

Application of QSAR Principles in the Regulatory Environment: The US EPA New Chemicals Program

Louis Scarano

U.S. Environmental Protection Agency

A large, faint watermark of the Environmental Protection Agency (EPA) logo is centered in the background. The logo features a stylized flower with three leaves and a circular top containing a sun and a cloud. The words "UNITED STATES" are arched above the flower, and "ENVIRONMENTAL PROTECTION AGENCY" is arched below it.

The views expressed in this presentation are those of the author
and do not represent Agency policy or endorsement.

No confidential business information (CBI) was used in this
presentation



Outline of Presentation

- The Toxic Substances Control Act (TSCA) and Regulation of New Chemicals in the US (Premanufacture Notifications or PMNs)
- Use of Structure-Activity Relationships (SAR)
- Some data on PMN submissions...



Part I

The Toxic Substances Control Act (TSCA) and Regulation of New Chemicals in the US



Section 5 of TSCA

TSCA, Section 5, requires a manufacturer or importer of a new chemical substance to submit a “premanufacture notice” (PMN) to EPA 90 days before the date of intended start of production or import of the subject chemical.



The US New Chemicals Program is **NOT** a Registration Program...

...it is a **notification** program.

- During that 90-day period, EPA reviews whether the manufacture, processing, distribution in commerce, use or disposal of the substance **may present an unreasonable risk to human health or the environment**
- Designed to prevent health and/or environmental risks before they occur



Information Required in PMN

- Chemical identity
- Byproducts
- Production/Import volume
- Description of uses
- Description of human exposure
- Description of disposal practices
- **Available** test data in submitters' control



What are Available Data?

TSCA requires new chemical manufacturers to submit only studies/data in their possession or control at the time of the PMN application (i.e., **no minimum set of toxicity or other studies are required**)



Data Received with Notifications

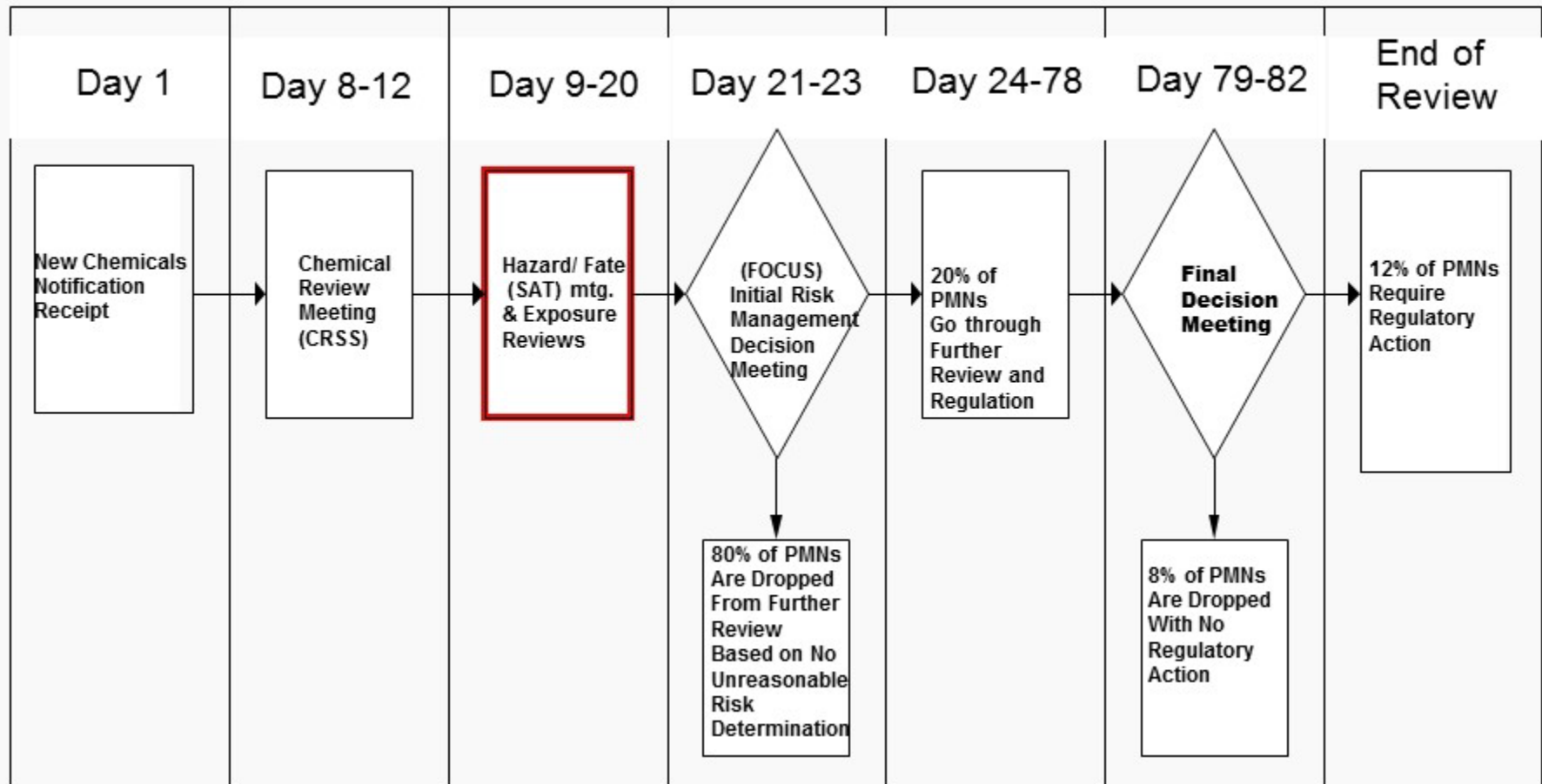
- About 15-20% of current notices contain acute toxicity testing in mammals
- About 10% of current notices contain environmental effects (ecotox) or environmental fate data
- Because no test data are required to be submitted, predictive models/technical tools and professional judgment are used by EPA to assess potential risks

