The Effects of Down the Drain Disposal of Drugs on the Environment

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This curriculum unit is recommended for: AP Environmental Science/ Grades 10th-12th

Keywords: toxicology, LD50, EC50, NOEL, T25, wastewater treatment plant, mode of action, side effects, mechanism, endocrine disruptors, feminization, vitellogenin, therapeutic dose, toxicity, ADME

Teaching Standards: See Appendix 1 for teaching standards addressed in this unit.

Synopsis: This unit will focus on highlighting the possible effects of introducing drugs into the water supply. Students will explore how drugs are introduced to the aquatic environment. They will take an in depth look at endocrine disruptors, and studies that have linked their presence in water to male feminization. Students will also research popular drugs in the United States and hypothesize their effects on the aquatic environment, and ultimately human health. One problem posed to students is to determine how wastewater treatment plants can effectively remove a particular drug out of the water supply. Students will practice calculating LD_{50} without a calculator and create a model explaining the LD_{50} of their assigned drug. This unit also contains a service learning component where students will educate the public about the hazards associated with improper drug disposal.

I plan to use this curriculum unit in my AP Environmental Science (APES) class (10th, 11th and 12th graders) and it is designed to be an overarching theme throughout the year, but can also be taught continuously in the month following the AP exam. This curriculum unit incorporates several concepts including toxicology, water quality, ecology, and sustainability.

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The Effects of Down the Drain Disposal of Drugs on the Environment

Monica High

Rationale

According to the College Board, the AP Environmental Science course is designed to help students understand the interrelationships of the environment and the analyze how human activity can contribute to environmental problems.When students leave my classroom in the spring I want them to have a greater appreciation for the environment, and I want their lifestyle to have been impacted in some way. I do not expect all of my students to become environmentalist or crusaders, but I want them to understand that small adjustments can make a big impact.

Sustainability is an overarching theme in this course. Environmental sustainability is defined as "the ability to meet the needs of the current generation without limiting the ability of future generations to meet their needs. At the beginning of the year I always ask my students, "How can you be more sustainable?", and I usually get the standard responses: "Recycle", "Carpool", "Turn off the lights". While these are all good ideas I want them to understand that there are so many little things we do on a daily basis that are ultimately destroying our planet. I teach at a health science academy and the majority of my students want to become doctors and nurses, and most of them do not have a true interest in the environment and they are either taking it because North Carolina requires all students to take an earth science course, or they are taking this class for the AP credits; but linking this course to something that they are interested in (healthcare) may elevate their interest in the environment.

At the end of this curriculum unit students will understand how improper drug disposal adversely impacts the aquatic environment both directly and indirectly. Students will discover which drugs are most commonly flushed and poured down the drain. They will also learn about proper drug disposal in both residential and commercial settings. This curriculum is divided into four main sections. In the beginning students will learn about endocrine disruptors and how their presence in the aquatic environment can lead to male feminization in some aquatic species. Then students will assess the toxicological profile of a commonly used drug, and create a model to demonstrate the LD_{50} of that particular drug. Next students will learn about water quality and WWTP and investigate how (or if) WWTP are able to efficiently remove drugs from the water supply. Lastly, students will complete a service learning project in which they educate the public about improper drug disposal.

Student and School Background

Hawthorne Academy: Health Science Magnet, Military and Global Leadership and Public Safety Academy (Hawthorne Academy) is located in the center of Mecklenburg County. This year Hawthorne Academy of Health Science recently merged with Marie G. Davis Military and Global Leadership Academy, and currently the school operates as two different schools in one building. We serve approximately 500 students. Prior to the 2017-2018 school year, students were granted admission based on their science and math test scores. As a result all of the students in my AP Environmental Science class are high achieving. This class is a year long course, taught every other day for 90 minutes a day. We are a 1:1 school so all students have access to technology, and teachers are encouraged to incorporate technology into our daily lesson plans.

Curriculum Objective

As stated before, this curriculum unit is designed to help students understand how human activity can change the world around them, by having them study this effect through a topic to which they can relate. Pollution and its effects is roughly 30% of the AP exam, and this is a fun and relatable way for them to explore this topic. Students will be exposed to activities that explain the concept of toxicology and how safe exposure limits are established. They will also learn about specific acts and government regulations including the Safe Drinking Water Act and the Clean Water Act and research the economic impact of these and other environmental laws. They will learn how to analyze data and graphs from research journals, and they will use raw data to create their own graphs which demonstrates the LD_{50} of a drug. In addition to just learning the facts associated with pollution students will hopefully be mindful of what they pour down the drain.

