U.S. EPA Experiences Using Category Approaches

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Categories – Old and New

- Classical Categorization (Plato & Aristotle)
  - grouping objects based on similar properties and analyzing differences between
  - clearly defined, mutually exclusive and collectively exhaustive; any entity of the given classification belongs unequivocally to one, and only one, category

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- Conceptual Clustering (modern; since

New Chemical Categories - Why

- TSCA Section 5 (1976) - Pre-manufacture Notice (PMN)
  - little or no hazard data/information submitted
  - ~2,000 per year (35-40 per week)
- Prior to 1987, nearly 20% of PMNs submitted underwent a detailed review ("standard review") by EPA
  - highly resource-intensive
  - consumes most of the mandated 90-day PMN review period
- After 1987, based on accumulated experience, EPA began grouping PMN chemicals with shared chemical and toxicological properties into categories
  - to facilitate consistency and efficiency in review
  - focused on chemical classes that most often triggered "unreasonable risk" finding, i.e. impetus was 'risk-based'
- 2002 - EPA published TSCA New Chemicals Program Chemical Categories Report: http://www.epa.gov/oppt/newchems/pubs/chemcat.htm

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New Chemical Categories - What

- New Chemicals Category:
  - Human Health, Environmental, or both
  - Category Statement - describing molecular structure
  - Boundary Conditions - e.g. molecular weight, log Kow, or water solubility
  - Tiered Testing Strategy (hazard and fate)
- Hazard concerns and testing recommendations vary little from chemical to chemical within the category (based on cumulative experience)
- NOT necessarily the most hazardous substances; rather those that most often result in "unreasonable risk"
- NOT comprehensive lists of all substances that may be hazardous or subject to further action
- Currently, 54 New Chemical Categories:
  - 46 Environmental
  - 25 Human Health

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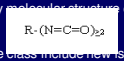
ABBREVIATED EXAMPLE NEW CHEMICALS CATEGORY – HUMAN HEALTH

Category: Diisocyanates Human Health
Definition. Any molecular structure containing two or more isocyanate groups is considered to be a member of the category for new chemical purposes:



Members of the class include new isocyanate monomers as well as new oligomers, polymers, prepolymers, or reaction products of existing isocyanate monomers. Most new chemical diisocyanates of concern are polymers or oligomers containing well-known diisocyanate monomers such as toluene diisocyanate (TDI) or 4,4'-methylenediphenyl diisocyanate (MDI).
Hazard Concerns. Diisocyanates are of concern for potential dermal and respiratory sensitization, and for pulmonary toxicity. Based on conflicting animal and human data for respiratory sensitization, the Agency has determined that there is presently not a reliable animal model for testing diisocyanates for potential respiratory sensitization. At this time, it is assumed that all diisocyanates may be potential human respiratory sensitizers. Most members of the diisocyanate category have not been tested for carcinogenic potential. Though the aromatic diisocyanates [MDI, TDI, dianisidine diisocyanate (DADI)] tested positive and one aliphatic diisocyanate [hexamethylene diisocyanate (HDI)] tested negative in one species, it is premature to make any generalizations about the carcinogenic potential of aromatic versus aliphatic diisocyanates.
Boundaries. Structures with an isocyanate equivalent weight of ≥5,000 are presumed not to pose a hazard under any conditions. Typically, concerns are confined to those species with molecular weights <1,000.
General Testing Strategy. The following testing is recommended to address the potential for pulmonary toxicity and dermal sensitization.
1. Dermal sensitization (OPPTS 870.2600).
2. 90-day Subchronic inhalation toxicity test in rodents (OPPTS 870.3465).

