United States Environmental Protection Agency

# Profiling Chemicals Based on Toxicity from the U.S. EPA ToxRef Database

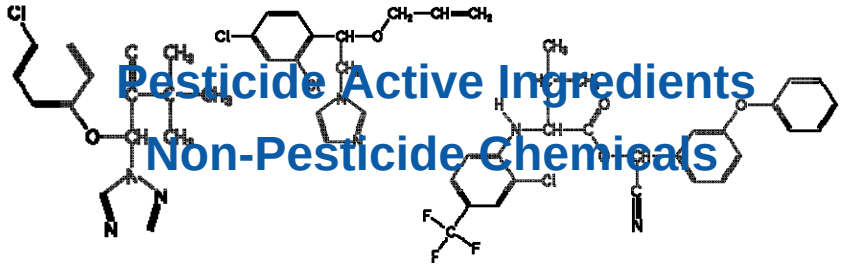
*Society for Risk Analysis Annual Meeting*
*Boston, Massachusetts*
*December 8, 2008*


Matthew T. Martin
http://www.epa.gov/ncct/toxrefdb

**Office of Research and Development**
National Center for Computational Toxicology

# Overview

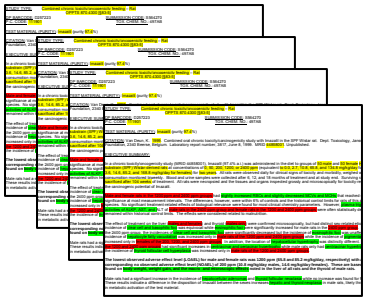
- **Source Data**



Pesticide Active Ingredients

Non-Pesticide Chemicals

DER



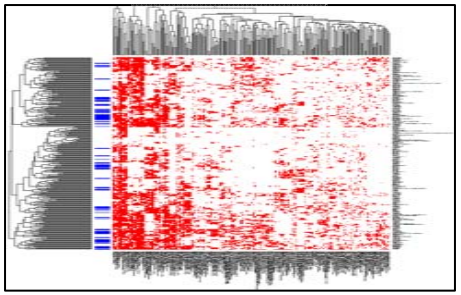
- **Database**

ToxRefDB

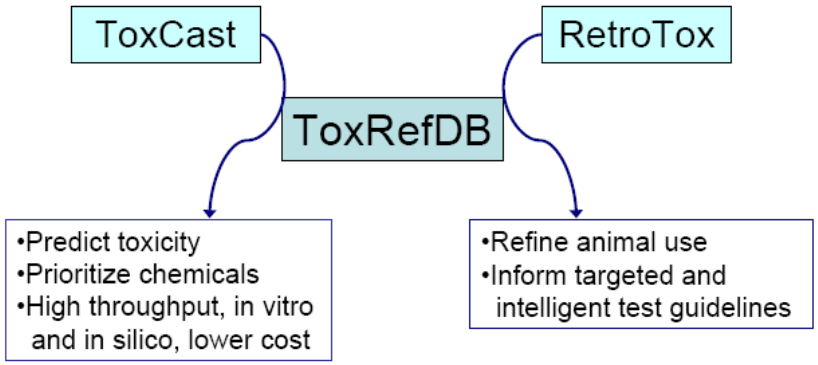
Structure

Input


Output

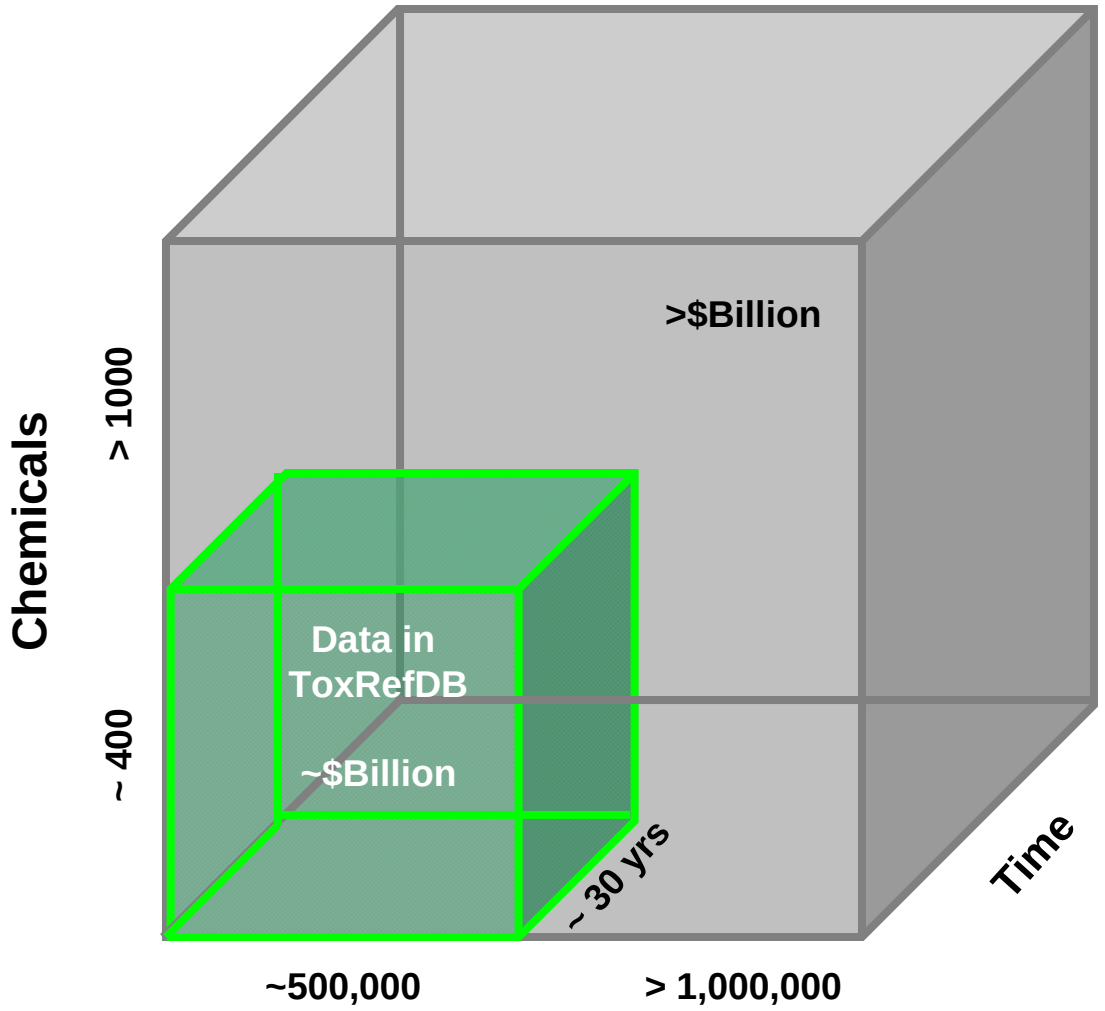


- **Applications**



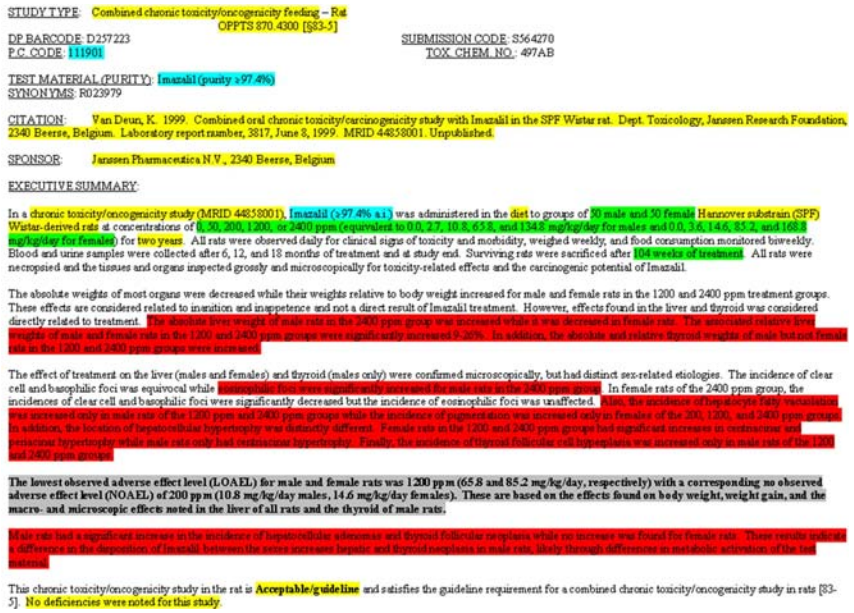
United States Environmental Protection Agency

# Pesticide Toxicity Dataset



# Data Evaluation Record (DER)

- Reviews of guideline toxicity studies
  - Used for hazard identification and characterization
- Study design
  - Chronic : Cancer : Subchronic : Multigeneration : Developmental
  - Detailed test material, animal, and dosing information
- Derive NOAEL/LOAEL & 'critical effects'
  - Systemic
  - Parental : Offspring : Reproductive
  - Maternal : Developmental
- Dose response (all treatment-related effects)



STUDY TYPE: Combined chronic toxicity/oncogenicity feeding – Rat
OPPTS 870.4300 [§83-5]

DP BARCODE: D257223
P.C. CODE: 111901

SUBMISSION CODE: S564270
TOX. CHEM. NO.: 497AB

TEST MATERIAL (PURITY): Imazalil (purity >97.4%)
SYNONYMS: R023979

CITATION: Van Deun, K. 1999. Combined oral chronic toxicity/carcinogenicity study with Imazalil in the SPF Wistar rat. Dept. Toxicology, Janssen Research Foundation, 2340 Beerse, Belgium. Laboratory report number, 3817, June 8, 1999. MRID 44858001. Unpublished.

