



AACT

American Academy
of Clinical Toxicology

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Archived Question's of the Day Jan-July 2017

Date:

1/9/2017

Question:

Botulism is an uncommon disorder caused by toxins produced by *Clostridium botulinum*. Seven subtypes of botulinum toxin exist (subtypes A, B, C, D, E, F and G). Which subtypes have been noted to cause human disease and which ones have been reported to cause infant botulism specifically in the United States?

Answer:

According to the cited reference "Only subtypes A, B, E and F cause disease in humans, and almost all cases of infant botulism in the United States are caused by subtypes A and B. Botulinum-like toxins E and F are produced by *Clostridium baratii* and *Clostridium butyricum* and are only rarely implicated in infant botulism" (Rosow RK and Strober JB. Infant botulism: Review and clinical update. 2015 *Pediatr Neurol* 52: 487-492)

Date:

1/10/2017

Question:

A variety of clinical forms of botulism have been recognized. These include wound botulism, food borne botulism, and infant botulism. What is the most common form of botulism reported in the United States?

Answer:

According to the cited reference, "In the United States, infant botulism is by far the most common form [of botulism], constituting approximately 65% of reported botulism cases per year. Outside the United States, infant botulism is less common." (Rosow RK and Strober JB. Infant botulism: Review and clinical update. 2015 *Pediatr Neurol* 52: 487-492)

Date:

1/11/2017

Question:

Which foodborne pathogen accounts for approximately 20 percent of bacterial meningitis in individuals older than 60 years of age and has been associated with unpasteurized milk and soft cheese ingestion?

Answer:

According to the cited reference, “*Listeria monocytogenes*, a gram-positive rod, is a foodborne pathogen with a tropism for the central nervous system. *L. monocytogenes* outbreaks have been associated with unpasteurized milk, soft cheeses, and deli-style meats. Illness, though rare in the general population, is an important cause of disease in newborns, pregnant women, the elderly, and people with impaired, cell-mediated immunity, such as transplant recipients and patients with AIDS. In 1995, the Centers for Disease Control and Prevention reported that *L. monocytogenes* accounted for 20% of bacterial meningitis cases among people >60 years of age.

Presentation may be more subacute (>24 hours) than it is with other forms of bacterial meningitis.

Cerebrospinal fluid Gram’s stain may be positive in only 30% to 40% of cases. Pregnant women are also at increased risk for listeria infection. In this population, it causes chorioamnionitis in the woman (not meningitis), which at the time of delivery can lead to neonatal meningitis. Because of this risk, pregnant women are advised to avoid foods that may be sources of listeria infection, such as soft cheeses and deli meats”. (New England Journal of Medicine “Question of the Week” December 27, 2016)

Date:

1/12/2017

Question:

What is rotenone?

Answer:

According to the cited reference, “Rotenone is a natural toxin present in plants from the genera *Derris* and *Lonchocarpus*. For centuries natives of the Amazon basin have used this compound to induce narcosis in fish and facilitate fishing for human consumption; this practice is still used by many Amazon riverine groups. Rotenone is also commercialized worldwide as a pesticide. In aquaculture, rotenone is used to eliminate fish and other unwanted organisms from production systems.” Trade names for products containing rotenone include Chem-Fish, Cuberol, Fish Tox, Noxfire, Rotacide, Sinid and Tox-R. It is also marketed as Curex Flea Duster, Derrin, Cenol Garden Dust, Chem-Mite, Cibe Extract and Green Cross Warble Powder. The compound may be used in formulations with other pesticides such as carbaryl, lindane, thiram, piperonyl butoxide, pyrethrins and quassia. (Melo KM et al. Short term exposure to low doses of rotenone induces developmental, biochemical, behavioral and histological changes in fish. 2015 Env Sci Poll Res Int 22(18): 13926-13938)

Date:
1/13/2017

Question:
What does the term “signal word”, as used by U.S. EPA, signify?

Answer:
Signal words” are the words used on a pesticide label- Danger, Warning, Caution- to indicate level of toxicity. Signal words “describe the acute (short-term) toxicity of the formulated pesticide product. The signal word can be either: DANGER, WARNING or CAUTION. Products with the DANGER signal word are the most toxic. Products with the signal word CAUTION are lower in toxicity. The U.S. Environmental Protection Agency (EPA) requires a signal word on most pesticide product labels. They also require it to be printed on the front panel, in all capital letters, to make it easy for users to find. The only pesticide products that are not required to display a signal word are those that fall into the lowest toxicity category by all routes of exposure (oral, dermal, inhalation, and other effects like eye and skin irritation).([https://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=Terms%20of%20Env%20\(2009\)#formTop](https://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=Terms%20of%20Env%20(2009)#formTop); accessed December 2016 and <http://www.npic.orst.edu/factsheets/signalwords.pdf>; accessed December 2016)

Date:
1/16/2017

Question:
Lithium is widely used as long-term therapy for bipolar disorder. What are the clinically important adverse risks for patients on long-term lithium therapy?

Answer:
According to one systematic review and meta-analysis of randomized controlled trials and observational studies (more than 385 studies included): “Lithium is associated with increased risk of reduced urinary concentrating ability, hypothyroidism, hyperparathyroidism, and weight gain. There is little evidence for a clinically significant reduction in renal function in most patients, and the risk of end-stage renal failure is low. The risk of congenital malformations is uncertain; the balance of risks should be considered before lithium is withdrawn during pregnancy. Because of the consistent finding of a high prevalence of hyperparathyroidism, calcium concentrations should be checked before and during treatment.” (McKnight RF et al. Lithium toxicity profile: a systematic review and meta-analysis. 2012 Lancet 379:721-728)

Date:

1/17/2017

Question:

How do electronic cigarettes produce the vapor inhaled by users of these products?

Answer:

According to the cited reference, "Electronic cigarettes (e-cigarettes), also known as electronic nicotine-delivery systems, are devices that produce an aerosol by heating a liquid that contains a solvent (vegetable glycerin, propylene glycol, or a mixture of these), one or more flavorings, and nicotine, although the nicotine may be omitted. The evaporation of the liquid at the heating element is followed by rapid cooling to form an aerosol. This process is fundamentally different from the combustion of tobacco, and consequently the composition of the aerosol from e-cigarettes and the smoke from tobacco is quite different. E-cigarette aerosol is directly inhaled (or "vaped") by the user through a mouthpiece. Each device includes a battery, a reservoir that contains the liquid, and a vaporization chamber with heating element. (Dinakar C and O'Connor GT. The health effects of electronic cigarettes. 2016 NEJM 375:1372-1381)

Date:

1/18/2017

Question:

What is the elimination half-life of smoked crystal methamphetamine?

