# Pathology 438 Final Examination due: 15 June 2015

Spring 2015

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The electronic responses to this examination are due on Monday, 15 June 2015 at end of day (5:00 pm). Submit them to [shalloran@lifewest.edu](mailto:shalloran@lifewest.edu) OR to [smhbizness@gmail.com](mailto:smhbizness@gmail.com). You will be sent an acknowledgement receipt.

You are not allowed to consult with classmates or any individuals *other than* the instructor as you research, prepare and compose your responses to the questions posed in this examination. Lecture content (slides) and your oral presentations are on MOODLE for you to use in preparing answers, in addition to access to the LCCW library, reference books and course text books, and on-line resources. Please proofread and organize your work and assemble the exam before submitting it.

Some answers require you to include a citation of the sources you consult to formulate your response. Format your citation according to MLA or APA standards. (If you wish, you can use the built-in Word feature that formats your references: under the References tab, use Insert Citation and fill in the fields as much as possible. Later you will use Bibliography->Insert Bibliography at the point of the cursor. You might learn how to use Section Break too in order to insert bibliographies under separate answers. I have put in section breaks in this document between questions.)

By working the examination and submitting it for grading you are agreeing to work independently of all other individuals and you are certifying that all the responses and answers to the examination questions are your own work.

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Within group A through C, choose ONE of any of the choices answer.  
Choose between D or E, and within D, choose ONE of any of the choices

* 1. **Environmental Toxicants. Pick one from the three classes of substances below and discuss exposure (places where it might be encountered), its toxicokinetics (ADME) and toxicodynamics (acute, chronic toxicity, effects on physiology and eliciting pathologies. You are allowed to focus on one compound in the class or discuss the toxicology of the class generally**

***Polychlorinated Biphenyls (PCBs)***

Polychlorinated Biphenyls (PCBs) are man-made organic chemicals classified as chlorinated hydrocarbons. PCBs are non-flammable and were used in industrial and commercial materials such as hydraulic and electrical equipment, and as plasticizers in paint, plastic, and rubber, just to name a few. PCB is no longer produced in the USA, but may still be present in electrical equipment, motor and hydraulic oils, fluorescent light ballasts, oil-based paint, fiberglass and plastics made pre-1979. PCBs used were chemical mixtures made up of individual chlorinated biphenyl components known as [congeners](http://www.epa.gov/epawaste/hazard/tsd/pcbs/pubs/congeners.htm). Today, the environment is littered with PCBs as they have leached into water from run-offs in landfills. PCBs don’t break down, therefore they accumulate and can travel via water, soil and air. According to the United States Environment Protection Agency (EPA), clear evidence shows that PCBs have toxic effects in animals. Systems affected by PCBs are the immune system, reproductive system, nervous system and endocrine system, just to name a few. The EPA states that through research, PCBs have been found to cause cancer in animals, and analysis suggests that PCBs are most likely human carcinogens as well (U.S. Environmental Protection Agency, 2013).

Main exposure routes in occupational/work settings are through inhalation and dermal contact, while most of the population is exposure via oral routes. Inhalation absorption data is unreliable and cannot sufficiently state absorption rates. Data suggesting inhalation absorption varies significantly, however, data summarized by Wolf (1985) suggests that up to 80% of levels seen in the adipose tissue of workers exposed to capacitors, was most likely caused by inhalation (Wolf, 1985). Dermal absorption is also a major way that BCPs accumulate in adipose tissue of these workers. Oral exposure through food consumption is postulated to be the most common route of exposure, with vegetables accounting for most lower chlorinated PCBs, with fish, dairy products, and meat contributing the higher chlorinated PCBs.

In the GI tract, PCBs are absorbed as congeners. Once absorbed into the bloodstream, they are transported via lipoproteins and then accumulate in tissues with high fat content, such as the liver, adipose, skin, and breast milk. Initially, the liver and muscles experience the highest levels of PCB uptake, due to the high blood perfusion in both areas. Absorbed PCBs are either excreted or stored in adipose tissue, skin, and other organs and bodily fluids. Usually, less chlorinated congeners are readily metabolized and excreted, whereas highly chlorinated congeners are metabolized slowly and are the ones that tend to accumulate. Breast milk is a mode of transmission of PCBs from mother to child. Metabolism of PCBs is the rate limiting step, therefore in order to eliminate PCBs, the liver must hydroxylate and conjugate PCBs with glucuronic acid and sulfates. Generally, PCB’s with more than five chlorines and para-chlorine atoms are less susceptible to hydroxylation and have the longest half-lives. Conjugation increases water solubility of these compounds, which aids excretion in bile. Metabolites of all congeners are eliminated primarily through bile and feces. Only a small degree of elimination (<5%) can occur through urine for less chlorinated congeners (Schlummer, Moser, & McLachlan, 1998).

