Module 10: Safer Chemical Design Game – worksheet for students and instructors playing www.gwiz.yale.edu

Teacher's Notes

This activity (including game play time) is estimated to take approximately 2 hours.

Human and aquatic toxicity are complicated processes which depend on several variables. Most of these variables are related to physical and chemical properties of the chemical.

This activity is based on the educational game "Safer Chemical Design Game" and is intended to introduce students to safer chemical design concepts by focusing on manipulating physicochemical parameters to minimize toxicity of a hypothetical commercial chemical. The game simulates various real-world constraints that may affect chemical product development as students design a novel detergent. The students (players) are challenged to design a safer, and more sustainable chemical product using multi-criteria decision analysis. They can select different combinations of molecular parameters that lead to qualitative outputs related to toxicity, biodegradability, biotransformation, and overall chemical performance. In doing so, the player must navigate potential trade-offs that result from their choices.

The game has two levels - each level is divided into three challenges, or tasks, that are related to the attributes of the chemical product, including potential for human toxicity, aquatic toxicity, and performance (function). As students progress through different challenges, they are offered "Tips" which include additional information to aid their parameter choices. Both levels require the lower order learning objective of fact memorization as well as the higher order learning objective of knowledge transfer. The design of the chemical product is evaluated on function and avoidance of toxicity. A key feature of the game is the ability of the player to redesign and improve their product based on real-time feedback. Feedback is included after every task which allows the student to change their selection criteria and improve design.

Lesson planning: Introduce key concepts related to human and aquatic toxicity (see below) and use the game to reinforce the message. Use the eight questions in the worksheet as an individual assignment or as an in-class discussion. These questions are designed to be answered as student plays the game.

MoDRN Molecular Design Research Network

Supplemental Readings:

ToxTutor – National Institute of Health. Retrieved from: https://toxtutor.nlm.nih.gov Accessed May 2018

Voutchkova, A. M.; Osimitz, T. G.; Anastas, P. T., Toward a Comprehensive Molecular Design Framework for Reduced Hazard. *Chemical reviews* 2010, *110* (10), 5845-5882

Anastas, P. T.; Zimmerman, J. B., Safer by Design. *Green Chemistry* 2016, *18* (16), 4324-4324.

Zimmerman, J. B.; Anastas, P. T., Toward designing safer chemicals. *Science* 2015, *347* (6219), 215-215.

Zimmerman, J. B.; Anastas, P. T., Toward substitution with no regrets. *Science* 2015, *347* (6227), 1198-1199.

Cowan-Ellsberry C, Belanger S, Dorn P, et al. Environmental Safety of the Use of Major Surfactant Classes in North America. *Critical Reviews in Environmental Science and Technology*. 2014;44(17):1893-1993. doi:10.1080/10739149.2013.803777.

Student Learning Objectives: By the end of this module, the student will be able to:

- Define the four key components of ADME
- Relate physicochemical properties of chemicals to the impact they have on ADME and performance
- Predict which physicochemical properties of chemicals have an impact on ADME and performance

Background and Information:

What will affect toxicity?

(Module 3: ADME and Toxicity by Dr. Grace Lasker of Molecular Design Research Network. NSF Division of Chemistry and the Environmental Protection Agency under Grant No. 1339637.)

Chemical impact on health is usually investigated via the concept of ADME. This is how a chemical is Absorbed, Distributed, Metabolized, or Eliminated in living systems. Not all chemicals are impactful in the same ways, sometimes metabolism, for example, may not be an issue because of the way our liver metabolizes some compounds and converts them into inert substances. Some chemicals have means to be excreted, while others may not. Considering all aspects of how chemicals get into the body, how they move within the body, and how they get out of the body can help us assess the toxicity of a chemical.

ADME (standing for Absorption, Distribution, Metabolism, and Elimination) is an important concept that describes the potential impact a chemical or drug may have on a living system within the context of cellular biology and biochemistry. This is because movement and metabolism of molecules is determined by physicochemical properties of the molecule as well as the host system. The movement of molecules is called "kinetics" or "pharmacokinetics" and chemical properties such as polarity, molecule weight, molecular size, chirality, HOMO/LUMO, and many more all have an impact on the ADME potential of a molecule/toxin. ADME is generally used to describe the impact or a drug or pharmaceutical compound. However, the concept of ADME is applicable to non-pharmaceutical compounds, including from toxic exposure. Drugs are specifically designed using ADME principles; however, chemicals for commercial use are not designed with any guidelines targeting ADME.