Content Background

Drugs in Our Water

It has long been suspected that over-the-counter and prescription drugs were slowly making their way into our water supply. Data from recent studies indicate that these levels are higher than we originally suspected.[5] In the United States, water intended for human consumption is treated at wastewater treatment plants (WWTP), and is widely considered clean and safe. However, some experts question if WWTPs are efficient at completely removing drugs from our drinking water. A study from 2000 found measurable amounts of drugs in more than 80% of water samples tested.[10] There is no data that indicates that humans are harmed by trace amount of drugs in our water supply, but data from numerous studies suggests that they are harmful to the aquatic environment.[5]

Absorption, Distribution, Metabolism, Excretion (ADME)

ADME (Absorption, Distribution, Metabolism, Excretion) is a term used in pharmacology that describes how pharmaceutical compounds enter the body (A), move throughout the body (D), breakdown in the body (M) and ultimately leave the body (E).[2] In order for a drug to be effective it has to be delivered to the appropriate site in the body. Most drugs travel around the body through the bloodstream. Some drugs directly enter the bloodstream vis intravenous (IV) administration, drugs that are taken orally or nasally enter the bloodstream by crossing the mucus lining of the intestines or nose; this process is referred to as *absorption*. Once in the bloodstream a drug will travel through the body and get deposited in various tissues (*distribution*).[8] In reference to pharmacology, *metabolism* is the process of the body breaking down a pharmaceutical compound.[11] When compounds are metabolized their entire structure and function is altered; this can be either a good or a bad thing. Metabolism is a necessary because organisms frequently take in substances that may be harmful if not destroyed or not helpful/ beneficial in their whole form (ie. food).[8] Drug metabolism begins the moment a drug enters the body, but the majority of metabolism occurs by enzymes found in the liver such as CYP450.[2] In terms of drugs, metabolism usually deactivates drugs and reduces its effects on the body, in some instances a metabolite may be more active than the parent compound. Accumulation of metabolites in the body can have adverse effects so the body has to eliminate all of the metabolites. The body eliminates waste through urine, feces, or by exhaling. Drug metabolites are primarily removed from the body in the urine (*excretion*).[8]

Overall ADME is a simple process; however there are numerous factors that can make the journey of a drug through the body quite complex. Chemical properties of a compound such as solubility, polarity and ionization will affect its ability to leave the bloodstream and enter the tissues of the body. The ability of a drug to exit the bloodstream in know as the volume of distribution (V_D); drugs with higher a V_D are distributed throughout the body more completely

than those with a lower V_D value.[12] Typically drugs with low V_D are quickly metabolized (noted by a short half life) and removed from the body. However, some drugs are so large that they will remain in the body for weeks regardless of their V_D.[12] For example, the V_D of adalimumab (Humira) is 0.086 L/kg, indicating that this drug does not readily enter tissues and therefore should be easily metabolized. However, because adalimumab is so large (144190.3 g/mol) it is not easily metabolized and can stay in the body for weeks before it is effectively metabolized and excreted.[12]

Endocrine Disruptors

Endocrine disruptors refer to any chemical that interferes with the natural processes of the endocrine system, which can result in adverse effects to the immune, reproductive or neurological systems.[4] Researchers have been studying endocrine disruptors for the past 80 years; however, in recent years (last 10 years), there has been increasing interest in how endocrine disruptors affect the environment.[7] Endocrine disruptors interrupt normal cell signaling by mimicking naturally occurring hormones like estrogen and androgen. While mimicking these hormones they are able to bind to and activate or deactivate specific receptors in the body, which may lead to undesirable effects.[5] **Figure 1** illustrates the process of endocrine disruption.