Skin conditions such as acne and rashes are the most common health effects that PCBs cause, as well as irritation of the respiratory tract, depression, fatigue, liver, thyroid, dermal, ocular, immunological, and neurodevelopmental effects. Additionally, reduced birth weight, reproductive toxicity, and cancer can be noted. Mechanisms of toxicity are complicated, but seem to involve what is known as an Ah receptor, with dependent and independent mechanisms. This Ah receptor is a ligand-activated transcription factor which regulates gene transcription, and when bound to PCBs, normal gene expression is halted. An example of this transcription block is the liver’s production of UDP-glucuronyl **transferase, which stimulates T4 elimination, therefore depleting T4 hormone levels in the body.** Also, additional research shows that independent and unknown factors cause hypothyroidism in humans; hypotheses suggest that this is due to the decreased secretion of adrenal steroids seen in animal studies (Guo, Yu, Hsu, et al., 1999). Human studies have shown increased volume and goiter risk in the Thyroid, increased liver T4 and T3 elimination and decreased circulating thyroid hormone levels of TSH, T4 and T3 with correlated PCB exposure (Langer, Tajtakova, Fofor et al., 1998). PCBs also exhibits estrogenic by inhibiting the metabolism of estradiol (Kester, Bulduk, Tibboel, et al., 2000). Anti-estrogenic effects seem mediated by PCBs that are Ah receptor agonists. In women, PCBs have shown association with menstrual irregularities, increased uterus size, reduced conception, and increased miscarriage (Gerhard, Daniel, and Link, 1998; Bae, Peters-Golden, and Loch-Caruso, 1999). Reproductive effects in men are unknown as research is scarce, but based on research in male laboratory animals; fertility will most likely be compromised, as well as teste size and testosterone levels (Cooke, Zhao, and Hansen, 1996; Lundkvist, 1990).

* 1. **Food Toxicants.**

1. **Sulfur dioxide (SO2) is added to wine during its production. Discuss what is known about acute and chronic toxicity and other toxicodynamic features. Can wine be produced without using it? Are there are alternatives?**

Sulfur dioxide is known as a closely related chemical oxide to sulfites, which are the most commonly used additives in wine. Sulfites are used in wine making to kill unwanted bacteria and yeast, as well as a preservative, preventing the wine from oxidizing. Foods such as jam, gelatin, cheese, deli meat, pizza dough, and even medications contain sulfites! Natural exposure to sulfur dioxides is seen with volcanic eruptions, however, high levels of sulfur dioxide would most likely be seen with burning coal or oil.

In the air, 100ppm is a dangerously toxic level of sulfur dioxide, and can burn the nose and throat. Long-term exposure has been seen to have decreased lung function, especially affecting asthmatics even in low doses. (Agency for Toxic Substances and Disease Registry (ATSDR), 1999). Through research on sulfur dioxides, no clear non-conflicting research was found regarding its toxicity and levels found in wine. Apparently, not using sulfites is more of a risk regarding bacteria exposure than its toxic effects, therefore it is not commonly done. In conventional wines, up to 350ppm of sulfites are allowed in the United States, with organic wines usually limited to 100ppm. Additional standards set in place by the USDA has listed that in “organic wines”, only 10ppm of naturally occurring sulfites are allowed in order for the wine to be sold as “organic (Organic Wine Company). Only non-scientific, informational companies spoke about it’s possible concerns with regards to allergies, saying asthmatics are the only true population effected by these sulfites. The only recommendations for avoid sulfite allergies was to consume organic wines, as they contain less pesticides, which may be the cause. Although all mainstream wine is made with sulfur dioxides, wines made by natural wine makers only use sulfur when bottling white wines. Again, the risks vs. benefits of drinking wines without the use of sulfites must be further explored with more research on its toxic effects.