In addition, appropriate hazard communication needs to be developed and implemented.
Health and Safety Information. The following information provides guidance in developing hazard communication and protective measures language to accompany new diisocyanate chemicals and formulations. It is based on the Agency's current understanding of the hazards associated with diisocyanates and the most effective means to limit exposure.
Warnings. Exposure to diisocyanates may cause the following human health effects: skin irritation and allergic reactions, respiratory irritation, respiratory sensitization, and lung toxicity; some diisocyanates also may cause cancer. The likelihood that these effects will occur depends on a number of factors; among them, the level of exposure, frequency of exposure, part of the body exposed, and sensitivity of the exposed individual.
Symptoms of allergic reaction and respiratory sensitization include rashes, cough, shortness of breath, asthma, chest tightness and other breathing difficulties. There is uncertainty as to the mechanism by which sensitization occurs. In sensitized individuals, exposure to even small amounts of diisocyanates (below government-recommended workplace exposure levels) may cause allergic respiratory reactions like asthma and severe breathing difficulties**….**
Protective Measures. In workplaces where individuals handle diisocyanates or coatings or other formulations that contain them, an industrial hygiene and safety program should be operative. Important components of this program include: hazard communication and training on safe handling practices; use of efficient and well-maintained application equipment, engineering controls and personal protective equipment; housekeeping procedures including spill prevention and cleanup practices; and, if feasible, means to measure airborne levels of polyisocyanates and diisocyanates.
During spray applications, workers should take precautions to avoid breathing vapors, mists or aerosols. Inhalation exposures should be limited to <0.05 mg/m^3 as an 8-hour time-weighted average (TWA) for combined polyisocyanates and diisocyanates. [1/] Engineering controls should serve as the first, most effective means of reducing airborne polyisocyanate and diisocyanate concentrations; an appropriate NIOSH/MSHA-approved respirator should be used as a secondary tool to lower exposures**…**
May 1990, revised July 1993, February 1995, and February, 1997

EXAMPLE NEW CHEMICALS CATEGORY – ENVIRONMENTAL

Category: Anilines Environmental Toxicity
Definition: This category includes all anilines, both monoanilines and polyanilines. It is assumed that these compounds need to be absorbed to be toxic, therefore, compounds with MWs > 1000 will be excluded from this category. Above a log Kow value of => 7.38, anilines show no effects at saturation during 96-h exposures (Veith and Broderius (1987). Anilines which are solids at room temperature may show no toxicity at saturation at lower Kow values depending on the melting point, i.e., the higher the melting point at a given Kow, the greater the likelihood that no toxicity will be observed at saturation. For solids, the no effects at saturation has to be determined on a case-by-case basis.

Hazard Concerns. The acute toxicity for anilines has been determined through SAR Analysis:
Fish 96-h LC50 (**Veith and Broderius** 1987); Fish 14-d LC50 (Deneer et al 1987); Fish 14-d LC50 (Hermens et al 1984); Daphnids 48-h LC100 (Nendza and Seydel 1988a and 1988b); and Green algal 96-h EC50 (Nendza and Seydel 1988a and 1988b); Aromatic diamines (i.e., two amines on one benzene) and dinitroanilines are known to be more toxic than predicted by these SARs.

Boundaries. There are no known lower boundaries. The upper boundaries will be based on Kow and MW. Acute toxicity expected with log Kow < 7.38; no effects at saturation during 96-h exposures when log Kow >= 7.38. Chronic toxicity has no known upper bound for log Kow, but it is probably near 8. MW will be < 1000. The environmental base set of tests will be requested for aquatic releases and the terrestrial base set of tests will be recommended for terrestrial exposures. When the log Kow is >= 7.38, chronic toxicity testing with fish and daphnids will be recommended.

General Testing Strategy.
I. Release to Aquatic Ecosystems:
Tier 1. The aquatic base set of environmental toxicity tests will be recommended for aquatic exposures. The acute toxicity tests for fish (40 CFR 797.1400) and daphnids (40 CFR 797.1300) will be done using the flow-through method with measured concentrations; …
The algal toxicity testing (40 CFR 797.1050), should be done with static methods; measured concentrations.; …
Tier 2. Direct and Indirect Photolysis Screening Test (40 CFR 796.3765). If t½ ≤ 2 days, go to Tier 3; if t½ > 2 days, go to Tier 4.
Tier 3a. If t½ ≤ 2 days and photolysis products are known and/or identified, then assess photolysis products for environmental hazards.
Tier 3b. If t½ ≤ 2 days and photolysis products are not known and/or identifiable, then prepare a stock solution of PMN using the standard humic-containing solution described in the direct and indirect photolysis screening test [40.796.3765 (b)(2) and (c)(2)], …
Tier 4.
Fish chronic toxicity testing, i.e., fish early life stage (ELS) toxicity testing (40 CFR 797.1600), with flow-through methods; measured concentrations; … and the 7-d ELS stage toxicity test cannot be substituted for the 28-d ELS toxicity test because Van Leeuwen et al (1990) have demonstrated that the 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen);

Daphnid chronic toxicity testing (40 CFR 797.1330), with flow-through methods; measured concentrations; …and the 7-d daphnid chronic toxicity test cannot be substituted for the 21-d toxicity test because Van Leeuwen et al (1990) have demonstrated that the fish 7-d ELS toxicity test underestimated the chronic toxicity of anilines measured by the fish 28-d ELS toxicity test by >5.3 times when the NOECs were compared (see Table VII in Van Leeuwen).

