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Linking Molecular Structure to Functional Group and Chemical Literature Using a Chemical Reaction Database

American Institute of Chemical Engineers Annual Meeting
Big Data and Sustainability
October 29, 2018

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Chemical Alternatives Assessment

- **Involves comparing the potential human health and environmental effects of an identified alternate to a chemical of concern (CoC) throughout their life cycle.**
- **Focus of this work is identifying sustainable chemical synthesis routes that can be used for manufacturing of an identified alternate chemical.**
- **Inputs (reactants, catalysts and other reaction aids), as well as outputs (desired products and by-products) can be identified based upon the type of reaction used.**
- **The life cycle risk evaluation of a candidate manufacturing process can then be developed based upon the reaction participants throughout the lineage.**

Chemical Lineage

- A chemical compound (child) is produced by a chemical reaction from reactants (parents).
- The parent compounds are produced from their parents.
- Forms a lineage where a chemical has ancestors.
- Life Cycle Inventory (LCI) information for a chemical can be obtained by aggregating the LCI information for its ancestors combined with the emissions that occur during the chemical's manufacture.
- Ancestor chemicals can be evaluated as CoCs and alternatives identified.

Mittal, Vinit K., Sidney C. Bailin, Michael A. Gonzalez, David E. Meyer, William M. Barrett, and Raymond L. Smith. 2018. 'Toward Automated Inventory Modeling in Life Cycle Assessment: The Utility of Semantic Data Modeling to Predict Real-World Chemical Production', ACS Sustainable Chemistry & Engineering, 6: 1961-76.

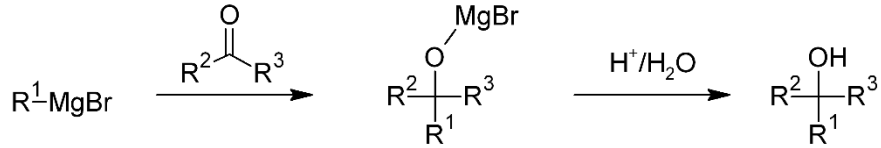
EPA Chemical Manufacturing Ontologies

- **Chemical Lineage Ontology:**
  - **Traces and identifies synthesis steps for producing a chemical from raw materials (*e.g.* crude oil, coal, natural gas).**
  - **Synthesis steps are typically name chemical reactions (*e.g.* Diels–Alder reaction).**
  - **For each step of the reaction sequence, a chemical has parents (reactants) and children (products).**
  - **Reaction conditions for each step are part of the ontology.**
- **Process Ontology**
  - **Unit operations that are required to carry out each of the synthesis steps.**
  - **Includes reactors, separation processes, storage, etc.**
  - **Emissions can be evaluated for each process step.**

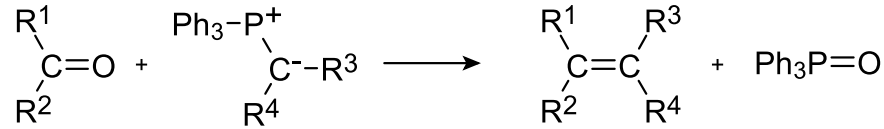
Mittal, V. K., S.C. Balin, M.A. Gonzalez, D.E. Meyer, W.M. Barrett, R.L. Smith (2018). "Toward Automated Inventory Modeling in Life Cycle Assessment: The Utility of Semantic Data Modeling to Predict Real-World Chemical Production." ACS Sustainable Chemistry & Engineering 6(2): 1961-1976.

Named Chemical Reaction

- General class of chemical reactions.
- Represent the mechanism used to produce a class of chemicals from a class of reactants under similar conditions.
- Involves formation of one functional group from one or more other functional groups.
- Examples:
  - Grignard reaction – alkylation of a carbonyl group.



  - Wittig reaction – alkene from carbonyl group.