Answer:

Per the cited references, "The elimination half-life of smoked crystal methamphetamine (and methamphetamine) administered by intranasal or IV routes is about 11 hours." (Kish SJ. Pharmacologic mechanisms of crystal meth. 2008 CMAJ 178(13): 1679-1682 and Schifano F, et al. Smokable ("ice," "crystal meth") and non-smokable amphetamine-type stimulants: clinical pharmacological and epidemiological issues, with special reference to the UK. Ann Ist Super Sanita 2007;43:110-115)

Date:

1/19/2017

Question:

MEK inhibitors (inhibit the mitogen- activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) kinase) are a relatively new class of chemotherapeutic agents used in the treatment of a variety of metastatic cancers. These agents have been associated with the development of ocular toxicity. What is the nature of this toxicity?

Answer:

According to the cited reference "As the ocular toxicity associated with MEK inhibitors is a relatively new discovery, very little is known about the mechanism of these ocular events. The majority of ocular toxicities reported with MEK inhibitors have occurred at the level of the retina with the two most common and sight-

threatening events being retinal vein occlusion and sub-retinal fluid accumulation.” (Duncan KE et al. MEK inhibitors: a new class of chemotherapeutic agents with ocular toxicity. 2015 Eye 29:1003-1012)

Date:

1/20/2017

Question:

Individuals requiring chronic transfusion therapy are often treated with the iron chelator deferoxamine in order to address transfusion-induced hemochromatosis and associated complications. Which toxicities have been associated with the use of deferoxamine?

Answer:

According to the cited reference, “In the 1980’s a number of investigators reported ototoxicity and ocular toxicity induced by deferoxamine, although others have suggested that doses less than 50 mg/kg/d are not associated with otic or ocular toxicity. The reported otologic disturbance is bilateral high frequency sensorineural hearing loss. The ocular disturbances include decreased acuity, peripheral field loss, abnormal color vision, defective dark adaptation, thinning of retinal vessels, retinal stippling, and abnormal visual evoked potentials.” (Chen SH et al. Auditory and visual toxicity during deferoxamine therapy in transfusion dependent patients. 2005 J Pediatr Hematol Oncol 27:651-653)

Date:

1/23/2017

Question:

What is “nanging” and what clinical symptoms may result from repeated nanging?

Answer:

Nanging” is the practice of repeated inhalation of nitrous oxide. According to the cited reference, “Nitrous oxide causes irreversible oxidation of the cobalt atom of vitamin B12 rendering the vitamin inactive. Vitamin B 12 is essential for the formation of methionine by methylation of homocysteine. In turn, methionine is converted to S-adenosyl-methionine (SAM) which is required for all methylation reactions including those of myelin phospholipids. Vitamin B12 deficiency can produce spinal cord disease particularly affecting the dorsal columns causing subacute combined degeneration. Clinical symptoms result from myopathy, peripheral axonal neuropathy or both, with combinations of paresthesias, gait ataxia, sphincter disturbances and pyramidal weakness. Impaired cognition and altered mentation may occur. (Ng J and Frith R. Nanging. 2002 Lancet 360:384)

Date:

1/24/2017

Question:

What is the classic presentation of tick paralysis?

Answer:

According to the cited reference, “The classic presentation is that of an acute symmetric ascending flaccid paralysis that evolves over hours to days, sometimes preceded by prodromal symptoms, including paresthesias, restlessness, irritability, fatigue, and myalgias. These symptoms are followed hours later by flaccid weakness that generally begins in the lower extremities. Fever is absent. The deep tendon reflexes are diminished or absent. If the tick continues to feed, the weakness ascends to the upper extremities over the ensuing 12 to 24 hours. Finally the respiratory muscles fail. (Edlow JA and McGillicuddy DC. Tick paralysis. 2008 Infect Dis Clin No Amer. 22:397-413)

Date:

1/25/2017

Question:

Who were the “radium girls”?

Answer:

According to the cited reference, the so-called “radium girls” were “Teenage girls and young women, whose job it was to apply luminous paint containing radium to watches [and instrument dials] during World War I, were among the first industrial radiation poisoning victims in the United States.” They attained dangerous exposures to radium “through licking their brushes to attain a fine point, through inhaling fine particles of radium laden dust and radon (a radioactive gas)...”(Clark C. Physicians, reformers and occupational disease: The discovery of radium poisoning. 1987 Women & Health 12(2):147-167)

Date:

1/26/2017

Question:

What is NEPA?

Answer:

NEPA is the National Environmental Policy Act. This act was signed into law on January 1, 1970. NEPA requires federal agencies to assess the environmental effects of their proposed actions prior to making decisions. The range of actions covered by NEPA is broad and includes: making decisions on permit applications, adopting federal land management actions, and constructing highways and other publicly-owned facilities. Using the NEPA process, agencies evaluate the environmental and related social and economic effects of their proposed actions. Agencies also provide opportunities for public review and comment on those evaluations. (<https://www.epa.gov/nepa/what-national-environmental-policy-act>; accessed January 2017)

Date:

1/27/2017

Question:

What are the primary environmental sources for the chemical sulfur dioxide?

Answer:

Sulfur dioxide in the air comes mainly from activities such as the burning of coal and oil at power plants or from copper smelting. In nature, sulfur dioxide can be released to the air from volcanic eruptions.

(<https://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=46>; accessed December 2016)

Date:

1/30/2017

Question:

The recognition of chemicals as potential carcinogens had its inception with observations made by Sir Percival Pott in the 1770's. What was this individual's contribution to the science of chemical carcinogenesis?

Answer:

According to the cited reference, "...Sir Percival Pott in 1775 described the frequent occurrence of cancer of the scrotum in chimney sweeps in England. He hypothesized that this was because of their significant exposure to soot. More importantly, he also proposed a mechanism to reduce the incidence of these cancers simply by requiring these individuals to bathe on a regular basis. This was instituted and the incidence of scrotal cancer was essentially eliminated." (Cohen SM and Arnold LL. Chemical carcinogenesis. 2011 Tox Sci 120(S1): S76-S92)

Date:

1/31/2017

Question:

The aromatic amine 4-aminobiphenyl (4-ABP) is present in tobacco smoke. The development of which human cancer has been linked to exposure to this chemical?

