?

Rajagopal et al., Front. Toxicol., 07 March 2022
https://doi.org/10.3389/ftox.2022.838466

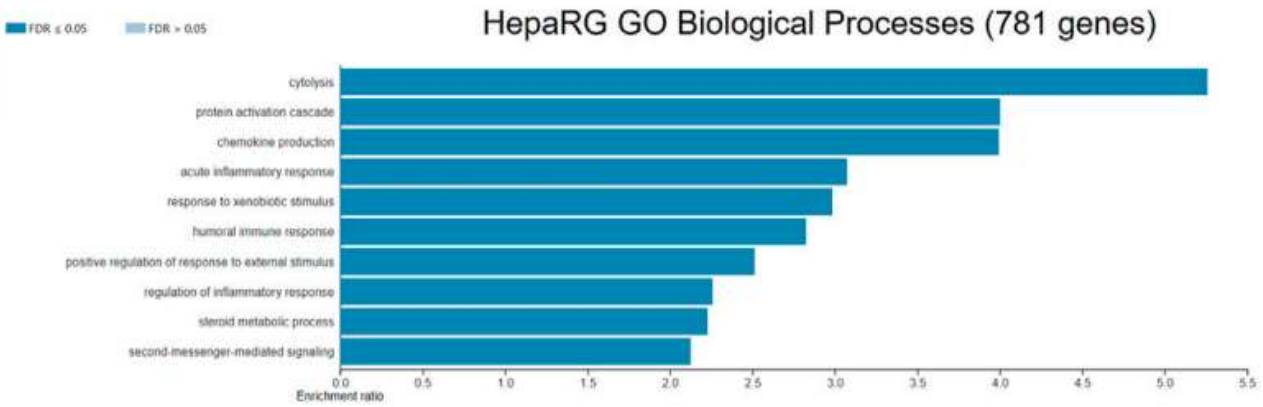
# Baseline expression of the cell lines within the NGRA DART

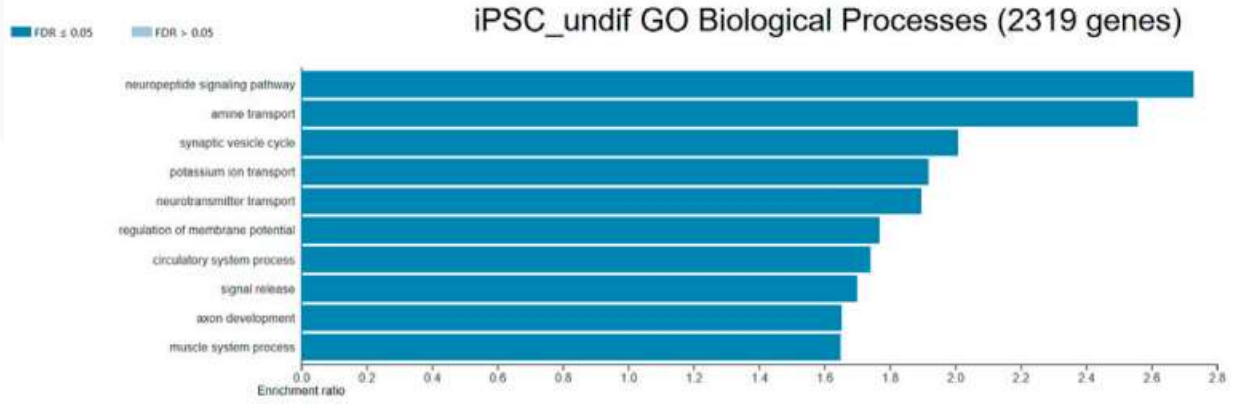
HepG2, MCF-7, HepaRG- Systemic Toolbox
hiPSCs- ReproTracker®, devTOXquickPredict™




**14,225 genes in total**




Differentiated hiPSCs not included in this study but in scope for future work

Rajagopal et al., Front. Toxicol., 07 March 2022
https://doi.org/10.3389/ftox.2022.838466

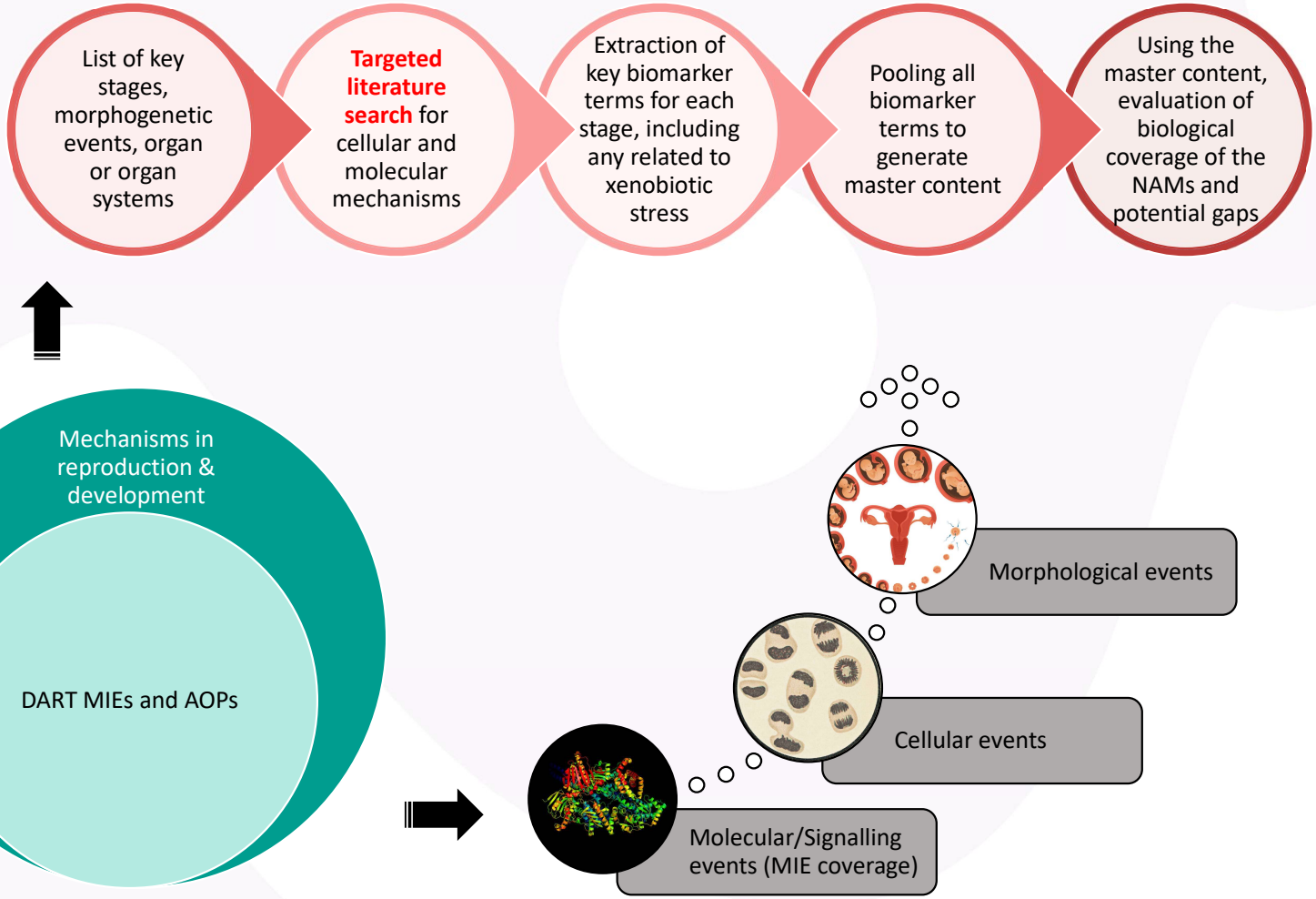
# Key Biomarkers for DART - Systematic literature search

