

Profiling Developmental Toxicity of 387 Environmental Chemicals using EPA's Toxicity Reference Database (ToxRefDB)

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Disclaimer: views are those of the presenter and do not necessarily reflect Agency policy nor imply endorsement of software used here

INTRODUCTION

- ❖ ToxCast™ goal is to prioritize chemicals based on the biological pathways and cellular processes they perturb
- ❖ high-throughput screens (HTS) test the broad chemical landscape across multiple biological targets (assays)
- ❖ computational methods identify significant correlations between chemicals, assays, and effects
- ❖ predictive power depends upon building associations with multivariate endpoints in toxicity
- ❖ ultimately relies on structured data from high-quality *in vivo* studies available in a computable form

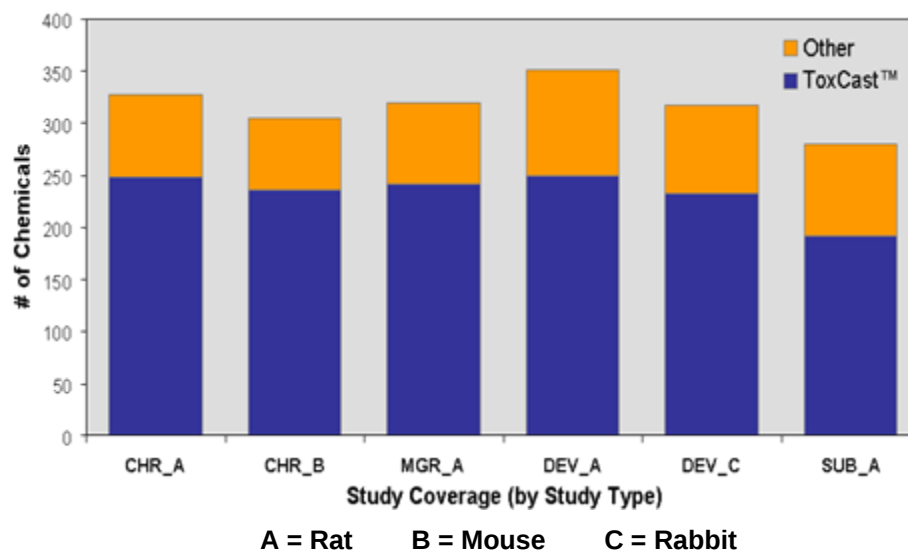
ToxRefDB



Martin et al. (2008) Environ Hlth Persp
doi:10.1289/ehp.0800074

Martin et al. (2009) Toxicol Sci
doi: 10.1093/toxsci/kfp080

Knudsen et al. (2009) Reprod Toxicol
doi: 10.1016/j.reprotox.2009.03.016



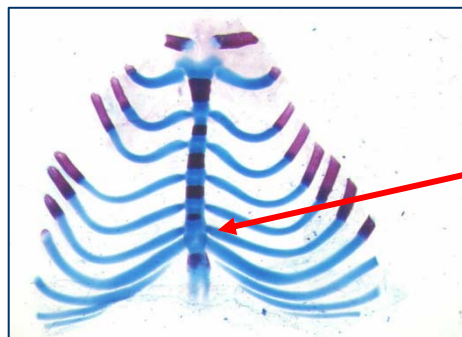
- ❖ **source data:** 2073 guideline studies for 480 chemicals, mostly pesticides and antimicrobials (>\$2B worth)
- ❖ **prenatal studies:** 751, mostly rat and rabbit, testing 387 chemicals (283 chemicals tested in both species)
- ❖ **annotation:** 988 terms for maternal and fetal effects based on enhanced *DevTox.org* lexicon
- ❖ **endpoints:** lowest effect levels for maternal (mLEL) and developmental (dLEL) parameters