Answer:

The cited reference points out that "The aromatic amine 4-aminobiphenyl is present in cigarette smoke and is excreted in the urine in forms that lead to DNA adduct formation.....this combination of increased mutagenic DNA adduct formation by 4-ABP and increased [bladder] cell proliferation leads to a significant incidence of bladder tumors, with cigarette smoking being the major cause of bladder cancer in the United States. (Cohen SM and Arnold LL. Chemical carcinogenesis. 2011 Tox Sci 120(S1): S76-S92)

Date:

2/1/2017

Question:

What are the landmark principles regarding expert testimony as established by the well-known case of Daubert v Merrell Dow Pharmaceuticals, Inc.?

Answer:

According to the cited reference, "First, it recognized the trial judge as the "gatekeeper" who must screen proffered expert testimony. Second, the objective of the screening is to ensure that expert testimony, in order to be admissible, must be "not only relevant, but reliable..... To determine whether proffered scientific testimony or evidence satisfies the standard of evidentiary reliability, a judge must ascertain whether it is "ground[ed] in the methods and procedures of science.....The Court also mentioned as indicators of good science whether the technique or theory has been subjected to peer review or publication, whether the existence of known or potential error rates has been determined, and whether standards exist for controlling the technique's operation. In addition, although general acceptance of the methodology within the scientific community is no longer dispositive, it remains a factor to be considered." (Reference Manual on Scientific Evidence, Third Edition, The National Academies Press, Washington, DC)

Date:

2/2/2017

Question:

What is the prevalence rate for intentional volatile solvent use/abuse among American adolescents?

Answer:

According to the cited reference, "Abused inhalants are voluntarily inhaled for their euphorigenic effects by a surprisingly high proportion of American adolescents. According to the 2013 Monitoring the Future study, the 30-day prevalence rate for intentional volatile solvent use among American 8th graders, or mostly 12- to 14-year-olds, was 2.7%. This prevalence is higher than all usage rates for all other illicit drugs except marijuana, and this trend has held steady for the past two decades. Moreover, the true prevalence of solvent use may be higher due to incorrect self-reporting of inhalant use. To wit, in a longitudinal study, 49% of 7th graders who admitted to volatile solvent misuse recanted the following year, and the researchers predicted that the vast majority of recanters were actual solvent users. Volatile solvents are most commonly misused by young adolescents, with an age at peak use of 14 years." (Beckley JT and Woodward JJ. Volatile solvents as drugs of abuse: Focus on the cortico-mesolimbic circuitry.2013 Neuropsychopharm 38:2555-2567)

Date:

2/3/2017

Question:

Based on the presumed cardiovascular fluctuations affecting the uteroplacental unit in pregnant cocaine users what are the overall risks of labor-related adverse events in this population?

Answer:

According to the cited reference, based on the presumed cardiovascular fluctuations affecting the uteroplacental unit in pregnant cocaine users “the overall risks of labor-related adverse events in this population are increased as follows: preterm labor 17.4%, precipitous labor 13.4%, placental abruption 17.3%, abnormal fetal monitoring 15.3%, and meconium-stained fluid 25%” (Chasnoff IJ, et al. Cocaine use in pregnancy: perinatal morbidity and mortality. *Neurotoxicol Teratol.* 1987, 9:291–293 as cited in Cain MA et al. The Maternal, fetal, and neonatal effects of cocaine exposure in pregnancy. 2013 *Clin Obstet Gyn*, 56 (1): 124-132)

Date:

2/6/2017

Question:

What characterizes the orolingual angioedema associated with the administration of tissue plasminogen activator?

Answer:

According to the cited reference, “orolingual angioedema is a rare adverse effect of tissue plasminogen activator (tPA) treatment of acute ischemic stroke with a reported incidence of between 1% and 5%. The frontal, insular, and peri-insular regions are often involved and are believed to play a role in the pathophysiology of stroke-associated angioedema.....Orolingual angioedema developing after tPA administration for acute ischemic stroke may manifest as unilateral swelling of the lips tongue and face. The resultant edema is commonly contralateral to the ischemic lesion that is believed to be due to the infarction’s triggering autonomic dysfunction and vasomotor changes in the hemiparetic side. Despite this distinct presentation, available literature has demonstrated equal representation of bilateral, contralateral and ipsilateral edema.” (Pahs L et al. A novel approach to the treatment of orolingual angioedema after tissue plasminogen activator administration. 2016 *Ann Emerg Med* 68(3):345-348)

Date:

2/7/2017

Question:

What is the epidemiology and what are the risk factors for infant botulism?

Answer:

The cited reference points out that “Botulism affects infants ranging from less than 1 week to 1 year of age with a median age of 10 weeks. Up to 95% of infant botulism cases occur in children younger than 6 months of age. Geographically the prevalence of infant botulism in the United States is highest in California, Utah, and the eastern Pennsylvania-New Jersey-Delaware area. Type A disease tends to be more prevalent in the Western U.S., whereas type B disease is more prevalent in the eastern United States. Infants living in rural/farm environments appear to be at higher risk for contracting botulism than those living in more urban environments, presumably because of higher exposure to dust particles. It has been suggested that exposure to soil from active construction sites may also increase the risk of contracting botulism, whether by living near a construction site or by having a parent who works in construction; however this link has not been conclusively established.” (Rosow LK and Strober JB. Infant botulism: Review and clinical update. 2015 *Pediatric Neurol* 52:487-492)

Date:

2/8/2017

Question:

What is a “cancer cluster”?

Answer:

The cited reference describes “The term cancer cluster usually implies that more cases of cancer (usually of the same type) are identified within a certain group of people, geographic area, and time period than are expected, based on the size and age of the population. Usually the term refers to a highly localized situation such as a school, neighborhood, or workplace, although it is sometimes used to refer to a broader geographic area or larger subgroup of the population.” (Thum MJ and Sinks T. Understanding Cancer Clusters. CA Cancer J Clin 2004; 54:273–280)

Date:

2/9/2017

Question:

Which substance has recently been described as causing a “zombie outbreak” in New York?