Absorption

There are four main routes of exposure:

- Inhalation through the respiratory system: a chemical in the form of a gas, vapor or particulate that is inhaled and can be excreted or deposited in the respiratory system.
- Dermal through skin or eye contact.
- Ingestion through the gastrointestinal system: Absorption through the digestive tract. Ingestion can occur through eating or smoking with contaminated hands or in contaminated work areas.
- Injection: Introducing the material directly into the bloodstream. Injection may occur through mechanical injury from "sharps".

To be absorbed, a substance must cross one of the layers of cells that keeps “us” “in” and the rest of the world “out”: skin (including mucus membranes), lung, and the gastrointestinal (GI) tract. Most substances are absorbed by passive diffusion through membranes. A small number of biologically important atoms and molecules are actively taken up by cells. Examples include sodium, potassium, and calcium ions, amino acids, small sugars (mono- and di-saccarides). If your substance is very similar to one of these, there is an increased chance of cellular uptake.

Absorption depends on chemical properties such as molecular weight, lipid solubility (log P), and physical state. These parameters determine if the chemical passes through the cell membranes into the body. Absorption of a chemical will result in the chemical circulating inside the body and potentially causing adverse effects.

Distribution

In order to be distributed, the compound needs to be able to move from the site of absorption to other areas of the living system. Not all compounds move easily. Most often movement is via the bloodstream but other compounds may move cell-to-cell as well. In general, there are four main ways by which small molecules cross biological lipid membranes:

- Passive diffusion. Diffusion occurs through the lipid membrane from a high to low concentration (aka concentration gradient).
- Filtration. Diffusion occurs through aqueous pores, still from high to low concentration as a driving mechanism.
- Special transport. Transport is aided by a carrier molecule. Can move against the concentration gradient (low to high).
- Endocytosis. Transport takes the form of pinocytosis for liquids and phagocytosis for solids.

The mechanism of transport for a certain chemical is frequently unknown, and so we must judge its potential toxicity using other variables (such as molecular weight, ionization (pKa), and octanol/water partition coefficient (log P).

Metabolism

Compounds begin to break down in the body by a family of enzymes in the liver called the Cytochrome P450 system. These enzymes can convert chemicals to reactive oxygen species (ROS), reactive intermediates, free radicals, and others. For example, redox reactions and potential, with a transfer of electrons, influence the toxicity of a chemical at the intracellular level. Scientific advances in toxicology and chemistry are starting to allow scientists to better understand these kinds of interactions, and they have begun to map out more specific pathways, called Adverse Outcome pathways (AOPs). It is through understanding these pathways that a new generation of chemicals can be safely designed by chemists and other scientists.

Excretion

Most excretion occurs through the kidneys as urine or as feces. Excretion is dependent on the process of kidney filtration at the glomerulus, and is largely based on molecular size and charge. Some molecules can be excreted through the skin as sweat and some may be excreted through the lungs via gas exchange. If excretion is not a complete process, the molecule or metabolic by-product can bioaccumulate and impact living systems adversely. If a compound is lipid-soluble, it will bioaccumulate more quickly in adipose tissue. Bioaccumulation of lipid-soluble compounds such as DDT has been shown to be correlated with adverse health effects such as diabetes, heart disease, obesity, etc.

Objective of the game

Imagine you are a chemist at a large chemical company. Your department is requesting that you develop environmentally friendly chemicals. As a part of this initiative, you were asked to design a detergent that not only has an optimal cleaning performance, but also is safer for humans and environment. If your product is successful, it will be widely produced and distributed in major chain stores.

Goal

Your task is to design a benign detergent that has optimal cleaning capabilities. As a chemist, you can thoughtfully design a chemical to have certain characteristics (e.g., be an efficient cleaning agent or have a reduced toxicity). You can achieve this by manipulating its physical and chemical properties. Your goal is to adjust these properties such that the detergent does not cause harmful (adverse) effects to humans and fish without sacrificing the product's cleaning ability.

Game Play

This game has two levels:

In Level 1, you will address detergent toxicity by limiting its absorption through the membranes. You will design a detergent that will not be absorbed into the body through skin, lungs, or intestines, and will not harm fish in bodies of water, like lakes or ponds.

In Level 2 the detergent is absorbed into the body. This is problematic, but as a chemist, you are able to minimize its toxicity and effects on the body. Note: Distribution, Metabolism, and Excretion are processes that occur when a chemical enters the body. Taken together with Absorption, the processes are referred to as "ADME" (Absorption-Distribution-Metabolism-Excretion).

