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LESSON:

Depleted Uranium and the Brain

Summary: Students look at data from real-life current research on the effects of depleted uranium on the brain. Depleted uranium was used for ammunition in both wars in Iraq. Students develop graph reading skills and learn important concepts in the scientific process like 1) the fact that research is ongoing and often yields unexpected and/or dead-end results and 2) how to use data as a guide for the "next steps" in research.

Students are introduced to the issue of depleted uranium by reading the article "Battle Scars: Global Conflicts and Environmental Health" and reading a hand-out with information on uranium and depleted uranium, basic physiology of the nose and brain, and the research being done by environmental health scientist Johnnye Lewis. Students are asked to write a summary of the data (presented in graph format) and come up with ideas about "next steps" in the research on the effects of uranium on the brain. Extension Lesson—This lesson extends the discussion of a topic addressed within an article in the *EHP Student Edition*.

EHP Article: "Battle Scars: Global Conflicts and Environmental Health"
EHP Student Edition, March 2005: A994–A1003
http://ehp.niehs.nih.gov/members/2004/112-17/focus.html

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

1. Write a clear, accurate description of the data presented in a graph.
2. Write a clear, accurate description of the combined results of several studies.
3. Look at the scientific process and the data collected, and suggest next steps in the research.

Class Time: 2–3 hours

Grade Level: 11–12 (It helps if the students are familiar with standard deviation)

Subjects Addressed: Life Science, Biology, Health, Anatomy and Physiology, Environmental Science

Prepping the Lesson (5–10 minutes)

INSTRUCTIONS:

1. Obtain a class set of *EHP Student Edition*, March 2005, or download the article at http://www.ehponline.org/science-ed and make copies.
2. Make copies of the student instructions.

MATERIALS (per student):

- 1 copy of the *EHP Student Edition* , March 2005, or 1 copy of the article "Battle Scars: Global Conflict and Environmental Health"
- 1 copy of the student instructions

VOCABULARY:

Antibody
Absorption
Blood–brain barrier
Central nervous system (CNS)

National Institute of Environmental Health Sciences
Community Outreach & Education Program

Cortex
Depleted uranium (DU)
Glial fibrillary acidic protein (GFAP)
Inhalation
Ingestion
Injection
Limbic system
Nose-brain barrier
Null hypothesis
Olfactory bulb and system
Route of exposure
Solubility
Toxicant
Toxicologist

BACKGROUND INFORMATION:

Introductory information about depleted uranium (DU) is included in the article "Battle Scars: Global Conflicts and Environmental Health."

In addition to being radioactive, uranium is a heavy metal that is toxic to the kidney and bone. In humans, acute toxicity for uranium exposure can produce severe nausea, vomiting, diarrhea, and kidney damage at 2 mg uranium/kg of body weight (Butterworth, 1955; Zhao and Zhao, 1990; Pavlakis et al., 1996). Uranium mineworkers sustained kidney damage after several months to several years of uranium exposure at 0.079–1.0 mg/kg body weight (Bernard et al., 1956; Hursh and Spoor, 1973; Luessenhop et al., 1958; Struxness et al., 1956).

The health effects from certain exposure levels of DU, particularly effects of the central nervous system (CNS), have not been firmly established. The standard scientific approach is to assume that the null hypothesis (i.e., there is no adverse effect) is correct. The Army spokeswoman in the article states that DU "has not been demonstrated to have ill effects." She may state this because of deference to the null hypothesis, political pressure, or both. Sometimes, these opinions may be an accurate description of available research results, but in reality existing studies are not able to answer questions about current exposures. For example, existing research may have looked at higher exposure doses, shorter exposure times, or different forms of uranium. Or a study may have looked at different exposure routes—for example, drinking water rather than inhaling dust. All of these factors, as well as the species tested, can influence the ability to *extrapolate*, or interpret existing results with respect to new situations outside of the laboratory. The accumulation of consistent data from animal research and human epidemiological studies is what ultimately leads scientists to confirm the adverse health effects of a substance, and politicians and other decision makers to accept these results.