Answer:

The cited article reports “a synthetic cannabinoid caused mass intoxication of 33 persons in one New York City neighborhood, in an event described in the popular press as a “zombie” outbreak because of the appearance of the intoxicated persons.” This report goes on to state: “The potency of the synthetic cannabinoid identified in these analyses is consistent with strong depressant effects that account for the “zombielike” behavior reported in this mass intoxication. AMB-FUBINACA is an example of the emerging class of “ultrapotent” synthetic cannabinoids and poses a public health concern.” (Adams AJ et al. “Zombie” outbreak caused by the synthetic cannabinoid AMB-FUBINACA in New York. 2017 NEJM 376(3): 235-242)

Date:

2/10/2017

Question:

What percent of cases of acute liver failure in adults are due to drug-induced liver injury?

Answer:

According to the cited article, “In adults, 11% of cases of acute liver failure are caused by drug-induced liver injury”. (Olson KR et al. Case 2-2017: An 18-year-old woman with acute liver failure. 2017 NEJM 376(3): 268-278)

Date:
2/13/2017

Question:

Metronidazole is a commonly prescribed antibiotic that has been reported to rarely induce what has been termed “metronidazole-induced encephalopathy”. What are the clinical symptoms associated with this syndrome and what are the reported brain MRI findings associated with this entity?

Answer:

The cited reference notes: “Three types of symptoms have been reported: seizures, cerebellar dysfunction, and acute changes in mental status. These symptoms may develop alone or in combination. Brain MRI on T2 weighted FLAIR images reveals abnormalities, mostly within the cerebellar dentate nuclei and corpus callosum. The third cerebral ventricle [has been reported to be] sandwiched by bilateral cerebellar dentate nuclei taking the form of a “chestnut”. The abnormality within the cerebellar dentate nuclei has thus been termed the “chestnut sign” in Japan where several cases with metronidazole induced encephalopathy have been reported.” (Kuriyama A. Chestnut sign: metronidazole-induced encephalopathy. 2017 J Emerg Med 52(1): 101-102)

Date:
2/14/2017

Question:

How rapidly does physical dependence on benzodiazepines develop?

Answer:

The cited article states “Physical dependence to benzodiazepines can be seen after just 3-6 weeks of use at therapeutic doses and 40% of patients using benzodiazepines for longer than 6 months will experience moderate to severe withdrawal [upon discontinuation of the drug].” (Puening SE et al. Psychiatric emergencies for clinicians: Emergency department management of benzodiazepine withdrawal. J Emerg Med 52(1): 66-69)

Date:
2/15/2017

Question:

Which compound, reportedly absorbed through intact skin covered by a latex glove, was responsible for the death of Dartmouth researcher Dr. Karen Wetterhahn?

Answer:

Dr. Wetterhahn, a 48-year-old researcher, was reportedly working with dimethylmercury in her laboratory, under a chemical hood, when a small amount of this extraordinarily toxic chemical was spilled onto her gloved hand. This material was absorbed and she died 298 days following exposure having suffered severe neurotoxic effects of dimethylmercury. (Nierenberg DW et al. Delayed cerebellar disease and death after accidental exposure to dimethylmercury. 1998 NEJM 338(23): 1672-1676)

Date:

2/16/2017

Question:

What percent of adults and youth (people > 12 years of age) in the United States are current users of tobacco?

Answer:

The cited article notes: "More than a quarter (27.6%) of adults were current users of at least one type of tobacco product in 2013 and 2014, although the prevalence varied depending on use category. A total of 8.9% of youths had used a tobacco product in the previous 30 days; 1.6% of youths were daily users. Approximately 40% of tobacco users, adults and youths alike, used multiple tobacco products; cigarettes plus e-cigarettes was the most common combination. Young adults (18 to 24 years of age), male adults and youths, members of racial minorities, and members of sexual minorities generally had higher use of tobacco than their counterparts." (Kasza KA et al. Tobacco-product use by adults and youths in the United States in 2013 and 2014. 2017 NEJM 376(4): 342-353)

Date:

2/17/2017

Question:

In which human body tissue are polychlorinated biphenyls (PCBs) preferentially stored?

Answer:

The cited reference notes "PCBs are pervasive environmental contaminants that are found in body tissues and fluids of the general population. Because they are lipophilic and generally have half-lives longer than 1 week, PCBs are preferentially stored in adipose tissue and are present in serum, blood plasma, and human milk." (<https://www.atsdr.cdc.gov/toxprofiles/tp17.pdf>; accessed Jan 2017)

Date:

2/20/2017

Question:

What are neonicotinoids?

Answer:

The cited article notes; "Neonicotinoids (neonics) are a class of chemicals used as insecticides for their neurotoxic action on the nicotinic acetylcholine receptor (nAChRs). Developed to replace organophosphate and carbamate insecticides, neonics are systemic in design, transfusing into all parts of treated plants, including pollen, nectar, and guttation fluids, and the foods grown by those plants. They are used for pest management across hundreds of crops in agriculture, horticulture, and forestry; in timber conservation and aquaculture; in vector control treatments for pets and livestock; and in urban and household pest control products. They are highly effective against difficult-to-control sucking, boring, and root-feeding insects." (Cimino AM et al.

Effects of neonicotinoid pesticide exposure on human health: a systematic review. 2017 Env Health Persp 125(2): 155-162)

Date:

2/21/2017

Question:

What is chlorfenapyr?

Answer:

According to the cited reference, "Chlorfenapyr is the only pyrrole pesticide currently registered for use against bed bugs. The compound is a pro-insecticide, i.e. the biological activity depends on its activation to form another chemical. The new chemical disrupts certain functions in the bed bug's cells, causing its death." (<https://www.epa.gov/bedbugs/pesticides-control-bed-bugs>; accessed; January 2017)

Date:

2/22/2017

Question:

What is a PEHSU?

