Daily Lesson Plans for:
The Basics of Toxicology for Green Molecular Design

Day 1
The goal of the first day is to introduce the basic paradigms of toxicology: dose/response, exposure, susceptibility, hazard/risk, endpoints and modes of action. These concepts were covered in the introductory reading and were discussed during the first hour of class. Discussion was guided by in class activities including a comparison of chemicals using various data sources. The second hour of class was a presentation and discussion of where toxicity data can be found, In particular we focused on ToxNet as a good aggregator of available experimental data.

We also introduced bio-based chemicals as the basis for the class discussions. The class was divided into groups and each group was assigned 4 chemicals, 2 traditional petroleum feedstocks and two potential bio-based replacements. Each assignment is built around a comparison of these chemicals. The chemicals can be found in the first day’s lecture slides. Bio-based chemicals were chosen as a case study for this class for two reasons: 1) They are an emerging class of chemicals which if adopted could be produced in large volumes and be introduced into consumer products and 2) Their petroleum counter parts have been widely studied and therefore have good baseline data.

Day 1 slides

Reading:
1. "A Small Dose of Toxicology." By Steven Gilbert. This is a free e-book and associated wiki site that has good information for people interested in some toxicology that relates to everyday life. I want you to read chapters 1 & 2.

Homework 1

Day 2
Each day starts with a discussion of the previous homework assignment and review of material. The first day’s assignment focused on available, experimental information and our discussion focused on the wide range of experimental data including the very noticeable differences in data quality and availability. We used this discussion to transition into ways to differentiate between chemicals with radically different amounts of toxicity data.

Persistence and bioaccumulation were introduced as one way that chemicals without toxicity data can be classified. The lecture and class exercises introduce general biodegradation rules of thumb, PBT profiler, ChemSpider (EPI-Suite), and UM-BBD degradation pathway prediction system.

Day 2 Slides

Reading:

Homework 2
Day 3
The homework discussion focus on how useful PBT profiler was to differentiate between chemicals. Most groups were able to use PBT profiler to differentiate between at least a couple of their chemicals, making it one of the more useful tools used during the class.

The class exercises and lecture focused on structural alerts and chemical properties that predict toxicity. Electrophiles, radicals, reactive oxygen (redox active) generators, and organic cations were all discussed as potential structural alerts. Electrophiles were discussed in great depth and way of designing away-from or less reactive electrophiles were discussed.

Finally a general introduction to ToxPredict was given so that the students could compare the rules of thumb and structural alert approach to a QSAR program.

Day 3 slides

Reading:

Homework 3

Day 4

The discussion focused on the short-coming of ToxPredict as a plateform. Too many of the chemicals failed to give back any useable data. In the cases where predictions were made it was not clear how to interpret them, since there were often missing units and no baseline for comparison. It is likely that ToxPredict could be used by a trained computational toxicologist to compare chemicals, but this tool was not suitable for a general audience and raised many questions about the utility of QSAR based approached.

The lecture portion of the class focused on the theory and general approaches to QSAR modeling. This helped students get a better idea of what was going on the backend of ToxPredict, unfortunately it didn’t make the results any more usable. While QSARs are an essential tool to discuss, next time I would chose a different tool or try ToxCreate and have students build their own training sets. If there were time, this could be a better way to introduce QSARs to students since they would build their own.

Day 4 Slides

Reading:

Homework 4

Day 5
The class discussion briefly outlined some of the improvements that could be made to ToxPredict to make it more useful for a general audience and for chemists. There was also a discussion of other available resources and approached to predicting the toxicity of compounds.

Most of the class was spent introducing ADME and rules of thumb for predicting ADME properties based on chemical properties. The slides include a number of guidelines and useful reference for predicting chemical behavior in the body based on relatively easy to measure chemical properties.

During the metabolism discussion the SMARTcyp tool was introduced to predict where the cytochrome P450 system will react with a given chemical substrate. The discussion touched on the potential for reactive electrophile formation and toxicity.

Day 5 slides

Reading:


Homework 5

Day 6

The discussion of the homework for focused on the competing factors that dictate ADME behavior. Some of these factors could be incorporated into chemical design, but not as easily as the design of less reactive electrophiles. ADME was probable the 3\textsuperscript{rd} most useful thing for the students behind electrophiles and PBT concepts. In the future I would move this earlier in the semester.

The lecture portion of this class covered the basics of toxicity testing: high throughput, high content, and the development and validation of new assays. The Tox21 approach was discussed and issues were highlighted. The class ended with a very good discussion of what tests or assays would be useful for chemists to run at their own bench. This turned into a more general discussion of when and how much toxicity testing should be done on new chemicals.

Homework 6

Day 7

The final day of class was reserved for student presentations.

Slides, including the students’ presentations