Some believe that this approach is too conservative when it comes to human health. In all science there is some level of uncertainty involved. How this uncertainty is dealt with can be a major factor in determining whether or not a material is thought to adversely affect health.

Currently there is momentum building for the implementation of the "precautionary principle." The precautionary principle is defined by the European Environment Agency as "an overarching framework of thinking that governs the use of foresight in situations characterized by uncertainty and ignorance and where there are potentially large costs to both regulatory action and inaction." Use of the precautionary principle shifts the burden of proof in the direction of protecting public health if there is reasonable, credible scientific evidence to assume a material *may be* toxic, even if it has not been proven so.

If the precautionary principle is used to determine whether DU is safe, results of current research might introduce more caution into the decision. This is because even though there are relatively few studies published on the health effects of DU, particularly potential CNS effects, these studies illicit some early concern.

Some published, peer-reviewed results on DU's effects on the CNS, as well as work in progress using some likely exposure scenarios, are presented in this background section to demonstrate how researchers build on each others' results. Early data have led the Department of Defense to fund scientists like Johnnye Lewis, a toxicologist at the University of New Mexico, to further explore the DU issue and add to the body of knowledge that hopefully will be used in the future to fill gaps in current knowledge and make informed decisions.

Gulf War Illness

Following the Gulf War, veterans began to report a set of symptoms that did not fit with a known disease etiology. Symptoms included: aching joints (> 80%); chronic fatigue, memory loss, and sleep difficulties (60–80%); skin rashes, concentration loss, depression, muscle spasms, nervousness, diarrhea, blurred vision, anxiety, breathing problems, chest pain, dizziness, and nausea (40–60%); and less frequently other symptoms including stomach pain, other vision problems, sensitivity to light, and loss of balance (Nicolson et al., 1995).

Research on Gulf War illness has focused on a variety of potential environmental exposures that could produce any combination of the symptoms experienced by the soldiers. Some potential exposures during combat that have been identified include a variety of agents: combustion products of burning oil facilities and ammunition depots, vaccines and pyridostigmine bromide used to protect against potential biological and chemical weapons, pesticides, potential biological and chemical warfare agents, decontamination solutions, diesel and leaded fuel exhaust, and DU.

Given the complexity of environmental exposures that occurred during the Gulf War, it is likely that Gulf War illness is the result of several interacting factors. Although groups of symptoms for Gulf War illness are unique, many of the symptoms are consistent with CNS disorders including neuroimmune disorders. There is a growing recognition that stress (both emotional and physiological) and direct toxicant effects on the CNS can result in autoimmune responses such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis through involvement of the neuroendocrine axis controlling immune function (El-Fawal et al., 1999). Soldiers in the field are generally agreed to be under emotional stress, and the potential for physiological stressors such as inflammatory responses to occur was high given the exposures to high dust levels and oil-field smoke.

These observations pointed researchers toward the investigation of neurotoxicants, including heavy metal poisoning, compounded by inflammatory stressors. Lead and mercury, known neurotoxicants, quickly topped the list of potential agents. However, DU, which is traditionally known to be toxic to the kidneys, lung, and bone, kept arising in exposure scenarios. Recent studies have suggested a link with exposure to DU and neurotoxic responses (Pellmar et al., 1999; McDiarmid et al., 2000). Interestingly, these neurotoxic responses are observed at exposures where no adverse effects are observed in the kidney.

DU Exposure Scenarios

Recent studies have shown that animals with imbedded DU (i.e., that have DU shrapnel in the body) present some CNS toxicity symptoms (Pellmar et al., 1999). Thus, it appears that DU may not stay encapsulated as once thought, and that it can penetrate the blood–brain barrier. Although the behavior of imbedded DU is important, the Gulf War illness occurs in soldiers who have not been hit with shrapnel. This has led scientists, including Johnnye Lewis and her team, to inquire about exposure to DU via inhalation of aerosols.

