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Characteristics of the ToxRefDB *In Vivo* Datasets from Chronic, Reproductive and Developmental Assays

Matt Martin

ToxCast Data Analysis Summit : May 14-15 2009

http://www.epa.gov/ncct/toxrefdb

Office of Research and Development
National Center for Computational Toxicology

ToxRefDB Overview

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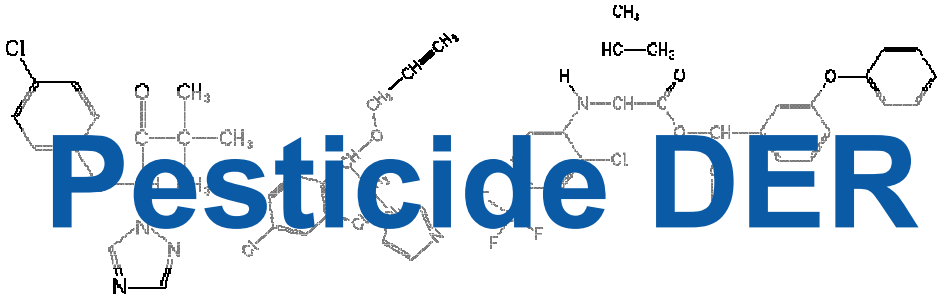
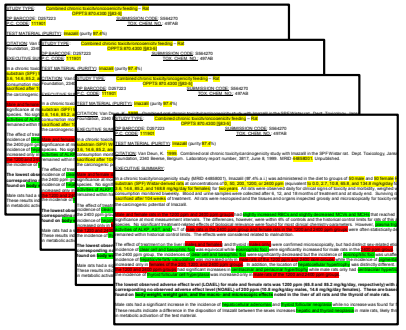
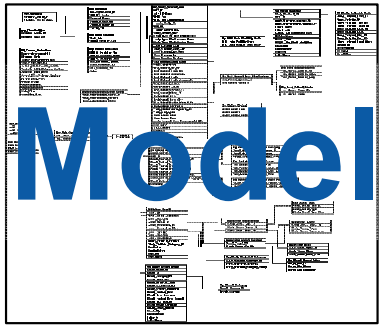
SOURCE DATA