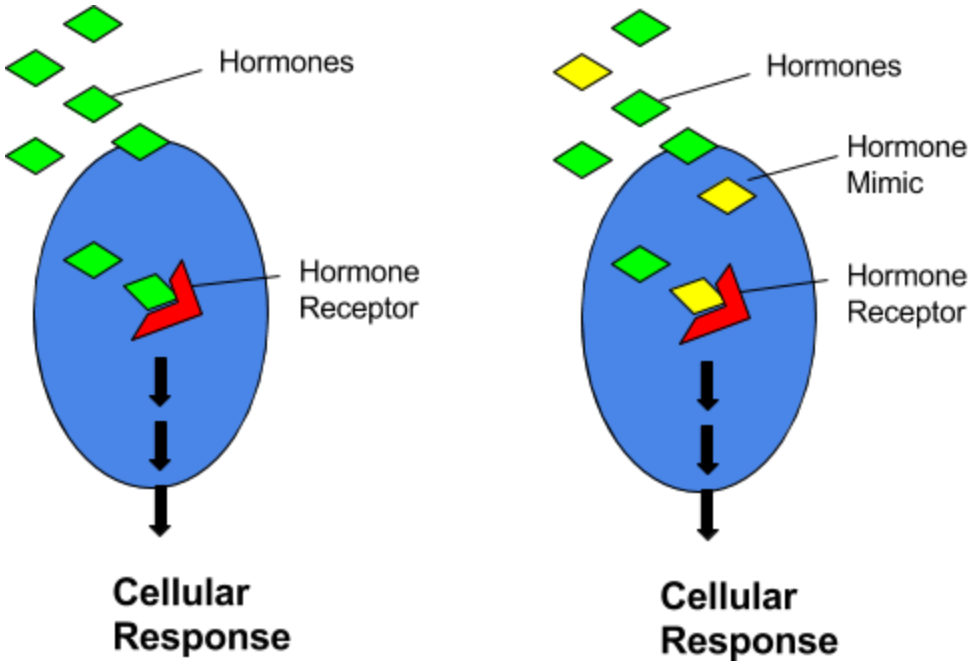

Figure 1.

Some endocrine disruptors are naturally occurring, but as our technology advances more man-made endocrine disruptors are making their way into our personal care products, cosmetics, insecticides, pesticides and plastics, all of which eventually land end their life cycle in the

environment.[5] Personal care products are typically washed off in shower and go down the drain and enter the water supply; after insecticides and pesticides are sprayed they too are washed off and will either seep into the ground and eventually make their way into the groundwater, or they may run-off directly into surface waters; and plastics containing endocrine disruptors are usually thrown away in landfills enabling the endocrine disruptors to enter the soil and groundwater. Some of the most popular endocrine disruptors include bisphenol A (BPA) (an estrogen agonist) and phthalates (an androgen antagonist). BPA is a chemical that is often found in plastics used to make food containers, water bottles and BPAs are also used to coat the inside of canned goods. In recent years BPAs have been in the news because a few studies have suggested that BPA can seep into food and may have an effect on the brain. Like BPA phthalates are found in plastic, but they are also used in detergents and personal care products. **Figure 2** illustrates exactly how endocrine disruptors enter the environment and ultimately return to humans.[4, b]