During Operation Desert Storm, American M1A1, M1, and M60 tanks and British Challenger tanks fired thousands of large caliber DU penetrators. American A-10 and AV-8B aircraft shot hundreds of thousands of small caliber DU rounds. American snipers shot 7.62 mm caliber bullets. It is estimated that the amount of expended DU ammunition is 290,000 kg (over 639,000 pounds) (OSAGWI, 1998). In addition, one-third (654) of the American tanks used in the war (2,054) were equipped with DU armor.

U.S. personnel in the gulf could have been exposed to DU in a variety of ways including during combat, during the recovery of contaminated vehicles, when they toured battlefields after the cease-fire, and during a fire in July 1991 at the U.S. base in Doha, Kuwait. It has been reported that in combat situations involving the use of DU munitions, the potential for inhalation, ingestion, or implantation of DU compounds can be significant (MEEDU, 1974). U.S. Army testing has found that 18–70% of a DU penetrator rod burns and oxidizes into small particles including micrometer-size uranium oxide particles during impact (ARDEC, 1991; U.S. Army EPI, 1995). The impact of one 120-mm DU penetrator fired from an American Abrams tank can therefore create between 900 and 3,400 grams of DUOx dust. U.S. Army testing has also found that 50–96% of the DUOx aerosol formed during the impact of DU into armor is of respirable size (less than 10 microns in diameter).

It is difficult to estimate the dose of uranium oxide soldiers would receive in a penetrator-impact scenario. There are a number of external factors that could influence the exposure, such as how much of the dust is released inside of the tank versus outside, the volume of the internal tank compartment, whether the soldiers were wearing protective equipment, and how rapidly the soldiers exit the tank. Once exposed, the dose that gets inside of a soldier's body will depend on the breathing rate of the soldier and how much of the uranium oxide is filtered out by protection mechanisms like nasal mucosa.

Inhalation Studies

This lesson focuses on some preliminary results from research conducted by Johnnye Lewis at the University of New Mexico in Albuquerque. Lewis is investigating the potential for uranium oxides to pass through the nose–brain barrier into the CNS. This research is essentially leading the field of DU exposure via inhalation; thus, students are getting information "hot off the press."

Lewis exposed groups of rats for 15 minutes to insoluble UO_2, soluble UO_3, or DUOx aerosols at varying concentrations. As a control, other groups of rats were exposed to clean-filtered air or TaO_2 (a non-uranium metal oxide) for the same duration. The exposure scenario is comparable to military combat, simulating the exposure of individuals inside of a tank armored with DU and hit by a DU penetrator. The research consists of multiple steps, investigating the potential for inflammation responses in the CNS (looking at glial fibrillary acidic protein [GFAP] intensity, which is the data presented in this lesson,GFAP is defined in the student instructions), the distribution of uranium oxides in the CNS, and neurodegeneration that might develop a long time after exposure.

A Note on Animal Studies

Controversy surrounds the use of animals for research. However, it is the use of animals in research that has greatly advanced our understanding of toxicants, pharmaceuticals, and diseases. There is no doubt that today we would be far behind in our understanding of health issues, their prevention, and their treatment, if we did not use animal models.

Scientists are very selective about when to conduct experiments using animals. There is typically a progression of data collected via other means, such as using bacteria, cell models, or epidemiology, to answer preliminary questions. However, there is a point at which non-animal research breaks down. For example, body systems often transform a toxicant into a different molecule to try to get rid of it. The amount of toxicant that gets transformed, what it gets transformed into, where it is distributed in the body (i.e., target organs), and how it is eliminated can only be determined through animal modeling or by "catching" a human exposure. Often, these animal studies will identify topics for research that again move back to a model system, again minimizing the use of animals.

Since ethics prevents exposing humans to known toxicants, the use of animals in research becomes necessary. Different types of animals are often used. This is because there are metabolic similarities and differences between species. Finding the similarities are important to be able to extend the results to humans.