Information on detergents

Detergents are substances that are used to remove grease and grime. Their performance is due to their unique structure. One end of their molecule, called head, is attracted to water (hydrophilic), while the other end, called tail, is attracted to dirt and grease (lipophilic).

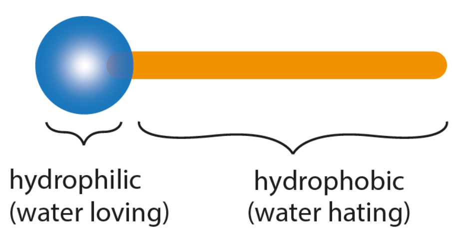


Figure 1: Detergent's structure.

Detergent heads and tails can vary, and they are made of different chemical functional groups. For example, tails consist of a hydrocarbon chain, which can be branched, linear, or aromatic. Heads, on the other hand, may include sulfonate, phosphate, sulfate or carboxylate functional group which define surfactant's character (antimicrobial & antifungal hand soap, versus cleaner or fragrance carrier).

The most common use is grease removal. Once the grease is detected, it is surrounded by hydrophobic (lipophilic) tails forming a structure called micelle. Micelle are typically spherical in shape and allow greasy compounds, which are normally insoluble, to dissolve.

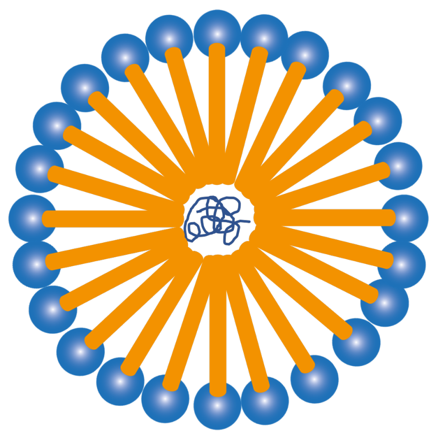


Figure 2: Structure of micelle.

Real World Application

- The computer game simulates the real-world constraints that may affect chemical product development as the student designs a novel product. It is important to think about the product holistically, and find a 'sweet spot' for reduced toxicity and increased performance.

- The game is made based on real world data.

Pre-Game Question

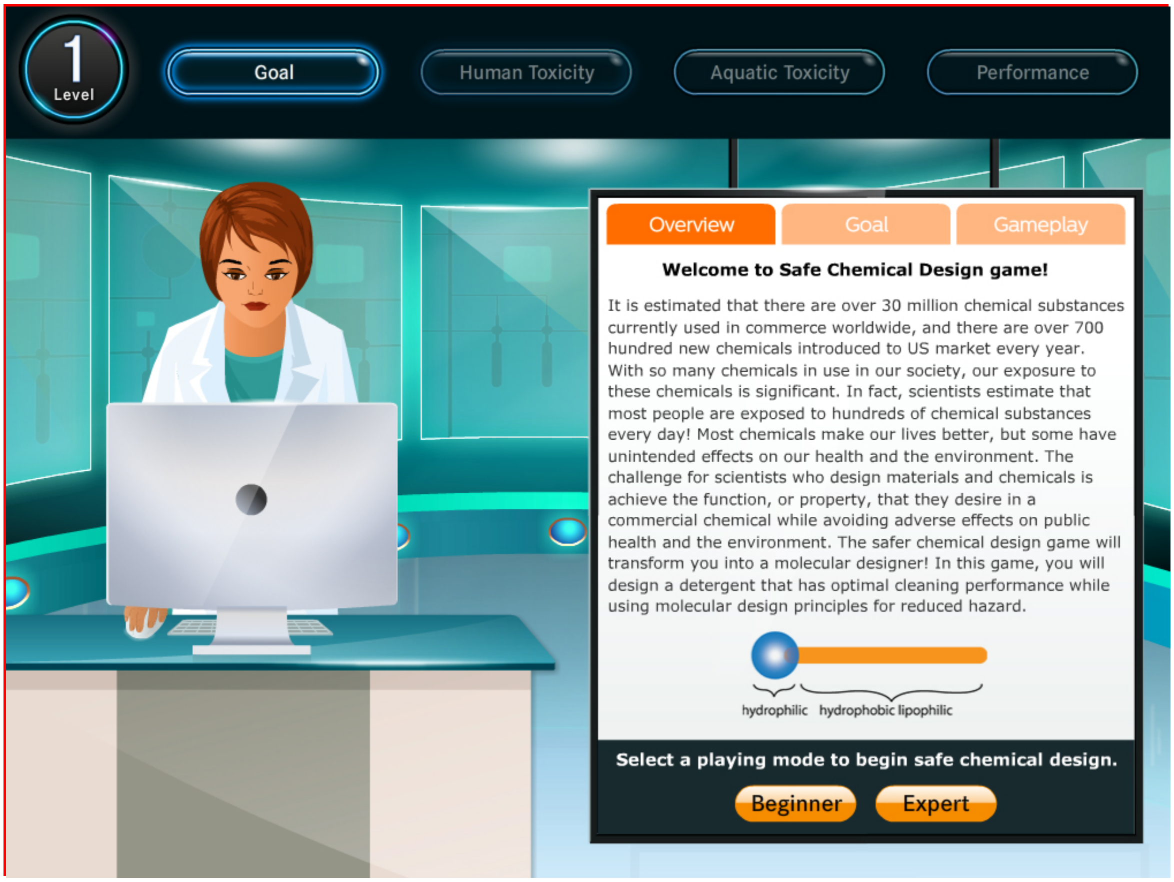
Speculate how molecular weight, lipid solubility, physical state (solid vs liquid) and vapor pressure of the detergent will impact absorption into the body.