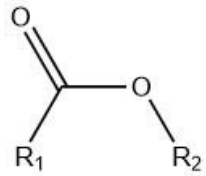
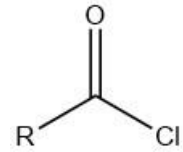
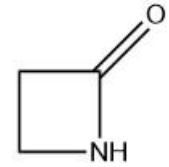
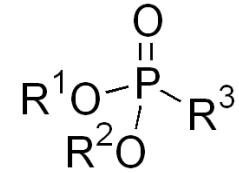


- Our current database contains about 200 named reactions.

Reaction images from Wikipedia.

Functional Group

- **Arrangement of atoms and bonds within a molecule with well characterized reaction properties.**
- **Examples:**

	Ester	Acyl halide	Lactam	Phosphonate
				
SMARTS	**C(=O)OC**	**C(=O)X**	**C(=O)NC In a ring**	**COP(C)(=O)OC**

- **Functional groups usually undergo the same or similar reactions typically regardless of the remainder of the molecule.**
- **Allows for systematic identification of reactions associated with a functional group.**

Application Overview

- Includes a chemical informatics class library.
- Class library can be exposed as a web service that allows users to obtain a list of functional groups and named chemical reactions associated with the functional groups within an identified chemical structure.
- Application currently written in C#.
- Accessed using a Windows Forms desktop application.
- Input is a structural representation of the molecule
  - Simplified Molecular-Input Line-Entry System (SMILES)
  - Chemical table (MOL) file from TEST.
- Output can either be a JSON serialized set of results or a web page.

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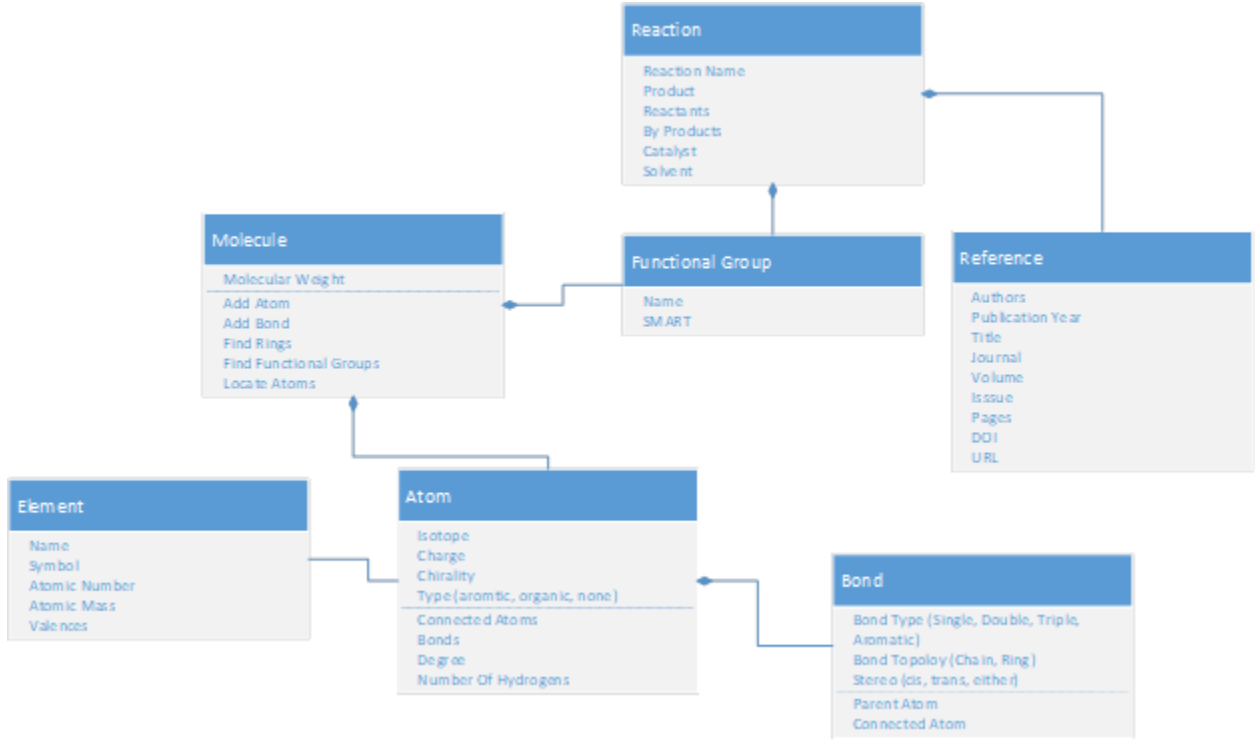
Chemical Informatics Class Diagram