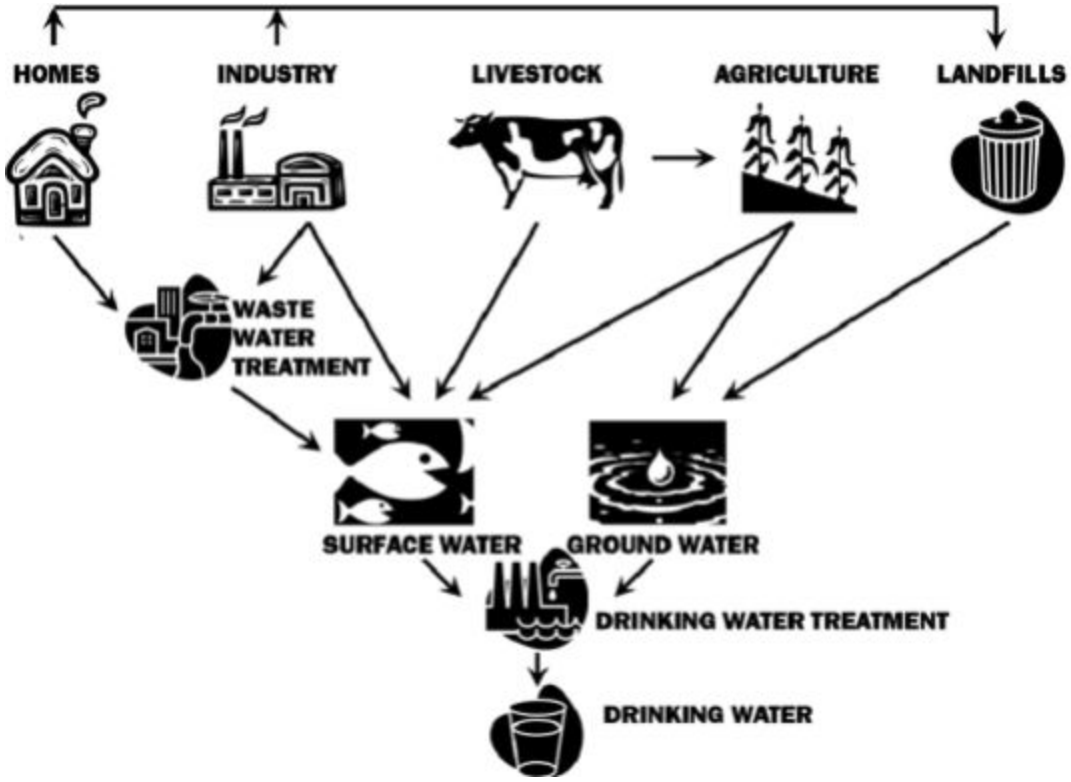

Figure 2.

The pesticide dichlorodiphenyltrichloroethane (DDT), is the known man-made endocrine disruptor.[9] In the 1930s wildlife biologists began noting unusual behavior in certain bird populations across the country. After studying these birds for a few years Charles Broley hypothesized that these birds were consuming fish contaminated by DDT run-off, which ultimately lead to neurological, behavioral and reproductive changes.[6] Subsequent researchers arrived at similar conclusions. Which eventually lead to Rachel Carson's book *Silent Spring*.[1] In

her book Carson highlights how pesticides are harming the environment, and she cautions that if the pesticide industry does not act responsibly they could ruin the planet for future generations.[5] As a result of public outcry from her book and other environmental studies, DDT was eventually banned for use in the United States.[1]

All endocrine disruptors interfere with normal endocrine functions; however, our perception of these compounds may vary significantly. For example, most people know that DDT is harmful and will go to great lengths to avoid it, but BPA has a similar chemical structure (Figure 3) and may be just as harmful but people do not think twice about storing their food in BPA products.[7]

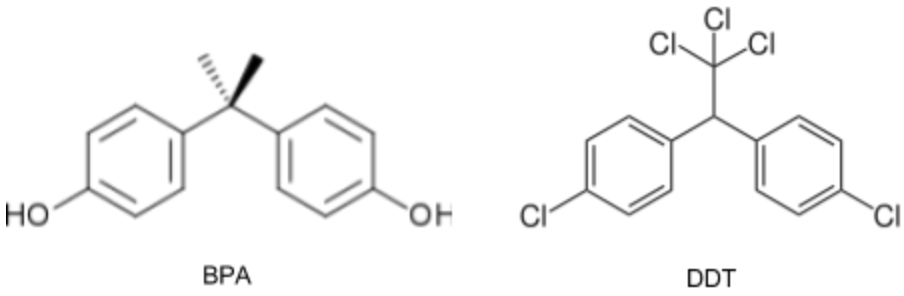

Figure 3.

Feminization of the Male

As previously mentioned, several common drugs and pesticides contain compounds that mimic estrogen, birth control being one of the more popular drugs. These drugs make their way into our water supply through improper disposal; however, the most common route of introduction is through human urine.[15] In 2007 Kidd et al. published a study which found that the presence of estrogen agonist (like birth control) in water lead to decreased sperm production and slower ovary maturation in fathead minnows. In this same study Kidd also noted that the male fish were beginning to produce VTG which would ultimately cause males to produce immature eggs within their testicular tissue.[c] Theoretically as more estrogen compounds enter the aquatic environment more and more aquatic species could become intersexed.[4] Some researchers believe that these same types of compounds are linked to gynecomastia (swollen male breast tissue), and certain cancers (prostate and breast) in humans.