II. Release to Terrestrial Ecosystems: The terrestrial base set of environmental toxicity tests (i.e., the early seeding growth test, the earthworm toxicity test and the soil microbial community bioassay) will be recommended for terrestrial exposures. Chronic toxicity testing for terrestrial organisms include: the plant whole life cycle test, the plant uptake test, and the soil microbial community bioassay.
May, 1991

New Chemical Categories - Lessons

Use of Categories:

- Benefits EPA reviewers and PMN submitters
- Increases confidence in the assessment a new substance with limited data
- Streamlines the review process and facilitates earlier decision-making
  - Only 2-3% of the total number of PMNs submitted undergo a standard review; down from 20% before categories
- Focuses program resources on development of risk management and control
  - ~ 10% of PMNs trigger "unreasonable risk" finding and require regulatory action by the Agency

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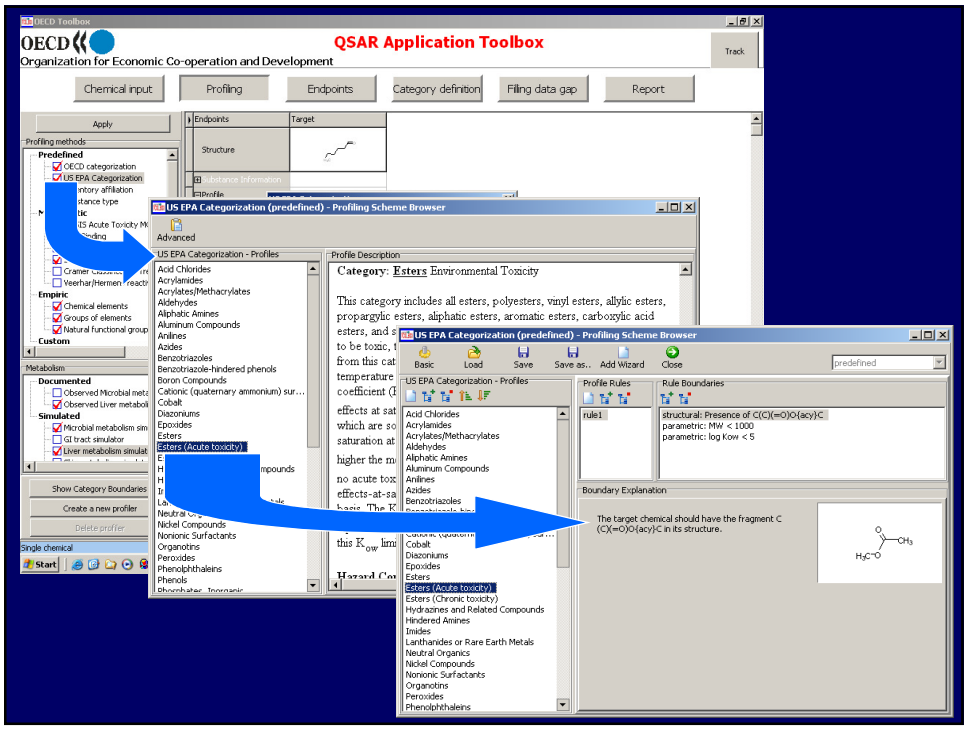

HPV Categories - Why

- 1998 – EPA Chemical Hazard Data Availability Study
  - US imports or produces ~ 3,000 High Production Volume Chemicals (HPV = more than 1 million lbs/yr)
  - 7% have a full set of basic test data
  - 43% have no test data
- 1998 – Chemical Right-to-Know Initiative launched, including the High Production Volume (HPV) "Challenge" Program
  - Essentially the same as OECD HPV Programme; U.S. EPA involved since inception
- 2007 – Companies have sponsored more than 2,200 HPVCs
  - Screening Information Data Set (SIDS) = 18 internationally agreed endpoints
- Categories accomplish the goal to obtain screening level hazard information, but using a strategic approach to testing across the category