Application Overview

- **Atom Class**
  - **Nodes of the molecule graph.**
  - **Contains a collection of connected atom objects and bonds.**
  - **Obtains information about atom from Element Class.**
- **Element Class**
  - **Chemical Element Information from Blue Obelisk Data Repository (https://sourceforge.net/projects/blueobelisk/).**
- **Bond Class**
  - **Edges of the molecule graph.**
  - **Bond type (single, double, triple, aromatic)**
  - **Stereo orientation (cis/trans)**

Application Overview

- **Molecule Class**
  - **Contains a collection of Atom objects.**
  - **Ring Identification using Tarjan Depth First Search**
  - **SMILES/SMARTS matching using VF2 Subgraph Isomorphism Algorithm**
  - **Aromaticity detection/Kekulization.**
- **SMILES/SMARTS Parser**
  - **Converts SMILES/SMARTS into an instance of the Molecule Class.**
  - **Grammar based upon OpenSMILES (http://opensmiles.org/)**
  - **Built using ANTLR4 (www.antlr.org).**
- **MOL File Parser**
  - **Used to import TEST output**

Chemical table file specification is available at http://download.accelrys.com/freeware/ctfile-formats/ctfile-formats.zip (December 2011)
Tarjan, R. (1972). "Depth-First Search and Linear Graph Algorithms." SIAM Journal on Computing 1(2): 146-160.
Cordella, L. P., et al. (2004). "A (Sub)Graph Isomorphism Algorithm for Matching Large Graphs." IEEE Trans. Pattern Anal. Mach. Intell. 26(10): 1367-1372.

Application Overview

- **Functional Group Class**
  - **SMiles ARbitrary Target Specification (SMARTS) string representing the functional group's structural subgraph of atoms/bonds.**
- **Named Reaction Class**
  - **List of reactant and product functional groups.**
  - **Associated with the desired functional group.**
  - **Keywords to enable online search using Google scholar, etc.**
- **Reference Class**
  - **Contains information for journal article associated with a reaction.**
  - **Input as an Endnote (RIS) file that can be obtained from the journal.**
  - **Has URL/DOI to enable access of the article from journal web site.**