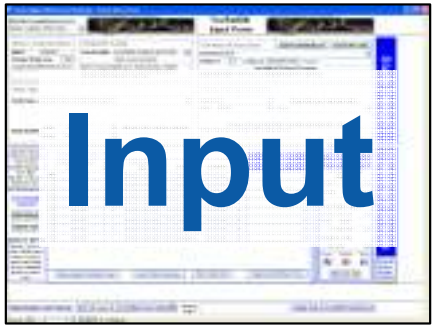
Pesticide DER



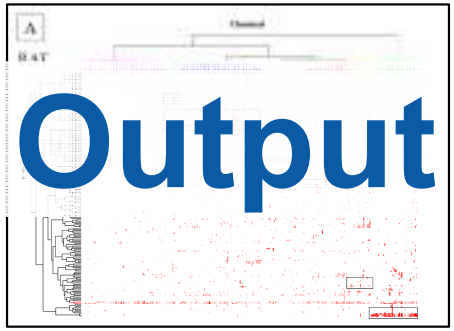
DATABASE



Model

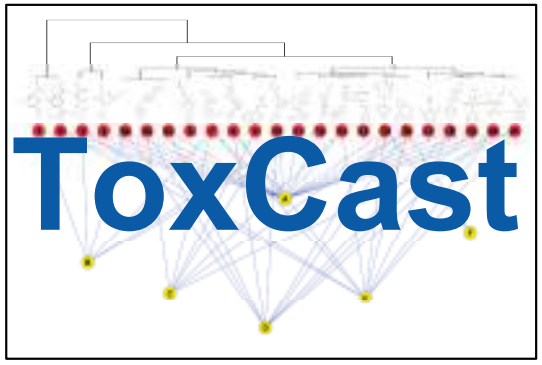


Input



Output

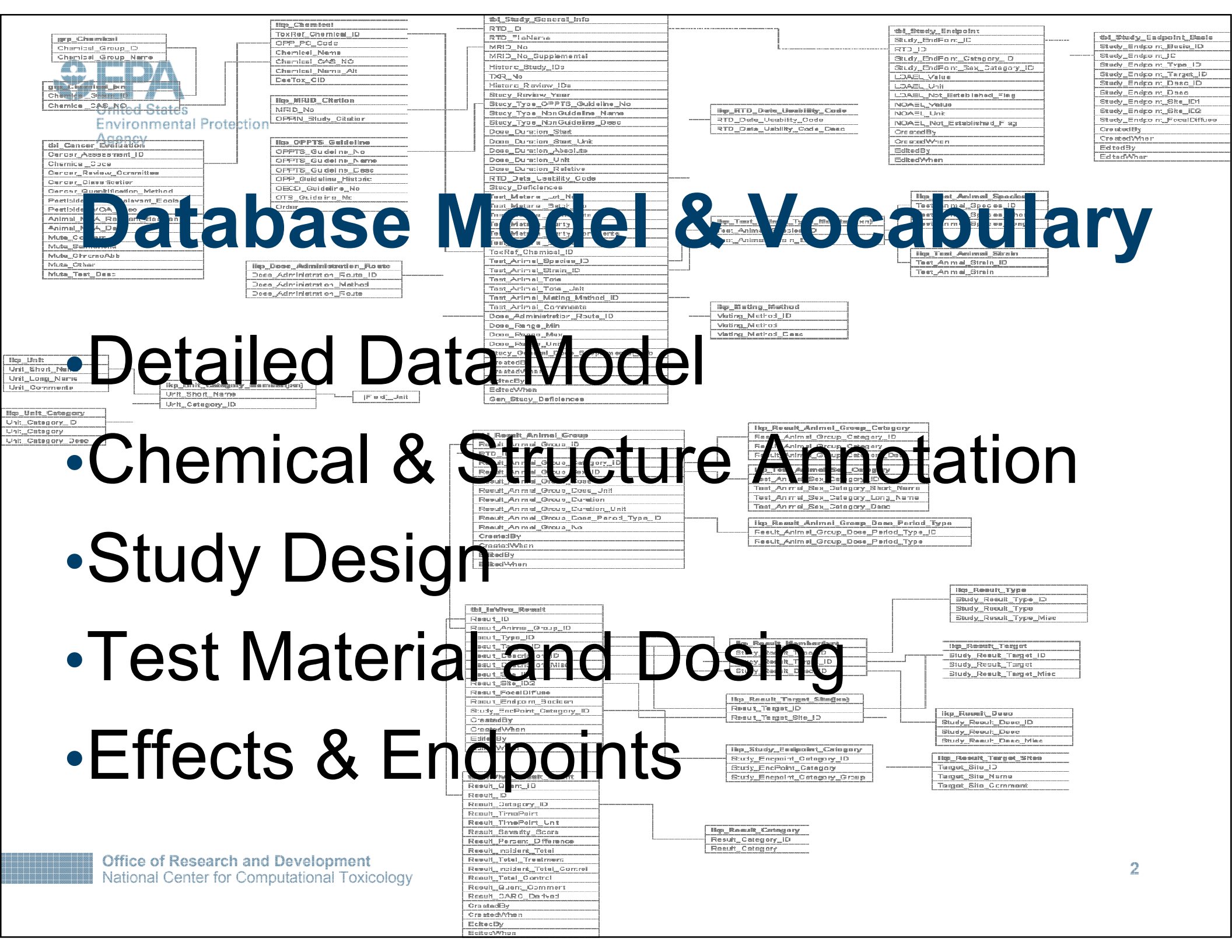
APPLICATION



ToxCast

Database Model & Vocabulary

- Detailed Data Model