SPONSOR: Janssen Pharmaceutica N.V., 2340 Beerse, Belgium

EXECUTIVE SUMMARY:

In a chronic toxicity/oncogenicity study (MRID 44858001), Imazalil (>97.4% a.i.) was administered in the diet to groups of 50 male and 50 female Hannover substrain (SPF) Wistar-derived rats at concentrations of 0, 50, 200, 1200, or 2400 ppm (equivalent to 0.0, 2.7, 10.8, 65.8, and 134.8 mg/kg/day for males and 0.0, 3.6, 14.6, 85.2, and 168.3 mg/kg/day for females) for two years. All rats were observed daily for clinical signs of toxicity and morbidity, weighed weekly, and food consumption monitored biweekly. Blood and urine samples were collected after 6, 12, and 18 months of treatment and at study end. Surviving rats were sacrificed after 104 weeks of treatment. All rats were necropsied and the tissues and organs inspected grossly and microscopically for toxicity-related effects and the carcinogenic potential of Imazalil.

The absolute weights of most organs were decreased while their weights relative to body weight increased for male and female rats in the 1200 and 2400 ppm treatment groups. These effects are considered related to inanition and inappetence and not a direct result of Imazalil treatment. However, effects found in the liver and thyroid was considered directly related to treatment. The absolute liver weight of male rats in the 2400 ppm group was increased while it was decreased in female rats. The associated relative liver weights of male and female rats in the 1200 and 2400 ppm groups were significantly increased 9-26%. In addition, the absolute and relative thyroid weights of male but not female rats in the 1200 and 2400 ppm groups were increased.

The effect of treatment on the liver (males and females) and thyroid (males only) were confirmed microscopically, but had distinct sex-related etiologies. The incidence of clear cell and basophilic foci was equivocal while eosinophilic foci were significantly increased for male rats in the 2400 ppm group. In female rats of the 2400 ppm group, the incidences of clear cell and basophilic foci were significantly decreased but the incidence of eosinophilic foci was unaffected. Also, the incidence of hepatocyte fatty vacuolation was increased only in male rats of the 1200 ppm and 2400 ppm groups while the incidence of pigmentation was increased only in females of the 200, 1200, and 2400 ppm groups. In addition, the location of hepatocellular hypertrophy was distinctly different. Female rats in the 1200 and 2400 ppm groups had significant increases in centrilobular and periacinar hypertrophy while male rats only had centrilobular hypertrophy. Finally, the incidence of thyroid follicular cell hyperplasia was increased only in male rats of the 1200 and 2400 ppm groups.

**The lowest observed adverse effect level (LOAEL) for male and female rats was 1200 ppm (65.8 and 85.2 mg/kg/day, respectively) with a corresponding no observed adverse effect level (NOAEL) of 200 ppm (10.8 mg/kg/day males, 14.6 mg/kg/day females). These are based on the effects found on body weight, weight gain, and the macro- and microscopic effects noted in the liver of all rats and the thyroid of male rats.**

Male rats had a significant increase in the incidence of hepatocellular adenomas and thyroid follicular neoplasia while no increase was found for female rats. These results indicate a difference in the disposition of Imazalil between the sexes increases hepatic and thyroid neoplasia in male rats, likely through difference in metabolic activation of the test material.

This chronic toxicity/oncogenicity study in the rat is **Acceptable/guideline** and satisfies the guideline requirement for a combined chronic toxicity/oncogenicity study in rats [83-5]. No deficiencies were noted for this study.

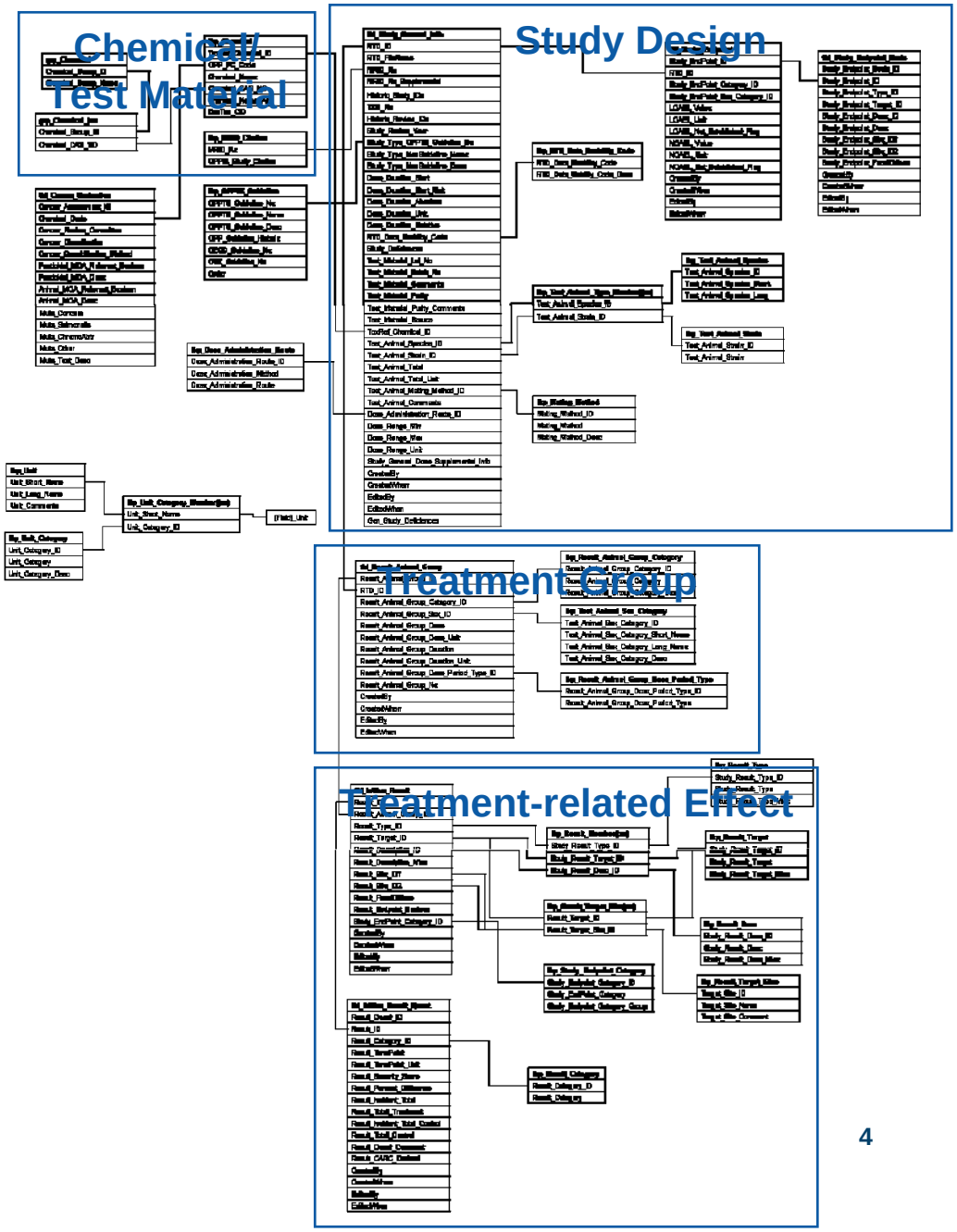
United States Environmental Protection Agency