When using animals in research, scientists are held to the highest of ethical standards. The exact experimental procedures have to be approved by university animal research ethical committees in order to minimize pain or discomfort in animals and to use the least possible number of animals. Most researchers use federal funds for research and are required to meet many strict criteria in the treatment of those animals before, during, and after the experiments. Any deviation from those ethical standards would result in a loss of funding, and potentially restrict future funding.

For additional resources on the use of animals in research, please refer to the *Resources* section of this lesson.

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RESOURCES:

Environmental Heath Perspectives, Environews by Topic page. Choose Alternative Test Methods, Hazardous Waste, Warfare http://ehp.niehs.nih.gov/topic

Confidence Intervals, http://web.uccs.edu/lbecker/SPSS/confintervals.htm

European Environment Agency: "Late Lessons from Early Warnings: The Precautionary Principle 1896–2000," http://reports.eea.eu.int/environmental_issue_report_2001_22/en/tab_content_RLR

MedicineNet.com: glial fibrillary acidic protein (GFAP) http://www.medterms.com/script/main/art.asp?articlekey=33140

Neuroscience for Kids: The Nose Knows, http://faculty.washington.edu/chudler/nosek.html

Society for Neuroscience: Smell and the Olfactory System, http://www.sfn.org/content/Publications/BrainBriefings/smell.html

Society for Neuroscience: The Blood-Brain Barrier, http://www.sfn.org/content/Publications/BrainBriefings/blood-brain.html

Society of Toxicology: Animals in Research, http://www.toxicology.org/publicoutreach/air/air.html

Standard Deviation, http://mathcentral.uregina.ca/rr/database/RR.09.95/weston2.html

Understanding the Standard Deviation, http://www.stats.org/record.jsp?type=news&ID=372

Implementing the Lesson

INSTRUCTIONS:

1. Hand out copies of the *EHP Student Edition*, March 2005, and refer your students to the article "Battle Scars: Global Conflicts and Environmental Health" (p. A994).
2. Hand out copies of the student materials.
3. Have the students read the student materials and discuss the background information as needed.
4. Review the assignment instructions with the students. The assignment instructions are found in the **Results** section of the student instructions.
5. After the students have turned in a satisfactory draft of their work, discuss the results and key points included in the Assessing the Lesson section of this lesson.

NOTES & HELPFUL HINTS:

- Students need to have a general understanding of standard deviation prior to doing this lesson. They do not need to have calculated standard deviation, but they should be able to look at two bar graphs and describe any difference between the two numbers shown. (Refer to the website provided in the Resources section for a "quick review" of standard deviation and confidence intervals.)
- Sentence starters have been provided in the student instructions to help those with less graph reading experience. You may want to use those "starters" with another graph to give them an example prior to the lesson.
- Give students the opportunity to revise their work multiple times. Most learning takes places in the revision process. They are learning to write more clearly and accurately. With each revision they understand how better to read a graph.

Aligning with Standards

SKILLS USED OR DEVELOPED:

Communication (written), comprehension (reading), critical thinking and response, experimentation (data analysis), graph reading

SPECIFIC CONTENT ADDRESSED:

Standard deviation, anatomy/physiology, toxicology/environmental health, scientific method, radioactivity (gamma rays), nervous system and its cells

NATIONAL SCIENCE EDUCATION STANDARDS MET:

Content Standards:

Science as Inquiry
- Identify questions and concepts that guide scientific investigations
- Use technology and mathematics to improve investigations and communications
- Formulate and revise scientific explanations and models using logic and evidence

Life Science
- The cell
- The behavior of organisms

Science in Personal and Social Perspectives
- Personal and community health
- Environmental quality
- Natural and human-induced hazards
- Science and technology in local, national, and global challenges

History and Nature of Science
- Science as a human endeavor
- Nature of scientific knowledge

Teaching Standards:

Teachers of science guide and facilitate learning
- Focus and support inquiries while working with students
- Encourage and model the skills of scientific inquiry, as well as the curiosity, openness to new ideas and data, and skepticism that characterize science

Assessing the Lesson

A complete student response would include the following information:

1. **Write an accurate description of the graphs (e.g., This graph shows . . .). Be sure to identify the title, x-axis, y-axis, independent variable, dependent variable, and the control.**

   Title: GFAP Intensity at 0 and 30 days after exposure to four uranium species (chemical forms).