- Chemical & Structure Annotation
- Study Design
- Test Material and Dosing
- Effects & Endpoints



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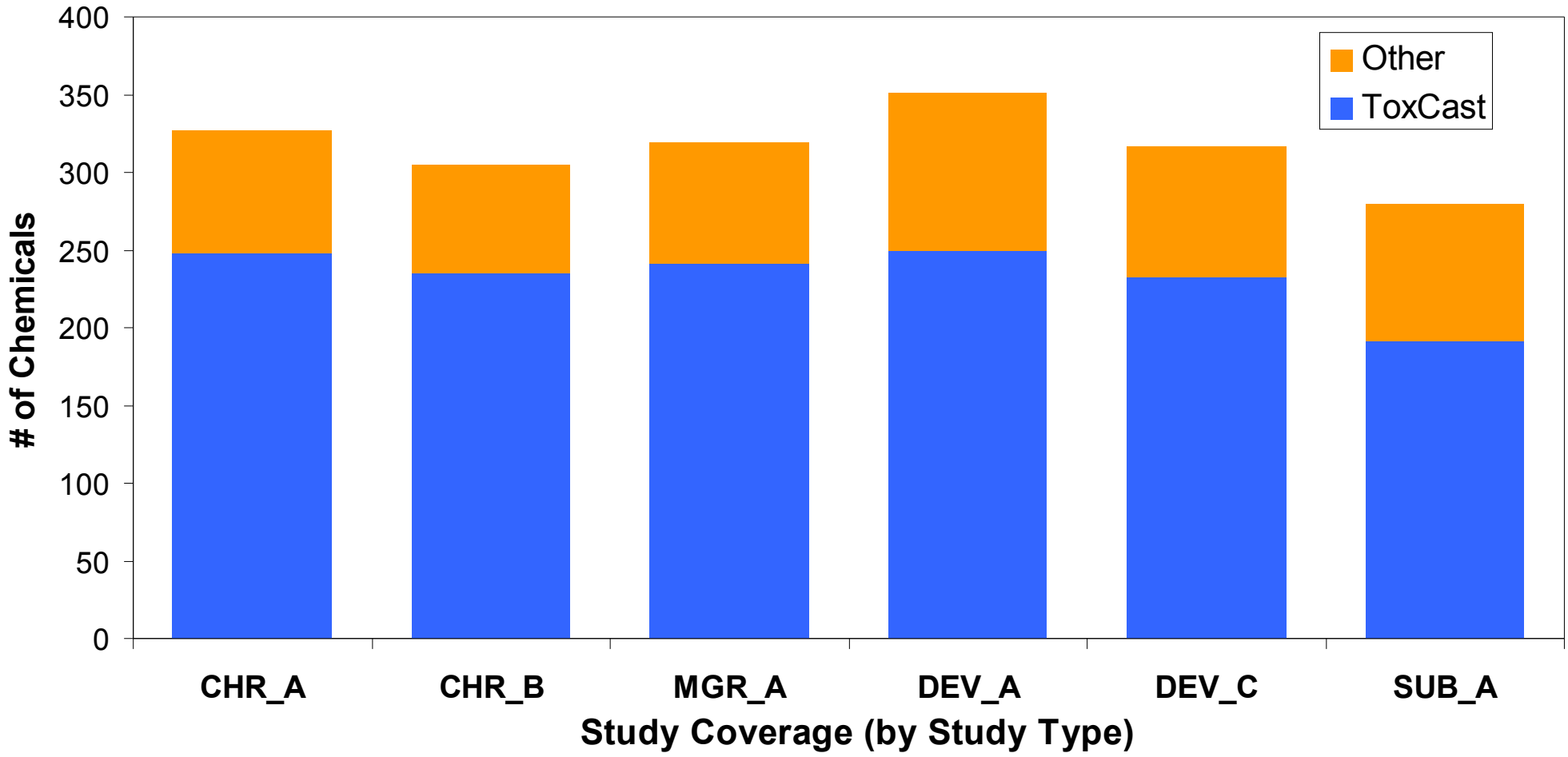
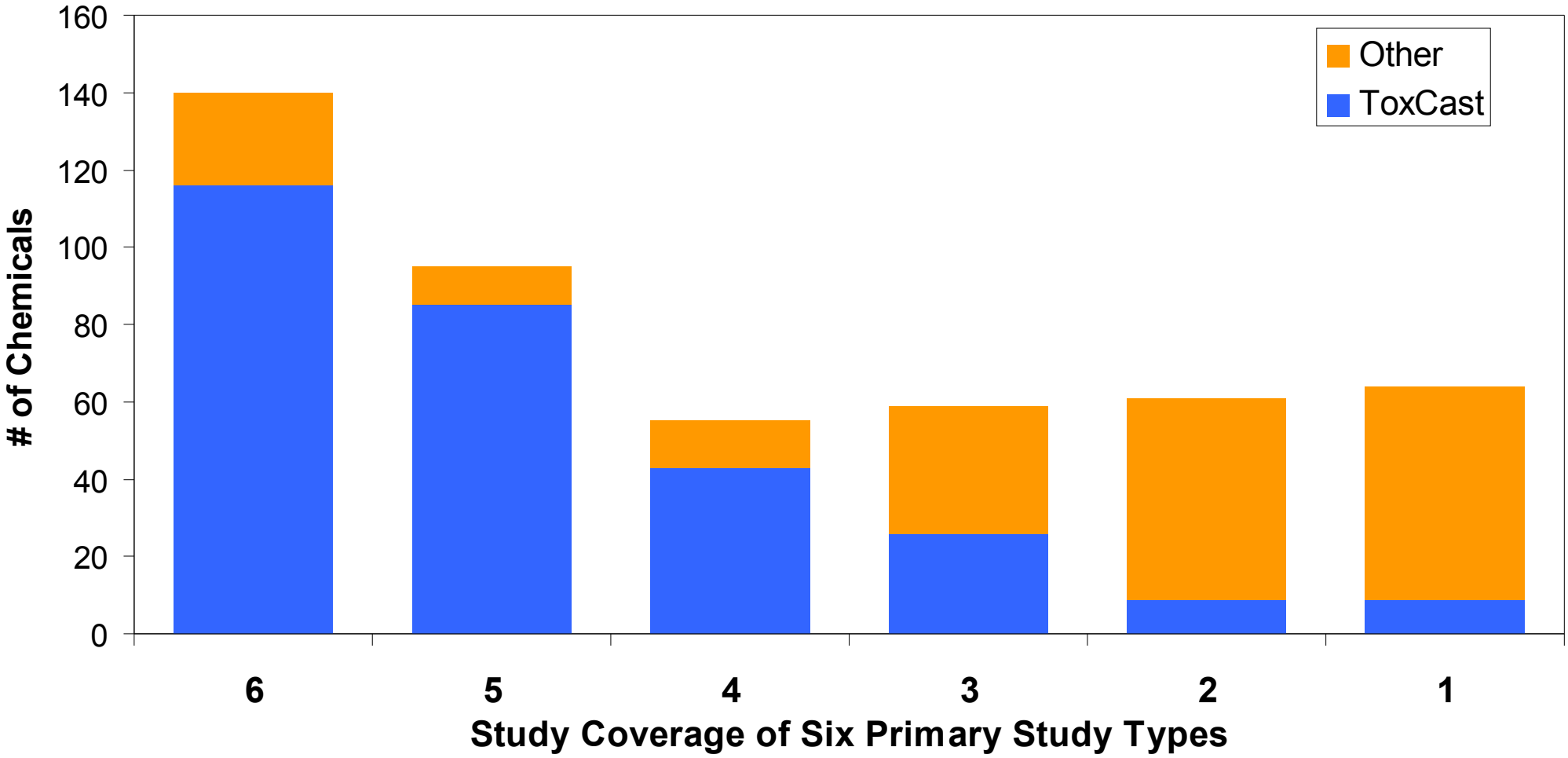
2073 Studies Entered For 480 Chemicals