**Chemicals & assays based approach**

- ReproTect (10 chemicals, 14 assays)
- ChemScreen (12 chemicals, 31 assays)
- ReproTracker®
- devTOXquickPredict™
- ToxCast

**AOPs based approach**

- Eleven DART-related Adverse Outcome Pathways (AOPs) published in 2015
- Over 90 AOPs in AOPWiki related to DART
- Network AOPs




Rajagopal et al., Front. Toxicol., 07 March 2022
https://doi.org/10.3389/ftox.2022.838466

# Key Stages, Morphogenetic Events and Derivatives Organs & Systems in Human Reproduction and Development

**Sex determination**

**Gametogenesis**

**Fertilization**

**Zygote formation**

**Implantation**

**Blastulation**

**Gastrulation**

**Placenta formation**

**Neurulation**

**Ectoderm formation and its derivatives**

- Central nervous system
- Peripheral nervous system
- Autonomous nervous system
- Integumentary system

**Mesoderm formation and its derivatives**

- Somitogenesis
- Hematopoiesis
- Heart and circulatory system
- Immune system
- Spleen
- Urinary system and urethra
- Reproductive system – testis
- Reproductive system – ovary
- Skeletal system
- Limbs

**Endoderm formation and its derivatives**

- Digestive system
- Respiratory system
- Thymus
- Parathyroid
- Thyroid

**Structures developing from mesenchyme or multiple germ layers**

- Adrenal glands
- Eyes
- Ears
- Face and neck

**Intrauterine growth**

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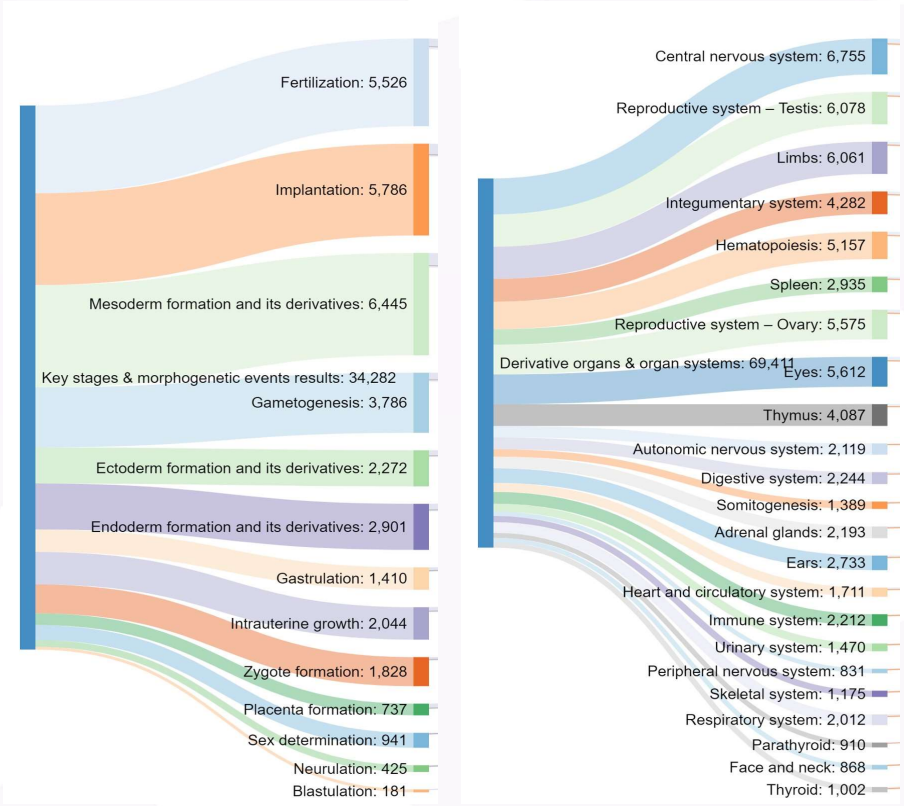
# Overview of Literature Search and Extraction of Key Markers Information

**Literature search**
**MeSH Ontology**
**37 million Articles**

**Validation and quality check of results; finalising the articles**




**Query run:** **("CNS") AND (embryonic development OR fetal development) AND (cell physiology OR nervous system physiology) OR (signalling OR pathway OR gene OR protein) AND (human OR mammalian) NOT (infections)**

**34,308 articles on key stages and morphogenetic events**

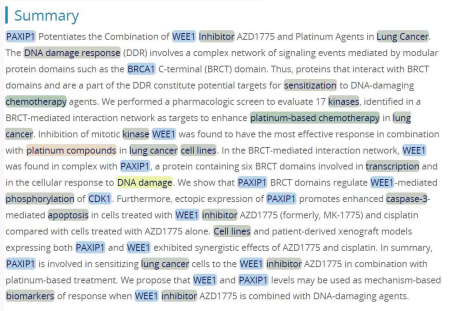
**69,299 articles on organs and organ systems development**

**103,607 total articles**

Pooling extractions, Thresholding of hit counts

Semantic enrichment using HGNC, miRNA and biological processes ontologies

Abstracts extracted and collated


Summary

PAXIP1 Potentiates the Combination of WEE1 Inhibitor AZD1775 and Platinum Agents in Lung Cancer. The DNA damage response (DDR) involves a complex network of signaling events mediated by modular protein domains such as the BRCA1 C-terminal (BRCT) domain. Thus, proteins that interact with BRCT domains and are a part of the DDR constitute potential targets for sensitization to DNA-damaging chemotherapy agents. We performed a pharmacologic screen to evaluate 17 kinases, identified in a BRCT-mediated interaction network as targets to enhance platinum-based chemotherapy in lung cancer. Inhibition of mitotic kinase WEE1 was found to have the most effective response in combination with platinum compounds in lung cancer cell lines. In the BRCT-mediated interaction network, WEE1 was found in complex with PAXIP1, a protein containing six BRCT domains involved in transcription and in the cellular response to DNA damage. We show that PAXIP1 BRCT domains regulate WEE1-mediated phosphorylation of CDK1. Furthermore, ectopic expression of PAXIP1 promotes enhanced caspase-3-mediated apoptosis in cells treated with WEE1 inhibitor AZD1775 (formerly, MK-1775) and cisplatin compared with cells treated with AZD1775 alone. Cell lines and patient-derived xenograft models expressing both PAXIP1 and WEE1 exhibited synergistic effects of AZD1775 and cisplatin. In summary, PAXIP1 is involved in sensitizing lung cancer cells to the WEE1 inhibitor AZD1775 in combination with platinum-based treatment. We propose that WEE1 and PAXIP1 levels may be used as mechanism-based biomarkers of response when WEE1 inhibitor AZD1775 is combined with DNA-damaging agents.