* 1. **Drug-Nutrient Interactions. Select any of the drugs or drug classes below and explain how it affects diet (nutrient absorption). Either suggest an alternative drug and/or explain how an individual can compensate for any effect on nutrition**

***Antacids***

Antacids, histamine-2 receptor antagonists (H2 blockers) and proton-pump inhibitors (PPIs) are commonly prescribed for treating heartburn, gastro-esophageal reflux disease and peptic ulcers. Antacids are notorious for their ability to interfere with good nutrition if they are taken regularly for an extended period of time. Antacids may decrease the absorption of a variety of compounds including copper, fluoride, and iron. Simultaneous intake of manganese or magnesium-containing antacids may decrease manganese absorption (Higdon & Drake, 2012). Drugs that treat acid reflux or heartburn raise the pH environment of the upper GI tract, which reduces absorption of needed vitamins and minerals. This is especially problematic among the elderly, who often are already low in stomach acid. Aluminum antacids and calcium carbonate act by buffering or neutralizing the acid pH of the stomach. A reduction of stomach acid impairs the breakdown of the ingested food. Reduced stomach acid also significantly increases the risk of vitamin B12 deficiency especially in the elderly, since vitamin B12 requires adequate gastric acid for absorption. This lack of stomach acid also decreases the absorption of folic acid, iron and zinc (McCabe, 2004). Aluminum-based antacids may interfere with normal calcium metabolism. Aluminum can form compounds with phosphates, removing them from the body. As a result of this imbalance, bones may lose the calcium that keeps them strong (The People's Pharmacy , 1993). Proton pump inhibitors, the most potent of acid-reducing medications, are increasingly popular. High doses of PPIs, used for a year or more, have been shown to make individuals more susceptible to hip fracture than control subjects. This heightened risk of osteoporosis is probably due to the drastic drop in calcium and vitamin D absorption that occurs with these drugs.

Occasional use should not pose a serious risk, but continual consumption might make osteoporosis worse. Should an individual require an antacid it is suggested not to take it at meal-time (The People's Pharmacy , 1993). For anyone taking acid-reducing medication, additional daily supplementation of the following vitamins and minerals is recommended: vitamin D3 (2,000+ IU), B12 (200 mcg), folic acid (800 mcg), calcium (1,000 mg), chromium (500 mcg), iron (15 mg), zinc (25 mg to 50 mg) and phosphorus (700 mg). (Cass M.D., 2013)

* 1. **Personal Care Products. Select one of the product types and the named compound usually contained in it. Discuss any facts on acute and chronic toxicity through dermal exposure, and discuss alternatives to:**

***Lipstick: lead acetate***

Lead acetate is a pigment stabilizer and potential impurity in many color cosmetics, including lipstick.  However this is by no means the most likely or most significant source of exposure. Lead is present in the environment, old batteries, old toys and old paint, just to name a few. Because lead has many uses including that of a pigment stabilizer, it has had many uses. However since the discovery of many of its negative health effects its use in everyday products has been drastically reduced.

According to the Material Safety Data Sheet (MSDS), lead acetate is a well-known carcinogen, and neurotoxin that has been linked to learning, language and behavioral problems (Needleman, Schell, Bellinger, Levinton, & Allred, 1990). Many of lead’s toxic properties are due to its ability to inhibit or mimic the action of calcium, this results in toxicity to almost every organ and system in the body (Agency for Toxic Substances and Disease Registry (ATSDR), 2014). It is known to have many negative health effects including irritation to the skin, eyes and respiratory system. Lead acetate can also affect the central nervous system, kidneys, blood and reproductive system. Lead is a cumulative poison and exposure even to small amounts can raise the body's content to toxic levels (Mallinckrodt Baker, Inc., 1999). Exposure to high amounts of lead may induce acute encephalopathy and can lead to death. Symptoms that develop after chronic exposure may include dullness, irritability, poor attention span, epigastric pain, constipation, vomiting, convulsions, coma, and death. The most sensitive targets for lead toxicity are the developing nervous system, the hematological and cardiovascular systems, and the kidney. Lead has been linked to reduced fertility in both men and women, hormonal changes and menstrual irregularities. Pregnant women are especially vulnerable because lead crosses the placenta and may enter the fetal brain, and has also been linked to miscarriage (Agency for Toxic Substances and Disease Registry (ATSDR), 2007).  In pre-adolescents lead exposure has been linked to a delay in the onset of puberty in girls, and the development of testes in boys.

Toxic effects of lead are most pronounced through ingestion or inhalation and are less pronounced via dermal or ocular exposure. In volunteers who applied lead acetate from cosmetic preparations, less than 0.3% of the applied lead dose was absorbed  (Mallinckrodt Baker, Inc., 1999). The most likely negative reaction to lead acetate based on absorptions such as this, would be mild skin irritation. Because it is so poorly absorbed from the skin and due to the small amount present in lipstick, it should not be a huge concern to the everyday user. However caution may be warranted in pregnant women and in the presence of young children to eliminate the risk of any toxic effects. It is also possible to look for alternative such as products with a lead-free claim.

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