CHR = Chronic/Cancer
MGR = Multigeneration Reproductive
DEV = Prenatal Developmental

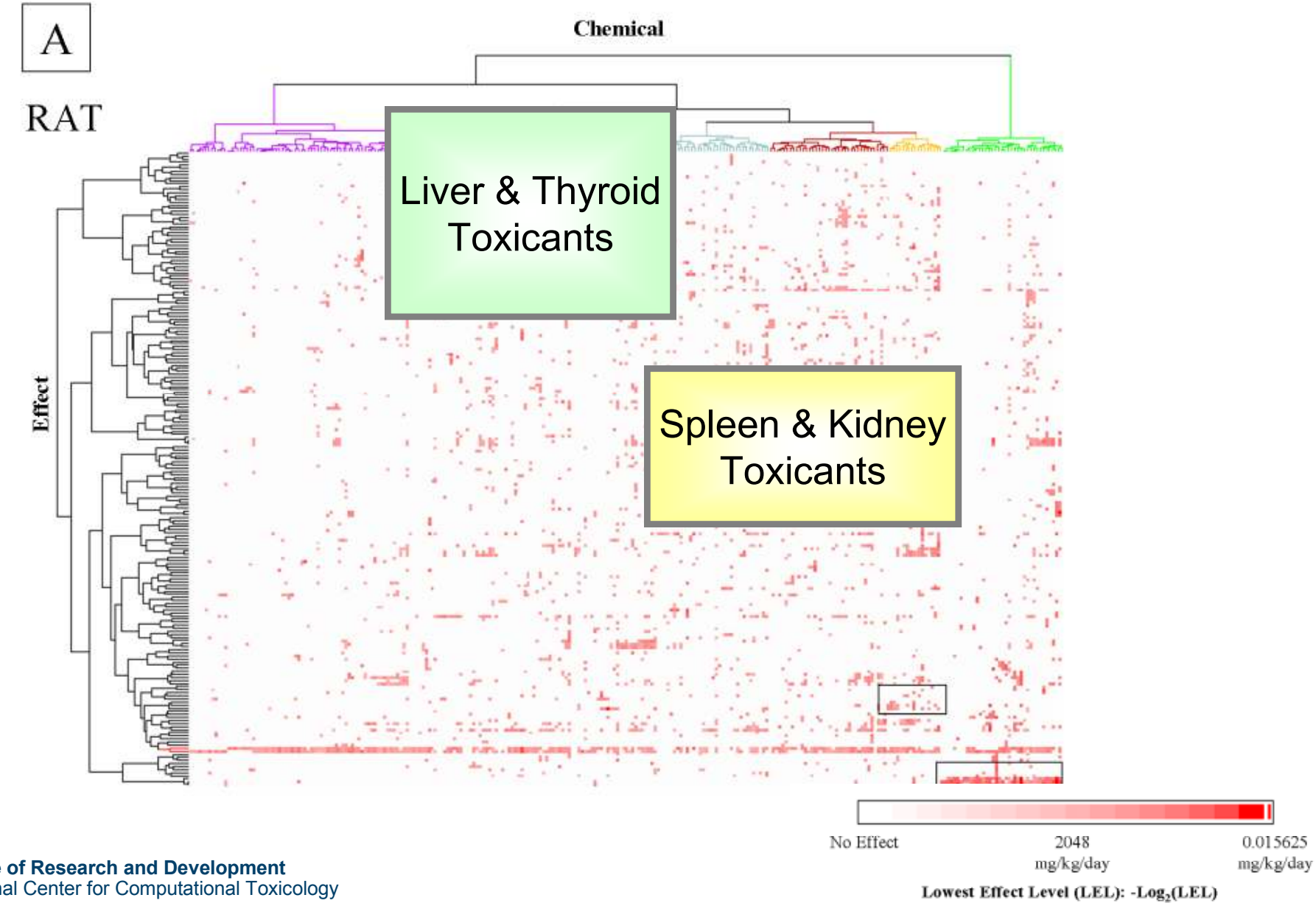
A = Rat
B = Mouse
C = Rabbit

Study Coverage



21 ToxCast Chemicals w/ No Studies

Chronic/Cancer Toxicity Profiling



http://www.ehponline.org/members/2008/0800074/0800074.pdf

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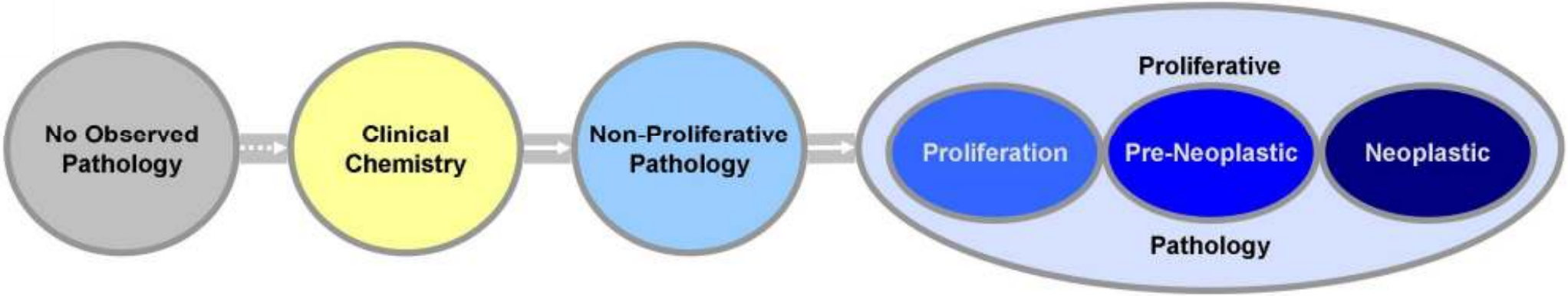
Endpoint Progression



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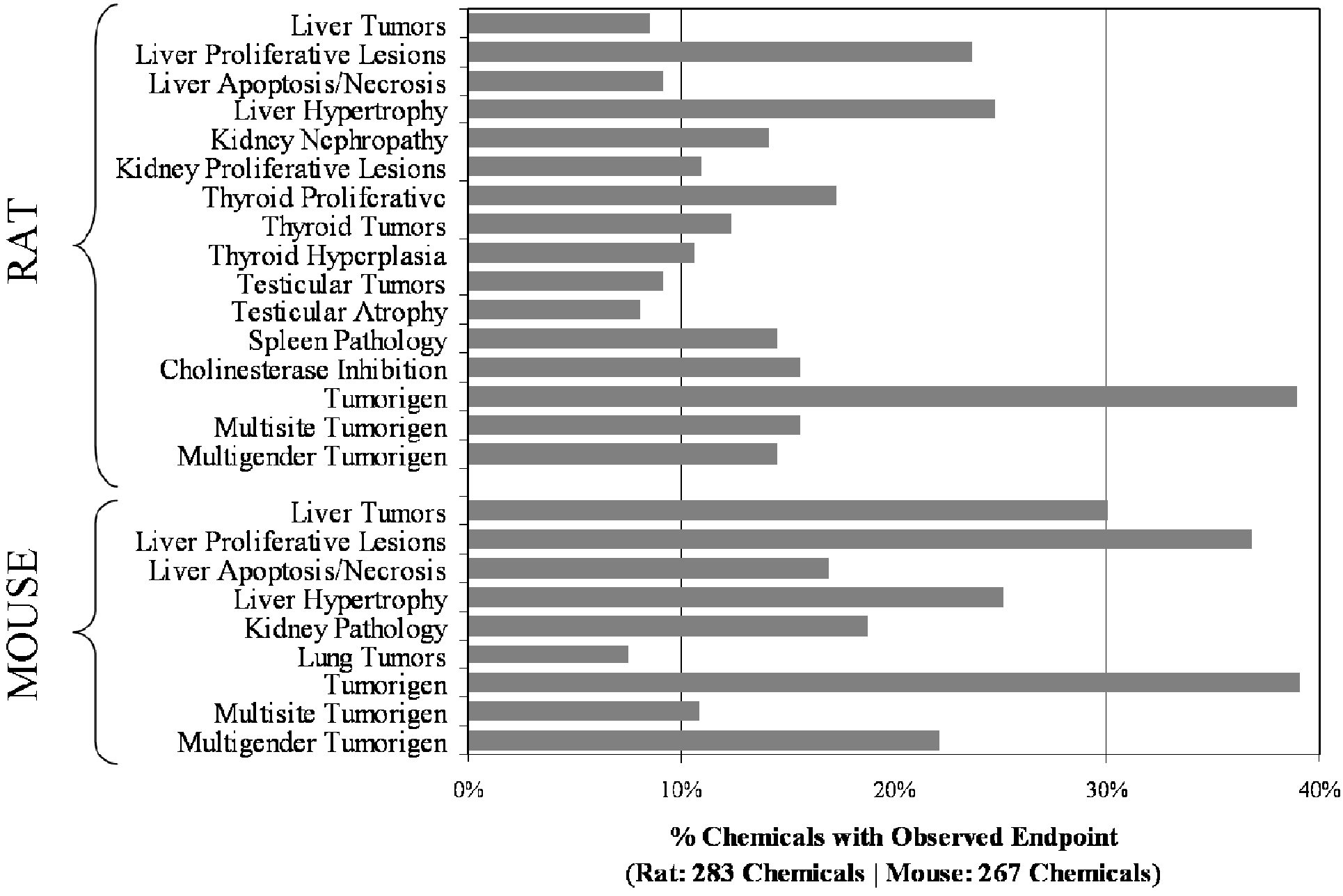
Initial Chronic Rat & Mouse Endpoints for Predictive Modeling