Answer:

According to the published website, "The Pediatric Environmental Health Specialty Units (PEHSUs) are a source of medical information and advice on environmental conditions that influence reproductive and children's health. PEHSUs are academically based, typically at university medical centers, and are located across the United States and Canada. These PEHSU form a network that is capable of responding to requests for information throughout North America and offering advice on prevention, diagnosis, management, and treatment of environmentally-related health effects in children. Because environmental factors have a variety of impacts on the health of children and reproductive age adults, the PEHSU network has experts in pediatrics, allergy/immunology, neurodevelopment, toxicology, occupational and environmental medicine, nursing, reproductive health and other specialized areas. PEHSU's work with health care professionals, parents, schools and community groups, and others to provide information on protecting children and reproductive-age adults from environmental hazards. They also work with Federal, State, and local agencies to address children's environmental health issues in homes, schools, and communities." (http://www.pehsu.net/About_PEHSU.html; accessed January 2017)

Date:
2/23/2017

Question:

Around the world, more than 600 million people reportedly use betel nut (*Areca catechu*), in part, for its purported euphoric effects. Is the use of betel nut currently legal in the United States?

Answer:

Yes, the use of betel nut is currently legal in the United States. (Milgrom P. et al. Symptoms with betel nut and betel nut with tobacco among Micronesian youth. 2016 Addictive Behaviors, 53:120-124)

Date:
2/24/2017

Question:

What is the relative potency of the drug carfentanyl in relation to morphine and fentanyl?

Answer:

A recent DEA "Officer Safety Alert" warns law enforcement personnel that "Carfentanil is a synthetic opioid approximately 10,000 times more potent than morphine and 100 times more potent than fentanyl. The presence of carfentanil in illicit U.S. drug markets is cause for concern, as the relative strength of this drug could lead to an increase in overdoses and overdose-related deaths, even among opioid-tolerant users. The presence of carfentanil poses a significant threat to first responders and law enforcement personnel who may come in contact with this substance. In any situation where any fentanyl-related substance, such as carfentanil, might be present, law enforcement should carefully follow safety protocols to avoid accidental exposure. (https://www.dea.gov/divisions/hq/2016/hq092216_attach.pdf; accessed February 2017)

Date:
2/27/2017

Question:

What is a cancer "cluster" and how many purported "cancer clusters" are reported to state health departments each year?

Answer:

The cited article states "The term cancer cluster implies that more cases of cancer (usually of the same type) are identified within a certain group of people, geographic area and time period than are expected, based on the size and age of the population. Usually the term refers to a highly localized situation such as a school, neighborhood, or workplace, although it is sometimes used to refer to a broader geographic area or larger subgroup of the population." "It is reported that more than 1,000 suspected cancer clusters are reported to state health departments each year." (Thun MJ and Sinks T. Understanding cancer clusters. 2004 CA Cancer J Clin 54:273-280)

Date:
2/28/2017

Question:

Which two drugs are considered to be associated with the highest risk for the development of drug-induced lupus (DIL)?

Answer:

The cited reference notes "Procainamide, with a DIL incidence during 1 year of therapy of approximately 20% and hydralazine, with a 1- year incidence of 5-8% are by far the highest risk drugs for inducing lupus-like disease..." (Rubin RL. Drug-induced lupus. 2015 Expert Opin Drug Saf 14(3):361-378)

Date:
3/1/2017

Question:

A strong association between which anticonvulsant drug and the HLA-B*1502 allele has been found in Asian populations suffering from Stevens-Johnson syndrome (SJS) and the related disorder toxic epidermal necrolysis (TEN).

Answer:

The cited article notes "A strong association between HLA-B*1502 and carbamazepine-induced SJS-TEN has been found in Asian populations other than the Han Chinese, including Malay, Thai, and South Asian Indians. In Malaysia, Thailand, and India studies have shown that carbamazepine as the major cause of drug induced SJS-TEN." (Chen P et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. 2011 NEJM 364:1126-1133)

Date:
3/2/2017

Question:

What are the clinical characteristics associated with acute clonidine overdose?

Answer:

The cited reference points out that "Clonidine overdose is characterized by CNS depression, bradycardia and miosis, and can mimic opioid poisoning. Other clinical effects include early hypertension, followed by hypotension, hypothermia and respiratory depression. Clonidine overdoses are uncommon, and the toxidromic triad of CNS depression, bradycardia and hypotension can often appear serious. In addition, the duration of some of the clinical effects may be prolonged, particularly the bradycardia. Case reports and reviews suggest clonidine may result in severe toxicity with ingestions of small amounts resulting in significant CNS depression and cardiovascular effects." (Isbister GK et al. Adult clonidine overdose: prolonged bradycardia and central nervous system depression, but not severe toxicity. 2017 Clin Tox 55(3): 187-192)

Date:
3/3/2017

Question:
What is the “exposome”?

Answer:
The “exposome” can be defined as the measure of all the exposures of an individual in a lifetime and how those exposures relate to health. An individual’s exposure begins before birth and includes insults from environmental and occupational sources. Understanding how exposures from our environment, diet, lifestyle, etc. interact with our own unique characteristics such as genetics, physiology, and epigenetics impact our health is how the exposome will be articulated. (<https://www.cdc.gov/niosh/topics/exposome/>; accessed February 2017)

Date:
3/6/2017

Question:
A recent analysis of counterfeit OxyContin seized in Canada demonstrated fentanyl to be present in 89% of all tablets. Fentanyl is also often found in counterfeit alprazolam as well as other counterfeit medications. Why is fentanyl apparently used so often in the production of illicit street drugs?

Answer:
The cited editorial notes: “Rising fentanyl use reflects the drugs potency and low production costs. Even with declining prices, heroin costs about \$65,000 per kilogram wholesale, whereas illicit fentanyl is available at roughly \$3500 per kilogram. Drug dealers thus face strong incentives to mix fentanyl with heroin and other street drugs.” (Frank RG and Pollack HA. Addressing the fentanyl threat to public health. 2017 NEJM 376(7):605-607)

Date:
3/7/2017

Question:
One population-based cohort study of older adults, observed that new use of an atypical antipsychotic drug was associated with a higher 90-day risk for hospitalization with acute kidney injury (AKI). What are the potential causes for this observed effect?

Answer:
The cited reference notes “Drug use was also associated with an increased risk for other adverse outcomes, including hypotension, acute urinary retention, pneumonia, and acute cardiac events. These outcomes are known potential causes of AKI.” (Hwamng YJ et al. Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults: a population-based cohort study. 2014 Ann Intern Med. 161:242-248)

Date:
3/8/2017

Question:

The concentration of melanin in human hair is recognized as affecting the amount of some drugs that might be incorporated into hair. As a consequence, at co-equal doses, higher drug levels are typically found in the hair of individuals with darker colored hair. This influence is particularly pronounced for which class of drugs?