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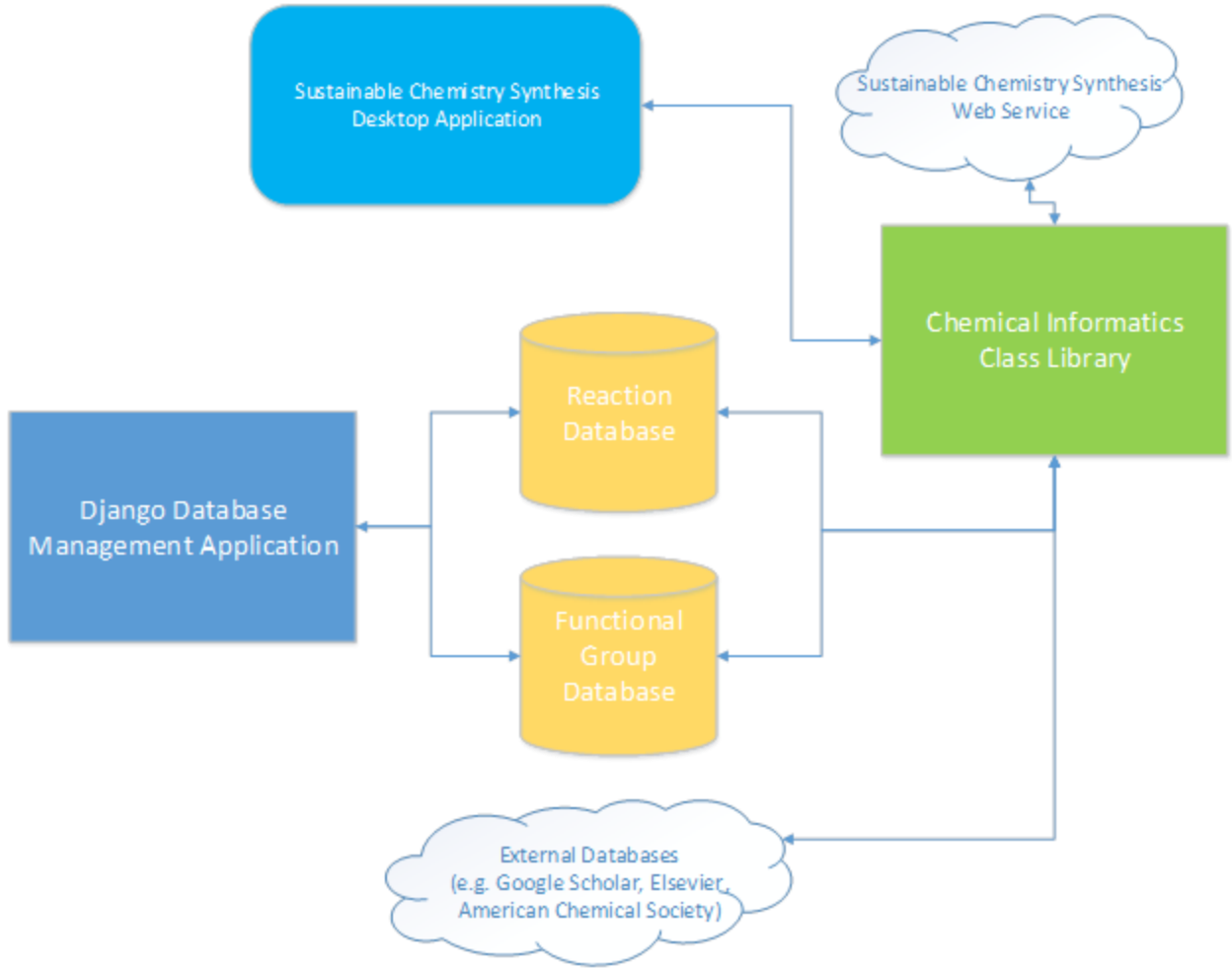
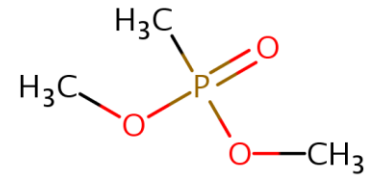
Application Block Diagram



Case Study

- **Brominated flame retardants**
  - **Persistent/Bioaccumulative**
  - **Toxic to humans**
  - **Banned by the European Union**
  - **No longer produced by some US manufacturers**

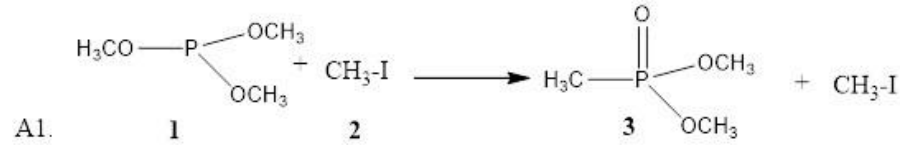
- **Proposed Alternative**
  - **Dimethyl methylphosphonate**



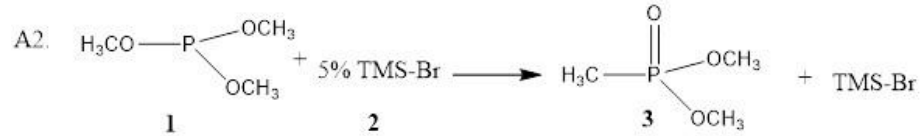
Covaci, Adrian, Stuart Harrad, Mohamed A. E. Abdallah, Nadeem Ali, Robin J. Law, Dorte Herzke, and Cynthia A. de Wit. 2011. 'Novel brominated flame retardants: A review of their analysis, environmental fate and behaviour', *Environment International*, 37: 532-56.
van der Veen, Ike, and Jacob de Boer. 2012. 'Phosphorus flame retardants: Properties, production, environmental occurrence, toxicity and analysis', Chemosphere, 88: 1119-53