____
____
____
____
____
____
____
____

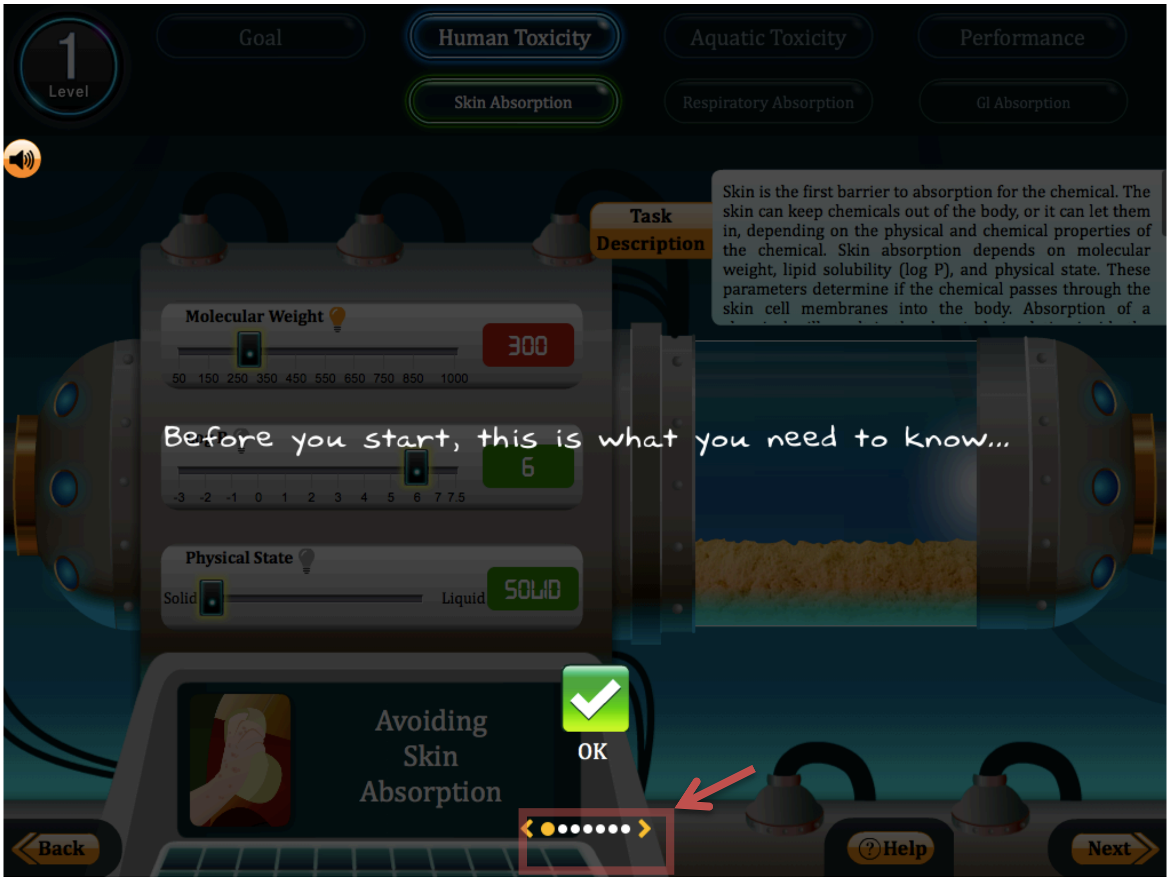
Activity Instructions

(Please note that the game is played online and it requires internet connection)

