Demonstration of the CIR Chemistry & Toxicology Database (CAT DB)

Presented at the 139th CIR Expert Panel Meeting
Washington, D.C.

Ivan J. Boyer, PhD, DABT
Cosmetics Ingredient Review (CIR)

June 6, 2016
CAT DB Demonstration: Outline

• Introduction
  – Project Purpose & Scope
  – Framework for Identifying & Evaluating Analogs

• Demonstration
  – CAT Database Search
  – CAT Database Predict Toxicity: Skin Sensitization

• Further Evaluation & Development
CAT DB Project: Purpose & Scope

• Purpose
  – Establish a CIR reference source
  – Evaluate computational methods for read-across

• Scope of initial phase (July-Dec 2015)
  – Foundation for development of structure-searchable CAT DB (“ground-floor” database)
  – CIR Inventory: all ingredients previously reviewed by CIR Expert Panel
  – knowledgebase (ChemTunes Studio)
    • Toxicity & safety assessment data
    • Weight-of-Evidence -based predictions (Rules based & QSAR)
CAT DB will support:

• Priority Setting
• Pre-Production Pack Development
• Read-Across Assessments
Framework for Identifying & Evaluating Analogs for Read-Across

- Formal, systematic, comprehensive, expert-driven*
- Objective, reproducible selection of analogs
- Transparent read-across assessments
- Identify, evaluate suitability, select analogs based on similarities
  - Chemical structure
  - Reactivity
  - Metabolic properties
  - Physicochemical properties
- Amenable to incorporating (Q)SAR analyses

Search for **candidate analogs** (requires databases)

Compare candidate analogs to SOI* to **identify features that could affect toxicity**
- Common structural **alerts**
- Key **functional groups and core substructure**
- Physicochemical **properties**

Evaluate potential **divergent metabolism** of analogs & SOI
- Metabolism databases
- Scientific literature searches
- Software prediction tools
- *in vitro* test results

*SOI = Structure of Interest (i.e. the structure with missing data)
Framework for Identifying & Evaluating Analogs for Read-Across (Continued)

- **Expert judgment of medicinal chemist**
  - Select candidate analogs
  - Categorize candidate analogs (suitable, suitable with interpretation, etc.)

- **Expert judgment of toxicologists**
  - Compile & Review toxicological data for SOI & analogs for consistency / concordance
  - All data taken together for weight-of-evidence assessment
    - Address uncertainty
Framework for Identifying & Evaluating Analogs for Read-Across (Concluded)

• Panel supported developing Framework as systematic approach to:
  – Identifying analogs for read-across assessments
  – Categorizing analogs as suitable, suitable with interpretation, and suitable with precondition

• Panel emphasized importance of:
  – Developing quantitative measures for key decision-making steps of the approach
  – Characterizing boundary conditions & assumptions of models applied
  – Using test data for the class of chemicals to which the ingredients belong to validate computational predictions
CAT Chemistry & Toxicology Database (CAT DB) & Tools Demo
CAT DB Search

Cat Database

Database Search

ChemTunes Workflows

Designed and Developed by Altamfra LLC and Molecular Networks
CAT DB: Main Search Menu

**Chemistry**
- Search options:
  - Name
  - Identifiers
  - CAS RN
  - Structure – sketch molecule
  - Structure - SMILES
- Search methods:
  - Exact
  - Substructure (partial)
  - Similarity (similar)

**Toxicity**
- Search options:
  - Study types (endpoints)
  - Species
  - Treatment duration
  - Dose level
  - Organ sites
  - Assay types
  - ...

Query Definitions: Chemistry
- Inventories: Selected 17 of 17 inventories
- Enter one name per line (you may enter the full name or a part of the name, autocomplete function is active)
- Examples: ASCORBIC ACID, beta-carotene, Saccharin

Query Definitions: Toxicity Studies
- Active Queries
- Search options:
CAT DB Search: Chemical Structure

Query Definitions: Chemistry
Inventories:
Selected 16 of 17 inventories

[Menu Options]

- Names
- Identifiers
- CAS Registry Number
- Structure: Sketch molecule
- Structure: SMILES

Add molecule
Clear

Right-click molecule to copy.
If you experience difficulties while using the chemical structure drawing tool on this page please consider entering your structures using the SMILES feature which requires no mouse.