www.epa.gov/ncct/toxrefdb/

Simple annotations



target: kidney
description: absent renal papilla
code: UG_REN_3.1060.5013



target: sternebra
description: incomplete ossification
code: SK_AXL_2.1099.5130



target: hindpaw
description: polydactyly (digit I)
code: SK_APP_2.1051.5234

images from www.DevTox.org

Complex annotation



www.DevTox.org

target: general
description: anasarca
code: GN_GRL_1.1043.5026

target: cranium
description: exencephaly
code: SK_CRN_1.1025.5101

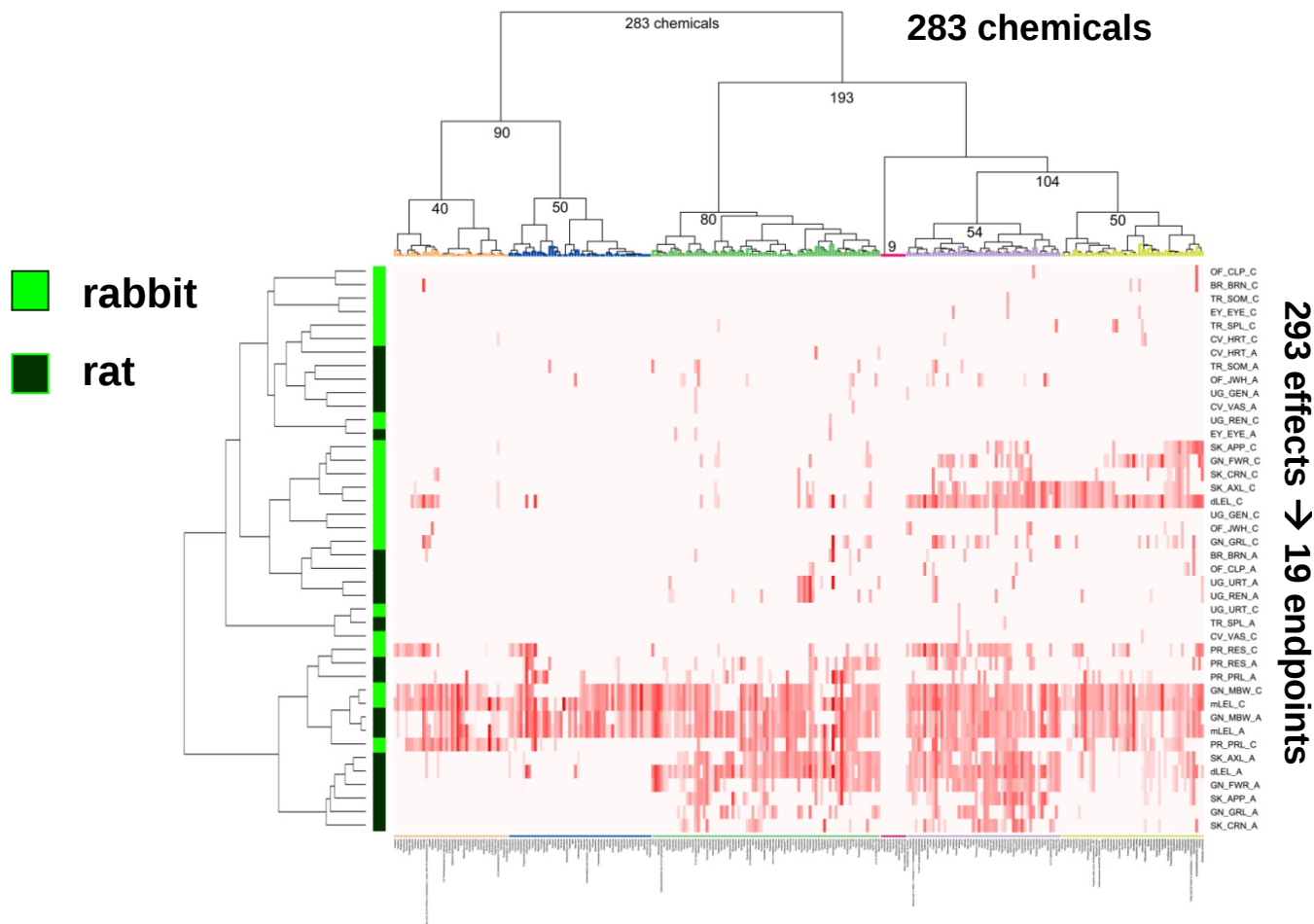
target: eye
description: open eye
code: NS_EYE_1.032.5162 (or 5187 or 5190)