Answer:

The cited reference notes “This influence is particularly pronounced for basic drugs, such as cocaine or codeine.” (Kronstrand R., et al. Codeine concentration in hair after oral administration is dependent on melanin content. 1999 Clin Chem 45:1485–94)

Date:
3/9/2017

Question:

As part of their risk management strategy for certain drugs, the Food and Drug Administration (FDA) requires a so-called “Risk Evaluation and Mitigation Strategy (REMS)”. What does a REMS include?

Answer:

The noted reference states: “A REMS includes at least one of the following component: a Medication Guide, a communication plan for health care providers, and “elements to assure safe use” (ETASUs).” (Gassman AL et al. FDA regulation of prescription drugs. 2017 NEJM 376:674-682 and FDA basics webinar: a brief overview of Risk Evaluation and Mitigation Strategies (REMS). Silver Spring, MD: Food and Drug Administration, September 2, 2016 (<http://www.fda.gov/AboutFDA/>)

Date:
3/10/2017

Question:

What are the factors that affect health care worker exposures to potentially hazardous antineoplastic drugs?

Answer:

According to the cited reference “The likelihood that a worker will experience adverse effects from hazardous drugs increases with the amount and frequency of exposure and the lack of proper work practices.” Specifically, “the factors that affect worker exposures include the following: Drug handling circumstances (preparation, administration, or disposal); Amount of drug prepared; Frequency and duration of drug handling; Potential for absorption; Use of ventilated cabinets; PPE; and General and specific work factors”. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health care Settings, available at (<https://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf>)

Date:
3/13/2017

Question:

Loperamide is an antidiarrheal agent available as an over the counter drug available to the public without a prescription. What is the mechanism by which this drug reduces diarrhea?

Answer:

The noted article states that loperamide “inhibits intestinal peristalsis through mu-opioid receptor agonism, calcium channel blockade, calmodulin inhibition and decreasing paracellular permeability”. (Eggleston W et al. Loperamide abuse associated with cardiac dysrhythmia and death. 2017 Ann Emerg Med 69(1):83-86 and Baker DE. Loperamide: a pharmacological review. 2007 Rev Gastroenterol Disord. 7(suppl 3): S11-S18)

Date:
3/14/2017

Question:

What is “iodide mumps”?

Answer:

The cited reference notes: “Iodide “mumps” was first described in a kidney-impaired patient after intravenous pyelography. It can develop after any imaging procedure that uses iodine-based contrast medium. Patients usually exhibit painless bilateral parotid or submandibular gland swellings that are rapid in onset (5 minutes to several days) and gradually disappear during the next 6-day period. At times, all salivary glands are enlarged, whereas sometimes only 1 gland is swollen, but either bilateral parotid or submandibular salivary gland swellings are the norm. No long-term consequences, other than 1 case of facial palsy, have been reported.” (Mandel L and Surattanont F. Bilateral parotid swelling: A review. 2002 Oral Surg, Oral Med, Oral Path, Oral Radiol and Endodont. 93(3): 221-237, see also “Image challenge”, NEJM 2017 at <http://www.nejm.org/image-challenge>)

Date:
3/15/2017

Question:

Hepatic veno-occlusive disease (HVOD) has been reported as a complication of herbals that contain pyrrolizidine alkaloids. What are the clinical characteristics of hepatic veno-occlusive disease?

Answer:

The cited article notes, “Hepatic veno-occlusive disease (HVOD) is a clinical syndrome characterized by hyperbilirubinemia, painful hepatomegaly and weight gain due to fluid retention, after hematopoietic stem cell transplantation (HSCT), HVOD is a well-recognized life threatening complication, with an incidence rate of 10% to 60%.” Similar clinical findings are reported following the ingestion of herbals containing pyrrolizidine alkaloids. The cited article cautions, “Confirmation of HVOD is based on the histology examination of liver

tissue.” (Dai N et al. Gynura root induces hepatic veno-occlusive disease: A case report and review of the literature. 2007 World J Gastroenterol 13(910): 1628-1631)

Date:

3/16/2017

Question:

What is the scientific basis for using nails (fingernails and/or toe nails) as a testing matrix for detecting drugs?

Answer:

The cited article notes, “Nails are made of keratin. The average growth rate for fingernails is 3 mm per month (range between 1.9 and 4.4 mm/month). Toenails grow 30 – 50% slower than fingernails and are much more susceptible to drug contamination from sweat. As the nail grows, [some] chemicals (illicit substances, drugs, alcohol biomarkers, etc.) incorporate into the keratin fibers where they can stay for extended periods of time (3 – 5 months in fingernails, and 8 – 14 months in toenails). The mechanisms of drug deposition in nails have not been extensively studied.” (Shu L., et al. Detection of drugs in nails: Three year experience. 2015 J Analytical Tox 39:624-628)

Date:

3/17/2017

Question:

Which potentially harmful drugs are most commonly identified in meconium?

Answer:

A recent study involving more than 76,000 assays of meconium revealed “The positivity rate was the highest for the cannabis metabolite 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (25.2%, n = 18,643), followed by opiates/oxycodone (23.2%, n = 17,778), amphetamine/methamphetamine (6.7%, n = 5134), cocaine metabolites (5.5%, n = 4205), methadone (5.3%, n = 4093), benzodiazepines (3.4%, n = 2603), barbiturates (1.1%, n = 834), propoxyphene (1.0%, n = 749), and phencyclidine (0.1%, n = 44). Based on documented pharmacy history, drugs administered to either the mother or newborn during the birth hospitalization were detected in meconium, providing evidence that drugs can be incorporated into meconium rapidly. Drugs administered directly to the newborn after birth were recovered in meconium as both parent drug and metabolites, providing evidence of neonatal metabolism. Overall, patterns observed in meconium exhibited many similarities to those patterns commonly reported with urine drug testing.” These authors concluded: “Interpretation of meconium drug testing results requires comparison of results with clinical and analytical expectations, including maternal admissions to drug use, pharmacy history, recognized metabolic patterns for drugs of interest, cutoff concentrations, and other performance characteristics of the test. Concentrations of drug(s) and drug metabolites(s) may not reliably predict timing of drug use, extent of drug use, or frequency of drug exposures.” (McMillin GA et al. Patterns of drugs and drug metabolites observed in meconium: What do they mean? 2015 Ther Drug Monit 37:568-580)

Date:
3/20/2017

Question:
What are “biosimilars”?