Options
- exact
- partial
- similar

Search
CAT DB Search: Sketch (picramic acid)
CAT DB Search: Exact Searching

Right-click molecule to copy.
If you experience difficulties while using the chemical structure drawing tool on this page please consider entering your structures using the SMILES feature which requires no mouse.

Options:
- exact
- partial
- similar

Search
CAT DB Search: Picramic Acid

<table>
<thead>
<tr>
<th>Query</th>
<th>Structure</th>
<th>System ID</th>
<th>Registry Numbers</th>
<th>Names</th>
</tr>
</thead>
<tbody>
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<td>96-91-8</td>
<td>PICRAMIC ACID [US FDA CFSAN Thesaurus] PICRAMIC ACID (PCPC [INCI], COSING [INCI])</td>
</tr>
</tbody>
</table>

Your search retrieved 1 hit. Click on a result for details.

Showing 1 to 1 of 1 entries

Structure query

Structure retrieved

4 Toxicity studies

in CIR inventory
Picramic Acid: Reported Functions

- Use function: Hair Dyeing
- IDs & Names
- Compound Annotation
- Use function: Hair Dyeing
- Compound Classification
- PAFA chemical information
- Safety assessment
- Toxicity Data
Picramic Acid: IDs & Synonyms

### Identifiers
- **CIR List ID**: 3151
- **COSING Refnum**: 35562
- **COSMOS ID**: CMS-3055
- **DSSTox CID**: 45529
- **DSSTox SID**: 29479

### Names
- **2-AMINO-5,6-DINITROPHENOL**
  - Name Source: DSSTox [Test Substance Name]
- **2-AMINO-5,6-DINITROPHENOL (CI 76540)**
  - Name Source: COSING [COSING_JUPAC_Description]
- **PICRAMIC ACID**
  - Name Source: PREFERRED NAME
- **PICRAMIC ACID**
  - Name Source: CIR [CIR Ingredient Name]
- **PICRAMIC ACID**
  - Name Source: CIR [U.S. INCI]
- **PICRAMIC ACID**
  - Name Source: COSING [INCI]
- **PICRAMIC ACID**
  - Name Source: PCPC [INCI]
- **PICRAMIC ACID**
  - Name Source: US FDA CFSAN Thesaurus [Preferred Term]

### Additional Information
- Compound Annotations
- Compound Classification
- PAFA Chemical Information
- Safety Evaluation
- Toxicity Data
**Picramic Acid: CIR Status Report**

**CIR Ingredient Status Report**

The following table provides a quick view of the status of CIR reports that include this ingredient. Clicking on any individual **INGREDIENT** will take you to the monograph for that ingredient in the ingredients area of the **On-Line INFObase**. Clicking on the **STATUS** will provide you an explanation of the status of the ingredient and a copy of the relevant report available from CIR.

For additional information about the Cosmetic Ingredient Review, see the [CIR Home Page](#).

<table>
<thead>
<tr>
<th>INGREDIENT</th>
<th>STATUS</th>
<th>DATE/REFERENCE</th>
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<tbody>
<tr>
<td>Picramic Acid</td>
<td>Published Report</td>
<td>IJT 28(Suppl. 3):205-216, 2009</td>
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<td></td>
<td>PDF may take a few minutes to download</td>
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</tr>
</tbody>
</table>
Amended Safety Assessment of Sodium Picramate and Picramic Acid

Lillian C. Becker,1 Wilma F. Bergfeld,2 Donald V. Belsito,2 Curtis D. Klaassen,2 James G. Marles, Jr.3 Ronald C. Shank,2 Thomas J. Slaga,2 Paul W. Snyder,2 and F. Alan Andersen3

Abstract
Sodium picramate is the sodium salt of picramic acid, a substituted phenolic compound. Sodium picramate and picramic acid function as hair colorants; they are reportedly used in 31 and 3 hair-dye products, respectively. No concentration-use data were available for sodium picramate, but picramic acid was reported to be used at 0.6%. The Cosmetic Ingredient Review Expert Panel recognized that adding picramic acid to a hair-dye formulation likely results in formation of a salt such as sodium picramate, which suggested that safety test data for one ingredient would be applicable to the other. Hair dyes containing these ingredients bear a caution statement and patch test instructions for determining whether the product causes skin irritation. The panel finds that the available data support the safety of these colorants in hair dyes and expects that sodium picramate would be used at concentrations comparable to those reported for picramic acid.