...and this is all done within 90 days for ~1200 cases/year!

Here is our general workflow:



New Chemicals Review Process for PMNs





Part II

Use of Structure-Activity Relationships (SAR) in the US EPA New Chemicals Program



SAR

- Sustainable Futures
 - Tools
 - Approach - finding analogous chemicals
- The Structure-Activity Team (SAT)
 - Human Health
 - Aquatic Ecotoxicity
- New Chem Categories



Sustainable Futures (SF) Initiative

- U.S. EPA provides training on risk-screening models and tools developed for new chemical screening level assessments to help companies find safer substitutes and/or processes before submitting them to the EPA.
<http://www.epa.gov/sustainable-futures>
- This program best describes how analogs are used in screening level new chemical assessments.
- It is a three-day workshop that is offered 1-3 times per year
- This presentation provides a VERY BRIEF overview of the hazard portion of the training...

Screening Level Tools/Models Used by EPA/OPPT

P-Chem and Fate

EPISuite™

Aquatic Toxicity

ECOSAR

Carcinogenicity

OncoLogic™

SF Chemical
Assessment

Non-Cancer Effects

**

E-FAST
ChemSTEER

Exposure Potential

**** OPPT currently has no computer models to quantitatively predict non-cancer effects but relies on traditional analog identification and read across**

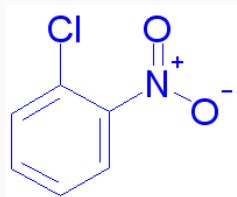


Analog Approaches

- Tools to Identify Analogs with Data
 - Analog Identification Methodology (AIM)
<http://www.epa.gov/tsca-screening-tools/analog-identification-methodology-aim-tool>
 - ChemID-U.S. National Library of Medicine
<http://www.chem.sis.nlm.nih.gov/chemidplus/>
 - CHEMFINDER
 - <http://chemfinder.cambridgesoft.com/>
 - OECD QSAR Toolbox
 - <http://www.oecd.org/env/ehs/risk-assessment/theoecdqsartoolbox.htm>
 - Internal sub-structure searchable databases.