Reproductive Toxicity Profiling

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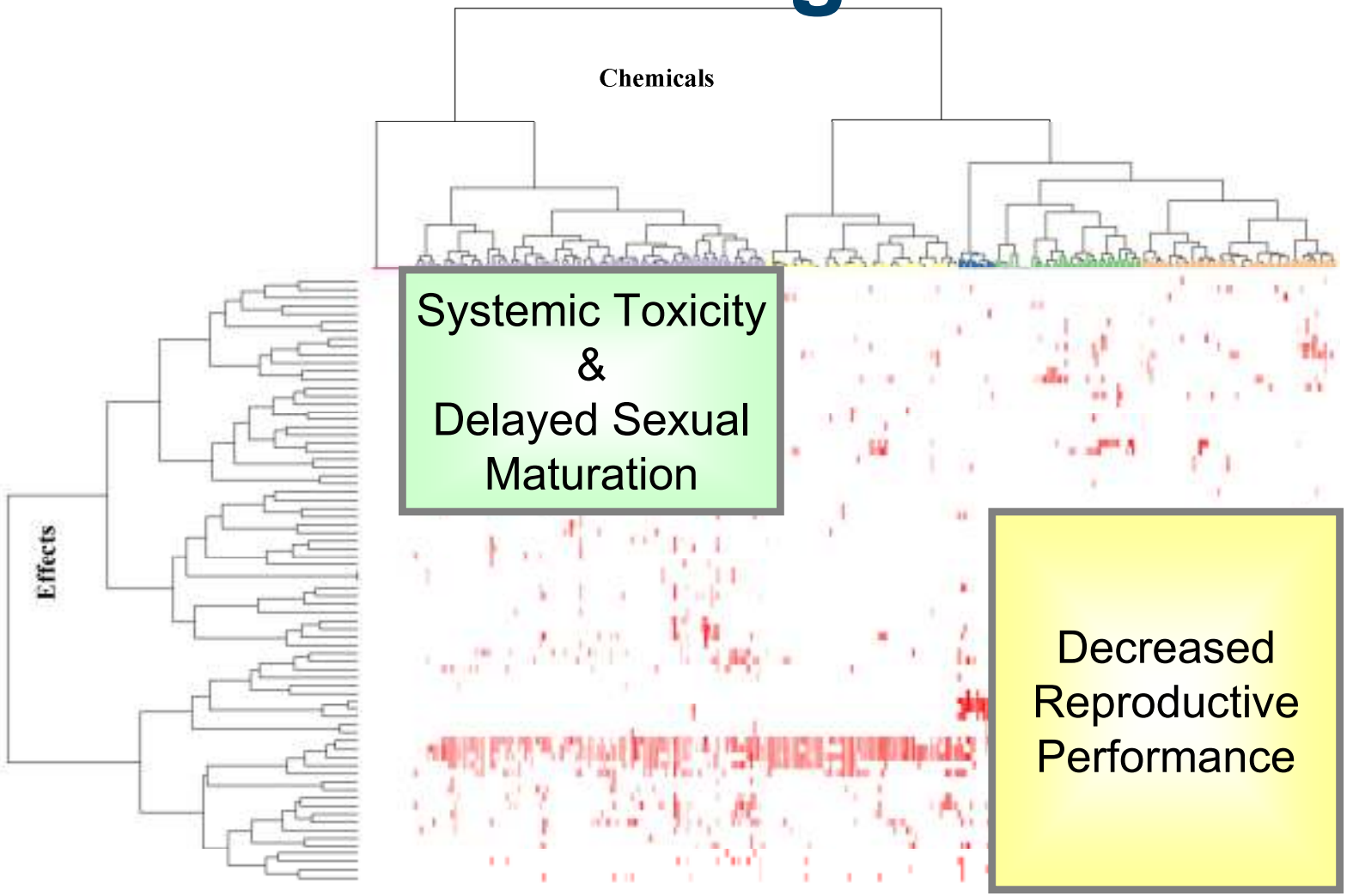

Chemical Clusters

- 1: No Observed Toxicities
- 2: General Systemic Toxicity & Delayed Sexual Maturation
- 3: Limited Toxicity - Primarily Body Weight Changes
- 4: Cholinesterase Inhibition
- 5: Male Reproductive Toxicity & Decrease Reproductive Performance
- 6: Offspring Viability & Decreased Reproductive Performance