Synthesis of Dimethyl Methylphosphonate

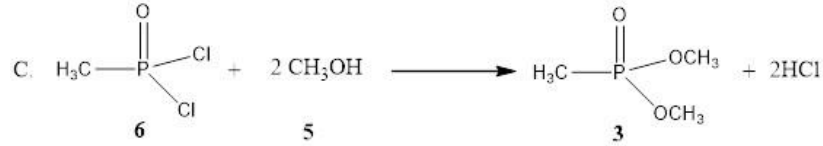
Michaelis-Abruzov Reaction



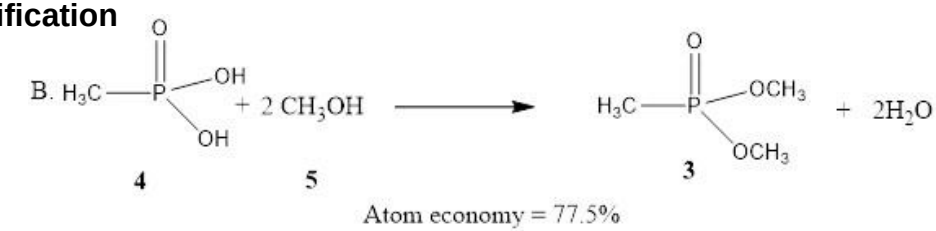
TMS-promoted Michaelis-Abruzov



Solid phase



Alkylphosphonic acid esterification



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Evaluation of Synthesis Sustainability

- **Based on the Twelve Principles of Green Chemistry and Green Engineering**

- **Emphasizes reduce or eliminate environmental impacts by reducing or eliminating the use and generation of hazardous materials in the design, manufacturing, and application of chemical products**

Anastas, P.T., and J.C. Warner. 1998. Green Chemistry: Theory and Practice (Oxford University Press).
Anastas, Paul T., and Julie B. Zimmerman. 2003. 'Peer Reviewed: Design Through the 12 Principles of Green Engineering', Environmental Science & Technology, 37: 94A-101A.

Synthesis Sustainability Metrics

- **Atom Economy - simplest green chemistry metric.**
  - **Ratio of the mass of the reactants that is incorporated into the final desired product.**
  - **Does not consider solvents, catalysts, or auxiliaries.**

- **E-Factor - Ratio of the mass of waste to mass of product.**

- **Effective Mass Yield (EMY) - percentage of the mass of the product relative to the mass of all non-benign materials used in the synthesis.**

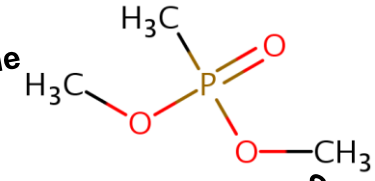
- **Process Mass Intensity (PMI) - ratio of the quantity of raw materials input to the quantity of bulk product output**

Trost, B. M. 1991. 'The atom economy--a search for synthetic efficiency', Science, 254: 1471.
Sheldon, Roger A. 1992. 'Organic synthesis - past, present and future. (advantages of incorporating catalysis to organic synthesis)', *Chemistry and Industry*, 23: 903-06.
Hudlicky, Tomas, Dean A. Frey, Lukasz Koroniak, Christopher D. Claeboe, and Larry E. Brammer Jr. 1999. 'Toward a 'reagent-free' synthesis', *Green Chemistry*, 1: 57-59.
ACS GCI PR. 2018. 'Tools for Green Chemistry & Engineering', ACS GCI Pharmaceutical Roundtable