Structure-based Approach for Identifying Analogs

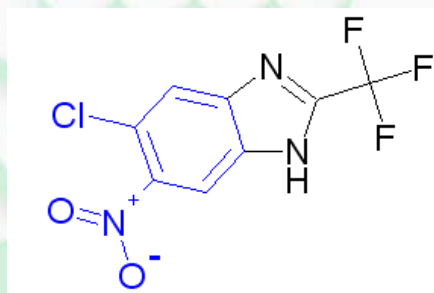
- Scientists typically conduct analog identification using sub-structure search engines (ISIS, ChemBase, ChemFinder, etc.)
- These programs identify a user-defined functional group from a predefined list and analogs returned will contain that fragment
- Limitation- additional functionalities on the identified analogs are not considered...giving rise to many odd results



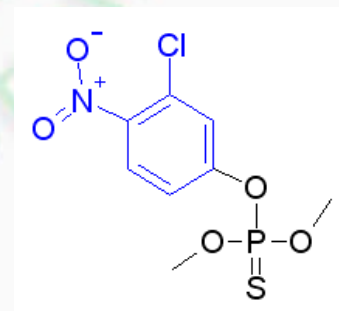
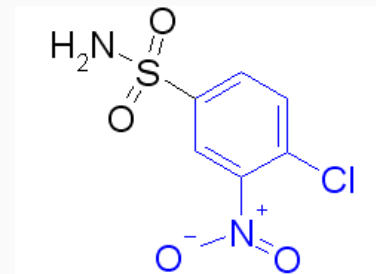
Chloro nitro benzene

Query chemical

Substructure Search

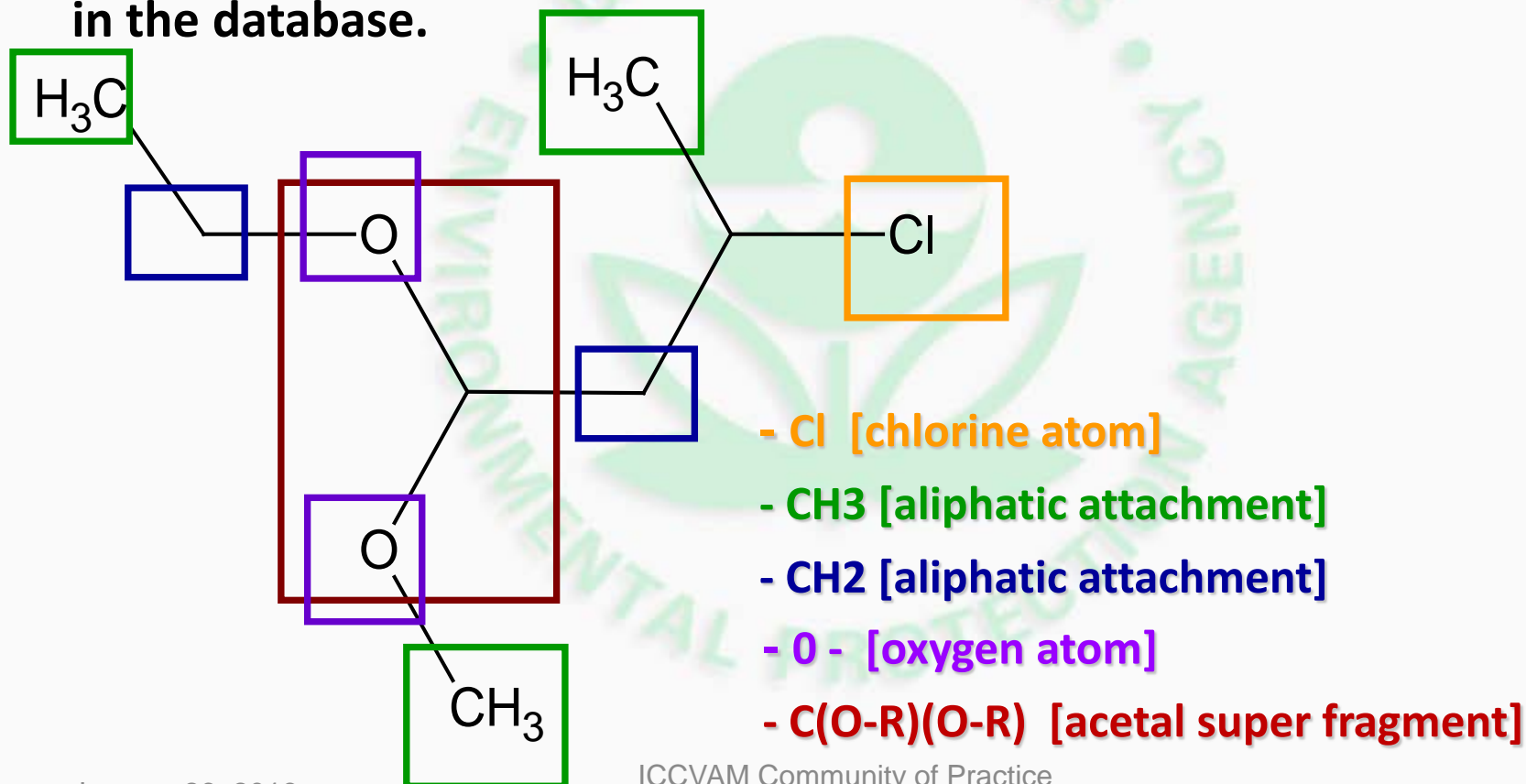


Analogs Returned??