Toxicology

Toxicology is the study of the ability of a drug to adversely affect the body. Drugs like antibiotics directly kill germs in your body; chemotherapeutics target cells that grow rapidly; a large percentage of drugs work by binding to cell receptors and either activate or block cell signaling (just like the previously mentioned endocrine disruptors). Regardless of how good a

drug works there are always side effects associated with the drug. While most drugs have a specific target that they are meant to bind to, it is possible that the drug will also bind to other receptors and activate or block unintended pathways. Even if a drug is specific and only binds to the intended target it may still set off a cascade of undesirable events. These side effects can range from minor to catastrophic. The deadly potential of a drug is directly linked to the dose of the drug. Toxicologists and risk assessors the median lethal dose (LD_{50}) to indicates the acute toxicity of a substance. The LD_{50} is defined as the dose of a substance at which 50% of the population is killed.after a predetermined period of time. Substances with a low LD_{50} are more toxic than those with higher LD_{50} values. Since some test subject have to die in order to calculate an LD_{50} value, they are not usually used or found in clinical trials.[2] In clinical trials, researchers use the NOAEL (No-observed-adverse-effect-level) as the safe level for a drug. The higher the NOAEL the safer the drug.[3]

Teaching Strategies

Quick Writes

If this unit is taught at the end of the course it will be helpful to have students brainstorm and use prior knowledge to reason how improper drug disposal can affect the environment. When you introduce this unit have students complete a quick write about "How can prescription and over the counter drugs affect the environment?". Students may struggle at first, but you can guide them by asking "What happens to drugs when you throw them away?". In my classroom quick-writes often look like a real life discussion board. I usually have students complete their initial quick write on a large (~5 x 7) post-it note and stick it on the board. Then I give students a few minutes to read over all of posts and respond to at least two. If a student initially had no idea what to write about, just reading their classmates' thoughts will get them thinking, linking concepts and you may get some very creative responses.

Closed reading with document based questions

As mentioned previously, this curriculum unit is designed for AP students, and at this level I really stress and work on their ability to acquire information on their own. After students have effectively brainstormed about the connection between drug disposal and adverse environmental effects they will read and annotate a pre-selected article. Then they will answer several text-dependent questions to gauge their understanding.

Gallery Walk

This strategy is not specifically mentioned in this curriculum unit; however, it may prove to be a useful tool. As an introduction to endocrine disruptors you can post graphs and data from

studies that link endocrine disruption with aquatic toxicity and have students walk around and interpret the data.

Class Discussion

This requires little participation from the teacher and provides the opportunity for students to teach each other. As students discuss a topic you can assess their understanding and uncover gaps in their knowledge. Class discussion can be used frequently throughout the curriculum especially at the end of each activity.

Case Studies

In my advanced classes I use case studies a lot. They are a great way students to see how concepts they have learned in class appear in the real world. Case studies also enable students to analyze a problem from several different viewpoints and encourages problem solving. In this curriculum unit student conduct a case study that examine the effects of improper drug disposal in an American city. They will learn about the main source of drug pollution in this city, how different stakeholders viewed the problem and how they proposed to handle the situation. Ultimately they will learn how this case was resolved and as a class they will reflect on the resolution.

Inquiry-Based Instruction and Peer-to-Peer Instruction

Throughout the course of this unit students will be conducting independent research and allowing their curiosity and observations to influence exactly what they learn or get from this unit. Students will research a commonly used drug of their choice and prepare a presentation about the drug. Students will be given a rubric that outlines what their presentation is expected to contain.

INSTRUCTION GUIDE

Part I- Introduction

Hook

This portion is designed to get your students thinking about how drugs enter the environment and what effects they may have on the environment. Show this comic[b] adapted by Doughton from Ternes to your class and have them brainstorm or discuss what could be the meaning behind the image. Make sure students notice that there are two routes depicted: directly down the drain and excretion.

Discussion prompts may include:

- What are some additional ways or scenarios in which drugs can enter our environment?
- How does the presence of drugs impact the environment?
- How do you or your parents dispose of medication?
- How can you prevent medication from entering the water supply?

To ensure that all students are engaged in the topic, you may choose to have students do a quick write about the comic on their own, then they can share out with the class or in small groups.

Closed Read

This 2016 article by Laurie Powell does a great job of summarizing how drugs enter our water supply.[a] After reading this article students should understand that when drugs are disposed of improperly they will enter our water supply; almost all of the water in the industrialized world is contaminated with some type of drug, and even bottled water is usually contaminated. Most students probably think that all traces of drugs are removed at the wastewater treatment plant (WWTP), but as this article points out WWTP mainly focus on removing bacteria from our water. Appendix 2 is a guided notes worksheet that is designed to accompany the article.