target: face
description: short snout
code: OF_JWH_1.033.5206

ToxRefDB_DEV summary statistics

<i>ToxRefDB_3700</i> ¹	<i>rat</i>	<i>rabbit</i>	<i>ratio</i> ⁵	<i>normalized</i> ⁶	<i>species bias</i> ⁷
<i>A. Input source information</i>					
number of studies entered (MRID)	383	368	1.04	0.00	
> studies passing acceptability criteria ²	357	325	1.10	0.08	
number of chemicals represented (CASN)	372	320	1.16	0.16	
number of dose groups (mg/kg/day) represented	2469	2327	1.06	0.03	
> dose groups by oral administration ³	2463	2307	1.07	0.04	
<i>B. Output endpoint effects</i>					
number of dose-effect groups recorded ⁴	5592	4749	1.18	0.15	
> maternal endpoint effects (pregnancy)	2429	2462	0.99	-0.10	Rabbit
>> reduced maternal weight gain	596	482	1.24	0.23	
>> resorptions / fetal loss	262	498	0.53	-1.00	Rabbit
> fetal endpoint effects (developmental)	1588	716	2.22	1.06	Rat
>> fetal weight reduction	182	95	1.92	0.86	Rat
>> developmental defects	1383	611	2.26	1.09	Rat

Chemical-endpoint relationships clustered by categorical LELs (cLEL)



Species dimorphism

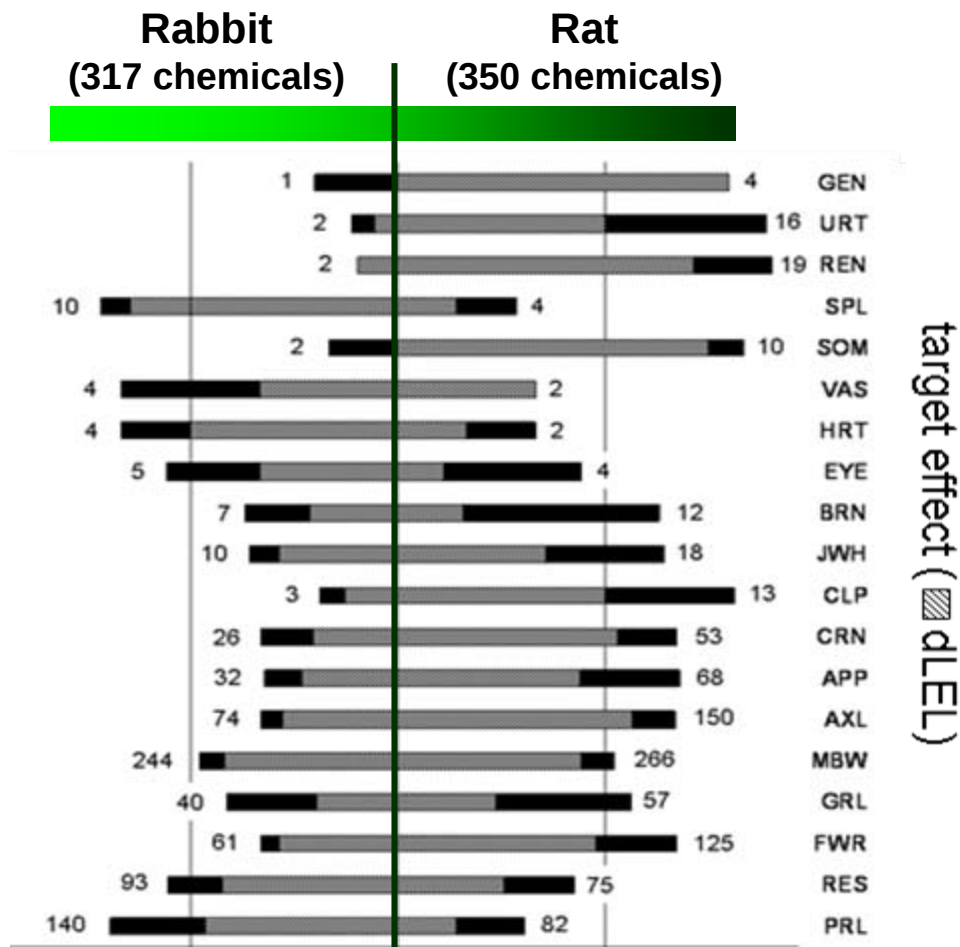
major target systems:

Rabbit

neurosensory and cardiovascular

Rat

urogenital and skeletal

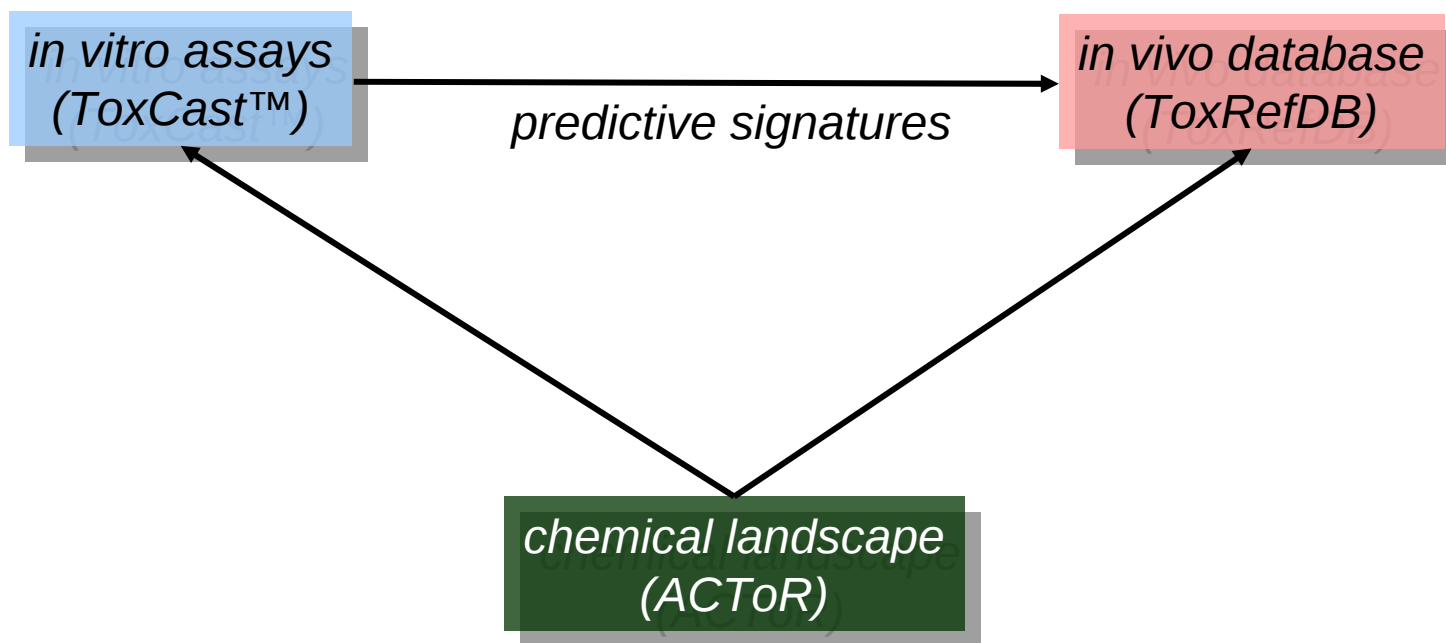


*SOURCE: Knudsen et al. (2009) Reproductive Toxicology
(in press) DOI 10.1016/j.reprotox.2009.03.016*

Developmental profiling

- ❖ 53 of 283 chemicals (18.7%) were specific (no maternal toxicity) or sensitive ($dLEL < mLEL$) for development
- ❖ sensitivity-specificity varies by species and system when expressed on an administered dose (mg/kg/day) basis:
 - FWR and skeletal defects (rat > rabbit)
 - pregnancy/fetal loss (rat < rabbit)
 - urogenital defects (rat > rabbit)
 - CNS defects (rat < rabbit)