# Overview of Literature Search and Extraction of Key Markers Information

Download Abstracts of Selected articles

Extract Genes

Vocabulary based on Hugo Gene Nomenclature Committee standard list of genes

Extract Cellular & Molecular Mechanisms

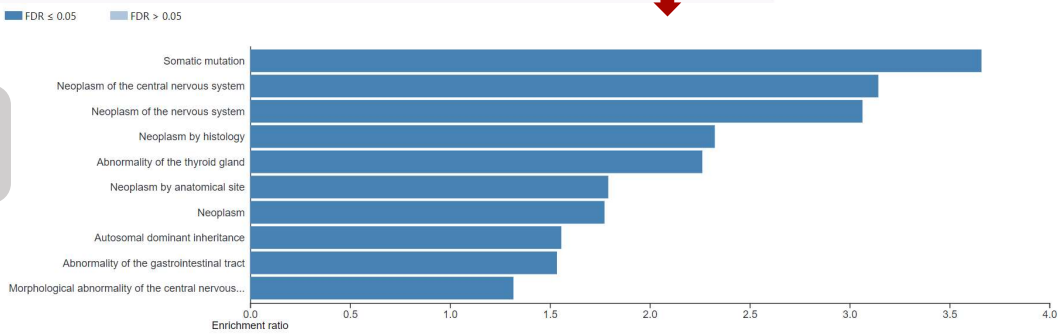
Extract miRNA

| A | B | C | D | E | F | G | H | I |
|---|---|---|---|---|---|---|---|---|
| PMID | Pub Yr | Title | Authors | Journal | | Issue | Pages | |
| 34332630 | 2021 | Brain organoid: a 3D technology for investigating cellu | Agboola OS, Hu X, Shan Z, Wu Y, | Stem cell research & therapy | | 1 | 430 | |
| 34325647 | 2021 | Activation of microglial GLP-1R in the trigeminal nucle | Jing F, Zou Q, Wang Y, Cai Z, Tang | The journal of headache and pa | 10.1 | 1 | 86 | |
| 34303983 | 2021 | Exposure to cadmium induces neuroinflammation an | Huang Y, Dai Y, Li M, Guo L, Cao | The Science of the total environ | 10.101 | | 149043 | |
| 34253646 | 2021 | Preclinical Evaluation of the Effects of Trazpiroben (TA | Whiting RL, Choppin A, Luehr G, | The Journal of pharmacology ar | 10.1124/ | | | |
| 34249938 | 2021 | The Altered Anatomical Distribution of ACE2 in the Br | Cui H, Su S, Cao Y, Ma C, Qiu W | Frontiers in cell and developme | 10.3389/fi | | 684874 | |
| 34162530 | 2021 | Regenerative medicine for neurological diseases-will r | Burns TC, Quinones-Hinojosa A | BMJ (Clinical research ed.) | 10.1136/b | | 955 | |
| 34130715 | 2021 | Programmed suppression of oxidative phosphorylatio | Chang RC, Thomas KN, Mehta N | Epigenetics & chromatin | 10.1186/s | 1 | 27 | |
| 34071978 | 2021 | Brain-Derived Neurotrophic Factor Signaling in the Pa | Numakawa T, Odaka H | International journal of molecul | 10.3390/ij | 22 | | |
| 34054129 | 2021 | Biallelic and monoallelic variants in PLXNA1 are implic | Dworschak GC, Punetha J, Kalan | Genetics in medicine : official jo | 10.1038/s41436-021-01126 | | | |
| 34040637 | 2021 | Gene Environment Interactions in the Etiology of Neu | Finnell RH, Caiaffa CD, Kim SE, Li | Frontiers in genetics | 10.3389/fg | 12 | | |
| 34019717 | 2021 | Neurotrophic factor levels in the serum and cerebrosp | Wang S, Zou F, Wu S, Wu Y, Yue Y | Microbiology and immunology | 10.1111/1348-0421.12918 | | | |
| 33946667 | 2021 | Therapeutic Effects of hiPSC-Derived Glial and Neuror | Salikhova D, Bukharova T, Cherki | International journal of molecul | 10.3390/ij | 22 | 9 | |
| 33917816 | 2021 | Potential Roles of the WNT Signaling Pathway in Amyc | Jiang X, Guan Y, Zhao Z, Meng F, | Cells | 10.3390/c | 10 | 4 | |
| 33804711 | 2021 | Investigating Primary Cilia during Peripheral Nervous | Yusifov E, Dumoulin A, Stoecklii E | International journal of molecul | 10.3390/ij | 22 | 6 | |
| 33803024 | 2021 | Microglia Development and Maturation and its Implic | Wurm J, Konttinen H, Andressen | International journal of molecul | 10.3390/ij | 22 | 6 | |
| 33801158 | 2021 | Involvement of Bcl-xL in Neuronal Function and Devel | Bas J, Nguyen T, Gillet G | International journal of molecul | 10.3390/ij | 22 | 6 | |
| 33766226 | 2021 | [Insulin-like growth factor 1 (IGF-1) promotes phagocy | Zhai L, Chen X, Lu S, Yang D, Li W | Xi bao yu fen zi mian yi xue za zl | | 37 | 3 | 199-204 |
| 33765252 | 2021 | Neurospheres: a potential in vitro model for the study | da Silva Siqueira L, Majolo F, da | Molecular biology reports | 10.1007/s | 48 | 4 | 3649-3663 |
| 33734615 | 2021 | Brain imaging features of children with Hoyeraal-Hreid | Zhang MJ, Cao YX, Wu HY, Li HH | Brain and behavior | 10.1002/b | 11 | 5 | e02079 |
| 33727946 | 2021 | The Neuroprotective Effect of Byu d Mar 25 in LPS-ind | Liu L, Zhang Y, Tang L, Zhong H, | Evidence-based complementary | 10.1155/2 | 2021 | | 8879014 |
| 33722788 | 2021 | Berberine-loaded M2 macrophage-derived exosomes | Gao ZS, Zhang CJ, Xia N, Tian H, | Acta biomaterialia | 10.1016/j | 126 | | 211-223 |
| 33705794 | 2021 | Adult astrocytes from reptiles are resistant to proinfla | Du N, Li H, Sun C, He B, Yang T, S | The Journal of biological chemis | 10.1016/j | 296 | | 100527 |
| 33679718 | 2020 | Different Functions of Recombinantly Expressed Dom | Bijelić D, Adžić M, Perić M, Jakov | Frontiers in immunology | 10.3389/fi | 11 | | 624612 |
| 33677027 | 2021 | Early life stress exposure worsens adult remote micro | Catale C, Bisicchia E, Carola V, Vi | Brain, behavior, and immunity | 10.1016/j | 94 | | 89-103 |
| 33670341 | 2021 | Linear Skin Defects with Multiple Congenital Anomalii | Indrieri A, Franco B | Genes | 10.3390/g | 12 | 2 | |