At this point students should understand that improper drug disposal will cause our water supply to become contaminated, but they do not fully understand why that is significant. In Laurie Powell's article she mentions that a lot of the drugs found in our water supply are a direct result of unmetabolized drugs found in excreted waste.

Assessment

As the teacher you will lead a class discussion about drugs in the water. Using their notes students will discuss what they have learned so far about drugs in the water; how they got their and why it is dangerous. They should also start brainstorming feasible solutions and different

stakeholders will respond to these solutions. Once you get them started this discussion should be entirely student driven, you can use this discussion as a way the assess how much your students under the concept of drugs in the water and also how it relates to other topics previously covered in the course.

Part II- ADME

A lot of information about the ability of a drug to be absorbed, distributed, metabolized and excreted can be predicted by studying the structure of the compound. This activity is designed to have your students explore how scientist can manipulate the structure of a compound in order to get desired therapeutic effects.

If your students read the article mentioned in the previous section they should know that antidepressants, antibiotics and pain relievers are some of the most prominent drugs found in tap water. For this activity you will assign each student a CAS (chemical abstract services) number for a popular drug but do not give them the drug name. Using the internet and the CAS number, students should be able to find the SMILES (simplified molecular-input line-entry system) structure and name of their compound. Now that they have the SMILES structure students will use admetsar or SwissADME, an online interactive site that will predict the drug properties (ADME) solely based on the structure. Using molinspiration students can alter their drug compound, get a new SMILES and see how the drug properties were altered. Protox will allow students to see the adverse effects associated with their drug/compound. Appendix 3 contains a worksheet that will help guide your students through this activity and the websites.

Assessment

Students will complete the worksheet in Appendix 3 as they work through this activity. The worksheet is a great way to assess if they understand how drugs are processed in the body. You can take this activity a step further and have students research how individual differences between people (weight, genetics, gender, ethnicity) will affect ADME, and how can this information be used to create personalized medicine.

Part III- Endocrine Disruptors and Feminization of the Male

By this point your students know that traces of drugs are found in our water supply, and they also have a surface understanding of how drugs are broken down and eliminated from the body. They can probably even tell you that the presence of these drugs is bad for the environment, but they probably cannot speak in depth about why or how drugs adversely impact

the environment. This activity highlights one possible adverse effect drugs may have on the environment, but should help peak students interest and get them to think critically about drugs in the environment.

Before starting this activity make sure to briefly discuss endocrine disruptors (What are they? Where are they found?) with your students. Up until this point your students have only focused on how drugs in the traditional sense impact the environment, so it is important that you stress that endocrine disruptors can be found in benign products that they use daily such as water bottles, cosmetics, and personal care products.

Have students analyze the graph below from Kidd *et al*.[c] In this 2007 study, a fish population was studied before and after exposure to synthetic estrogen. Researchers noticed that exposure to synthetic estrogen (vitellogenin aka. VTG: a precursor for egg yolk that is used as a biomarker for male femnization) leads to egg production in males and results in an intersexed fish. You can even take this a step further and incorporate the gallery walk mentioned in the teaching strategies section. Following a class discussion about the graph from Kidd *et al.* students can further explore the effects of endocrine disruptors through the case study Kermit or Kermette from the University of Buffalo.[d]

> The study from Kidd et al. "...explores the unintended side effects of chemicals introduced into the environment, specifically organic compounds that can act as environmental estrogens (chemical castration agents that can interfere with the sexual development of embryonic males). The case was developed for a non-majors chemistry course and focuses on the science that underlies the controversy surrounding the sale of the herbicide atrazine in the U.S. as well as the political and economic issues that impact this science."[c]

Assessment

The previously mentioned case study (Kermit or Kermette) is designed to walk students through an actual environmental crisis involving endocrine disruptors, and should be used as an assessment tool.