Answer:

A biosimilar product is a biological product that is approved based on a showing that it is highly similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products. The Patient Protection and Affordable Care Act (Affordable Care Act), signed into law by President Obama on March 23, 2010, amends the Public Health Service Act (PHS Act) to create an abbreviated licensure pathway for biological products that are demonstrated to be “biosimilar” to or “interchangeable” with an FDA-licensed biological product. This pathway is provided in the part of the law known as the Biologics Price Competition and Innovation Act (BPCI Act). Under the BPCI Act, a biological product may be demonstrated to be “biosimilar” if data show that, among other things, the product is “highly similar” to an already-approved biological product. (<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm>; accessed February 2017)

Date:
3/21/2017

Question:
What is the nerve agent known as “VR”?

Answer:

The cited article notes: “A product of the arms race during the Cold War, the Russian VX, or VR, is an organophosphorus compound that is a structural isomer of the western VX compound (or A4), with which it shares a very high toxicity. It is much less studied and known than VX because the knowledge of its existence is relatively recent. A very low volatility and high resistance in the environment make it a persistent agent. Poisoning occurs mainly following penetration through skin and mucosa but vapour inhalation is a credible risk in some circumstances. The clinical presentation may be differed by several hours and despite the absence of signs and symptoms, the casualty should not be considered as contamination or intoxication-free. This agent has a long residence time in blood, a characteristics that clearly differentiates it from other compounds such as sarin. The protocols for antidote administration may thus have to be changed accordingly. The fact that VR poisoned individuals will less respond to the current oxime therapy used in France, the 2-PAM and that VR represents a higher threat than VX, being probably possessed by some proliferating states, justify the interest for this toxic product. (Cuquel AC et al. The VR, the Russian version of the nerve agent VX. 2015 Anns Pharm Francaises 73(3): 180-189)

Date:
3/22/2017

Question:
What is the vascular toxicity commonly associated with platinum based chemotherapy?

Answer:
The cited reference reports on a large group of patients receiving platinum based chemotherapy for bladder cancer. These authors concluded "Patients receiving platinum based chemotherapy were at higher risk for thromboembolism but not other vascular events, particularly in the first year after diagnosis. This risk of thromboembolism is similar for cisplatin and carboplatin."

Date:
3/23/2017

Question:
What is the usual time frame for the onset of alcohol withdrawal symptoms?

Answer:
The cited reference notes "Alcohol withdrawal symptoms can be seen within 8 hours of a patient's last drink and as long as 7 days after." (Schuckit MA Recognition and management of withdrawal delirium (delirium tremens). 2014 NEJM 371(22):2109-2113)

Date:
3/24/2017

Question:
What is the explanation for a "rebound" in INR that may be seen following the successful treatment of warfarin overdose with vitamin K1?

Answer:
The cited article notes "Treatment with early doses of vitamin K1 will result in initial INR improvement, which can be falsely reassuring. If the patient's INR is not closely monitored, there is a risk of a rebound increase in the INR. The reason for this rebound is that warfarin has a much longer half-life (estimates of 44 hours in overdose) than vitamin K1 (elimination half life of 1.7 hours)." (Berling I. et al. Warfarin poisoning with delayed rebound toxicity. 2017 J Emerg Med 52(2): 194-196)

Date:
3/27/2017

Question:

Gases that trap heat in the atmosphere are called greenhouse gases. What are the main gases considered to be “greenhouse gases”?

Answer:

The main gases considered to be “greenhouse gases” are carbon dioxide (CO₂), methane, nitrous oxide and the fluorinated gases (hydrofluorocarbons, perfluorocarbons, sulfur hexafluoride, and nitrogen trifluoride) (<https://www.epa.gov/ghgemissions/overview-greenhouse-gases>; accessed; January 2017)

Date:
3/28/2017

Question:

Which adverse health effects have been attributed by some to so-called “carbonless carbon paper”?

Answer:

The cited reference notes: “According to available data, exposure to certain types of carbonless copy paper or its components has resulted, under some conditions, in mild to moderate symptoms of skin irritation and irritation of the mucosal membranes of the eyes and upper respiratory tract. In most cases, good industrial hygiene and work practices should be adequate to reduce or eliminate symptoms. These include adequate ventilation, humidity, and temperature controls; proper housekeeping; minimal hand-to-mouth and hand-to-eye contact; and periodic cleansing of hands.” (<https://www.cdc.gov/niosh/docs/2001-107/>; accessed; January 2017)

Date:
3/29/2017

Question:

The reference cited below notes “Histamine fish poisoning, also known as scombroid poisoning, is the most common cause of ichthyotoxicosis worldwide and often results from the ingestion of histamine-contaminated fish in the Scombridae and Scomberesocidae families, including mackerel, bonito, albacore, and skipjack.” Ingestion of which two fish make up more than 80% of histamine fish poisoning in the United States?

Answer:

Tuna and mahi mahi make up more than 80 % of reported cases of histamine fish poisoning. (Feng C et al. Histamine (Scombroid) fish poisoning: A comprehensive review. 2016 Clin Rev Allerg Immunol 50:64-69)

Date:
3/30/2017

Question:

The reference cited below notes “Workers in industries where beryllium is present may be exposed to beryllium by inhaling or contacting beryllium in the air or on surfaces. Inhaling or contacting beryllium can cause an immune response that results in an individual becoming sensitized to beryllium.” How is beryllium used in industry?

Answer:

The cited reference reports: “Beryllium is used industrially in three forms: as a pure metal, as beryllium oxide, and most commonly, as an alloy with copper, aluminum, magnesium, or nickel. Beryllium oxide (called beryllia) is known for its high heat capacity and is an important component of certain sensitive electronic equipment. Beryllium alloys are classified into two types: high beryllium content (up to 30% beryllium) and low beryllium content (2 – 3% beryllium). Copper-beryllium alloy is commonly used to make bushings, bearings, and springs. Beryllium is also found as a trace metal in slags and fly ash.”
(<https://www.osha.gov/SLTC/beryllium/index.html>; accessed January 2017)

Date:
3/31/2017

Question:

What is the so-called “General Duty Clause” promulgated by OSHA?

