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LESSON:

A Whiff of Danger

Summary: Students review common chemistry and biochemistry concepts by exploring real data related to the article "A Whiff of Danger: Synthetic Musks May Encourage Toxic Bioaccumulation."

EHP Article: "A Whiff of Danger: Synthetic Musks May Encourage Toxic Bioaccumulation" *EHP Student Edition*, April 2005, p. A50
http://ehp.niehs.nih.gov/docs/2005/113-1/ss.html

Objectives: By the end of this lesson, students should be able to:

1. define and use the following terminology: aromatic hydrocarbons, chemosensitizer, chemical formula, hydrophobic, inverse relationship, octanol–water coefficient (Log K_{ow}), molecular weight, multidrug/multixenobiotic resistance efflux transporters, musk, paradox, synthetic transport proteins, xenobiotic;
2. read the table and graph presented in the lesson.

Class Time: 1–2 hours

Grade Level: 11–12

Subjects Addressed: Chemistry, Biochemistry

Prepping the Lesson (10–15 minutes)

INSTRUCTIONS:

1. Obtain a class set of *EHP Student Edition*, April 2005, or download the article at http://ehp.niehs.nih.gov/docs/2005/113-1/ss.html
2. Make copies of the student instructions.

MATERIALS (per student):

- Copy of *EHP Student Edition*, April 2005, or 1 copy of "A Whiff of Danger: Synthetic Musks May Encourage Toxic Bioaccumulation"
- Copy of student instructions

VOCABULARY:

aromatic hydrocarbons, chemosensitizer, chemical formula, hydrophilic, hydrophobic, inverse relationship, octanol–water coefficient (Log K_{ow}), molecular weight, multidrug/multixenobiotic resistance efflux transporters, musk, paradox, polycyclic, synthetic transport proteins, xenobiotic

BACKGROUND INFORMATION:

The articles "A Whiff of Danger: Synthetic Musks May Encourage Toxic Bioaccumulation" (http://ehp.niehs.nih.gov/docs/2005/113-1/ss.html) and "Nitromusk and Polycyclic Musk Compounds as Long-Term Inhibitors of Cellular Xenobiotic Defense Systems Mediated by Multidrug Transporters" (http://ehp.niehs.nih.gov/members/2004/7301/7301.html) provide sufficient background information to complete the lesson.

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RESOURCES:

Environmental Heath Perspectives, Environews by Topic page. Choose Chemical Exposures, http://ehp.niehs.nih.gov/topic

Definition of octanol–water partition coefficient, USGS, http://toxics.usgs.gov/definitions/kow.html

Log octanol–water partition coefficient, http://www.tiem.utk.edu/~sada/help/TH_479.htm

Animal cell structure, molecular expressions, http://micro.magnet.fsu.edu/cells/animalcell.html

Transport in and out of cells, http://www.emc.maricopa.edu/faculty/farabee/BIOBK/BioBooktransp.html

Implementing the Lesson

INSTRUCTIONS:

1. Hand out copies of the *EHP News Magazine*, April 2005, and refer your students to the article "A Whiff of Danger: Synthetic Musks May Encourage Toxic Bioaccumulation" (p. A50).
2. Hand out copies of the student instructions.
3. Have the students read the article and answer the questions on the student instructions.
4. Discuss any vocabulary or concepts as needed.

NOTES & HELPFUL HINTS:

- You may want to discuss animal cell structure and transport in and out of cells (see Resources) in association with this lesson.

Aligning with Standards

SKILLS USED OR DEVELOPED:

Communication (written—including summarization), Comprehension (reading), Critical thinking and response, Graph reading, Observation, Tables and Figures (reading)

SPECIFIC CONTENT ADDRESSED:

Molecular weight, chemical structure, chemical formulas, hydrophobic, musks, chemosensitizers

NATIONAL SCIENCE EDUCATION STANDARDS MET:

Unifying Concepts and Processes

- Systems, order, and organization
- Evidence, models, and explanation
- Form and function

Physical Science

- Structure and properties of matter
- Chemical reactions

Life Science

- The cell
- Matter, energy, and organization in living systems
- Behavior of organisms