CNS - 6757 Abstracts

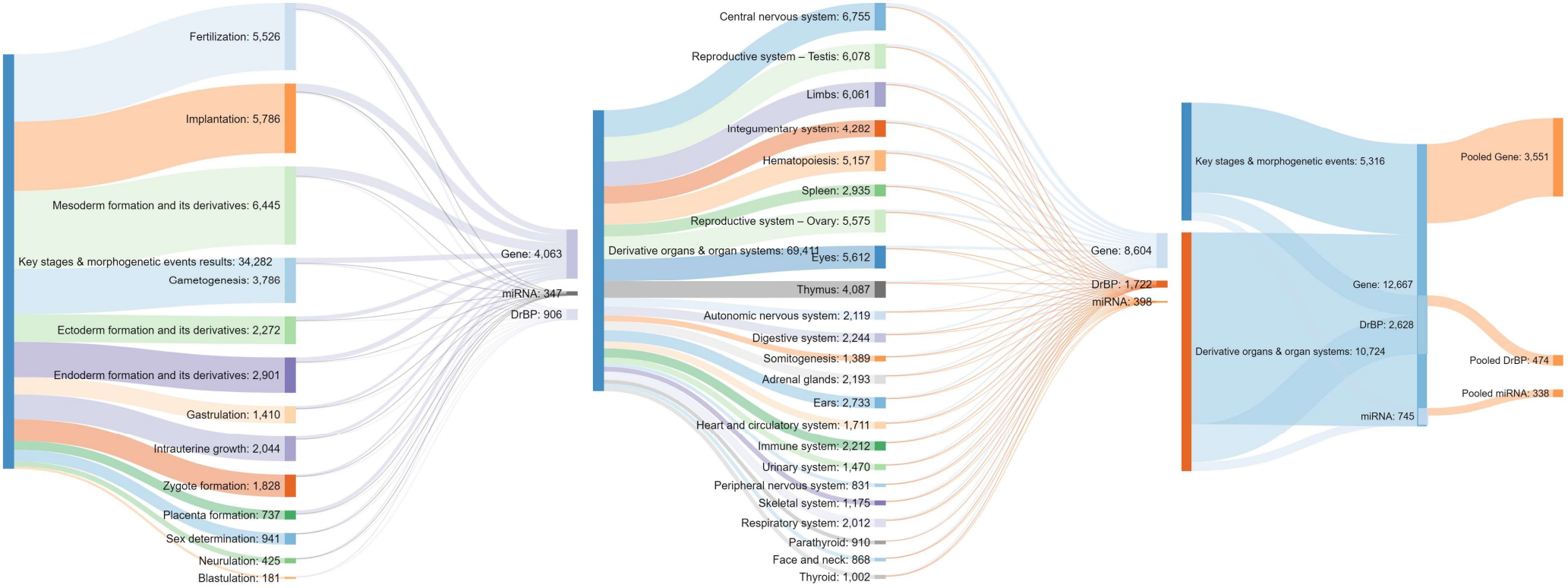
| | A | B | C |
|---|---|---|---|
| 1 | Gene symbol | Name | HitCount |
| 2 | GFAP | glial fibrillary acidic protein | 554 |
| 3 | SHH | sonic hedgehog | 505 |
| 4 | WNT1 | Wnt family member 1 | 441 |
| 5 | BDNF | brain derived neurotrophic factor | 379 |
| 6 | AQP1 | aquaporin 1 (Colton blood group) | 360 |
| 7 | NES | nestin | 346 |
| 8 | FGF2 | fibroblast growth factor 2 | 345 |
| 9 | IGF1 | insulin like growth factor 1 | 341 |
| 10 | GNRH1 | gonadotropin releasing hormone 1 | 334 |
| 11 | TH | tyrosine hydroxylase | 329 |
| 12 | NGF | nerve growth factor | 327 |
| 13 | CSPG4 | chondroitin sulfate proteoglycan 4 | 295 |
| 14 | MBP | myelin basic protein | 294 |
| 15 | PAX6 | paired box 6 | 288 |
| 16 | TGFB1 | transforming growth factor beta 1 | 267 |
| 17 | EGF | epidermal growth factor | 232 |
| 18 | TP53 | tumor protein p53 | 193 |
| 19 | INS | insulin | 189 |
| 20 | INSR | insulin receptor | 186 |
| 21 | NCAM1 | neural cell adhesion molecule 1 | 182 |
| 22 | TNF | tumor necrosis factor | 180 |
| 23 | CDKN2A | cyclin dependent kinase inhibitor 2A | 176 |
| 24 | APP | amyloid beta precursor protein | 173 |
| 25 | TNC | tenascin C | 166 |
| 26 | OLIG2 | oligodendrocyte transcription factor 2 | 163 |
| 27 | SOX2 | SRY-box 2 | 163 |
| 28 | CTNNB1 | catenin beta 1 | 158 |
| 29 | IL6 | interleukin 6 | 154 |
| 30 | RTN4 | reticulon 4 | 142 |
| 31 | VIP | vasoactive intestinal peptide | 142 |

902 genes




Human Phenotype Ontology

# Pooled List of DARS biomarkers

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https://doi.org/10.3389/ftox.2022.838466

# Pooled List of DARS biomarkers

## 3551 DARS Genes

| | A | B | C |
|---|---|---|---|
| 1 | Gene symbol | Name | HitCount |
| 2 | CGA | glycoprotein hormones, alpha polypeptide | 11924 |
| 3 | SHH | sonic hedgehog | 6622 |
| 4 | WNT1 | Wnt family member 1 | 6428 |
| 5 | TGFB1 | transforming growth factor beta 1 | 6056 |
| 6 | IGF1 | insulin like growth factor 1 | 4556 |
| 7 | INS | insulin | 4395 |
| 8 | GNRH1 | gonadotropin releasing hormone 1 | 3943 |
| 9 | CTNNB1 | catenin beta 1 | 3912 |
| 10 | VEGFA | vascular endothelial growth factor A | 3777 |
| 11 | SRY | sex determining region Y | 3479 |
| 12 | POMC | proopiomelanocortin | 3454 |
| 13 | EGF | epidermal growth factor | 3396 |
| 14 | KIT | KIT proto-oncogene receptor tyrosine kinase | 3380 |
| 15 | POU5F1 | POU class 5 homeobox 1 | 3307 |
| 16 | CD4 | CD4 molecule | 3152 |
| 17 | PAX6 | paired box 6 | 3124 |
| 18 | LIF | LIF, interleukin 6 family cytokine | 3070 |
| 19 | BMP4 | bone morphogenetic protein 4 | 3027 |
| 20 | CD34 | CD34 molecule | 3027 |
| 21 | ESR1 | estrogen receptor 1 | 2946 |
| 22 | SOX9 | SRY-box 9 | 2649 |
| 23 | TNF | tumor necrosis factor | 2620 |
| 24 | TP53 | tumor protein p53 | 2520 |
| 25 | PTHLH | parathyroid hormone like hormone | 2436 |
| 26 | AMH | anti-Mullerian hormone | 2431 |
| 27 | NR5A1 | nuclear receptor subfamily 5 group A member 1 | 2341 |
| 28 | IGF2 | insulin like growth factor 2 | 2290 |
| 29 | LEP | leptin | 2058 |
| 30 | AKT1 | AKT serine/threonine kinase 1 | 1977 |
| 31 | FGF2 | fibroblast growth factor 2 | 1912 |