What the application does…

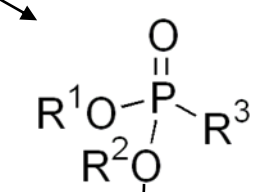
Enter Molecule's SMILES
O=P(OC)(OC)C

Step 1: Construct Molecule

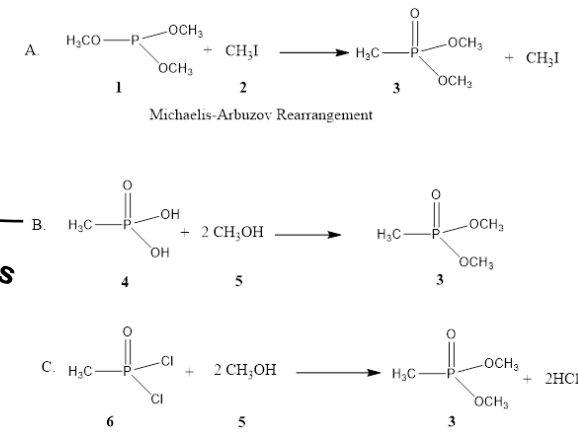


Step 2: Identify Functional Group

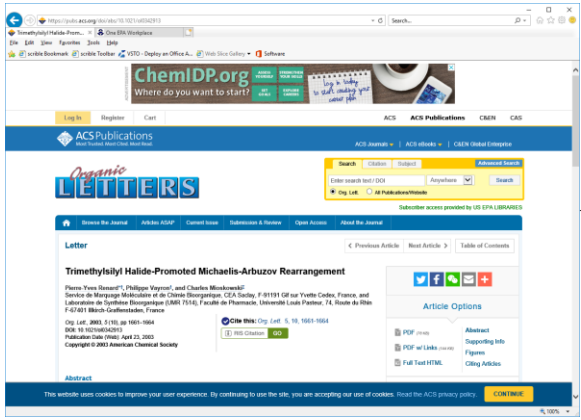
Dimethyl methylphosphonate



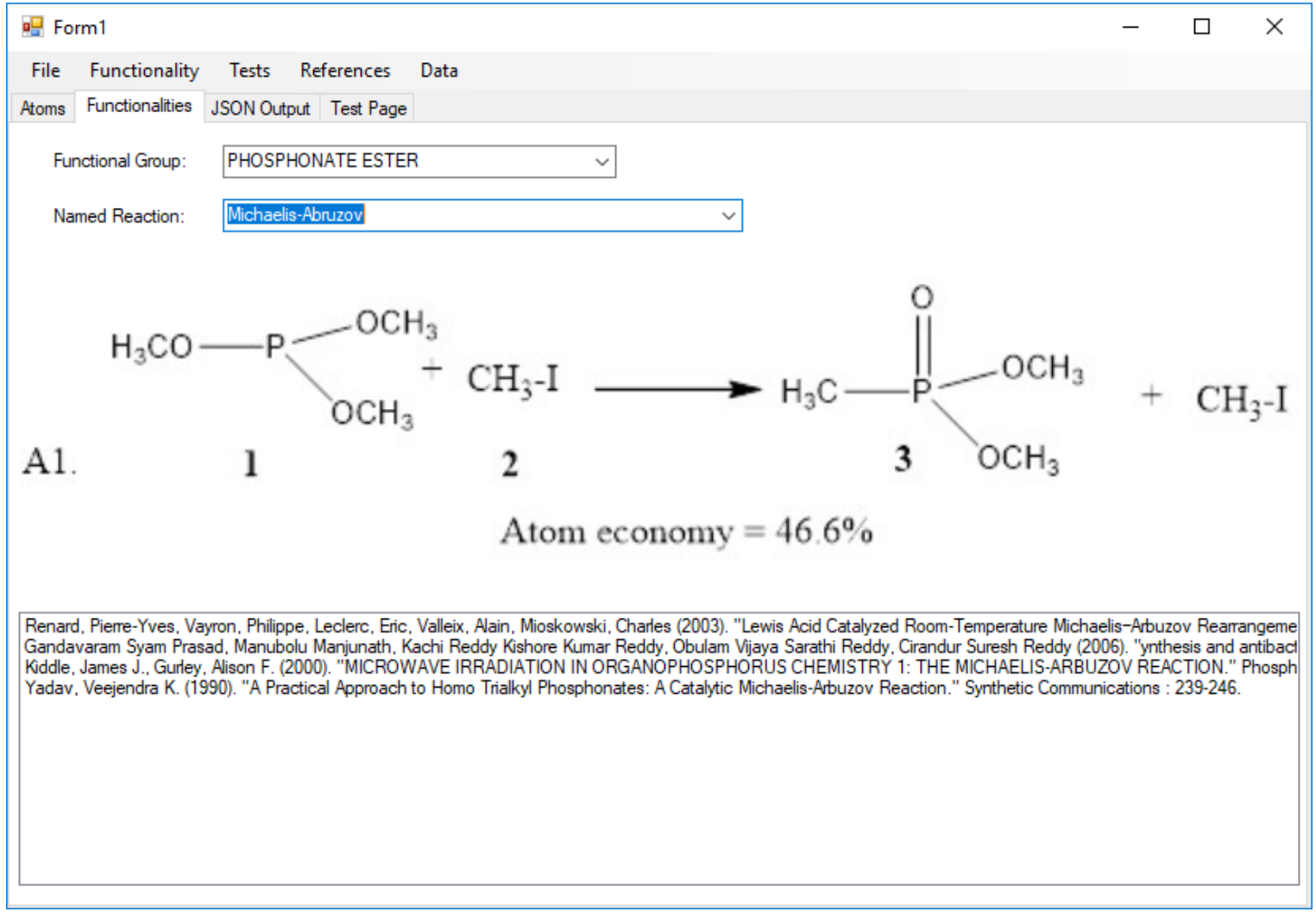
Step 3: Look Up Reactions



Step 4: Obtain References



Application Screen Shot



Alternatives Assessments Dashboard Hazard Profiles for the Synthesis of Dimethyl Methyl Phosphonate

	Acute Mammalian Toxicity Oral	Acute Mammalian Toxicity Inhalation	Acute Mammalian Toxicity Dermal	Carcinogenicity	Genotoxicity Mutagenicity	Endocrine Disruption	Reproductive	Developmental	Neurotoxicity Repeat Exposure	Neurotoxicity Single Exposure	Systemic Toxicity Repeat Exposure	Systemic Toxicity Single Exposure	Skin Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation
121-45-9 Trimethyl phosphite	M	N/A	M	N/A	L	L	H	H	N/A	N/A	M	N/A	N/A	H	H	L	N/A	L	L
74-88-4 Methyl iodide	H	H	M	VH	H	L	N/A	N/A	N/A	N/A	N/A	M	N/A	H	VH	VH	VH	H	L
2857-97-8 Bromotrimethylsilane	M	L	N/A	N/A	N/A	L	N/A	N/A	N/A	N/A	N/A	N/A	N/A	VH	VH	N/A	N/A	N/A	N/A