1. Go to www.gwiz.yale.edu and wait until it loads. Depending on the internet connection, the process can take up to 2 minutes.
2. Accept Copyright and all Terms of Use.
3. Begin the game by reading the instruction in Overview, Goal and Gameplay tabs.
4. We recommend playing in the Beginner mode.



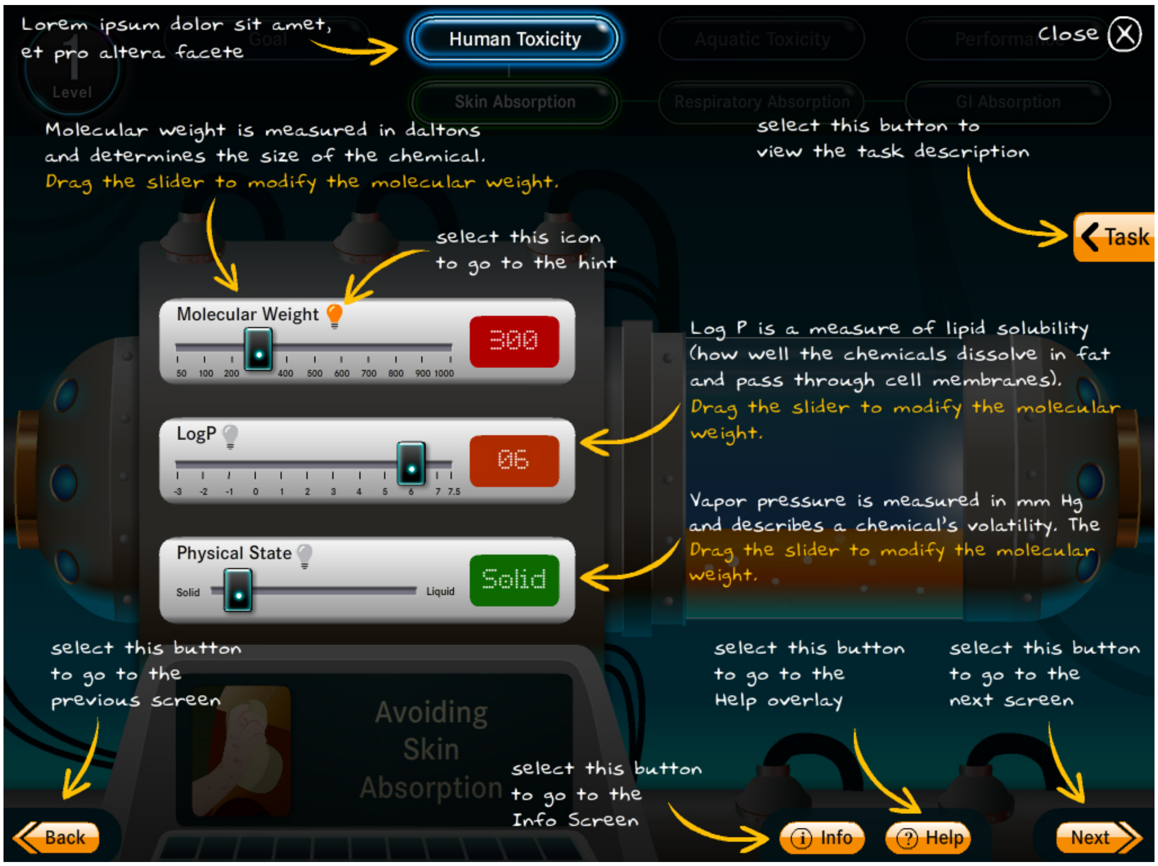
5. Familiarize yourself with the game mechanics by clicking on the small arrow button, rather than clicking OK.



Note: In level 1, you will have Human Toxicity Challenge, Aquatic Toxicity Challenge and Performance Challenge. You need to complete all three to progress to Level 2. All three challenges are interdependent, which means that selection that you will make in one challenge, will carry over to another one. Remember, the goal is to design one detergent which is not toxic to human and aquatic life while being an efficient detergent.