Keywords
cosmetics, safety, sodium picramate, picramic acid

In an earlier safety assessment of sodium picramate, the Cosmetic Ingredient Review (CIR) Expert Panel stated that this ingredient “is safe as a cosmetic ingredient at concentrations not to exceed 0.1%.” Upon re-review of the safety assessment, the Expert Panel decided to reopen the assessment of this permanent hair-dye to include picramic acid and to reconsider the 0.1% concentration limit, because picramic acid is used at higher concentrations.

Chemistry
Definition and Structure
Picramic acid (CAS No. 96-91-3) is the substituted phenolic compound that conforms to the formula in Figure 1A.2 It is listed in this dictionary in the chemical classes of color additives—hair and phenoxy. Technical/other names for picramic acid are the following: 1-amino-3,5-dinitro-2-hydroxybenzene; 2-amino-4,6-dinitrophenol; Cl 76540; 2,4-dinitro-6-amino-phenol; oxidation base 21; and phenol, 2-amino-4,6-dinitro-2.2 Picramic acid is also known as the following: 4,6-dinitro-2-aminophenol; 1-amino-2-hydroxy-3,5-dinitrobenezene; 4,6-dinitro-2-aminophenol; 6-amino-2,4-dinitrophenol; and acids picramique (French).3 Sodium picramate (CAS No. 831-52-7) is the sodium salt of picramic acid that conforms to the formula in Figure 1B. The chemical classes of sodium picramate are amines, color additives—hair and organic amines.7 Sodium picramate is also known as 2-amino-4,6-dinitrophenol, sodium salt; phenol, 2-amino-4,6-dinitro-, sodium salt; and picramic acid, sodium salts.4,5 Other names listed for sodium picramate are sodium 2-aminio-4,6-dinitrophenoxide and sodium (2-aminio-4,6-dinitrophenoxide)-7(CI).4

Physical and Chemical Properties
Picramic acid, a metabolite of picric acid, has a molecular weight of 199.12 and a melting point of 168°C. It is soluble in water (0.065 g per 100 mL of water, 22°C), alcohol, benzene, glacial acetic acid, aniline, and ether.7 Sodium picramate is a low-level explosive.6 It is a yellow, water-soluble salt with a molecular weight of 221.27.7,8 RCC Cytotoxic Cell Research GmbH (RCC) reported the log Po/w of sodium picramate to be less than −2.97 using the flask-shaking method.18
Sodium picramate was included in a list of shock-sensitive materials that may decompose violently if struck or heated and/or are prone to explosive decomposition if ground in the solid state.11


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Picramic Acid: VCRP Product Category

VCRP (2015) Use Frequency
Picramic Acid: 10
Sodium Picramate: 1

Product category
- Hair dyes and colors

VCRP Cosmetic Product Category (2015)
Cosmetic Product Category: 06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)
Picramic Acid: Toxicology (Subchronic)

Toxicity data
- NTP
- Genetic
- SCCS
- Genetic
- COSMOS
- Target organ
- Subchronic

Doses tested

Study quality and OECD guideline compliance noted
Picramic Acid: Toxicology (Subchronic) Detailed
CAT DB Similarity Searching Options
Example: 1,10-Decanediol

Partial & similarity search options
## CAT DB Search: 1,10-Decanediol

Your search retrieved 1 hit. **Click on a result for details.**

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<tr>
<th>Query</th>
<th>Structure</th>
<th>System ID</th>
<th>Registry Numbers</th>
<th>Names</th>
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Showing 1 to 1 of 1 entries
1,10-Decanediol: Reported Functions

VCRP (2015) Use Frequency
14
1,10-Decanediol: Similarity (85%) Search

Set similarity cut-off (Tanimoto score)
1,10-Decanediol: Similarity Search

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Sorted
Hexyl Alcohol (Candidate Analog #1): Reported Functions

VCRP (2015) Use Frequency = 0

Not Reported to be Used
Hexyl Alcohol (Candidate Analog #1): Toxicology Studies

12 Studies

- Title: US FDA CFSAN PAPA Study
- Study call: US FDA CFSAN PAPA
- Study inventories: US FDA CFSAN PAPA
- Study number: 26
- Reference: Study completeness (US FDA CFSAN PAPA): B