Science in Personal and Social Perspectives

- Personal and community health

Assessing the Lesson

Guidelines for student answers:

a) The paradox is that musks are considered nontoxic, however they may enhance the toxicity of other substances.
b)–c) Students define the words.
d)–e) Students identify the chemical formulas, elements, and number of atoms.
f) Students show how to calculate the molecular weight.
g) The two nitromusks are musk xylene (MX) and musk ketone (MK).
h) The independent variable is the Log K_{ow} and the dependent variable is the IC_{50}.

i) It appears that the lower the Log K_{ow} of the musk, the lower the IC_{50}. This means that if the substance is more hydrophilic it can inhibit 50% of the efflux transporters at lower concentrations of the musk.
j) MK is potentially more potent than HHCB. This means it is more likely to allow toxic chemicals into the cell.
k) The new title for the research article should provide an accurate reflection of the research topic. Some examples of answers to the question "Why do you think the title of the original research article is so long?" are to give readers a good idea of the research discussed in the article and to improve the keyword/title searchability of the article.

Authors and Reviewers

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Student Instructions: A Whiff of Danger

Step 1: Read "A Whiff of Danger: Synthetic Musks May Encourage Toxic Bioaccumulation," *EHP Student Edition*, April 2005, p. A50, http://ehp.niehs.nih.gov/docs/2005/113-1/ss.html .

Step 2: Answer the following questions about the research:

a)The author refers to a paradox with respect to synthetic musks. Using your own words, describe the paradox.

b)Using your own words, summarize the results of the study and why they are important to human health. Please use and define the following terminology in your summary: chemosensitizer, multidrug/multixenobiotic resistance efflux transporters, molecular weight, musk, transport proteins, xenobiotic.

Step 3: Referring to Table 1 (next page), answer the following questions.

Chemical Formula

c) Define **chemical formula**.

d)The two most widely used musks are Galaxolide and Tonalide. In the year 2000, approximately 1,800 metric tons were produced in Europe alone. What is the chemical formula for each musk?

Galaxolide:

Tonalide:

e)Break down the chemical formula for each musk by naming each element and the number of atoms represented per molecule.

Galaxolide:

Tonalide:

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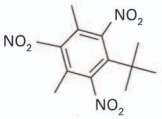
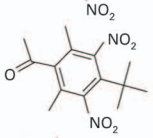
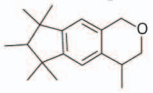
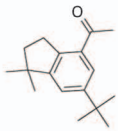
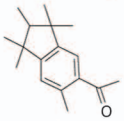
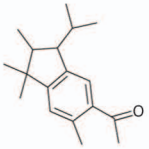
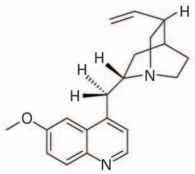
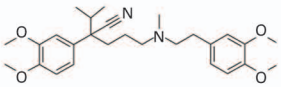
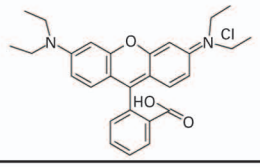
Table 1. Names, CAS numbers, formulas, structures, molecular weights, and log K_{ow} values for artificial musks and MXR model substrates and inhibitors.

Chemical and trade names	CAS No.	Formula	Structure	Molecular weight	Log K_{ow}
Musk xylene (MX) 1-*tert*-Butyl-3,5-dimethyl-2,4,6-trinitrobenzene	81–15–2	$C_{12}H_{15}N_3O_6$		297.3	4.9[a]
Musk ketone (MK) 1-*tert*-Butyl-3,5-dimethyl-2,6-dinitro-4-acetylbenzene	81–14–1	$C_{14}H_{18}N_2O_5$		294.3	4.3[a]
Galaxolide (HHCB) 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethyl-cyclopenta-γ-[2]-benzopyran	1222–05–5	$C_{18}H_{26}O$		258.4	5.9[a]
Celestolide, Crysolide (ADBI) 4-Acetyl-1,1-dimethyl-6-*tert*-butylindane	13171–00–1	$C_{17}H_{24}O$		244.4	5.9[a]
Tonalide, Tetralide, Fixolide (AHTN) 7-Acetyl-1,1,3,4,4,6-hexamethyl-tetrahydronaphthalene	21145–77–7	$C_{18}H_{26}O$		244.4	5.7[a]
Traseolide (ATII) 5-Acetyl-1,1,2,6-tetramethyl-3-isopropylindane	68140–48–7	$C_{18}H_{26}O$		258.4	6.3[a]
Quinidine	56–54–2	$C_{20}H_{24}N_2O_2$		324.4	2.8[b]
Verapamil	52–53–9	$C_{27}H_{38}N_2O_4$		454.6	4.5[b]
Rhodamine B	81–88–9	$C_{28}H_{31}ClN_2O_3$		479.0	1.5[c]