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HPV Categories - What

- A group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity.
- Similarities based on:
  - a common functional group (e.g., aldehyde, epoxide, ester, etc.)
  - common precursors and/or breakdown products
  - an incremental and constant change across the category
- Categories can apply to series of chemical reaction products or chemical mixtures that are related in some regular fashion
- NOT Mutually Exclusive – a substance can belong to more than one category
  - Endpoint-specific - i.e., those selected for environmental effects endpoints may not be suitable for assessing human health effect endpoints
  - Subcategories
- NOT Comprehensive or Exhaustive
  - defined by high volume manufacture
  - dependent on which chemicals manufactured by a sponsoring company or consortium

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- EPA and OECD HPV Categories are hazard-based; no outcomes included

HPV Categories - Examples

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HPV Categories - Lessons

- Data from tested category member(s) can be interpolated/extrapolated to untested members; do not need to test every endpoint for every chemical
- Category evaluation of hazard
  - is based on a greater weight of evidence
  - provides better basis for establishing biological plausibility
  - increases robustness of the evaluation
- Category analysis facilitates strategic testing
  - weight of evidence used for deciding need for additional testing
  - defines the nature and scope of any testing needs
  - testing often completed faster
- Categories can be reduced (subcategories) or expanded

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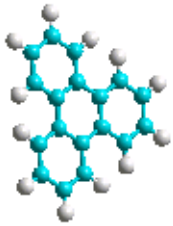
Integration of Category Approaches



Analog Identification Methodology

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AIM Methodology

- A pre-indexed database of 645 molecular fragments
  - Flags chemicals that 'fit' structural definition for New Chemicals Human Health Categories
  - Flags chemicals where metabolites may be of concern
- A second database with links to publicly available toxicity data
  - 31,031 potential analogs with publicly available toxicity data
  - On-Line Databases: TSCATS, HSDB, IRIS
  - U.S. Government Documents
    NTP, ATSDR, HPV Challenge Program
  - Other Sources: DSSTox, RTECS, IUCLID, AEGLS

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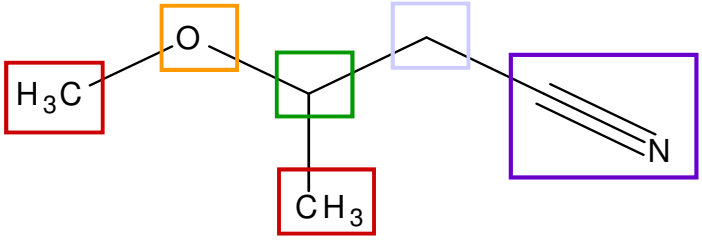
AIM Methodology

Analog Identification Methodology

AIM identifies analogous compounds using a chemical fragment-based approach with 645 individual *fragments* indexed in the database.



-CH3 [aliphatic carbon]

-O- [oxygen, aliphatic attach]

-CH2- [aliphatic carbon]

-CH [aliphatic carbon]

-C#N [cyano, aliphatic attachment]

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Analog Identification Methodology

Analog Identification Methodology

The Analog Identification Methodology (AIM) was designed to help identify publicly available, experimental toxicity data on closely related chemical structures

Main | CAS | SMILES | Name | Draw | Results

The AIM database contains 31,031 chemicals.

Home
Methodology
Data Sources
Security and Anonymity
Terms of Use
Comments

The following chemical will be run in AIM:

CAS Number:	141322	Update CAS
Chemical Name:	2-Propenoic acid, butyl ester	Update Name
Smiles Notation:	O=C(OCCCC)C=C	
Chemical Structure:		

Find Analogs Clear All

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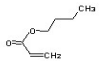
Found 12 Analog(s) for 2-Propenoic acid, butyl ester:

Analog Identification Methodology

Exact Chemical Match:

# of Studies: 3	BUTYL ACRYLATE [CAS No. 141-32-2]		
	Toxicity Data Available for this Compound		
	On-Line Databases	U.S. Government Documents	Other Sources
	TSCATS HSDB		RTECS IUCLID

- Based on its structure, this chemical may belong to the acrylates/methacrylates. Members of this category may have potential human health concerns. More information and category definitions
- This compound may metabolize in the body to products that may cause concerns for human health. Analogs for metabolites should also be investigated. Metabolism classes found: terminal double bond, ester, and acrylate