...the AIM Approach

AIM uses a more comprehensive structural analysis of all functionalities to identify analogs using a fragment-based approach with over 700 individual *atoms, groups and super fragments* indexed in the database.





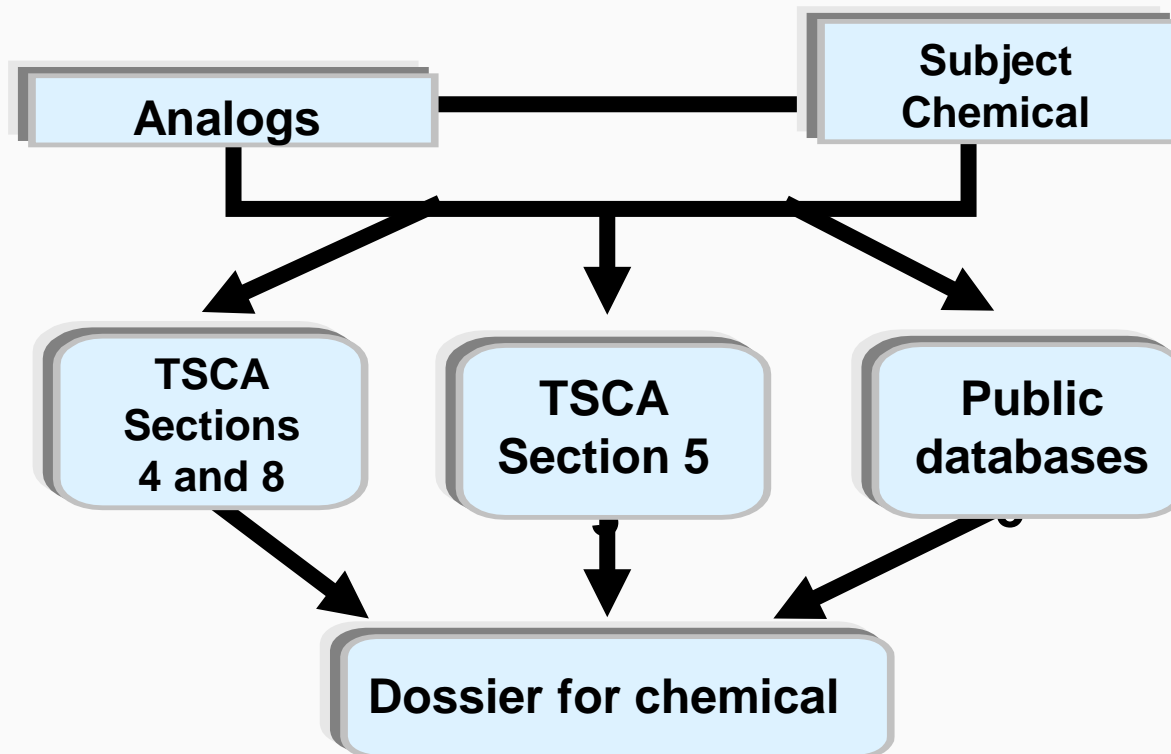
AIM Approach (cont.)

- AIM provides higher selectivity for analog identification than a substructure search engine.
- AIM focuses on analogs with available measured data from public sources focused on eco and health hazard data
- The AIM approach yields smaller groups of more closely related analogs than general substructure engines
 - users spend less time searching through analogs and data points.
- This also means sometimes AIM won't provide any analogs - when other search engines may



Structure Activity Team Search Strategies

Identify information for the subject chemical and analogs from the submission, in-house sources, public databases





Structure Activity Team (SAT) Meeting

Human Health Hazard Evaluation

- Determine the likelihood of absorption (by all routes)
- Identify possible effects/concerns based on all the information (submitted data, analogs with data, professional judgement)
- HOW WE USE: Occupational risk assessment, M(SDS) and Personal Protective Equipment (PPE) recommendation, to identify data gaps and inform testing strategies