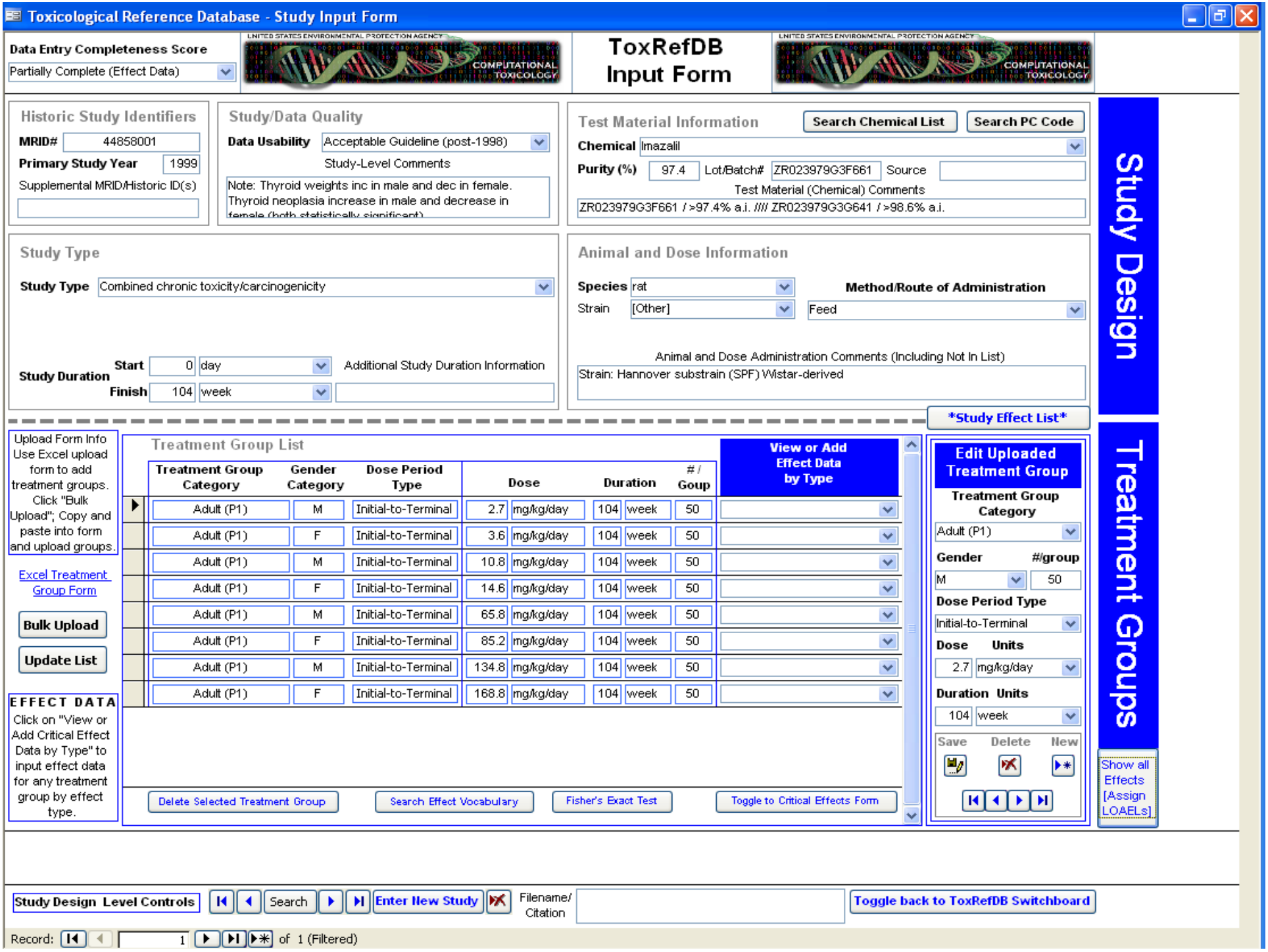
# ToxRefDB Standardized Vocabulary

Fields/Data Elements Utilizing Standardized Vocabulary

- Chemical
- Study Quality
- Study Type
- Method & Route of Admin
- Species
- Strain
- Generation
- Dosing Period
- Gender
- Dosing Duration
- Effect Type
- Effect Target
- Effect Description
- Target Cell Type
- Target Region

## ToxRefDB Data Model

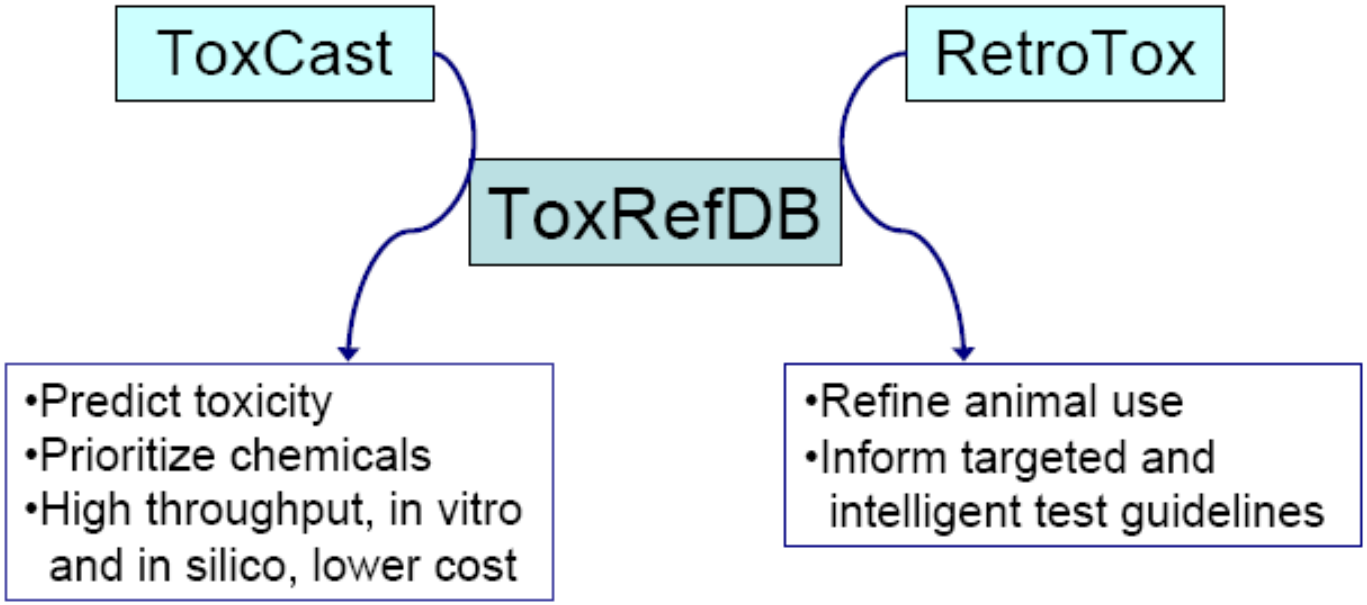



Toxicological Reference Database - Study Input Form
Data Entry Completeness Score
Partially Complete (Effect Data)
ToxRefDB Input Form
Historic Study Identifiers
MRID# 44858001
Primary Study Year 1999
Supplemental MRID/Historic ID(s)
Study/Data Quality
Data Usability Acceptable Guideline (post-1998)
Study-Level Comments
Note: Thyroid weights inc in male and dec in female. Thyroid neoplasia increase in male and decrease in female (both statistically significant)
Test Material Information
Search Chemical List
Search PC Code
Chemical Imazalil
Purity (%) 97.4
Lot/Batch# ZR023979G3F661
Source
Test Material (Chemical) Comments
ZR023979G3F661 / >97.4% a.i. /// ZR023979G3G641 / >98.6% a.i.
Study Type
Study Type Combined chronic toxicity/carcinogenicity
Study Duration Start 0 day
Finish 104 week
Additional Study Duration Information
Animal and Dose Information
Species rat
Strain [Other]
Method/Route of Administration
Feed
Animal and Dose Administration Comments (Including Not In List)
Strain: Hannover substrain (SPF) Wistar-derived
*Study Effect List*
Study Design
Treatment Groups
Upload Form Info
Use Excel upload form to add treatment groups. Click "Bulk Upload"; Copy and paste into form and upload groups.
Excel Treatment Group Form
Bulk Upload
Update List
EFFECT DATA
Click on "View or Add Critical Effect Data by Type" to input effect data for any treatment group by effect type.
Treatment Group List
Treatment Group Category | Gender Category | Dose Period Type | Dose | Duration | # / Goup | View or Add Effect Data by Type
Adult (P1) | M | Initial-to-Terminal | 2.7 mg/kg/day | 104 week | 50
Adult (P1) | F | Initial-to-Terminal | 3.6 mg/kg/day | 104 week | 50
Adult (P1) | M | Initial-to-Terminal | 10.8 mg/kg/day | 104 week | 50
Adult (P1) | F | Initial-to-Terminal | 14.6 mg/kg/day | 104 week | 50
Adult (P1) | M | Initial-to-Terminal | 65.8 mg/kg/day | 104 week | 50
Adult (P1) | F | Initial-to-Terminal | 85.2 mg/kg/day | 104 week | 50
Adult (P1) | M | Initial-to-Terminal | 134.8 mg/kg/day | 104 week | 50
Adult (P1) | F | Initial-to-Terminal | 168.8 mg/kg/day | 104 week | 50
Delete Selected Treatment Group
Search Effect Vocabulary
Fisher's Exact Test
Toggle to Critical Effects Form
Edit Uploaded Treatment Group
Treatment Group Category
Adult (P1)
Gender
M
#/group
50
Dose Period Type
Initial-to-Terminal
Dose
2.7
Units
mg/kg/day
Duration
104
Units
week
Save
Delete
New
Show all Effects [Assign LOAELs]
Study Design Level Controls
Search
Enter New Study
Filename/ Citation
Toggle back to ToxRefDB Switchboard
Record: 1 of 1 (Filtered)