Part IV- Exploration

By now students should begin to see the connection between improper drug disposal and its impact on the aquatic environment. In this activity students will assume the role of an environmental risk assessor. Students will be divided into groups and each group will select a drug that to research. Each group will determine the following for their drug:

- Common name or name brand
- any recent news or deaths

- mechanism/ mode of action
- purpose of the drug
- side effects (Explain the cause of the side effects)
- popularity/ demographic (rough estimate of the number of people on this drug)
- therapeutic dose
- toxicity information (LD_{50}, NOAEL, T25)
- aquatic/ environmental toxicity information
- Conclusion: Possible environmental ramifications

Historically research was not focused on the environmental effects of drugs, resulting in very little environmental data. It is important to stress to students that environmental toxicologist/ risk assessors sometimes have to use data from other species to determine aquatic toxicity. Students will write-up their findings in the form of a toxicological risk assessment. Students will us this EPA site to help them.

Assessment

The completed risk assessment is used to assess student in this section.

Part V- Service Learning (optional)

Your students have explored drug toxicity and learned about how improper disposal can impact the environment; now they can focus on educating the public about this issue. The FDA and several other local agencies stress the importance of proper drug disposal. In this activity students will design a service project that address improper drug disposal. Students may decide start a campaign designed to raise awareness to the hazards associated with drugs in the environment, or start an action campaign where they tell other how to properly dispose of drugs. These are just a couple of suggestions, but let students come up with their own idea and implement their own service project.

Appendix 1

AP Environmental Science Course Topics

Pollution

A. Pollution Types
    a. Water pollution
        i. Cause and Effects
        ii. Groundwater pollution
        iii. Maintaining Water Quality
        iv. Water Purification
        v. Sewage Treatment/ Septic Systems
        vi. Clean Water Act
    b. Solid waste
        i. Disposal
        ii. reduction
B. Impacts on the Environment and Human Health
    a. Hazards to Human Health
        i. Environmental Risk Assessment
        ii. Dose-response relationship/ LD_{50} and Threshold

Appendix 2

Are You Drinking Prescription Drugs in Your Tap Water?

Laurie Powell

Follow the link and read the article published on Focus for Health
http://bit.ly/2gIm012

According to the article, how do drugs get into the water supply?

1.

2.

3.

Why aren't drugs removed by wastewater treatment plants (WWTP)?

How should you properly dispose of medication?

The author mentions that she is concerned that water bottles contain Bisphenol-A (BPA). What is BPA and why do you think she is concerned?

What is an adverse effect of having trace amounts of drugs in the water?

After reading this article, what are your thoughts about drugs and our water?

Appendix 3

Drug Absorption, Distribution, Metabolism & Excretion (ADME)

Use the internet and information that you've learned in class to answer the following questions.

Define the following in terms of drug delivery.

- Absorption:
- Distribution:
- Metabolism:
- Excretion:

Using only your current knowledge, what do you think could impact ADME of a drug?

CAS #: _____ Name of compound: _____

SMILES structure: _____

Why do you think scientist use CAS numbers instead of a name to identify a compound?

Go to the SwissADME website (www.swissadme.ch/index.php). Enter your SMILES structure into the search bar. Use the results to complete the Trial 1 column of the table below.

	Trial 1	Trial 2
CAS #		
Name		
Structure (drawing)		
Absorption		
Distribution		
Metabolism		
Excretion		

Go to molinspiration (molinspiration.com) and enter your SMILES structure. Using the drawing tools on the site alter the structure of your compound. Draw your new structure in the Trial 2 column and with your nes CAS # use admetSAR to predict the properties of your new compound.

Referencing your chart, what effect did your alteration have on your compound?

How could this be used for drug discovery?

What is the relationship between absorption, distribution, metabolism and excretion?

Do you think smaller or larger molecules are more effective drugs? Explain your reasoning.

Using the internet and the online tools introduced in this activity and research a drug you are familiar with. Write your findings in the space below.

Resources

Classroom Materials

- Internet
- Laptops,
- Worksheets/ handouts (Appendix 2 and 3)
- Sticky notes

Teaching Resources

a. "Are You Drinking Prescription Drugs in Your Tap Water?" Focus for Health. December 16, 2016. Accessed October 27, 2017. https://www.focusforhealth.org/drinking-prescription-drugs-tap-water/.
b. T.mettens. "Pharmaceutical Estrogens in the Water Are Feminizing Male Fish. Are We Next?" Transyanimalphys. November 02, 2013. Accessed June 07, 2017. https://transyanimalphys.wordpress.com/2013/11/02/pharmaceutical-estrogens-in-the-water-are-feminizing-male-fish-are-we-next/.
c. Kidd, K. A., P. J. Blanchfield, K. H. Mills, V. P. Palace, R. E. Evans, J. M. Lazorchak, and R. W. Flick. "Collapse of a fish population after exposure to a synthetic estrogen." *Proceedings of the National Academy of Sciences* 104, no. 21 (2007): 8897-901.
d. "Kermit to Kermette?" Kermit to Kermette? - National Center for Case Study Teaching in Science. Accessed October 28, 2017. http://sciencecases.lib.buffalo.edu/cs/collection/detail.asp?case_id=189&id=189.