   X-Axis (independent variable) = exposure type—air (the control) or uranium species.

   Y-Axis (dependent variable) = GFAP Intensity

   Writing Example: These graphs show the "GFAP intensity at 0 and 30 days after exposure to four uranium species." The x-axis, which is the independent variable, shows the type of exposure which includes air (the control) and the uranium species used in the experiment (UO_2 by itself, UO_3 by itself, UO_3 and UO_2 combined, depleted uranium, and TaO_2). The y-axis shows the dependent variable which is the GFAP intensity.

2. **Write an accurate and detailed description of the results (e.g., The research results show . . .). Be sure to include the standard deviation in your discussion (i.e. whether there is any difference between the control group and the experiment group).**

   Results: After the exposure (at day 0) there is a significant difference between the amount of GFAP in the rats exposed to air compared to the uranium species UO_3 by itself. There may be a significant difference between the GFAP intensity and the other uranium species, but there is some overlap in the standard deviation bars which decreases the confidence in any difference.

   Thirty days after the exposure there is no significant difference between the GFAP intensities for the control compared to all of the uranium species except for TaO_2. This is because all of the averages fall within the standard deviations of the control except for TaO_2. In the TaO_2 case, there may be a significant difference (because the averages fall outside of the standard deviation of the other species of uranium and controls tested), but any difference is small because the standard deviation for the control and TaO_2 overlap. Statistical tests are done to really determine significance rather than "eye-balling" it off a graph. But reading significance from a graph is an excellent skill for students to acquire.

3. **Describe what you think these results may mean (e.g., It appears that . . .). Be sure to mention any assumptions, "if–then" scenarios, or unknowns that influence your answer.**
   A variety of answers are possible here. The answers just need to be consistent with and supported by the data and assumptions or unknowns stated.

   The conclusion Lewis's lab reached was that uranium-exposed animals had more inflammation (GFAP) than the air controls at zero days. The most soluble form of uranium, UO_3, leads to the highest degree of inflammation (or injury) at this time point. A difference between air- and uranium-exposed rats was not evident at 30 days. The early inflammation may be a sign of damage by uranium.

4. **Describe the next steps you would take if you were continuing with this research. Be sure to include why you would take those next steps.**
   A variety of answers are also possible here. The answers just need to be consistent with and supported by the data and assumptions or unknowns stated.

   Since the inflammation (high GFAP response) is an indication of potential injury, the next step for Lewis's lab is to investigate if there is actually neuronal cell death, or if this cell death develops later in life. The alternative would be that the early injury is repaired and no long-term consequences are seen.

   This would be a good time to review with students how these data, in their current level of understanding (and uncertainty,) might change decisions in circumstances where the precautionary principle is used versus one in which decisions are based solely on scientifically proven toxic responses. Using the precautionary principle, these results might raise concerns that inhalation of high concentrations of uranium dusts might result in neuronal damage, and urge caution in the use of uranium to protect public health until the uncertainty is resolved.

   This is a good time to discuss with students that scientific research is an ongoing process where scientists can be baffled by results or not fully understand what they mean. At this stage they often ask questions like:

   Do I need to make adjustments in the experimental design or set-up (i.e., did we do something wrong)?

   Are there different processes happening than what I originally thought?

   Are these results real and they are simply supporting the null hypothesis?