EPA
United States
Environmental Protection
Agency

# 1983 Studies Entered For 451 Chemicals

# Applications

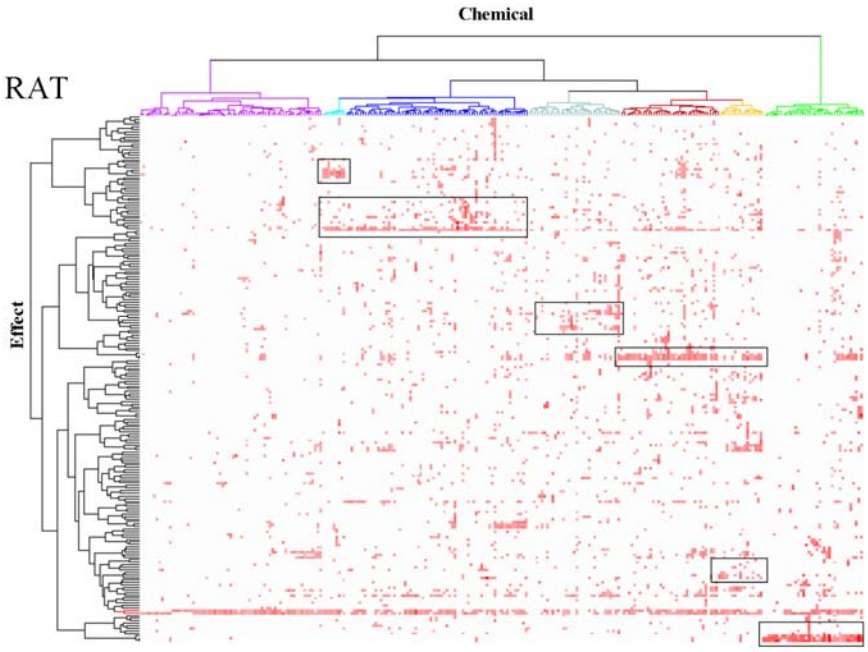


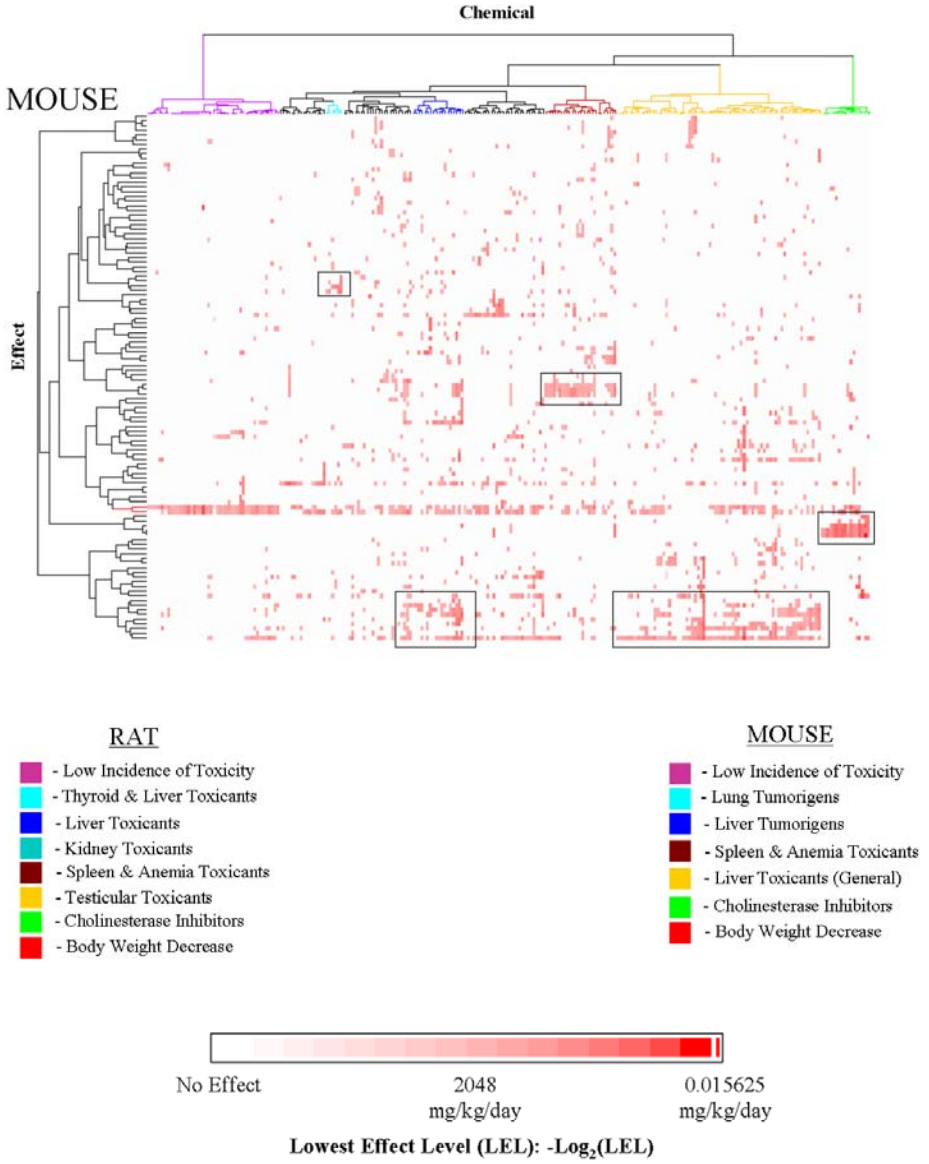

- Research (link to HTS and genomic data)
  - Inform modeling and systems biology
  - ***In Vivo* Toxicity-based Profiling**

- Retrospective Analysis
  - 2-yr Bioassay: Rat vs. Mouse
  - Multigeneration: F1 vs. F2
  - Developmental: Rat vs. Rabbit