## 474 DARS Biological Processes

| | A | B | C |
|---|---|---|---|
| 1 | HitID | Name | HitCount |
| 2 | GO_0023052 | signaling | 21733 |
| 3 | GO_0007049 | cell cycle | 3228 |
| 4 | GO_0008219 | cell death | 2514 |
| 5 | GO_0006306 | DNA methylation | 2440 |
| 6 | GO_0001837 | epithelial to mesenchymal transition | 2422 |
| 7 | GO_0016310 | phosphorylation | 2372 |
| 8 | GO_0030154 | cell differentiation | 2262 |
| 9 | GO_0048468 | cell development | 2248 |
| 10 | GO_0001556 | oocyte maturation | 1973 |
| 11 | GO_0022008 | neurogenesis | 1567 |
| 12 | GO_0006412 | translation | 1541 |
| 13 | NCIT_C17741 | Oxidative Stress | 1449 |
| 14 | GO_0048477 | oogenesis | 1243 |
| 15 | GO_0001171 | reverse transcription | 1235 |
| 16 | GO_0016477 | cell migration | 1209 |
| 17 | GO_0007165 | signal transduction | 1146 |
| 18 | GO_0030218 | erythrocyte differentiation | 1134 |
| 19 | GO_0016049 | cell growth | 1041 |
| 20 | GO_0006914 | autophagy | 1021 |

## 338 DARS miRNA

| | A | B |
|---|---|---|
| 1 | HitID | HitCount |
| 2 | LET7 | 155 |
| 3 | MIR-21 | 127 |
| 4 | MIR-145 | 85 |
| 5 | MIR-125B | 73 |
| 6 | MIR-17 | 73 |
| 7 | MIR-17-92 | 65 |
| 8 | MIR-1 | 64 |
| 9 | MIR-302 | 62 |
| 10 | MIR-124 | 56 |
| 11 | MIR-29B | 55 |
| 12 | MIR-34C | 52 |
| 13 | MIR-34A | 51 |
| 14 | MIR-130B | 51 |
| 15 | MIR-375 | 49 |
| 16 | MIR-200C | 46 |
| 17 | MIR-24 | 45 |
| 18 | MIR-29A | 44 |
| 19 | MIR-429 | 41 |
| 20 | MIR-223 | 41 |

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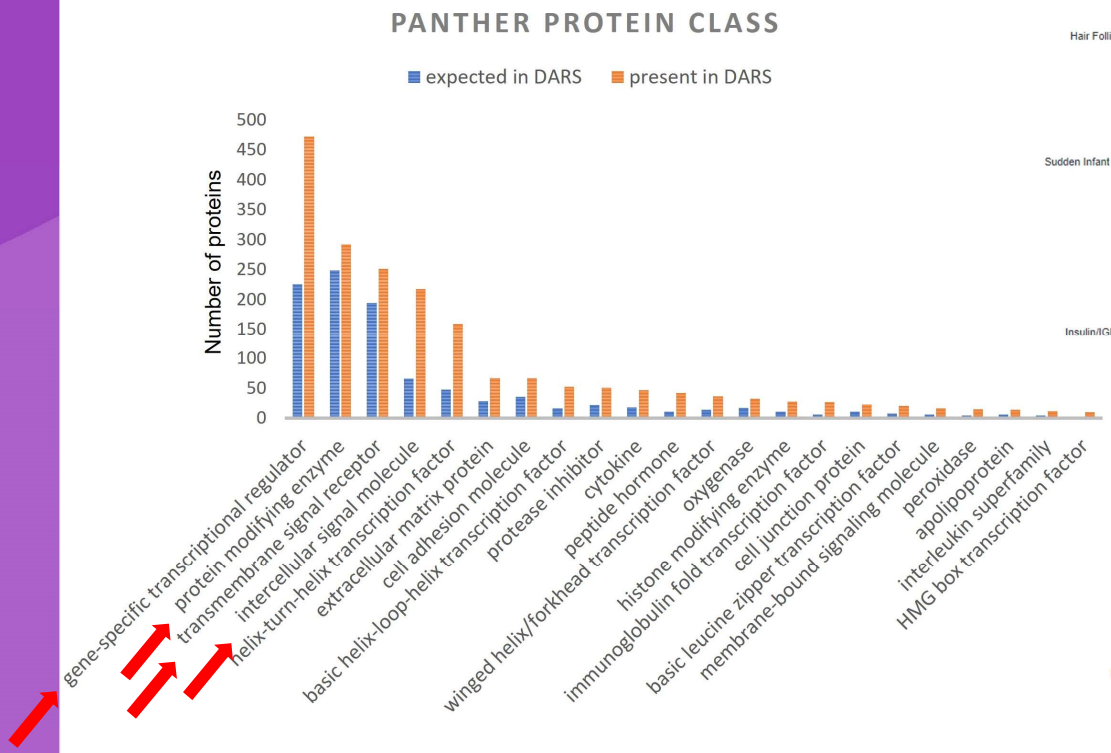
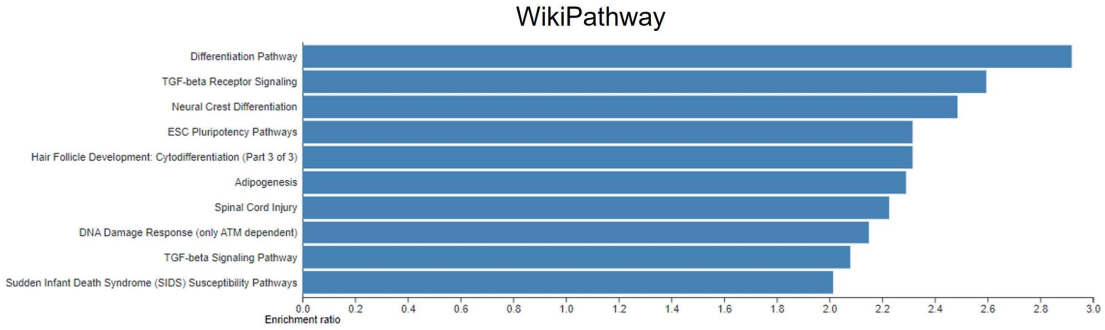
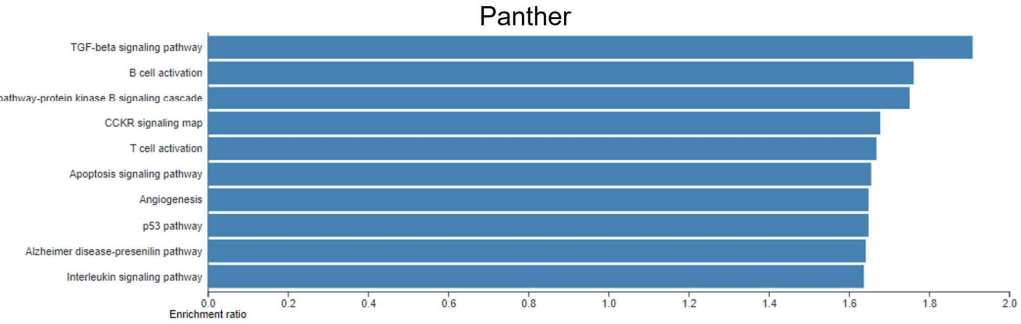
Rajagopal et al., Front. Toxicol., 07 March 2022
https://doi.org/10.3389/ftox.2022.838466