Authors and Reviewers

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Reviewer(s): Susan Booker, Laura Hemminger, Liam O'Fallon, Kimberly Thigpen Tart

Student Instructions: Depleted Uranium and the Brain

Background Information

You just read the article "Battle Scars: Global Conflicts and Environmental Health." As you can see, there are many environmental health issues to consider in war. Some of those issues can be quite severe and can result in premature death or substantial injury of infants, children, adults, and the elderly. The physical combat alone in wars in Iraq presents substantial risk to the population, and is a significant contributor to the problem Iraqis are facing now and in the future. One perhaps not so obvious problem is the lingering presence of **depleted uranium (DU)** from shielding and armor-piercing bullets used by American soldiers. This lesson introduces you to the use of DU in military conflict and the potential health effects from exposure to the toxic substance.

You will be introduced to a scientist from the University of New Mexico in Albuquerque, who is studying the potential effects of DU on the brain. You will analyze real data from her current research.

DU and Research

The article "Battle Scars: Global Conflicts and Environmental Health" supplies basic background information about DU. It is important to note that DU is a known kidney and bone **toxicant**, but only recently have questions been raised about its potential effects on the **central nervous system (CNS)**. The toxicity of a substance depends on the amount in the body and the **route of exposure** (**inhalation, ingestion, absorption,** or **injection**). Multiple forms of research, like epidemiology and animal studies, help identify the concentration at which a substance starts becoming toxic.

The standard scientific approach is to assume that the **null hypothesis** (i.e., there is no adverse effect) is correct. Hence, the Army spokeswoman in the article states that DU "has not been demonstrated to have ill effects." The accumulation of consistent data from repeated animal research and human epidemiological studies is what ultimately leads scientists (and politicians and decision makers) to confirm any adverse health effects of a substance.

Meet the Scientist: Dr. Johnnye Lewis

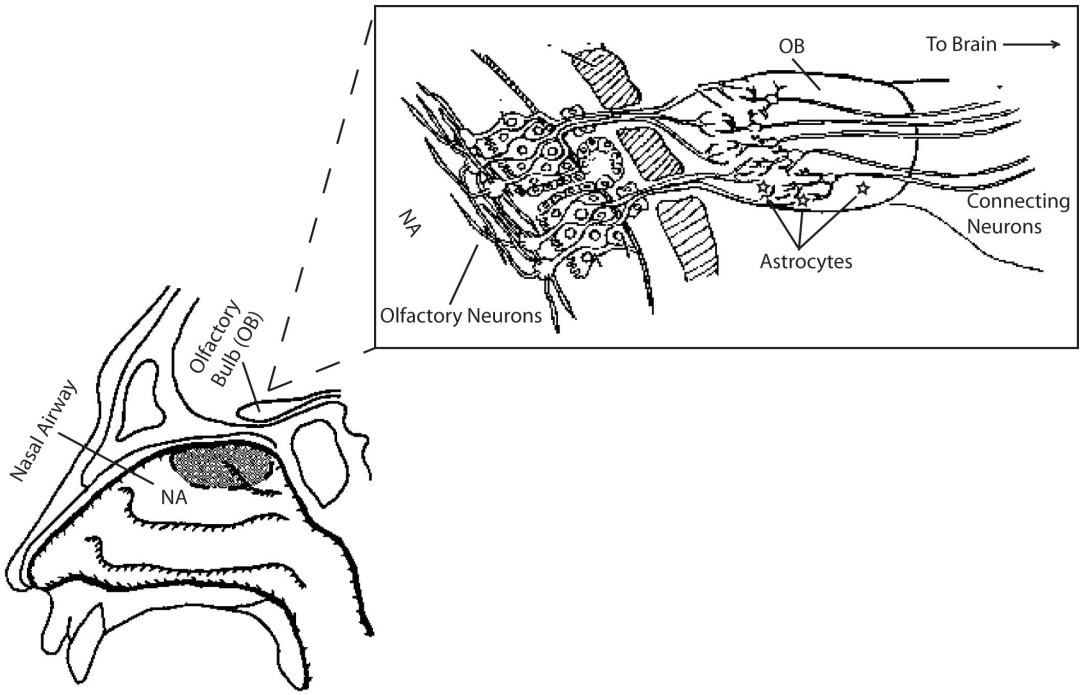
Johnnye Lewis is a **toxicologist** (a scientist who studies the health effects of toxic chemicals) and is the director of the Community Environmental Health Program at the University of New Mexico. She has worked on issues related to uranium contamination of groundwater with Navajo Native American communities for over 10 years, and she recently helped develop a new, lower health-based standard for uranium in groundwater in the state of New Mexico. Dr. Lewis does an interesting range of work in environmental health including population and community health work, as well as active laboratory research studying inhalation toxicity of metals (i.e., adverse effects from breathing a toxic substance).