United States Environmental Protection Agency

# Chronic/Cancer Toxicity Profiling



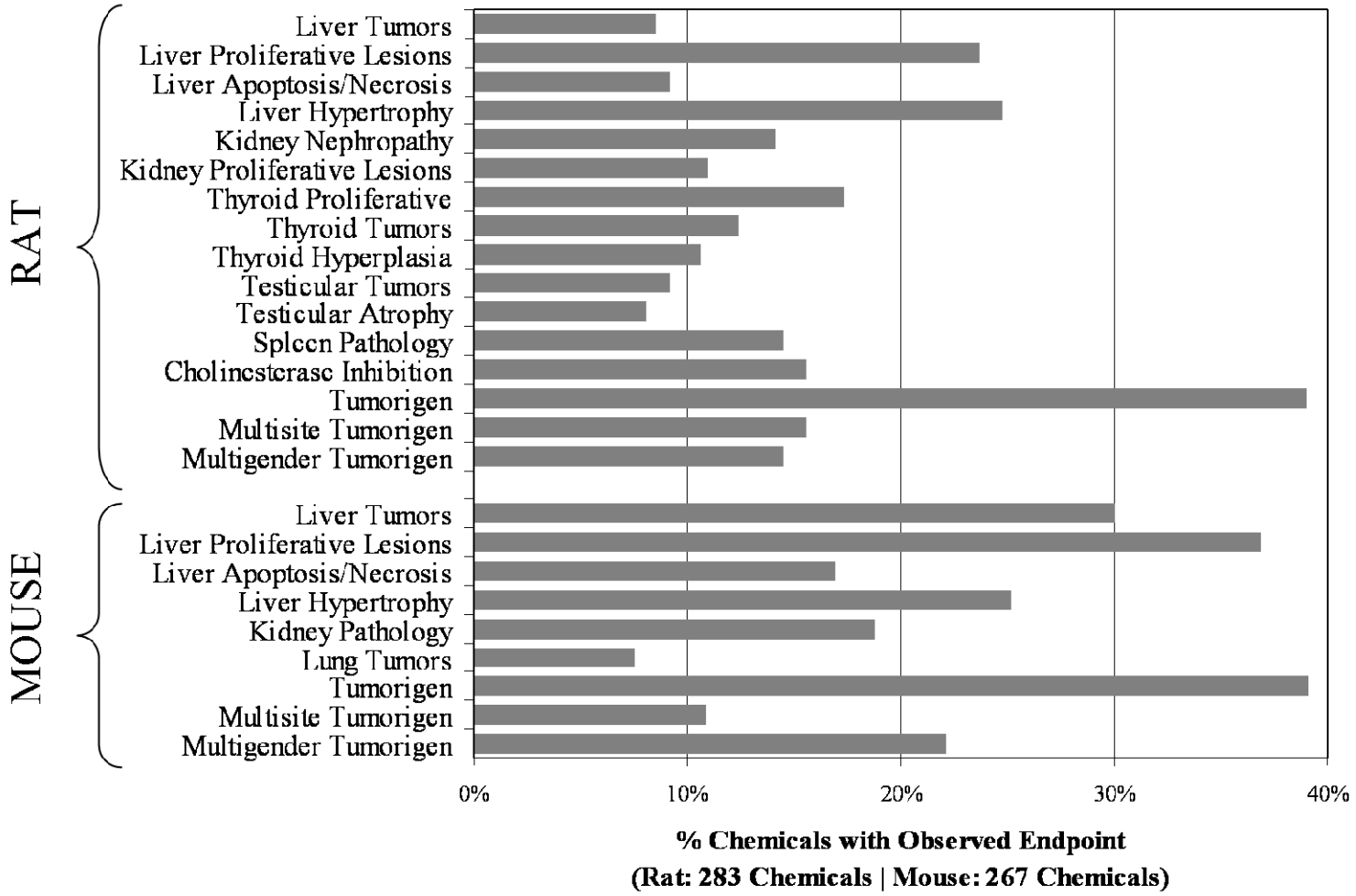




Two-way Unsupervised Hierarchical Clustering

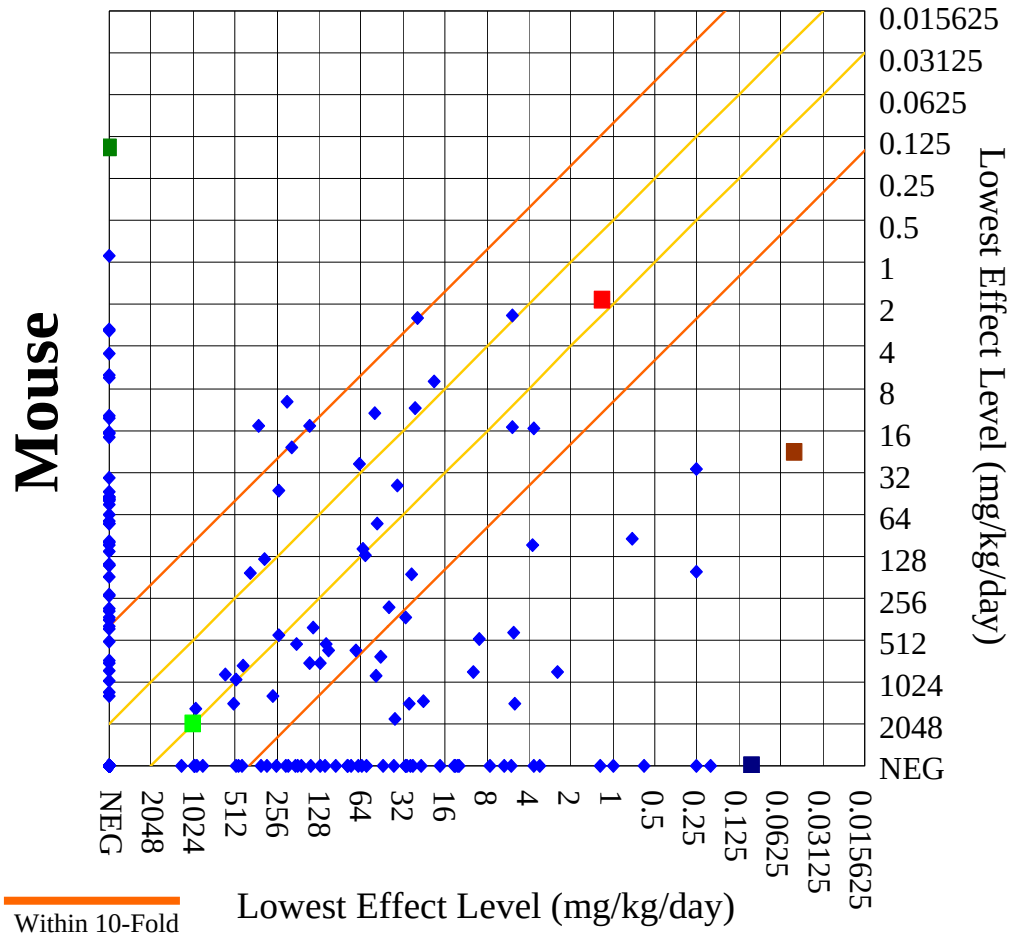


http://www.ehponline.org/members/2008/0800074/0800074.pdf

# Selected Chronic Rat & Mouse Endpoints for Predictive Modeling



# Rat vs. Mouse Tumorigenicity




Within 10-Fold

Within 2-Fold

NEG – Negative for Tumorigenicity

- **260** Chemicals w/ Rat & Mouse Chronic/Cancer Study
- **108** Non-tumorigens
- **51** Rat Only Tumorigens
- **48** Mouse Only Tumorigens
- **53** Rat & Mouse Tumorigens