The Human Toxicity challenge has three subtasks: Skin, Respiratory, and GI absorption. After adjusting physicochemical parameters for each subtask, you will receive feedback, which will allow you to go back and change your parameter selection.

If you have additional questions about the game mechanics, press the Help button.



6. Read the Task description for the Skin Absorption Subtask.
7. Go to Molecular Weight parameter and move the slider to 250. Do you see how the output window becomes red? Click on the light bulb to learn why.
8. Adjust the slider until the output window becomes green.
9. Repeat the process for log P and Physical State. Make sure to read light bulb tips for both parameters.
10. Once you are satisfied with your property selection, press Next button to continue and receive feedback.
    a. If one of parameters is outside of the preferred range, you can click Back and reselect your values.

11. Complete Respiratory and GI Absorption Subtasks and progress to Aquatic Toxicity Challenge.

QUESTION 1

How do high and low values of the selected physicochemical parameters (molecular weight, lipid solubility, physical state) affect absorption? Was your pre-game prediction correct/incorrect?

12. Continue to adjust parameters relevant to the performance of the detergent.

Note: Performance is a measure of a chemical's effectiveness. It tells us how well the detergent will do its job (a great cleaning ability). For detergents and soaps, performance is quantifiable through the hydrophilic-lipophilic balance (HLB).

In this phase of product development, you will optimize the HLB. You should know that the HLB value will vary with the log P value selected during earlier design phases. Thus, changing the HLB value will also impact the absorption of the molecule. Make sure that while adjusting HLB, you don't go out of preferred range for log P!

The consideration of multiple outcomes such as absorption and product performance is an example of the real-world constraints that may affect chemical product development.

QUESTION 2

Using the game outcome, what is the HLB "sweet spot" which enables the detergent to be an effective cleaner and be nontoxic?

QUESTION 3

Why do you think Log P and HLB are depended on each other? Tip: recall detergent's structure.

QUESTION 4

Many detergents available on the market are designed for a specific function: be a good cleaning agent. As you can see from the game, it is relatively easy to control one parameter. When a company decides to design a product with a dual function like safety AND high performance, the task becomes more challenging. Why do you think that is?

In the game, were you able to design a detergent that will not absorb and have a high performance?

Was it easy or difficult?

Can you think of other examples of products from your daily lives, which perform a dual function?

13. Progress to Level 2 and begin by reading Overview, Goal and Gameplay tabs.

Note: Level 2 has three Challenges: Human Toxicity Challenge, Aquatic Toxicity Challenge and Performance Challenge. You will need to complete all three to successfully finish the game. Similar to Level 1, parameter selection is carried over to another challenge, since you are still developing one product with one set of parameters.

In this level, you need to design a chemical that will have a limited distribution, increased degradation and limited bioaccumulation. You will also notice that properties and chemical functional groups which control these processes are different than in Level 1.

14. Read the Task Description for Distribution and adjust four given parameters. Click Next to receive feedback.

QUESTION 5

Which molecules (high or low surface area) will enhance distribution through the membrane and why?

____
____
____
____
____
____

15. Continue the Human Toxicity Challenge by completing Metabolism and Accumulation & Excretion Subtasks.

QUESTION 6

Which functional groups impair excretion and contribute to accumulation in the organism?

____
____
____
____
____
____

16. In Aquatic Toxicity Challenge, you are asked to select up to 3 functional groups which enhance biodegradation. You can access that feature by clicking on the arrow

button in the Functional Groups window. Make sure to scroll down to access all the functional groups you can choose from.

QUESTION 7

Why does branching play a critical role in biodegradation of the chemical?

____

____

____

17. Once you complete Aquatic Toxicity Challenge and receive feedback, please proceed to Performance Challenge. This time the HLB value which you see is the result of your functional group selection in the earlier challenge. If your HLB value is out of the preferred range, you need to change functional groups by clicking Edit Functional Groups. Please remember that your re-selection will also impact Aquatic Toxicity Challenge result.

QUESTION 8

Do the same functional groups that enhance biodegradation (Aquatic Toxicity Challenge) contribute to the increased performance?

As future chemists, why do you think this is important to consider different functional groups and the role they play in the design process?

What if instead of two parameters (safety and performance) you also need to consider cost as a third parameter?

This material is based upon work supported by the NSF Division of Chemistry and the Environmental Protection Agency under Grant No. 1339637.