Chemical Absorption

- Absorption is necessary for most chemicals to be systemically toxic
 - Degree of absorption often varies by exposure route (oral, dermal, inhalation)
 - Important when you are extrapolating across routes
- Absorption potential may be estimated using measured data or using physical/chemical properties
 - Molecular weight, Kow, water solubility, physical state
- Not appropriate for portal of entry effects



Assessing Non-Cancer Effects

- Currently OPPT does not use quantitatively predictive QSAR models to estimate non-cancer effects
 - Other commercial tools are available, but there are hurdles to implementing these techniques (cost, transparency, availability, etc.)
- Non-cancer assessment are based on available experimental data for the compound of interest and closely related analogs
- Assessments include a broad range of acute, subchronic, and chronic endpoints



Assigning Concern Levels for Non-Cancer Effects

Hazard Concern	Definition - Experimental Data
Low	No basis for concern identified <i>or</i> systemic toxicity with NOAEL > 1000 mg/kg/day; only minor signs of toxicity with LOAEL ≥ 500 mg/kg/day
Moderate	Suggestive animal studies for chemical or analog(s) <i>or</i> chemical class known to produce toxicity <i>or</i> organ pathology (gross and/or microscopic) with LOAEL < 500 mg/kg/day; NOAEL < 1000 mg/kg/day
High	Evidence of adverse effects in humans <i>or</i> conclusive evidence of severe effects in animal studies. Death, organ pathology (microscopic) at LOAEL ≤ 100 mg/kg/day; multiple organ toxicity; NOAEL ≤ 10 mg/kg/day.



Assessing Cancer Effects

- OncoLogic™ is an expert system that evaluates the likelihood that a chemical may cause cancer using an expert system SAR.
- Using a series of user provided inputs, OncoLogic™ mimics the judgment of experts by following sets of knowledge rules that are based on studies of how chemicals cause cancer in animals and humans.



Major Data Sources Used to Develop Cancer Knowledge Rules

- Chemical Induction of Cancer monograph series
- IARC monograph series
- NCI/NTP technical reports
- Survey of compounds which have been tested for carcinogenic activity, PHS Publ. 149
- Non-classified EPA submission data from various EPA program offices



Cancer Concern Levels

Concern Level	Definition
Low	Unlikely to be carcinogenic
Marginal	Likely to have equivocal carcinogenic activity
Low – Moderate	Likely to be weakly carcinogenic
Moderate	Likely to be a moderately active carcinogen
Moderate – High	Highly likely to be a moderately active carcinogen
High	Highly likely to be a potent carcinogen



Structure Activity Team (SAT) Meeting

Ecotoxicity (Aquatic) Hazard Evaluation

- Use of available data, analogs and ECOSAR approach/model
- ECOSAR: A computer program that integrates knowledge about chemical structure and toxic effects to predict aquatic toxicity
- Fish, aquatic invertebrates, algae, and others
- Has library of > 120 class-based QSARs for predicting toxicity of a chemical to aquatic organisms
- ECOSAR is freely available to download: <http://www.epa.gov/tsc-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model>
- HOW WE USE: Develop acceptable levels in receiving waters; mitigate water releases; identify data gaps and inform testing strategies



ECOSAR

- Computer program that uses collective knowledge about chemical structure to predict toxicity to aquatic organisms
- ECOSAR utilizes a combination of biology (mechanism) and chemistry (structural similarity principles) to organize the universe of chemicals into classes and derive class-specific QSARs
- This library of class-based QSARs for predicting aquatic toxicity is overlaid with an expert decision tree for selecting the appropriate chemical class.



How ECOSAR Predicts Toxicity

- Class equations are derived from measured toxicity data for chemicals in the class (training set chemicals)
 - Measured data must meet study criteria
- Most resulting regression equations are linear and relate *predicted** $\log K_{ow}$ to measured toxicity values within the class of interest

* Can also use measured $\log Kow$



Standard Aquatic Toxicity Profile

Endpoint	Measured or Predicted Value
Fish LC ₅₀	Experimental Data or ECOSAR Data
Daphnid LC ₅₀	
Green algae EC ₅₀	
Fish Chronic Value	
Daphnid Chronic Value	
Green algae Chronic Value	