Predictive modeling



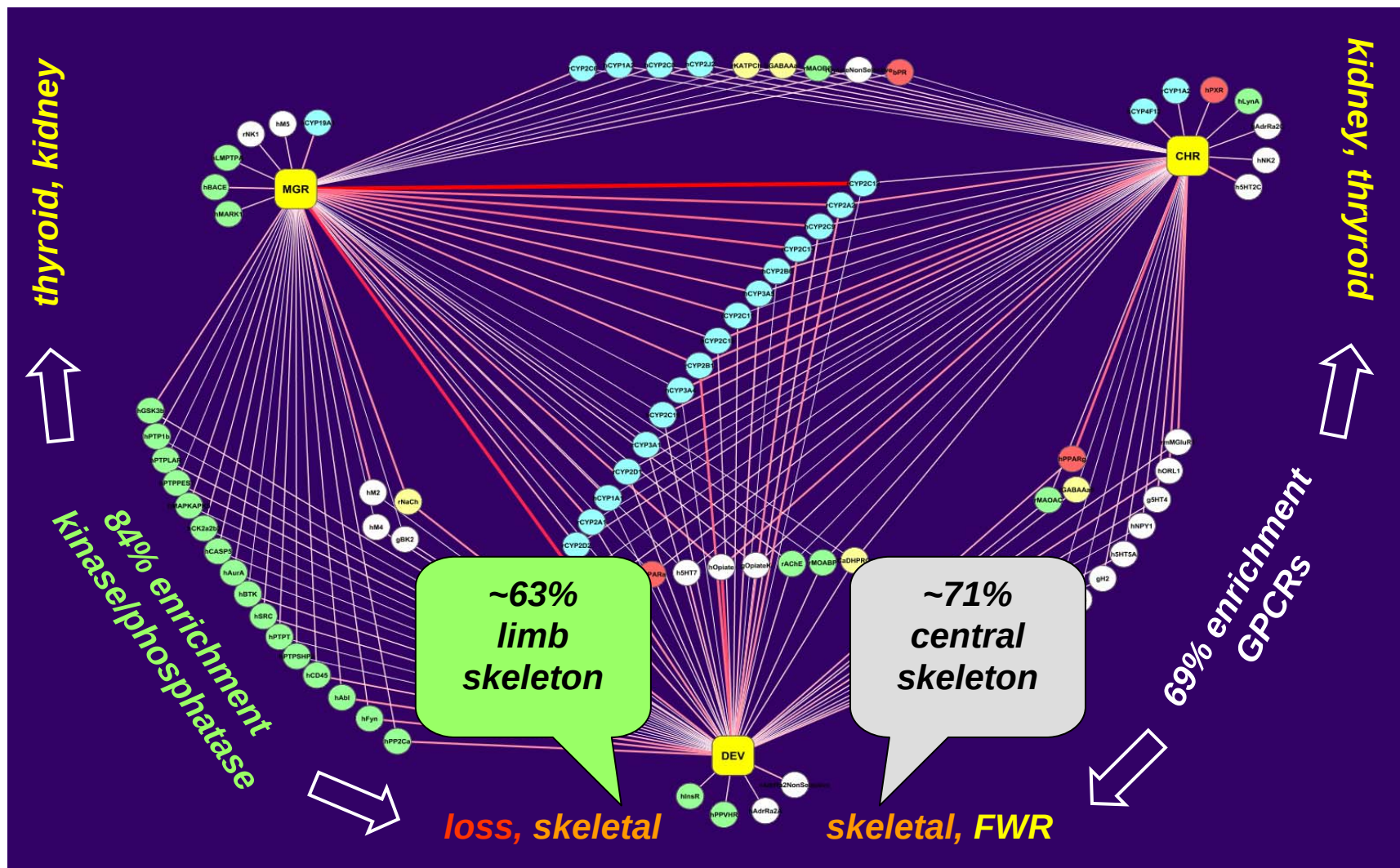
Biochemical HTS screen

- ❖ 239 functional targets (NovaScreen):
 - 79 G-protein coupled receptors (GPCRs)
 - 32 cytochrome P450 mono-oxygenase activities (CYPs)
 - 82 effector enzymes (kinases, phosphatases, proteases)
 - 15 nuclear receptors (NRs)
 - 31 other (ion channels, transporters, receptors)

- ❖ target protein sources:
 - 146 human, 67 rat, 26 other mammalian species
 - includes 26 assay orthologs

Significant assay-endpoint associations

239 *in vitro* assays x 76 *in vivo* endpoints



SUMMARY: ToxRefDB

STRENGTHS

- puts >\$2B worth of legacy data into a computable form
- unique effects scored by LEL (mLELs, dLELs, cLELs)
- enables comparison of endpoint occurrence between species
- broad biological coverage (DEV, MGR, CHR)
- *in vivo* database for anchoring effects from *in vitro* assays
- searchable database will be public (www.epa.gov/ncct/toxrefdb/)

LIMITATIONS

- endpoints represented in the database as independent features
- differential effects may reflect nuances in study design
- not all ToxCast™ chemicals represented in ToxRefDB
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Acknowledgements



Virtual Embryo

Tom Knudsen (NCCT)

Amar Singh (LHM)

Michael Rountree (SSC)

Richard Spencer (EMVL)

Rob DeWoskin (NCEA)

Nisha Sipes (September)

Sid Hunter (NHEERL)

ToxCast™ (NCCT)

Bob Kavlock

David Dix

Keith Houck

Richard Judson

Woody Setzer

Matt Martin

Ann Richard

David Reif

Holly Mortensen