- Study Comments
- Study Background
- Test Substance
- Study Endpoints

**Study result comments:** Test compound administered in gelatin capsules at the 1000 mg/kg dose level; at lower dose levels test compound mixed in diet; congestion of pancreas, liver, kidney and stomach; atrophy of the testis and epididymis; test compound administered in gelatin capsules at 1000 mg/kg, at lower dose levels test compound mixed in diet; congestion of pancreas, liver and stomach; atrophy of the testis and epididymis; test compound administered in gelatin capsules at 1000 mg/kg; at lower dose levels test compound mixed in diet; congestion of pancreas, liver, kidney and stomach; atrophy of the testis and epididymis

**Species:** dog
**Strain:** Oral
**Route of Exposure:** 91 day
**Test Duration:** 370.0, 1000.0 mg/kg bw/day
**Dose Levels / Range:** HNEL (Study): 370.0 mg/kg bw/day
**LEL (Study):** 1000.0 mg/kg bw/day

HNEL = Highest No-Effect Level
LEL = Lowest Effect Level
# 1,10-Decanediol & Candidate Analogs: CAT DB Systemic Toxicity Profile

<table>
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<tr>
<th>CAT DB Systemic Toxicity Data Profile for 1,10-Decanediol and Candidate Analogs</th>
<th>Similarity Score</th>
<th>INCI Dictionary Entry</th>
<th>In-Use (VCRP 2015)</th>
<th>Fragrance only (INCI)</th>
<th>CIR Safety Assessment</th>
<th>Acute Toxicity Studies</th>
<th>Repeated Dose Toxicity Studies</th>
<th>Repro./Develop. Toxicity Studies</th>
<th>Genotoxicity Studies</th>
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</tbody>
</table>

<sup>a</sup>Selected structure of interest (SOI)

<sup>b</sup>Identified as a candidate analog through similarity search

<sup>c</sup>Special toxicity study
CAT DB Workflows: Predict toxicity
CAT DB Workflows: Predict Toxicity

- Predict toxicity
- Export structures and data
- Compare compounds
- Calculate properties (in next release)
- TTC export (in next release)
- Read-across (in next release)
- WoE decisions (in next release)
- Find analogs (in next release)
- TTC workflow (in next release)
Need to find or estimate toxicity data for γ-Undecalactone & Analogs
Need to find or estimate toxicity data for γ-Undecalactone & Analogs

Selected file (multiple structures, SMILES, or IDs) loaded
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<tr>
<th>Compound</th>
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</table>

8 Tox studies, but no skin sensitization data.
Undecalactone: Predict Skin Sensitization Hazard & Potency

<table>
<thead>
<tr>
<th>Select</th>
<th>Query</th>
<th>Structure</th>
<th>System ID</th>
<th>Registry Number</th>
<th>Names</th>
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<td>GAMMA-OCTALACTONE [US FDA OCSAN Thesaurus] GAMMA-OCTALACTONE (COSING [INCI])</td>
<td>2</td>
<td>COSING&lt;br&gt;US FDA PAPA ORAL TOXICITY&lt;br&gt;COSMOS Cosmetic Substance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GAMMA-HEPTALACTONE</td>
<td>CMS-15256</td>
<td>104-50-7</td>
<td>GAMMA-OCTALACTONE [US FDA OCSAN Thesaurus] GAMMA-OCTALACTONE (COSING [INCI])</td>
<td>2</td>
<td>COSING&lt;br&gt;US FDA PAPA ORAL TOXICITY&lt;br&gt;COSMOS Cosmetic Substance</td>
<td></td>
</tr>
</tbody>
</table>

**Toxicity Predictions**

Please select the toxicity endpoints you want to predict:

- [ ] Bacterial Reverse Mutagenicity
- [ ] in vitro Chromosome Aberration
- [ ] in vivo Micronucleus
- [ ] Mouse Tumor
- [ ] Rat Tumor
- [ ] Cleft Palate
- [ ] Skin Sensitization Hazard
- [ ] Skin Sensitization Potency

[Select all] [Deselect all] [Predict] [Cancel]
γ-Undecalactone: Sensitization Predictions

Predictions for endpoint: Skin Sensitization Hazard

NEGATIVE

Probability (POSITIVE) = [0.027, 0.131]