No Effect — 2048 mg/kg/day — 0.015625 mg/kg/day

Lowest Effect Level (LEL): $-\text{Log}_2(\text{LEL})$

http://toxsci.oxfordjournals.org/cgi/reprint/kfp080

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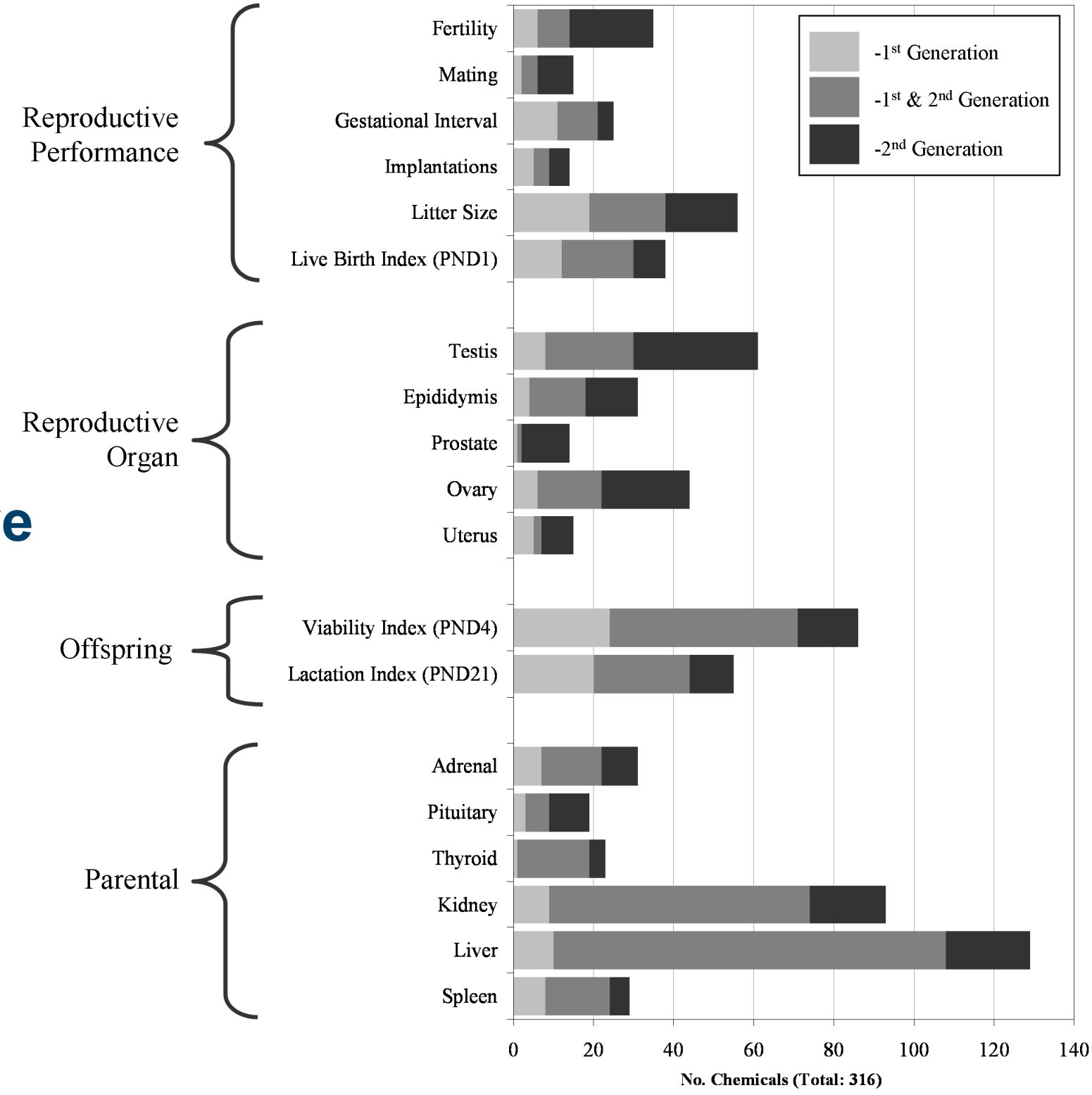
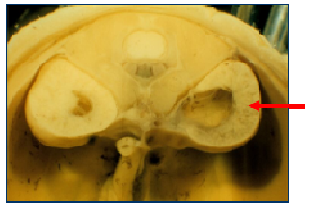
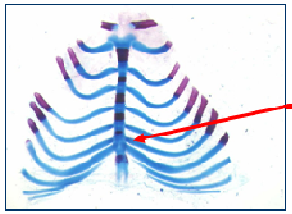
Initial Reproductive Endpoints