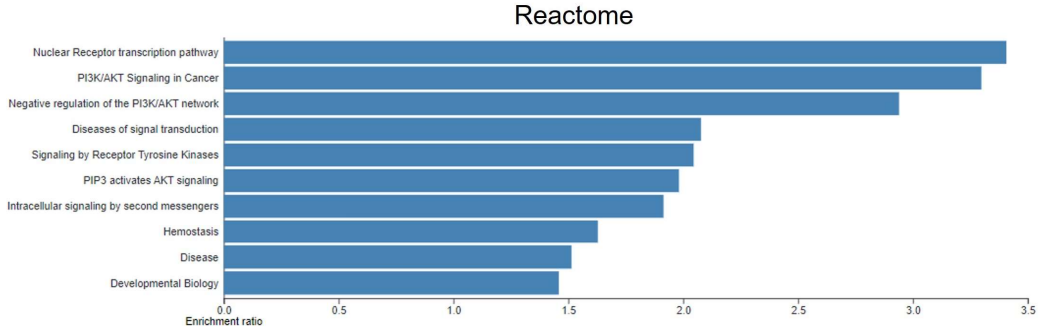
Rajagopal et al., Front. Toxicol., 2022

# Protein classes and signalling pathways over-represented in DARS biomarkers



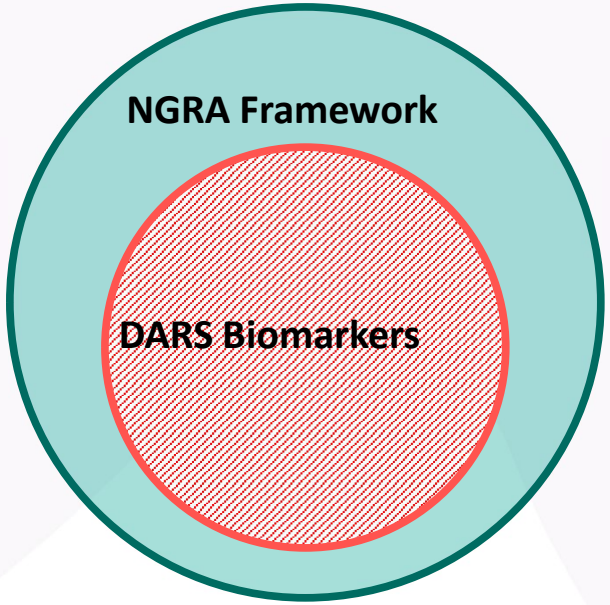




**DARS BP:** Signalling, cell cycle, cell death, DNA methylation, epithelial to mesenchymal transition, phosphorylation, cell differentiation, cell development, oocyte maturation and neurogenesis

**DARS miRNA:** LET-7, MIR-21 and MIR-145

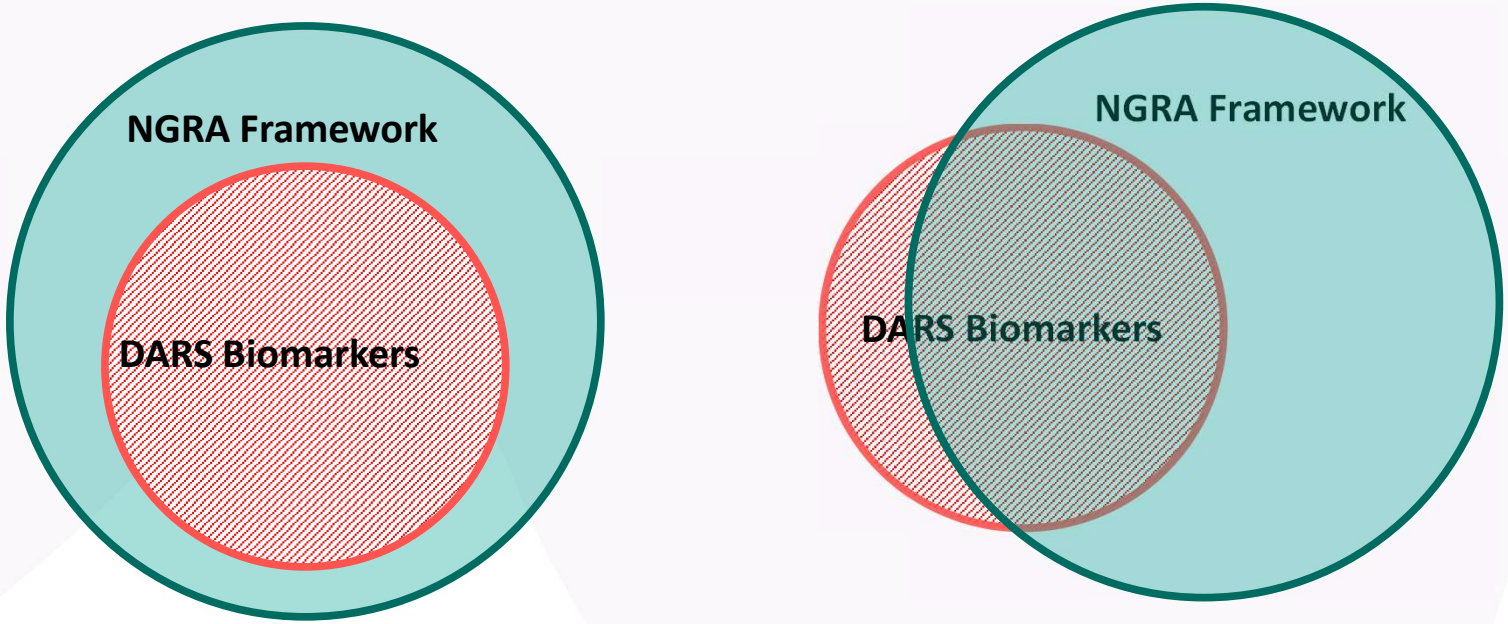
Rajagopal et al., Front. Toxicol., 2022

# Biological coverage of the DARS biomarkers by the DART NGRA




Expectation

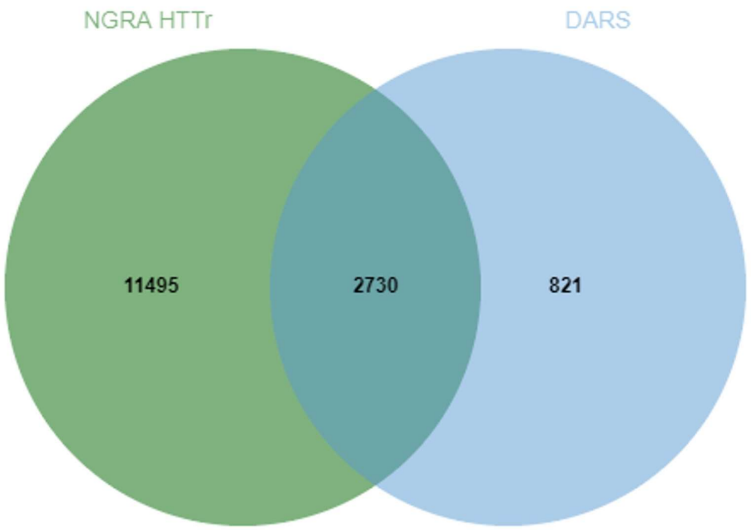
# Biological coverage of the DARS biomarkers by the DART NGRA