Analogs, Ordered by Number of Studies:

# of Studies: 5	ETHYL ACRYLATE [CAS No. 140-88-5]		
Analog # 1 	Toxicity Data Available for this Compound		
	On-Line Databases	U.S. Government Documents	Other Sources
	TSCATS HSDB	NTP	RTECS IUCLID DSSTox Cancer

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AIM Clustering Tool/Category Builder

- AIM fragment matching algorithm expanded to organize data sets to identify "structural clusters" of chemicals
- Applied to multiple EPA databases (PMNs, HPV, 8(e), IUR) to formulate structure-based categories; "structural clusters"

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Category Approaches in EPA's Pesticides Program

- Simple Read-Across (Bridging) has been used to bridge for structural and stereoisomers
  - EXAMPLE: environmental fate and ecotoxicity data for cypermethrin used in the ecological risk assessment for zeta-cypermethrin
- Category Approach has been used for sediment toxicity data for benthic organisms
  - EXAMPLE: The pyrethroids: bifenthrin, cyfluthrin, cypermethrin and esfenvalerate, were selected to represent the full distribution of pyrethroids persistence and toxicity to aquatic species (fish and invertebrates)
  - Based on structural similarity and same mode of action

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Pesticides Risk Assessment

- 1996 - Food Quality Protection Act (FQPA), mandates that the Agency must assess the cumulative risks of pesticides that share a common mechanism of toxicity
- 1999 – EPA published "Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity" http://www.epa.gov/fedrgstr/EPA-PEST/1999/February/Day-05/6055.pdf
- Cumulative risk assessments for four groups of pesticides:
  - Organophosphates (OPs)
  - N-methyl carbamates
  - Triazines
  - Chloroacetanilides

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Conclusions

- U.S. EPA and others have used Chemical Categories
  - For ~ 2 decades
  - To assess hazard and risk of 1000s of chemicals
- Chemical Categories are a practical way to:
  - Extrapolate data gathered for HPV chemicals (few thousand) to lower volume chemicals (several thousands),
  - To meet goals of assessing large number chemicals (U.S. EPA TSCA; REACH; Canadian DSL), and
  - Guide/Organize Integrated Testing Strategies (e.g., U.S. NAS Report; EU OSIRIS)

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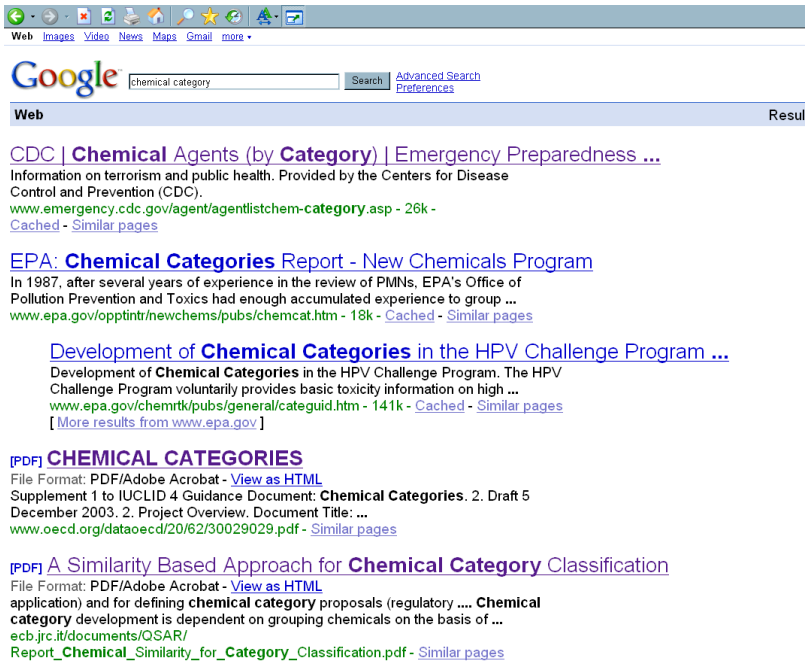

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Categorization

- The process in which idea and objects are recognized, differentiate, and understood
- Implies that objects are grouped into categories, usually for some specific purpose
- Ideally, a category illuminates a relationship between the subjects and objects of knowledge
- Is fundamental in language, prediction, inference, decision making and all kinds of interaction with the environment

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