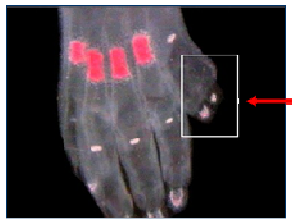
Profiling Developmental Toxicity



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

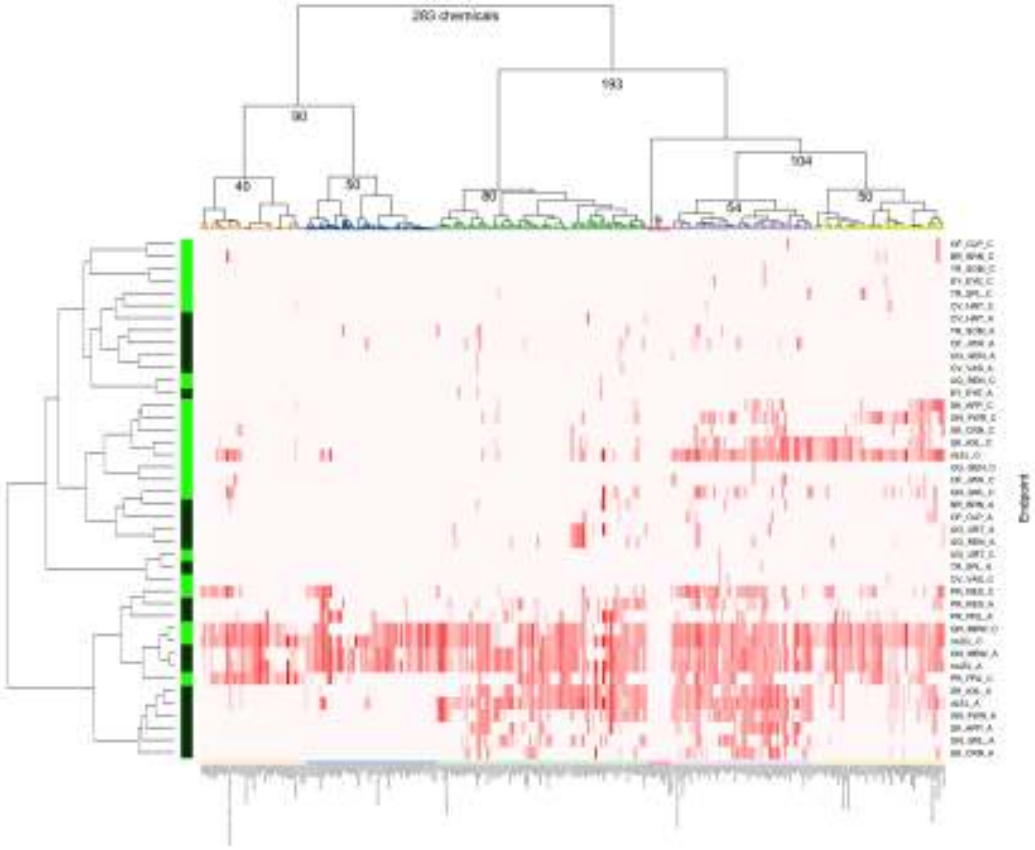


target: sternebra
description: incomplete ossification
code: SK_AXL_2.1099.5130



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

images from www.DevTox.org



ToxRefDB 387 chemicals, 751 prenatal studies, 988 total effects annotated (enhanced DevTox.org)

283 chemicals x **293** effects → **19** target systems from rat (■) and rabbit (■) studies

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

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Conclusions & Questions

- >$2Billion in Legacy In Vivo Data 'Recycled'
- Valuable Resource for Modeling Community
- Initial Datasets Available to Public via Website
- Initial Anchoring Endpoints vary by:
  - Incidence across chemicals
  - Biological specificity
  - General Aggregation Approach
- Searchable Database to be Made Publicly Available

ToxRefDB Homepage

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ToxRefDB Program

Toxicology Reference Database

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ToxRefDB was developed by the National Center for Computational Toxicology (NCCT) in partnership with EPA's Office of Pesticide Programs (OPP), to store data from in vivo animal toxicity studies. The initial focus was populating ToxRefDB with pesticide registration toxicity data that has been historically stored as hard-copy and scanned documents by OPP. A significant portion of these data have now been processed into ToxRefDB in a standardized and structured format. ToxRefDB currently includes chronic, cancer, sub-chronic, developmental, and reproductive studies on hundreds of chemicals, many of which are pesticide active ingredients. These data are now accessible and computable within ToxRefDB, and are serving as reference toxicity data for ORD research and OPP retrospective analyses. The primary research appliction of ToxRefDB is to provide toxicity endpoints for the development of ToxCast™ predictive signatures.

Data Set	Description	Download	Publication
Data Entry Tool & Controlled Vocabulary	The Data Entry Tool provided the user interface for all initial data input into ToxRefDB. The controlled vocabulary standardized the capturing of regulatory animal toxicity studies performed across various study types. (More Information)	Download (15.5 MB, ZIP)	Martin et al. (2008) "Profiling Chemicals Based on Chronic Toxicity Results from the U.S. EPA ToxRef Database" Environmental Health Perspectives doi:10.1289/ehp.0800074
Chronic & Cancer Endpoints	Based on incidence, severity and potency, 26 primarily tissue-specific pathology endpoints were selected to uniformly classify 310 chemicals included in the manuscript's analysis. The 310 chemicals in this analysis largely overlap with the 320 ToxCast Phase I chemicals. (More Information)	Download (2.7 MB, XLS)	Martin et al. (2008) "Profiling Chemicals Based on Chronic Toxicity Results from the U.S. EPA ToxRef Database" Environmental Health Perspectives doi:10.1289/ehp.0800074

www.epa.gov/ncct/toxrefdb

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Last updated on Tuesday, November 18th, 2008.
http://www.epa.gov/ncct/toxrefdb/
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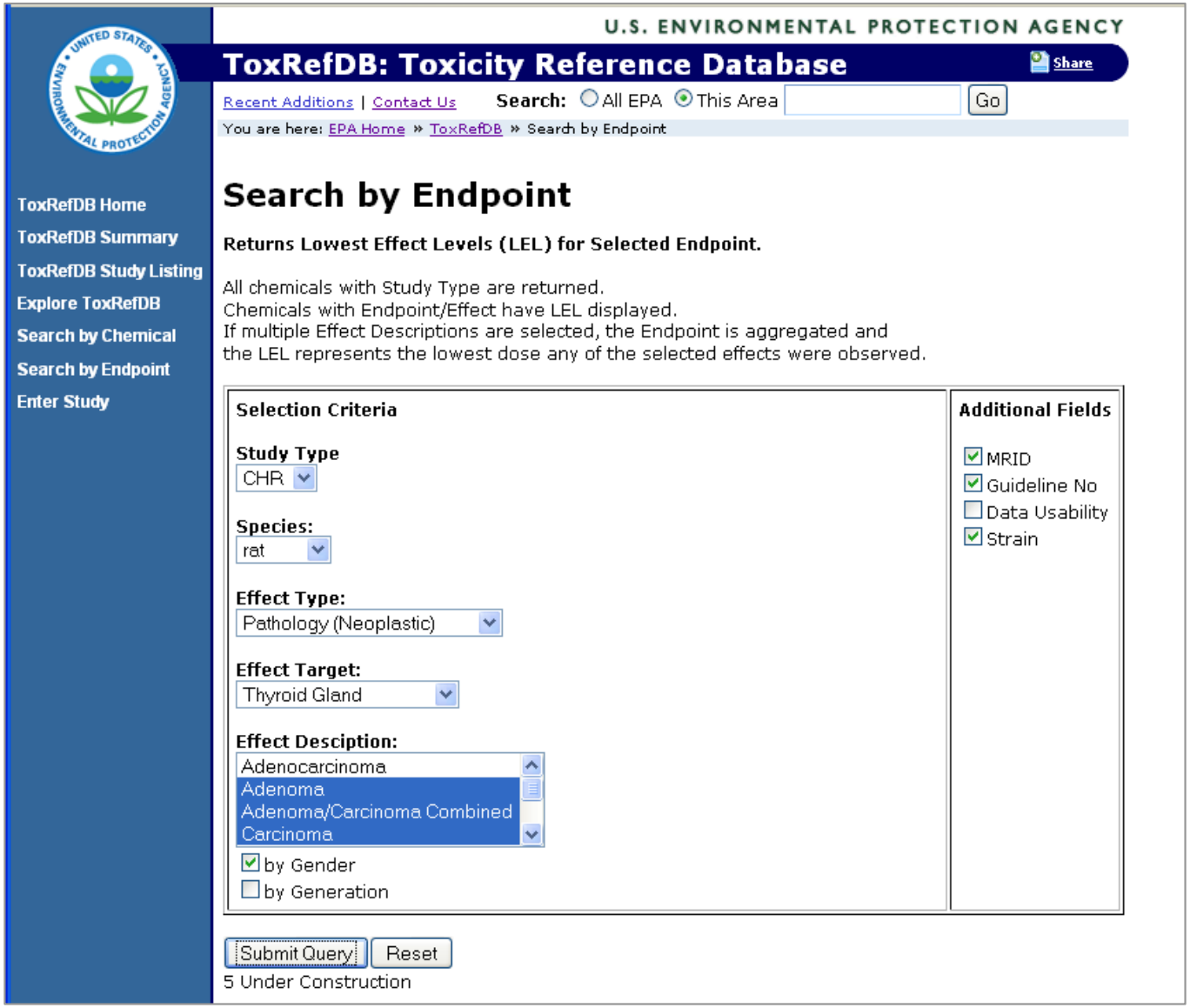
ToxRefDB Outputs