The research you will be working with is from Dr. Lewis's laboratory, where she and her staff are looking at the effects of DU on rat and mouse brains and nasal passages. This research is leading the field on this subject and is "hot off the press." You have the unique opportunity to see the data first-hand.

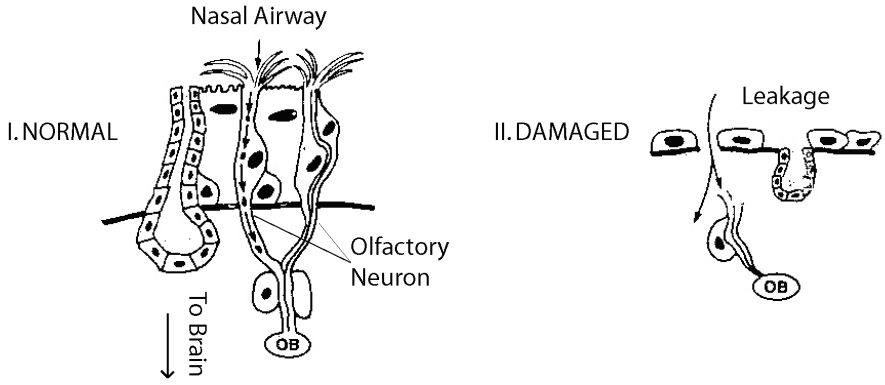
Dr. Johnnye Lewis

The Olfactory System and GFAP

Some basic background information on the **olfactory system** and the **glial fibrillary acidic protein (GFAP)** is important to understand the research you will be reviewing. The olfactory system is the tissue in the nose that receives smell stimuli, the junction between the nose and the brain, and the parts of the brain that interpret odors. Olfactory neurons in the nose are the only cells in the body in direct contact with both the CNS and the environment (i.e., the inside of the nose). The olfactory cells provide information to multiple parts of the brain including the **limbic** (primitive) system and the **cortex** (outer layer).



Hypothetical Function of the Nose-Brain Barrier



You have probably heard of the **blood–brain barrier**, which protects the brain by acting as a barrier by keeping many chemicals away from the brain. It is believed that the olfactory system has a **nose–brain barrier** for the same reason—to protect the brain. Dr. Lewis's work raises the question of whether the nose-brain barrier can be compromised if cells are injured. Recall the inflammation that happens in your nose on a windy day with lots of dust in the air. Your "stopped up" and "runny" nose are responses to injury within the nose. Those inflammation responses serve as self-protection, but because of the structure of the nose and the unique contact with the brain, repeated insults and injury may provide an opening for inhaled substances to enter the **olfactory bulb** and parts of the CNS.

All cells contain proteins that support the structure and other functions of the cell. Certain CNS cells (astrocytes) contain a protein called **GFAP**. If the CNS is injured, or inflamed, astrocytes are activated and produce more GFAP. The astrocytes themselves can subsequently release chemicals that injure brain cells. GFAP, as a marker of these astrocytes, is therefore used as an indicator of inflammation or possible cell injury. Recall that injury to the nasal mucosa and olfactory bulb may be an avenue for toxicants to access the brain.

Research Hypothesis

Scientific research is developed around a hypothesis, or an educated guess about what is happening. The hypothesis that is driving Dr. Lewis's research is:

Inhalation of uranium aerosols from weapons that used DU ammunition resulted in DU depositing in the CNS and was followed by neurodegeneration in a portion of rats exposed.