993-13-5 methyl phosphonic acid	M	N/A	N/A	N/A	L	L	N/A	H	N/A	N/A	N/A	N/A	N/A	N/A	N/A	M	N/A	N/A	L
67-56-1 Methanol	H	H	H	N/A	H	H	H	H	N/A	N/A	H	H	N/A	N/A	H	L	N/A	H	L
676-97-1 methyl phosphonic dichloride	VH	VH	N/A	N/A	L	L	N/A	H	N/A	N/A	N/A	N/A	N/A	N/A	N/A	L	N/A	N/A	L
67-56-1 Methanol	H	H	H	N/A	H	H	H	H	N/A	N/A	H	H	N/A	N/A	H	L	N/A	H	L

Martin, Todd M. 2017. 'A framework for an alternatives assessment dashboard for evaluating chemical alternatives applied to flame retardants for electronic applications', Clean Technologies and Environmental Policy, 19: 1067-86.

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Summary

- Named reactions can be identified as a starting point for the production of chemicals based upon functional groups present in a molecule.
- Chemical lineage information, including required reactants, by-products, catalysts, reaction conditions, etc. can be determined for each of the named reactions.
- Synthesis pathways can be built from the named reactions.
- Alternative assessment of the manufacturing phase of the chemical life cycle can then be performed.