Chlordane – Group B2

Lindane – Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential

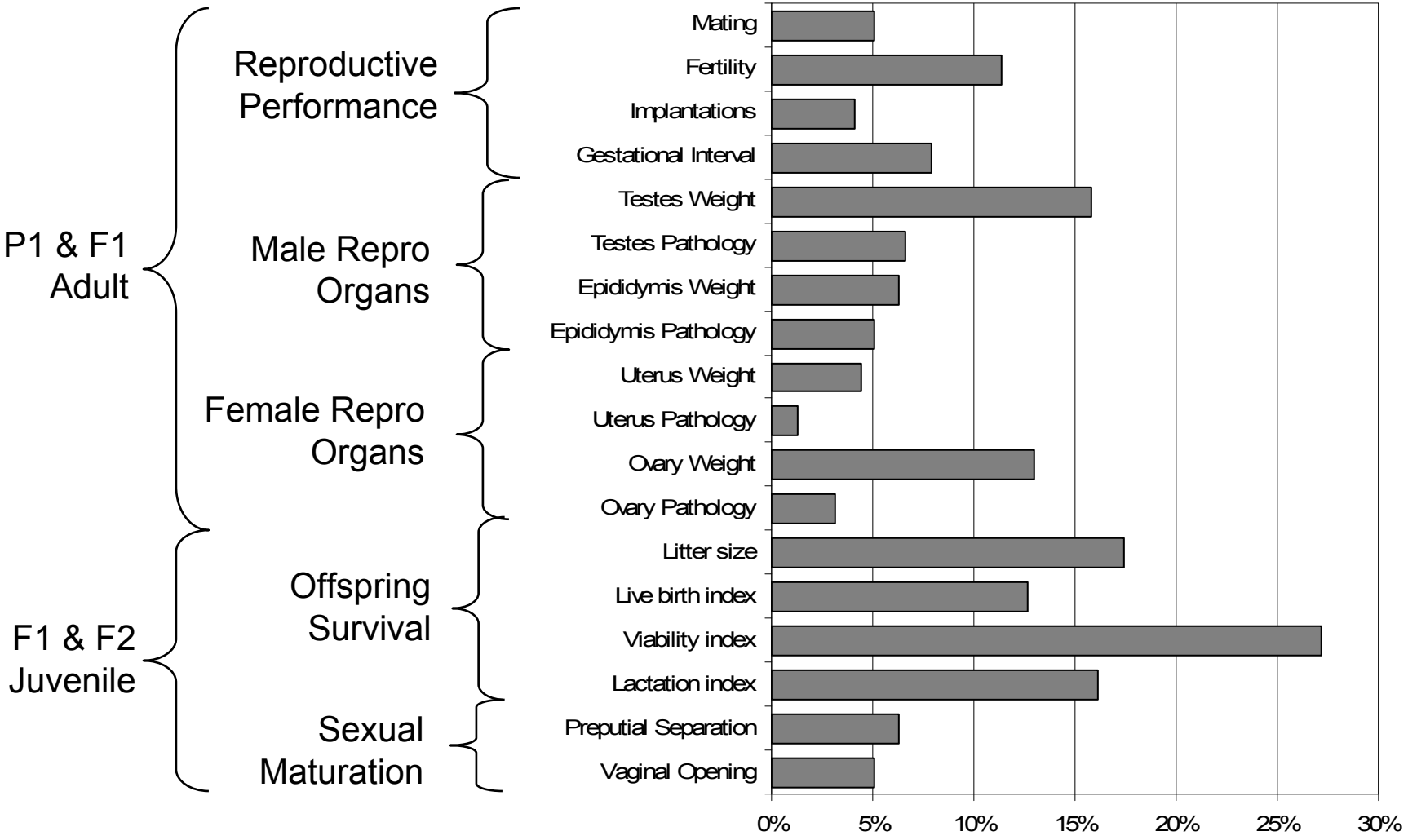
Dipropyl isocinchomeronate – Group B2

Chlorpyrifos-methyl – Not Likely to be Carcinogenic to Humans

Disulfoton – Group E

http://www.epa.gov/pesticides/carlist/

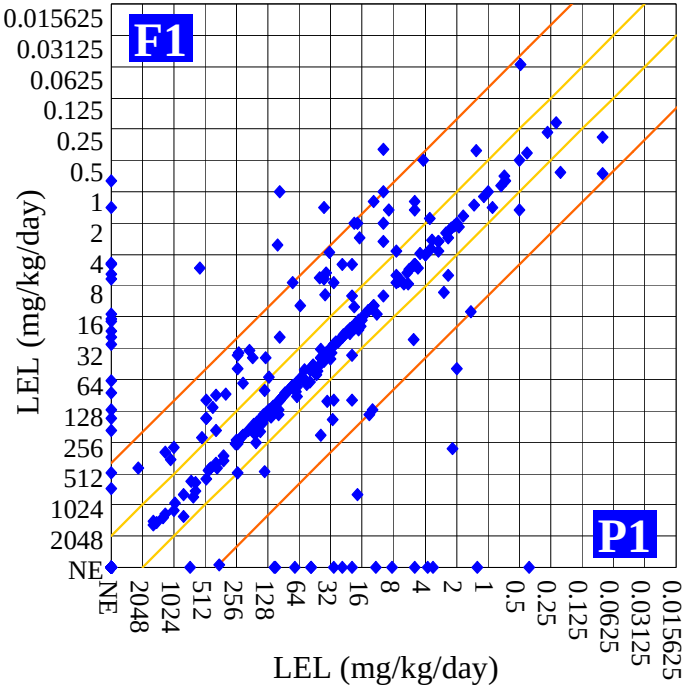
# Multigeneration Reproductive Toxicity Profiling



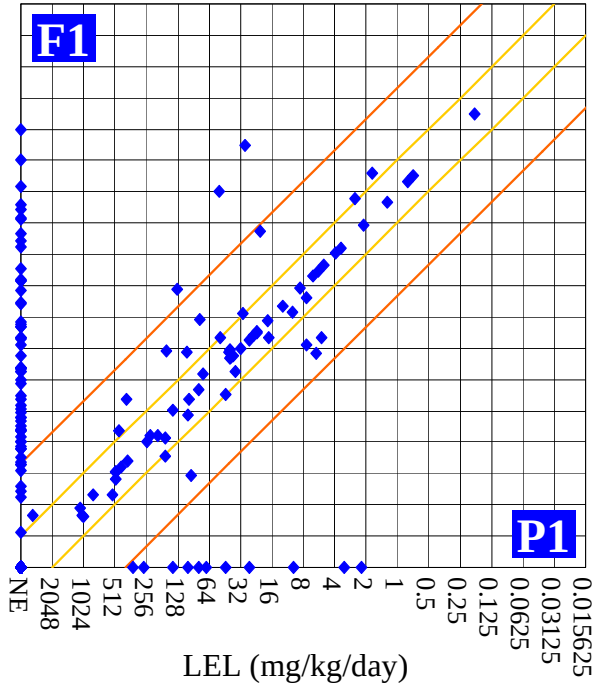

% Chemicals w/ Observed Endpoint
Total: 316 Chemicals

# Multigeneration Reproductive Toxicity Profiling

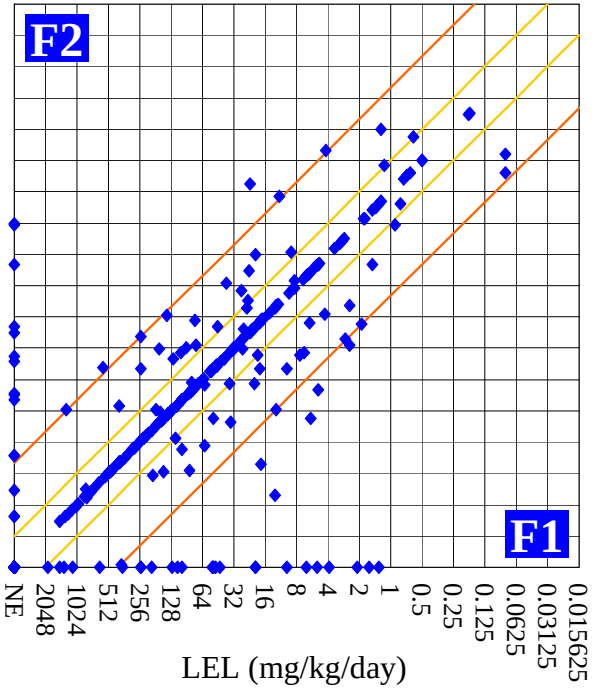
## Parental




## Reproductive




## Offspring




Within 10-Fold

Within 2-Fold

NE – Not Established
LEL – Lowest Effect Level
Total = 316 Chemicals

- Parental Toxicity
  - **19** F1 Specific
  - **5** F1 Sensitive
- Reproductive Toxicity
  - **61** F1 Specific
  - **3** F1 Sensitive
- Offspring Toxicity
  - **12** F2 Specific
  - **6** F2 Sensitive

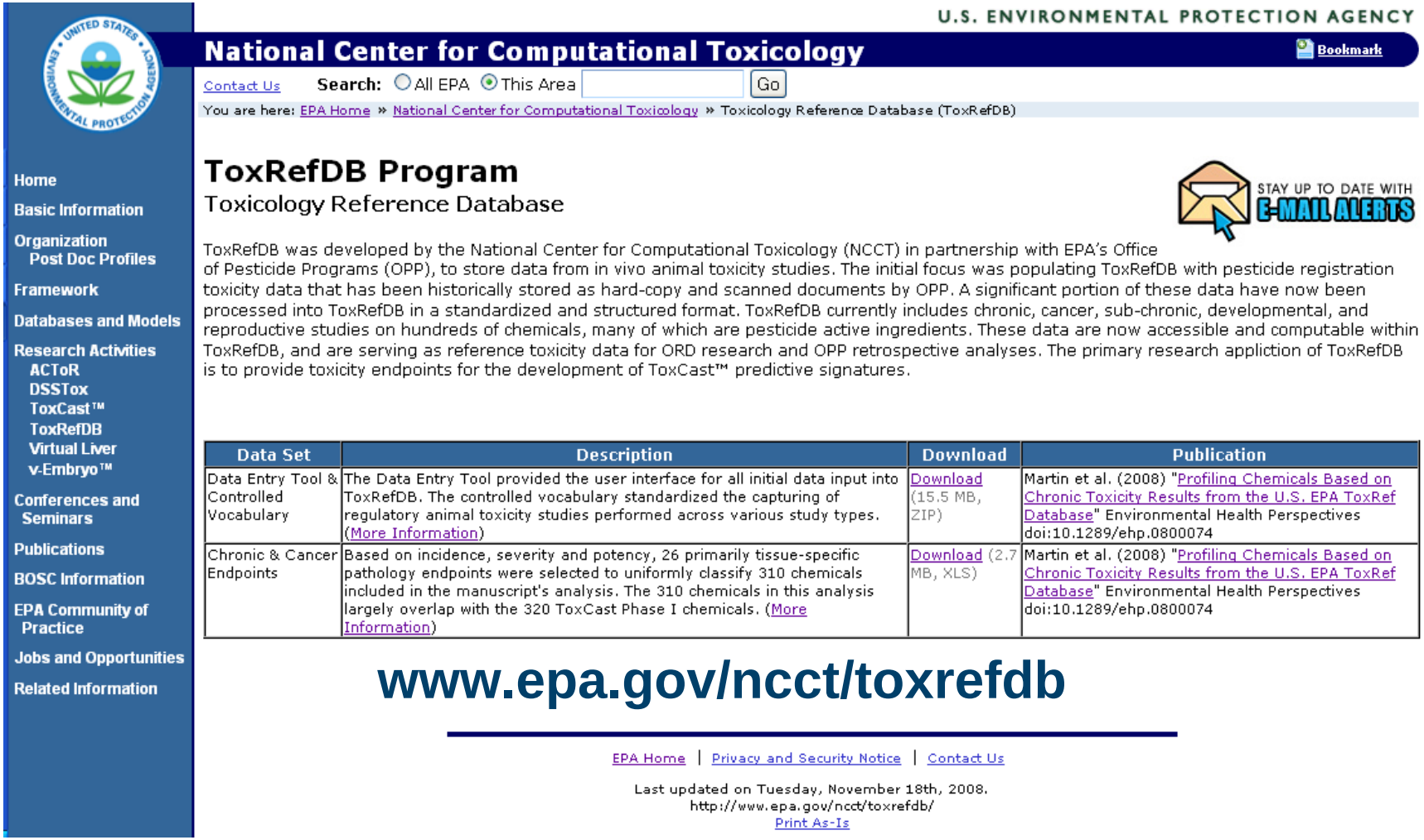
*10-Fold Cutoff

# Conclusions

- Current Status
  - Publication of Chronic/Cancer Endpoints for Predictive Modeling
  - ToxCast Phase I *In Vivo* Toxicity Data Entry Complete
  - Ongoing Internal QA/QC
  - Ongoing Stakeholder Review
  - ToxRefDB Homepage Online