Red: positive probability
Green: negative probability
Yellow: uncertainty
γ-Undecalactone: **Hazard, Models & Alerts**

**Prediction Results for compound #1**

In database: Yes
CHEMTUNES ID: CME-7803
Name: GAMMA-UNDECALACTONE
Registry number(s): 104-57-6
# studies in CHEMTUNES: 8

**Predictions for endpoint: Skin Sensitization Hazard**

NEGATIVE

Probability (POSITIVE) = [0.027, 0.131]

No MIE (Molecular Initiating Event) neighbors are found for this compound (only global model)

No structural alerts are found for this compound
γ-Undecalactone: Hazard, Nearest Neighbors

Quality of data used in the training set are noted. Toxicity study data are linked through this table.

- Data note
- OECD ToolBox
- Master table 1
- Master table 2
- OECD Toolbox
CAT DB Search: Exact Searching
Picramic Acid: Predict Toxicity

Predictions can be invoked at any point in the workflow.
Picramic Acid: Sensitization Hazard Models & Alerts

Red: positive probability
Green: negative probability
Yellow: uncertainty

Predictions for endpoint: Skin Sensitization Hazard

Positive
Probability (POSITIVE) = 0.999

Mon Models

<table>
<thead>
<tr>
<th>Model name</th>
<th>Probability (POSITIVE)</th>
<th>Probability Bar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>[0.855, 0.965]</td>
<td></td>
</tr>
<tr>
<td>Logic SSH-Hazard 2015 01 Alcohol</td>
<td>[0.734, 0.986]</td>
<td></td>
</tr>
<tr>
<td>Logic SSH-Hazard 2015 01 Amine</td>
<td>[0.833, 0.967]</td>
<td></td>
</tr>
<tr>
<td>Logic SSH-Hazard 2015 01 Phenquin</td>
<td>[0.696, 0.906]</td>
<td></td>
</tr>
</tbody>
</table>

Alerts

Chemotype Alert Match
Leaving group and nitro on aromatic ring (ortho or meta or para)

Predictions for endpoint: Skin Sensitization Potency

GHS 1A
Probability (POSITIVE) = [0.502, 0.532]
Picramic Acid: Sensitization Hazard, Nearest Neighbors

Prediction Results for compound #1

In database: Yes
CHEMTUNES ID: CMS-2056
Name: PICRAMIC ACID
Registry number(s): 96-91-3
# studies in CHEMTUNES: 4

Predictions for endpoint: Skin Sensitization Hazard

POSITIVE

Probability (POSITIVE) = 0.999

Nearest Neighbors in Training Set

System ID

CMS-56661

Experimental data: positive
Distance in model space: 0.017
Structural similarity:

Data Note

MasterTBL2; Regulatory

CMS-72053

Experimental data: positive
Distance in model space: 0.054
Structural similarity:

Regulatory

CMS-60587

Experimental data: positive
Distance in model space: 0.065
Structural similarity:

Regulatory

CMS-67

Experimental data: positive
Distance in model space: 0.067
Structural similarity:

OECD TBOX; NJCEATM+ICCVAM; OpenLIT | Kilimich Score=2
CAT DB: Update in Q3 2016

• Content update
  – Safety evaluation data (SCCS, EPA, COSMOS, etc.)
  – COSMOS TTC dataset
  – New ChemTunes databases: acute toxicity (done), skin sensitization (in progress)
  – Botanicals list

• Software update
  – Calculate Properties
  – TTC workflow
  – Read-across workflow (prototype)

• New predictions
  – Liver knowledge base (structural rules)
  – Acute toxicity QSAR model
Sneak Preview of the Read-Across Workflow

User workflow guided by the breadcrumbs

Analogs listed under each SOI in descending order of similarity to SOI

Metabolites Tautomers
Future work

• Enhance & Refine “ground-floor” CAT DB to Achieve Full-Featured Toxicity & Safety Assessment platform
• Develop Direct way to access & search for CIR Reports through CAT DB
• Mine & Incorporate published & unpublished data used in CIR Assessments
• Incorporate all CIR Conclusions, other Risk Assessments
• Incorporate all Fields of the PCPC Online InfoBase Ingredient DB
• Evaluate Additional ChemTunes Workflows (when released), such as:
  – Weight-of-Evidence (WoE)
  – Metabolism