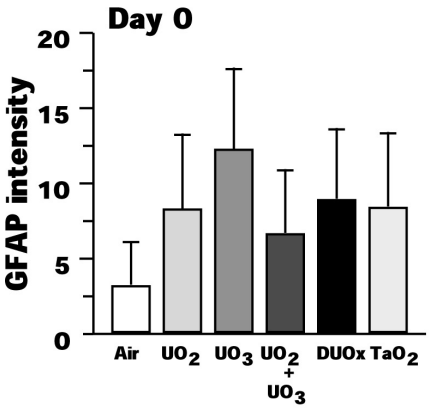
Experiment Information

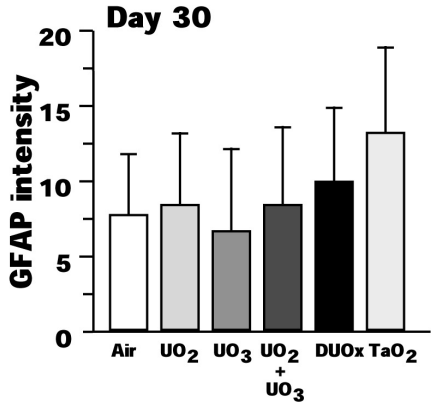
- The first set of experiments exposed rats to high doses of DU and other uranium species for a short period of time (acute exposure, i.e., tank impact scenario).
- The rats were exposed via inhalation through the nose only.
- The rats were exposed to four different types of uranium (including DU), each having different solubilities.
- The experiment measured the intensity of GFAP (which correlates with amount of GFAP produced).

Results

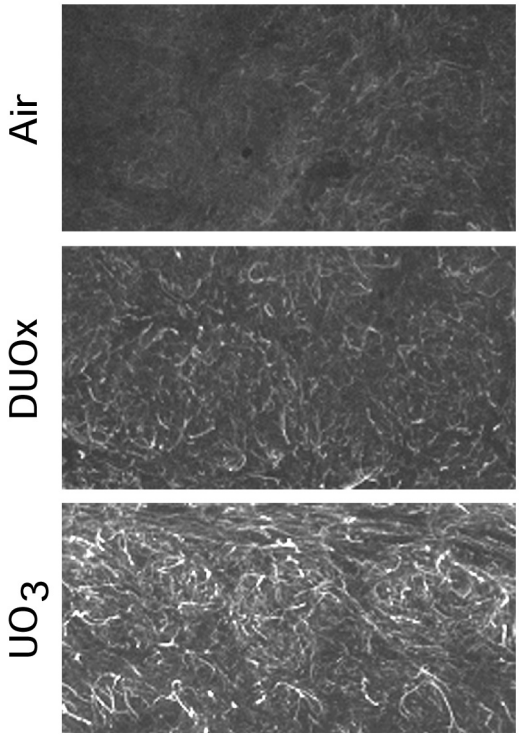
Below are two graphs of the results of the experiment. Photos of GFAP markers are included for your visual reference. You can see in the photos that at day zero the GFAP intensity in the tissue exposed to the UO_3 is much brighter compared to the DUOx and the air.

Step 1: Write an accurate description of the graphs (e.g., This graph shows . . .). Be sure to identify the title, x-axis, y-axis, independent variable, dependent variable, and the control.





Below are photos to show what the GFAP intensities looked like at Day 0



Step 2: Write an accurate and detailed description of the results (e.g., The research results show . . .). Be sure to include the standard deviation in your discussion (i.e., whether there is any difference between the control group and the experiment group).

Step 3: Describe what you think these results may mean (e.g., It appears that . . .). Be sure to mention any assumptions, "if–then" scenarios, or unknowns that influence your answer.

Step 4: Describe the next steps you would take if you were continuing with this research. Be sure to include why you would take those next steps.