- Next Steps
  - Publication of Reproductive & Developmental Endpoints for Predictive Modeling
  - ToxCast Phase II *In Vivo* Toxicity Data Entry
  - Public Release of Database via Web-based Tools
  - Expanding Study Types to Developmental Neurotoxicity, etc.
  - Integrate with other Toxicity Databases & Data Models

# ToxRefDB Homepage



U.S. ENVIRONMENTAL PROTECTION AGENCY

National Center for Computational Toxicology

Bookmark

Contact Us  Search: All EPA This Area  Go

You are here: EPA Home » National Center for Computational Toxicology » Toxicology Reference Database (ToxRefDB)

- Home
- Basic Information
- Organization
  - Post Doc Profiles
- Framework
- Databases and Models
- Research Activities
  - ACToR
  - DSSTox
  - ToxCast™
  - ToxRefDB
  - Virtual Liver
  - v-Embryo™
- Conferences and Seminars
- Publications
- BOSC Information
- EPA Community of Practice
- Jobs and Opportunities
- Related Information

## ToxRefDB Program

Toxicology Reference Database

STAY UP TO DATE WITH E-MAIL ALERTS

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.

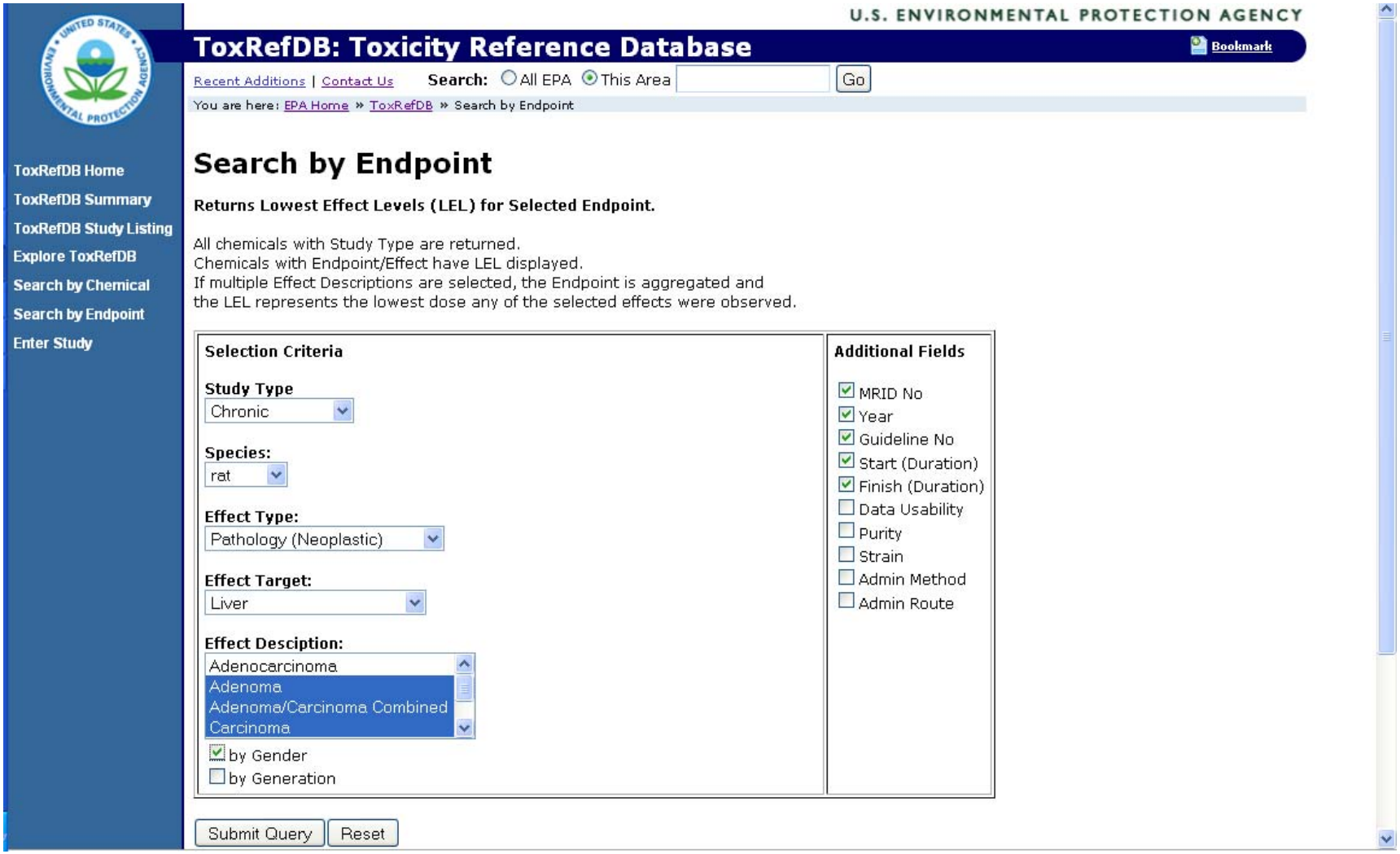
| Data Set | Description | Download | Publication |
|---|---|---|---|
| Data Entry Tool & Controlled Vocabulary | The Data Entry Tool provided the user interface for all initial data input into ToxRefDB. The controlled vocabulary standardized the capturing of regulatory animal toxicity studies performed 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 |

EPA Home | Privacy and Security Notice | Contact Us

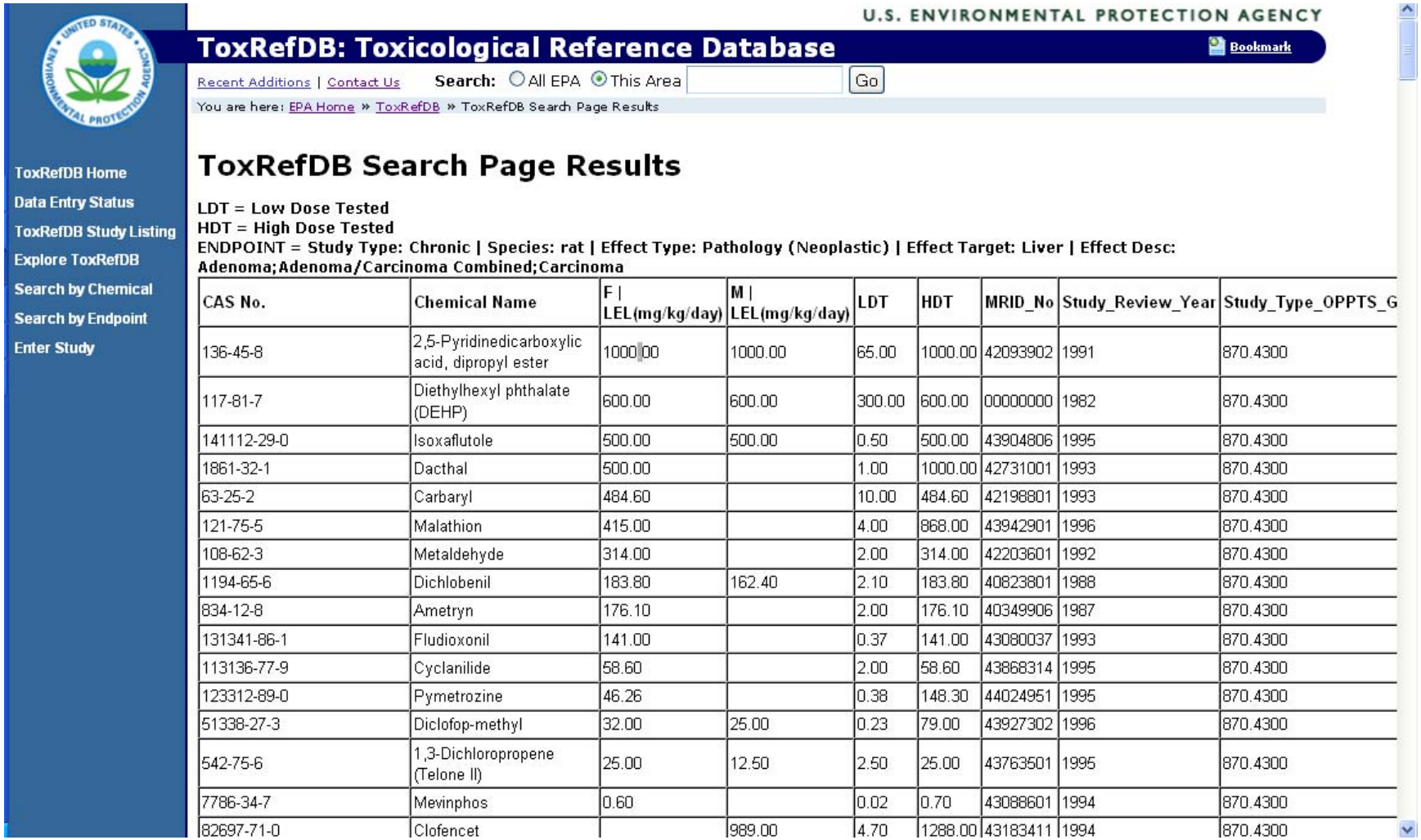
Last updated on Tuesday, November 18th, 2008.
http://www.epa.gov/ncct/toxrefdb/
Print As-Is