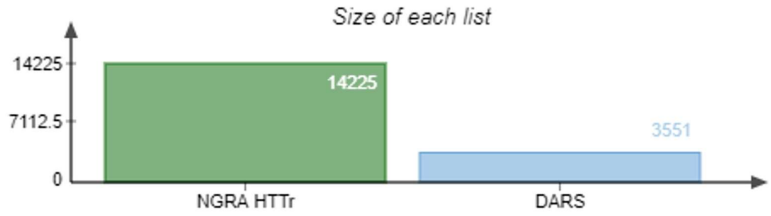



Expectation *versus* Reality

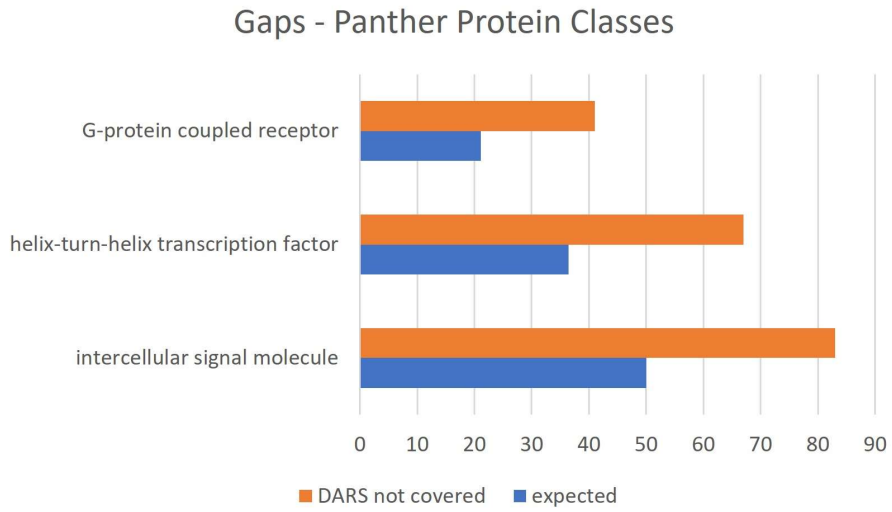
# Biological coverage of the DARS biomarkers by the DART NGRA

*Coverage*




*Gaps*




- 41 GPCRs (6 present in IPP)
- 60 HTH transcription factors (mainly homeobox transcription factors)
- Intercellular signal molecules (chemokines, cytokines, growth factors, neurotropic factors, peptide hormones)

Rajagopal et al., Front. Toxicol., 07 March 2022
https://doi.org/10.3389/ftox.2022.838466

Rajagopal et al., Front. Toxicol., 2022

# Biological coverage of the DARS biomarkers by the DART NGRA

## Coverage

General cellular & functional processes- cell survival, cytotoxicity

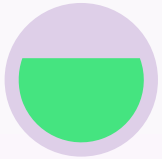
Receptor or enzyme activity- IPP covers about 13%

Signalling pathways- DARS genes

Specific differentiation- ReproTracker®

Specific cellular processes- devTOXQuickPredict™

Cellular stress- Cell stress panel assays

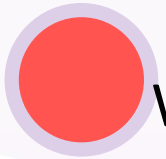


## Gaps

Specific cellular processes- E.g. cytokine secretion or myelination or androgen biosynthesis

Specific functional processes- E.g. sperm motility or axon guidance or lymphocyte migration

Receptor or enzyme activity- E.g. receptor tyrosine kinases or receptor serine/threonine kinases or GPCRs



## Weight of evidence

Integrating data from different NAMs

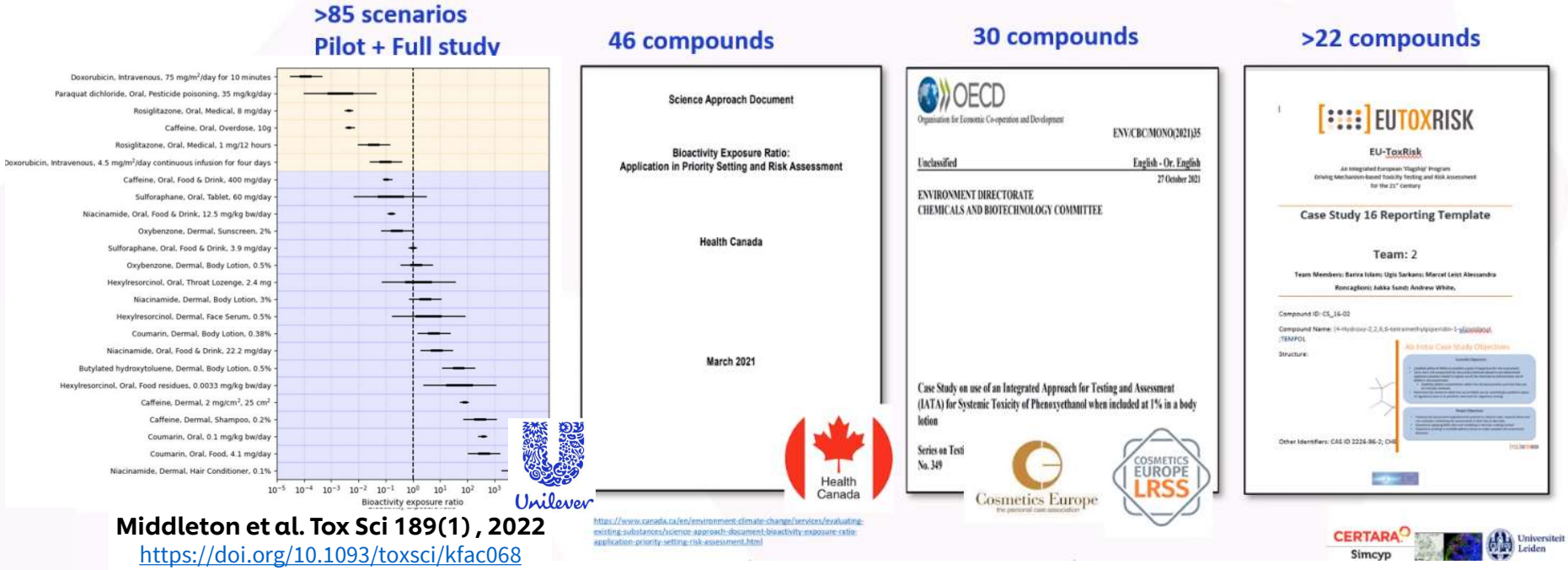
MIE -> KEs -> Adverse effects E.g. ADORA 2A binding, inhibition of PI3Kinase-AKT signalling, T cell development

Rajagopal et al., Front. Toxicol., 2022

# Case studies - flexible and fit for purpose validation of

# NGRA DART

# How PODs from NAMs compare to PODs coming from animal studies




**Middleton et al. Tox Sci 189(1) , 2022**
https://doi.org/10.1093/toxsci/kfac068

***Health Canada:*** ***"The purpose of this SciAD is to demonstrate that PODBioactivity can provide a lower bound estimate for in vivo based effect levels derived from oral repeat-dose, developmental, and reproductive studies considered under the Chemicals Management Plan (CMP). The PODBioactivity was lower than the lowest PODTraditional cited in the risk assessment for 43 of the 46 of the chemicals examined. These findings are consistent with other published case studies using similar methodology. This was done to demonstrate confidence in using in vitro bioactivity as a surrogate lower bound estimate of in vivo adverse effect levels."*** **From Health Canada**

