

Novel Structural Alerts to Group Liver Toxicants into Categories for Read-Across



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Introduction

- Prediction of chronic toxicity by *in silico* methods still remains an elusive goal. Traditional (quantitative) structure-activity relationship ((Q)SAR) approaches to predicting NO(A)ELs have significant shortcomings.
- A pragmatic approach for (repeat dose) toxicity prediction is to identify relevant molecular initiating events (MIE) and adverse outcome pathways (AOPs) and use this information to help guide the formation of chemical categories (grouping).
- To date, there is insufficient knowledge to create “profilers” for grouping and category formation.

Aims

The aims of this investigation were:

- To develop structural alerts for liver toxicity relating to human health effects.
- To use the novel structural alerts to screen the COSMOS Cosmetics Inventory to develop initial groupings of compounds relevant to toxicity.

Methods

Creation of Novel Structural Alerts. Structural alerts for liver toxicity, that go beyond protein binding, were created as follows (more details in Hewitt et al 2013):

- The Fourches et al (2010) data set of 951 compounds with human hepatotoxicity binary classification data was assessed.
- Compounds in the data set were clustered based on structural similarity with the ToxMatch software.
- Clusters associated with hepatotoxic compounds were analysed to identify structural alerts and mechanisms of action.

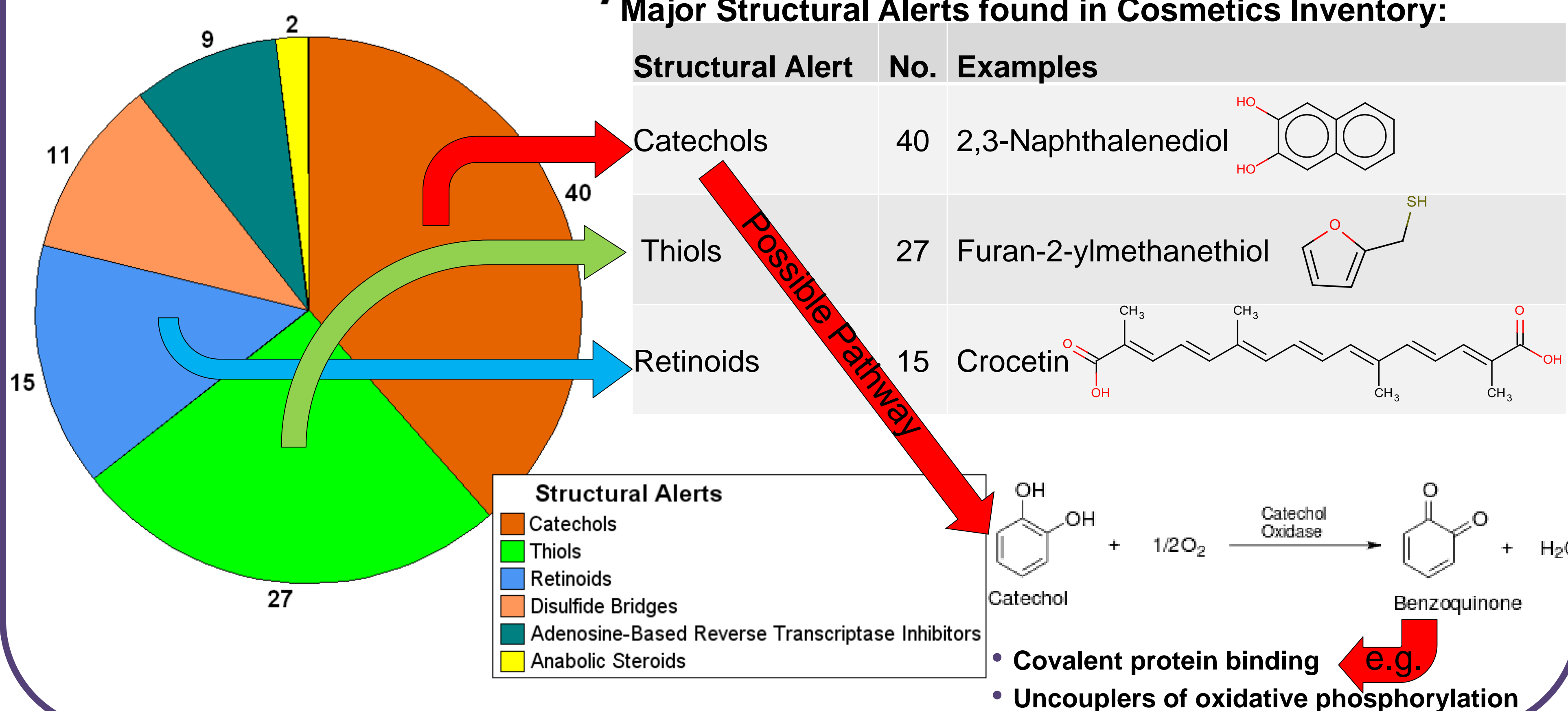
Groupings of Cosmetic Ingredients Relevant to Hepatotoxicity. Groupings were obtained as follows:

- The structural alerts were coded into SMARTS strings and captured in a KNIME workflow.
- The COSMOS Cosmetics Inventory (4,467 compounds) was screened for potential hepatotoxic (sub)structures and significant groupings of compounds were captured.

Results 2: Screening of COSMOS Cosmetics Inventory

- Screening of the COSMOS Cosmetics Inventory resulted in the six structural alerts shown top right (Results 1) been found to be present in the compounds. 103 compounds were found with one or more alert.
- Groups were formed on the basis of these alerts ranging from 40 compounds (catechols) to two compounds (anabolic steroids).
- The presence of an alert does NOT imply toxicity, but may suggest areas of chemistry for testing!

Structural Alerts for Liver Toxicity



Results 1: Structural Alerts

For liver toxicity 16 structural alerts were obtained in total. The following were found to be significant to the Cosmetics Inventory:

1. Catechols (Structural Alert 8)
2. Thiols (Structural Alert 11)
3. Retinoids (Structural Alert 3)
4. Disulfide bridges (Structural Alert 15)
5. Adenosine-based RTIs (Structural Alert 2)
6. Anabolic Steroids (Structural Alert 13)

Other structural alerts obtained were for the following groups, although these were not found to be relevant to the Cosmetics Inventory:

- Tamoxifen-like antioestrogen (Structural Alert 1)
- β -lactam substructure (Structural Alert 4)
- Barbitals (Structural Alert 5)
- Phenothiazines (Structural Alert 6)
- Cytidine-based RTIs (Structural Alert 7)
- ACE Inhibitors (Structural Alert 9)
- Oestrogen Steroids (Structural Alert 10)
- Nitrogen mustards (Structural Alert 12)
- Glucocorticoid steroids (Structural Alert 14)
- p-aminophenylsulphonamides (Structural Alert 16)

All structural alerts were supported by mechanistic information and preliminary AOPs.

Conclusions

- Clustering of molecules in a non-standard database, followed by careful mechanistic analysis, has revealed useful information and structural alerts.
- The sequence of reactive and non-reactive MIEs, defined by structural alerts and chemotypes, provides a basis for grouping (category formation) for potential liver toxicants.
- This approach could be extended to develop more structural alerts and so contribute to a predictive model for hepatotoxicity.
- The groupings of molecules determined for the COSMOS Cosmetics Inventory could provide a basis for testing with SEURAT-1.

References

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