## www.epa.gov/ncct/toxrefdb

# ToxRefDB
# Web-based Query Tool



# ToxRefDB
# Web-based Query Tool



U.S. ENVIRONMENTAL PROTECTION AGENCY

**ToxRefDB: Toxicological Reference Database**

Bookmark

Recent Additions | Contact Us  Search: All EPA This Area  Go

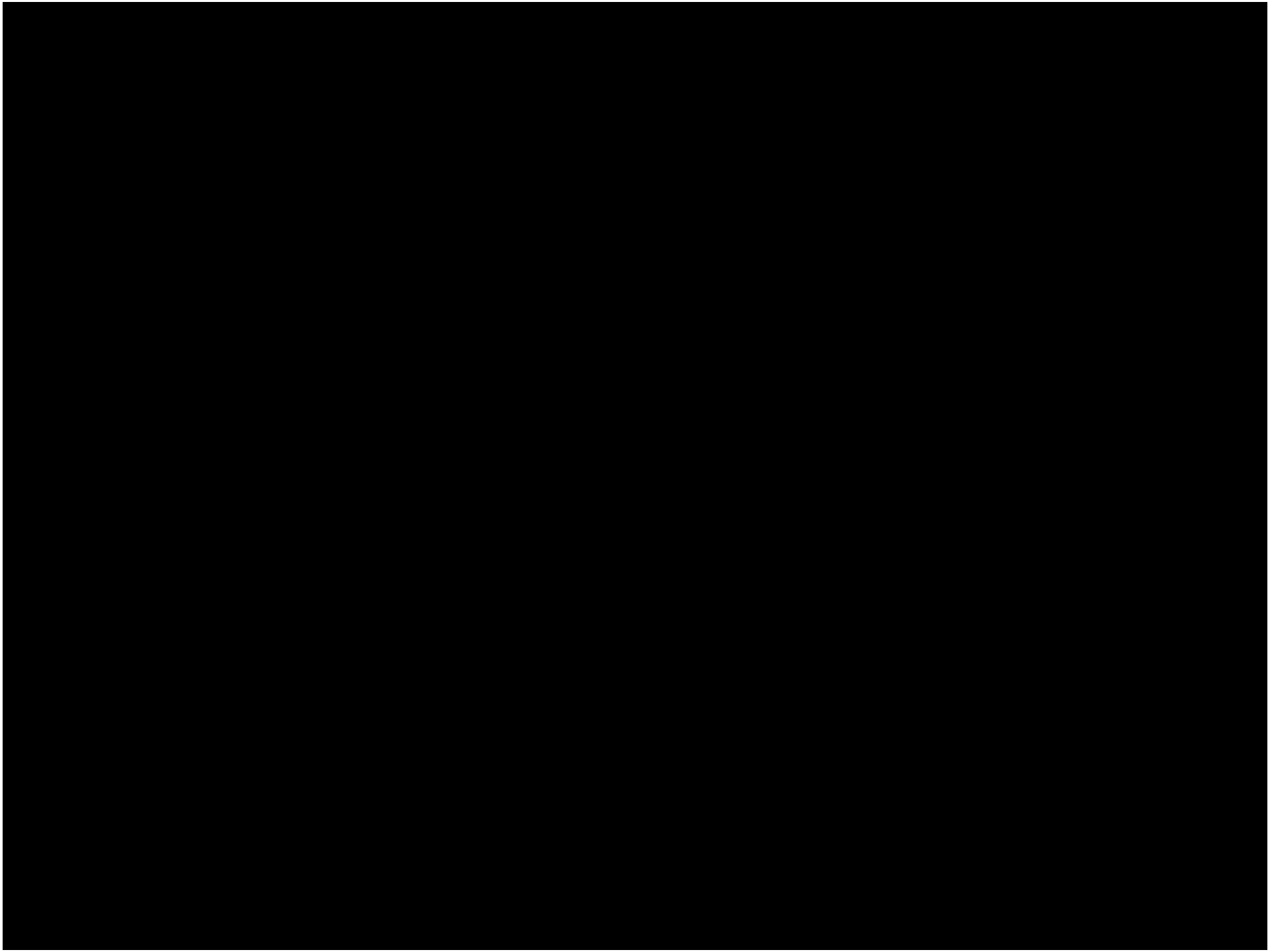
You are here: EPA Home » ToxRefDB » ToxRefDB Search Page Results

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: Chronic | Species: rat | Effect Type: Pathology (Neoplastic) | Effect Target: Liver | Effect Desc: Adenoma;Adenoma/Carcinoma Combined;Carcinoma**

| CAS No. | Chemical Name | F \| LEL(mg/kg/day) | M \| LEL(mg/kg/day) | LDT | HDT | MRID_No | Study_Review_Year | Study_Type_OPPTS_G |
|---|---|---|---|---|---|---|---|---|
| 136-45-8 | 2,5-Pyridinedicarboxylic acid, dipropyl ester | 1000.00 | 1000.00 | 65.00 | 1000.00 | 42093902 | 1991 | 870.4300 |
| 117-81-7 | Diethylhexyl phthalate (DEHP) | 600.00 | 600.00 | 300.00 | 600.00 | 00000000 | 1982 | 870.4300 |
| 141112-29-0 | Isoxaflutole | 500.00 | 500.00 | 0.50 | 500.00 | 43904806 | 1995 | 870.4300 |
| 1861-32-1 | Dacthal | 500.00 | | 1.00 | 1000.00 | 42731001 | 1993 | 870.4300 |
| 63-25-2 | Carbaryl | 484.60 | | 10.00 | 484.60 | 42198801 | 1993 | 870.4300 |
| 121-75-5 | Malathion | 415.00 | | 4.00 | 868.00 | 43942901 | 1996 | 870.4300 |
| 108-62-3 | Metaldehyde | 314.00 | | 2.00 | 314.00 | 42203601 | 1992 | 870.4300 |
| 1194-65-6 | Dichlobenil | 183.80 | 162.40 | 2.10 | 183.80 | 40823801 | 1988 | 870.4300 |
| 834-12-8 | Ametryn | 176.10 | | 2.00 | 176.10 | 40349906 | 1987 | 870.4300 |
| 131341-86-1 | Fludioxonil | 141.00 | | 0.37 | 141.00 | 43080037 | 1993 | 870.4300 |
| 113136-77-9 | Cyclanilide | 58.60 | | 2.00 | 58.60 | 43868314 | 1995 | 870.4300 |
| 123312-89-0 | Pymetrozine | 46.26 | | 0.38 | 148.30 | 44024951 | 1995 | 870.4300 |
| 51338-27-3 | Diclofop-methyl | 32.00 | 25.00 | 0.23 | 79.00 | 43927302 | 1996 | 870.4300 |
| 542-75-6 | 1,3-Dichloropropene (Telone II) | 25.00 | 12.50 | 2.50 | 25.00 | 43763501 | 1995 | 870.4300 |
| 7786-34-7 | Mevinphos | 0.60 | | 0.02 | 0.70 | 43088601 | 1994 | 870.4300 |
| 82697-71-0 | Clofencet | | 989.00 | 4.70 | 1288.00 | 43183411 | 1994 | 870.4300 |



# Aggregating Effects