ToxRefDB Outputs

ToxRefDB Search Page Results | ToxRefDB | US EPA - Mozilla Firefox

ToxRefDB Home
Data Entry Status
ToxRefDB Study Listing
Explore ToxRefDB
Search by Chemical
Search by Endpoint
Enter Study

ToxRefDB Search Page Results

LDT = Low Dose Tested
HDT = High Dose Tested
ENDPOINT = Study Type: CHR | Species: rat | Effect Type: Pathology (Neoplastic) | Effect Target: Thyroid Gland | Effect Desc: Adenoma;Adenoma/Carcinoma Combined;Carcinoma

CAS No.	Chemical Name	Female LEL(mg/kg/day)	Male LEL(mg/kg/day)	LDT	HDT	MRID	StudyTypeID	Strain
361377-29-9	Fluoxastrobin	1083.20		2.10	1083.20	45865703	870.4300	Wistar
34549-30-9	2,2-Bis(bromomethyl)1,3-propanediol	460.00	200.00	100.00	800.00	00000000	870.4200	Fischer 344
10453-86-8	Resmethrin	450.30	400.90	39.50	450.30	00041402	870.4300	Wistar
95-14-7	1,2,3-Benzotriazole	335.00		335.00	605.00	00000000	870.4200	Fischer 344
82-68-8	Quintozene	300.00	150.00	1.00	300.00	41987301	870.4300	[Other]
31512-74-0	Polixetonium chloride	300.00		100.00	900.00	41809101	870.4300	CD(SD)BR
53112-28-0	Pyrimethanil	291.00	221.00	1.30	291.00	43301612	870.4300	Sprague Dawley (CD)
40487-42-1	Pendimethalin	250.00	250.00	5.00	250.00	40174401	870.4300	CD(SD)BR
80844-07-1	Ethofenprox	249.10	186.70	1.10	249.10	40449707	870.4300	Sprague Dawley (CD)
104206-82-8	Mesotrione	189.48		0.06	189.48	44505035	870.4300	Alpk: APSD
188425-85-6	Boscalid	155.60	116.10	4.60	1024.40	45404828	870.4200	Wistar
29091-21-2	Prodiamine	151.00	720.00	1.80	720.00	40985901	870.4300	Sprague Dawley
19044-88-3	Oryzalin	135.86	112.46	12.16	135.86	00026779	870.4300	Fischer 344
148-79-8	Thiabendazole	91.80	30.20	10.10	91.80	43593201	870.4300	CD(SD)BR
542-75-6	1,3-Dichloropropene (Telone II)	50.00	25.00	25.00	50.00	00000000	870.4200	Fischer 344
51338-27-3	Diclofop-methyl	32.00		0.23	79.00	00000000	870.4300	Wistar
120068-37-3	Fipronil	16.75	12.68	0.02	16.75	42918648	870.4300	Sprague Dawley (CD)
1746-01-6	2,3,7,8-Tetrachlorodibenzo-p-dioxin	0.00	0.00	0.00	0.00	00000000	870.4200	[Other]
165252-70-0	Dinotefuran		991.00	2.96	1332.00	45640001	870.4300	[Not Reported]
82697-71-0	Clofencet		989.00	4.70	1288.00	43183411	870.4300	Sprague Dawley (CD)
69377-81-7	Fluroxypyr		500.00	100.00	1000.00	44080322	870.4300	Fischer 344
141112-29-0	Isoxaflutole		500.00	0.50	500.00	43904806	870.4300	CD(SD)BR
113-48-4	MGK 264		450.00	50.00	450.00	43005301	870.4300	[Other]
63-25-2	Carbaryl		349.50	10.00	484.60	42198801	870.4300	CD(SD)BR
34256-82-1	Acetochlor		250.00	22.00	343.00	00131088	870.4300	Sprague Dawley (CD)
40487-42-1	Pendimethalin		213.00	51.00	213.00	42027802	870.4300	CD(SD)BR
87818-31-3	Cinmethylin		150.00	1.50	150.00	00156541	870.4100	Fischer 344
15972-60-8	Alachlor		126.00	14.00	126.00	00109319	870.4300	[Other]

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ToxRefDB Data Integrity and QC Procedures

1. Develop controlled vocabulary for each study type
2. Integrate into ToxRefDB, if new
3. Develop data entry SOP for each study type
4. Primary data entry
5. Record new vocabulary, as needed
6. Secondary data review
7. Update ‘not in list’ records with new vocabulary
8. Random 10% internal expert review (must meet >98% accuracy)
9. External review (stakeholder) of >50% of studies to date
10. Update studies based on internal & external review