Annotated Bibliography

1. Carson, Rachel. *Silent spring*. London: Penguin Books, in association with Hamish Hamilton, 2015.

This book was originally published in 1962 and explains how the use of pesticides alters the environment and negatively impacts the food chain.

2. Doogue, Matthew P., and Thomas M. Polasek. "The ABCD of clinical pharmacokinetics." *Therapeutic Advances in Drug Safety* 4, no. 1 (2013): 5-7.

This article looks at how a drug is absorbed, distributed, metabolized and excreted in the body.

3. Dorato, Michael A., and Jeffery A. Engelhardt. "The no-observed-adverse-effect-level in drug safety evaluations: Use, issues, and definition(s)." *Regulatory Toxicology and Pharmacology* 42, no. 3 (2005): 265-74.

This article summarizes NOAELs and details how they are used in clinical risk assessments

4. "Endocrine Disruptors." National Institute of Environmental Health Sciences. Accessed August 22, 2017. https://www.niehs.nih.gov/health/topics/agents/endocrine/index.cfm.

This NIH article explains how endocrine disruptors work and how human encounter them on a daily basis.

5. Fallik, Dawn. "This New Study Found More Drugs in Our Drinking Water Than Anybody Knew." New Republic. December 11, 2013. Accessed May 20, 2017. https://newrepublic.com/article/115883/drugs-drinking-water-new-epa-study-finds-more-we-knew.

Interesting news article that discusses how the amount of drugs in our water supply is increasing and current regulations are not doing enough to curb the effects.

6. Gerrard, Jonathan M. *Charles Broley: an extraordinary naturalist*. Headingley, Man.: White Horse Plains Publishers, 1983.

Charles Broley was an ornithologist who first noticed a change in the mating habits and behaviors of bald eagles which was eventually linked to the use of insecticides.

7. Kabir, Eva Rahman, Monica Sharfin Rahman, and Imon Rahman. "A review on endocrine disruptors and their possible impacts on human health." *Environmental Toxicology and Pharmacology* 40, no. 1 (2015): 241-58.

This article summarizes the various health effects associated with exposure to endocrine disruptors

8. Lin, Jing, Diana Sahakian, Sonia De Morais, Jinghai Xu, Robert Polzer, and Steven Winter. "The Role of Absorption, Distribution, Metabolism, Excretion and Toxicity in Drug Discovery." *Current Topics in Medicinal Chemistry* 3, no. 10 (2003): 1125-154.

This scientific article details the concept of ADME. It could be a good article for a jigsaw activity.

9. Patisaul, Heather. "Long-term effects of environmental endocrine disruptors on reproductive physiology and behavior." *Frontiers in Behavioral Neuroscience* 3 (2009).
This scientific review article summarizes how exposure to endocrine disruptors at critical times of development can alter physiology and behavior in vertebrates.

10. Publications, Harvard Health. "Drugs in the water." Harvard Health. June 2011. Accessed May 20, 2017. http://www.health.harvard.edu/newsletter_article/drugs-in-the-water.
Not only does this article talk about drugs in our water supply, but it also identifies the most common drugs that are detected in drinking water.

11. Tetko, Igor V., Pierre Bruneau, Hans-Werner Mewes, Douglas C. Rohrer, and Gennadiy I. Poda. "Can we estimate the accuracy of ADME–Tox predictions?" *Drug Discovery Today* 11, no. 15-16 (2006): 700-07.
This article takes an in depth look at the link between ADME and toxicity and analyzes whether ADME can predict toxicity.

12. Toutain, PL, and A. Bousquet-Mélou. "Volumes of distribution." *J Vet Pharmacol Ther* 27, no. 6 (December 2004): 441-53.
This scientific review article summarizes volume of distribution and how it can be used in drug discovery.