Category and Class-based Information

- **U.S. EPA New Chemical Category Statements**
 - After several years of experience in the review of PMNs, EPA/OPPT had enough experience to group chemicals with shared chemical and toxicological properties into categories
 - Enabled submitters and EPA reviewers to benefit from the accumulated data and past decisional precedents
- **Currently, there are a total of 56 categories**
 - Categories are not necessarily the substances of greatest concern to EPA, but rather include chemicals for which sufficient history has been accumulated so that hazard concerns and testing recommendations vary little from chemical to chemical

<http://www.epa.gov/opptintr/newchems/pubs/chemcat.htm>



Example U.S. EPA Category Statement (Anhydrides, Carboxylic Acid)

- **Hazard Concerns**

- Carboxylic acid anhydrides are of concern for potential pulmonary sensitization based on data for phthalic, trimellitic, isopropylidene bis(phthalic), and sulfonyl bis(phthalic) anhydrides. Carboxylic acid anhydrides are also of concern for potential developmental or reproductive toxicity based on data for maleic, succinic.....
- The EPA New Chemical Program has thus far been concerned only with those carboxylic acid anhydrides with potentially significant inhalation exposure, and has pursued developmental toxicity only for low molecular weight (<500) carboxylic acid anhydrides that are thought to have a significant potential for systemic uptake via the lung. For pulmonary sensitization,



Part III

Some Data on PMN Submissions...



Since 1979...

▶ **New Chemical Notifications Reviewed**

- *Total Valid Notifications reviewed since 1979: > 56,000*
 - Total Valid Notifications: \simeq 41,000
 - Total Valid Exemption Notifications: \simeq 15,000
- EPA currently reviews 1,200 Notifications/Exemptions per year

....but, only about 50% of the PMNs are actually produced or imported into the US.



More Stats and Data...

- **TSCA Inventory**
 - Total Chemicals now on TSCA Inventory: >85,000*
 - New Chemicals as a % of the TSCA Inventory: ~27%
 - CBI Chemicals as a % of the TSCA Inventory: ~19%
- **Testing data received: ~10-15% (next two slides)**

* Roughly 62,000 from 1979 inventory plus 23,000 “new” chemicals



Health Study Stats

			Initial Submission Stats		Post Submission Stats	
			Notifications Initially Containing Health Data	% With Initial Health Data	Notifications with Post Submission Health Data	% With Post Submission Health Data
	Total Notifications	Notifications with No Health Data				
2004	1330	1031	268	20.15%	31	2.33%
2005	1184	946	200	16.89%	38	3.21%
2006	1137	905	203	17.85%	29	2.55%
2007	1097	896	169	15.41%	32	2.92%
2008	1114	893	181	16.25%	40	3.59%
2009	1009	833	136	13.48%	40	3.96%
2010	1021	857	143	14.01%	21	2.06%
2011	1129	933	150	13.29%	46	4.07%
2012	932	746	134	14.38%	52	5.58%
Averages	1106	893	176	15.74%	37	3.36%



Ecotox Study Stats

			Initial Submission Stats		Post Submission Stats	
			Notifications Initially Containing Ecotoxicity Data*	% With Initial Eco Data	Notifications with Post Submission Ecotox Data	% With Post Submission Ecotox Data
	Total Notifications	Notifications with No Ecotoxicity Data				
2004	1330	1167	154	11.58%	9	0.68%
2005	1184	1056	119	10.05%	9	0.76%
2006	1137	1017	110	9.67%	10	0.88%
2007	1097	981	112	10.21%	4	0.36%
2008	1114	996	105	9.43%	13	1.17%
2009	1009	923	76	7.53%	10	0.99%
2010	1021	927	89	8.72%	5	0.49%
2011	1129	1001	113	10.01%	15	1.33%
2012	932	847	82	8.80%	3	0.32%
Averages	1106	991	107	9.56%	9	0.78%

* On Average 15% of the data noted above for initial submission is actually studies for an analogous chemical - not the PMN itself. However, the analog data must still be reviewed for appropriateness (requires staff/contractor time) so it was included in this exercise.



Acknowledgements

- The New Chemicals Structure Activity Team (SAT):
 - Leonard Keifer
 - Becky Jones
 - Kendra Moran
 - Doritza Pagan-Rodriquez
- Others:
 - Kelly Mayo, Yintak Woo



Thank You!

scarano.louis@epa.gov

URL for New Chemicals Program:

<http://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca>

URL for OPPT Tools: <http://www.epa.gov/tsca-screening-tools>