[a]Data from Balk et al. (2001). [b]Data from Wang et al. (2003). [c]Data from Liu (2004).

The table is from the original research article "Nitromusk and Polycyclic Musk Compounds as Long-Term Inhibitors of Cellular Xenobiotic Defense Systems Mediated by Multidrug Transporters," *Environmental Health Perspectives*, January 2005, Volume113, Number 1, p. 17–24, http://ehp.niehs.nih.gov/members/2004/7301/7301.html .

Molecular Weight

The **molecular weight** is the total weight of the molecule, which is the sum of the weight of each atom present in the molecule.

f)Show how to calculate the molecular weight for Celestolide and rhodamine B.

- Celestolide:

- Rhodamine B:

Chemical Structure

Look at the chemical structure column in Table 1. All of the musk molecules contain six-sided ring structures called **aromatic rings**. In the study, the authors saw an effect from both types of musks tested. The nitromusks appeared to have a greater effect than the polycyclic musks.

g)In the table, there are two nitromusks and the rest are polycyclic. Look at the chemical structures and identify the two nitromusks.

Step 4: Refer to the graph at right and answer the following questions. The abbreviations for the substances on the graph are found in Table 1.

h)Identify the independent and dependent variables.

i)The **octanol–water coefficient (Log K_{ow})** tells whether a chemical has a greater attraction to water (is **hydrophilic**) or if it is water insoluble (**hydrophobic**)—the higher the K_{ow}, the more hydrophobic a substance. The octanol–water coefficient is important in biochemistry because it can give researchers an idea about how a substance may behave in the body. Substances with high Log K_{ow} (about 5.5 or higher) will probably be attracted to fatty tissues, like those in the brain or liver, and be stored in the body for a long period of time. The Log K_{ow} may also have an effect on how a substance interacts with cell membranes and transporters.

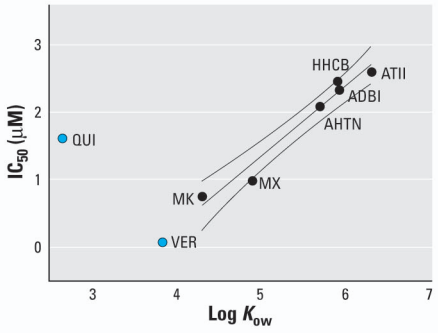


Figure 5. Correlation of MXR inhibitory efficiency (indicated by IC_{50} values) and log K_{ow} of test compounds. Abbreviations: QUI, quinidine; VER, verapamil. For the calculation of the regression curve, (with 95% confidence intervals) only musk compounds were included.

Describe the relationship between the Log K_{ow} of the synthetic musks and the IC_{50} (the concentration of musk that inhibits 50% of the efflux transporters). Be sure to address what this means with respect to the **water solubility** of the musk and its ability to **inhibit the efflux transport**.

HINT: Remember, inhibiting the efflux transporters allows unwanted chemicals into the cell that would normally be excluded. So the lower the IC_{50}, the more it inhibits the efflux transporters, and the more unwanted chemicals can get into the cell (this is called an inverse relationship).

NOTE: Quinadine (QUI) and verapamil (VER) are two reference substances that are known to inhibit efflux transporters.

j)Which musk appears to be more "potent"—MK or HHCB? Justify your answer and describe what "more potent" means.

k)The title for the original research publication is "Nitromusk and Polycyclic Musk Compounds as Long-Term Inhibitors of Cellular Xenobiotic Defense Systems Mediated by Multidrug Transporters." Can you come up with a title for the article that is descriptive and accurate but would be easy for a high school student to understand? Why do you think the title of the original research article is so long?