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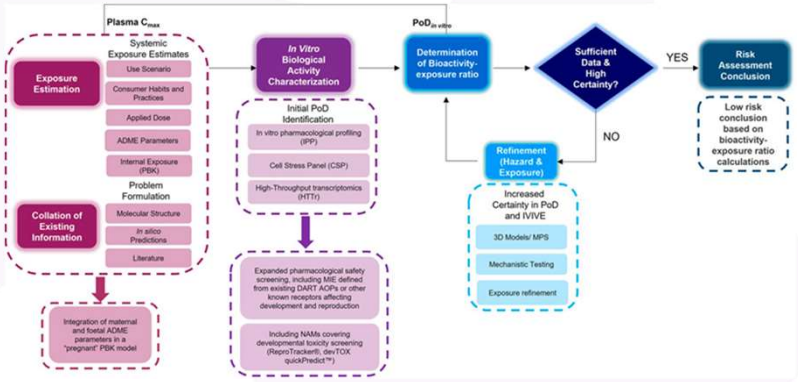
# Next Steps

- Evaluation of DART NGRA across many chemistries
- ReproTracker assay
  - Development and evaluation of an osteoblast differentiation protocol




Rajagopal et al., Front. Toxicol., 2022

- Identification and filling of existing gaps (PBK modelling e.g placenta transfer measurements, DNT, DIT, endocrine disruptors, multigenerational effects, studying epigenetics in germline development, advanced cell models for refinement)
- CLP/GHS hazard classification
- Use for regulatory purposes (REACH submission)

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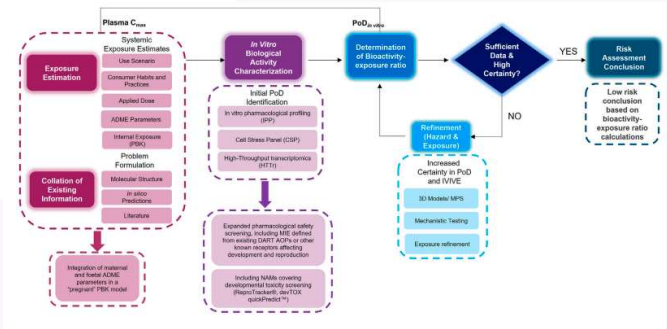
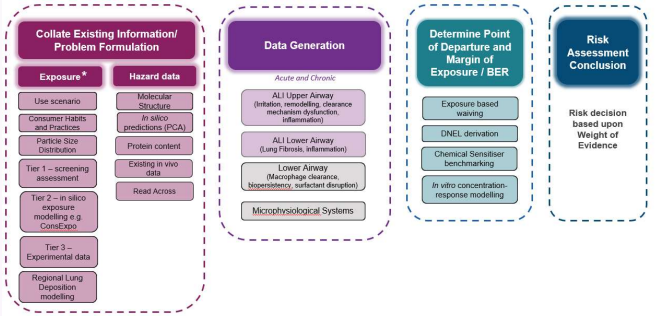
# Unilever NGRA frameworks for Consumer Safety decisions

## Developmental & Reproductive




Rajagopal et al (2022) *Frontiers in Toxicology*, doi: 10.3389/ftox.2022.838466

## Inhalation




## Ongoing Evaluations

EPA United States Environmental Protection Agency

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**EPA and Unilever Announce Major Research Collaboration to Advance Non-animal Approaches for Chemical Risk Assessment**

August 19, 2021

**Contact Information**
EPA Press Office (press@epa.gov)

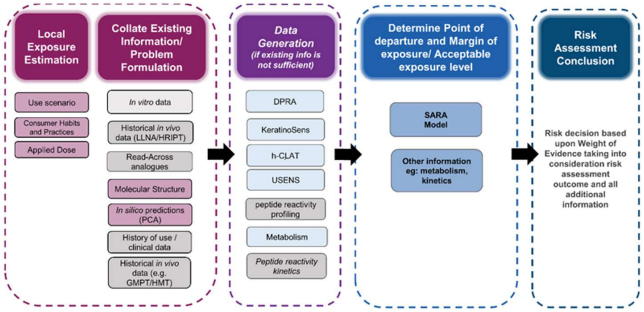
**WASHINGTON** – Today, the U.S. Environmental Protection Agency (EPA) and Unilever announced a collaborative agreement to explore better ways to assess chemical risks associated with consumer products. This agreement builds on prior cooperation between EPA and Unilever regarding New Approach Methods (NAMs), which are a promising alternative to conventional toxicity testing that are intended to reduce reliance on the use of animals.

EPA and Unilever have been jointly evaluating and using NAMs since 2015. This collaboration is helping EPA implement its New Approach Methods Work Plan and is the foundation for new efforts to demonstrate that these novel approaches can help decision makers better protect consumers, workers and the environment.

"EPA is a pioneer in developing and applying NAMs to identify and quantify risks to human health, while reducing the use of animals in chemical toxicity testing," said **H. Christopher Frey, Deputy Assistant Administrator for Science Policy in EPA's Office of Research and Development**. "We are excited to continue the collaboration with Unilever, which enhances the robustness of our mutual research to demonstrate the use of NAMs."

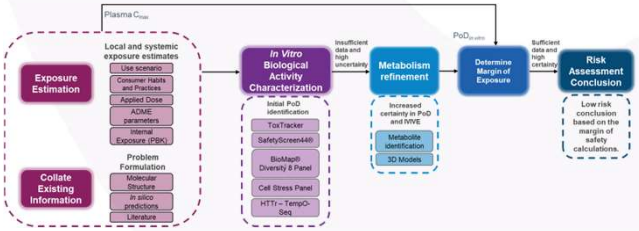
The new collaborative effort aims to establish a framework for the Next Generation of Risk Assessments based on NAMs. Such assessments are intended to quantify health risks to humans with sufficient scientific rigor to replace conventional animal-based methods and to support EPA's mission to protect human health and the environment.

## Skin Sensitisation




Reynolds et al (2021) *Reg Tox Pharmacol*, **127**, 105075

## Systemic




Baltazar et al (2020) *Toxicol Sci*, 176, 236-252

National Toxicology Program
U.S. Department of Health and Human Services

**NICEATM News** - 2021 Issue 25: May 27

**In this Newsletter:**

NICEATM to Collaborate with Unilever on Development of Predictive Model for Skin Sensitization

**NICEATM to Collaborate with Unilever on Development of Predictive Model for Skin Sensitization**

NICEATM has entered into an agreement with consumer products company Unilever to collaboratively test and further develop their Skin Allergy Risk Assessment (SARA) predictive model. SARA is a computational model that uses a variety of input data to estimate a probability that a chemical will cause an allergic skin reaction in humans. NICEATM will test the SARA model using a variety of chemical data sets, including chemicals of interest to U.S. and international regulatory agencies. NICEATM and Unilever will also work together to expand the SARA model to include data generated by NICEATM. The intent is to make the SARA model openly available for public use along with other NICEATM predictive models. Availability of the SARA model will help further reduce animal use for the endpoint of skin sensitization, and will improve upon existing efforts by providing points of departure for quantitative human risk assessment.

Information about other NICEATM projects to evaluate alternatives to animal use for skin sensitization is available at https://ntp.niehs.nih.gov/go/ACDtest.

Reference: Reynolds et al. Probabilistic prediction of human skin sensitizer potency for use in next generation risk assessment. Comput Toxiol 9:36-49. https://doi.org/10.1016/j.comtox.2018.10.004

Unilever

SEAC SAFETY & ENVIRONMENTAL ASSURANCE CENTRE
Scientific Excellence And Collaboration

OECD

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