Answer:

The “General Duty Clause” of the OSH Act of 1970 requires: (a) Each employer — (1) shall furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees; (2) shall comply with occupational safety and health standards promulgated under this Act.(b) Each employee shall comply with occupational safety and health standards and all rules, regulations, and orders issued pursuant to this Act which are applicable to his own actions and conduct.(https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=OSHACT&p_id=3359; accessed March 2017)

Date:
4/3/2017

Question:

What are the differences in the development of neuro-cognitive effects between healthy children with a single anesthesia exposure before age 36 months, compared with healthy siblings with no anesthesia exposure?

Answer:

One recent study of 105 sibling pairs reported “no statistically significant differences in mean scores were found between sibling pairs in memory/learning, motor/processing speed, visuospatial function, attention, executive

function, language, or behavior.” The authors concluded “Among healthy children with a single anesthesia exposure before age 36 months, compared with healthy siblings with no anesthesia exposure, there were no statistically significant differences in IQ scores in later childhood.” However these authors cautioned, “Further study of repeated exposure, prolonged exposure, and vulnerable subgroups is needed.” (Sun SL et al. Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. 2016 JAMA. 315(21): 2312-2320.

Date:

4/4/2017

Question:

What is the widely abused substance, first popularized in the Houston, Texas, hip-hop culture, known as “purple drank”?

Answer:

The cited reference notes, “Also known as “syrup,” “sizzurp,” “barre,” and “lean” (nicknamed for the posture that users assume when intoxicated), purple drank is a concoction that can take several forms. Most involve some form of codeine cough syrup containing the opiate painkiller codeine and promethazine hydrochloride, an antihistamine with sedative properties. The cough syrup is typically mixed with a soft drink and candy, with some variants including alcohol. Other forms of this mixture can include over-the-counter cough syrups, which are easier to obtain and much cheaper than prescription strength codeine cough syrup, but produce different effects. For example, misuse of dextromethorphan can result in hallucinogenic effects, rather than the sedative effects of the traditional form of purple drank containing codeine and promethazine. The high-profile arrest of former Oakland Raiders Quarterback JaMarcus Russell in 2010 for possession of codeine, and allegations of his habitual misuse, led to heightened awareness of a potential purple drank problem.” (Agnich LE et al. Purple drank prevalence and characteristics of misusers of codeine cough syrup mixtures. 2013 Addictive Behaviors 38:2445-2449)

Date:

4/5/2017

Question:

Candida endophthalmitis has been associated with the use of which illicit substance?

Answer:

Candida endophthalmitis has been associated with the use/abuse of brown heroin. (Melnychuk EM and Sole DP. A rare central nervous system fungal infection resulting from brown heroin use. 2017 J Emerg Med 52(3): 314-317)

Date:
4/6/2017

Question:

Which recombinant immunoglobulin has been suggested as a useful therapy in the reversal of dabigatran associated bleeding? What is the proposed mechanism for this reversal effect?

Answer:

The cited reference notes that “Idarucizumab is a recombinant immunoglobulin G1 iso-type molecule that binds specifically to the thrombin binding site of dabigatran and its metabolites with an affinity that is approximately 350 times greater than the affinity of dabigatran to thrombin, resulting in the inability of dabigatran to thrombin resulting in the inability of dabigatran to bind thrombin.” (Miller L et al. Idarucizumab for reversal of dabigatran-associated bleeding: misnomer or miracle? 2017 J Emerg Med 52(3): 341-347 and Schiele F et al. A specific antidote for dabigatran: functional and structural characterization. 2013 Blood 121: 3554-3562)

Date:
4/7/2017

Question:

What are the adverse health effects of concern associated with occupational exposure to hexavalent (VI) chromium?

Answer:

The cited reference notes: “The primary occupational health effect associated with hexavalent chromium compounds is an increased risk of lung cancer from inhalation exposures. In addition, health effects associated with exposure to chromium (VI) can include airway sensitizations, or asthma, skin sensitizations, e.g., allergic and irritant contact dermatitis, nasal and skin ulcerations, and eye irritation”.
(https://www.osha.gov/OshDoc/Directive_pdf/CPL_02-02-076.pdf; accessed March 2017)

Date:
4/10/2017

Question:

Listeriosis is caused by the Gram-positive organism, *Listeria monocytogenes*. This bacterium generally causes self limited and mild gastroenteritis. What is the disease profile often associated with *Listeria monocytogenes* infections in at risk populations (e.g. pregnant women, elderly people, immuno-compromised people, unborn babies, and neonates) with possible inadequate cell mediated immunity?

Answer:

The cited reference reports: “Mainly in patients with impaired cell-mediated immunity, listeriosis can lead to severe illnesses, including severe sepsis, meningitis, or encephalitis, and thereby cause lifelong consequences and even death. Infection during pregnancy can result in spontaneous abortions or stillbirths. Preterm birth is also a common consequence of listeriosis in pregnant women.” (de Noordhout CM et al. The global burden of listeriosis: a systematic review and meta-analysis. 2014 The Lancet Infectious Diseases 14:1073-1082)

Date:

4/11/2017

Question:

Which plant, known as the “heartbreak grass” has been posited as a homicidal agent used by the government of Vladimir Putin?

Answer:

Plants of the genus *Gelsemium* are also known as “heartbreak grass” and have been posited as a homicidal agent used by the government of Vladimir Putin. The cited reference notes “All three species of *Gelsemium* are highly poisonous. The leaves, stems and roots are equally toxic, and consuming the plant has been used as a method to commit suicide and homicide. Experimental work indicates that typical symptoms of intoxication include sweating, dizziness, nausea, vomiting, blurred vision, muscular weakness, limb paralysis, dilated pupils, breathing difficulty, coma and convulsion. In instances of severe poisoning, the nervous system is depressed and death is caused by respiratory depression. (Jin GL et al. Medicinal plants of the genus *Gelsemium* (Gelsemiaceae, Gentianales)—A review of their phytochemistry, pharmacology, toxicology and traditional use. 2014 *J Ethnopharm* 152:33-52)

Date:

4/12/2017

Question:

Valproic acid is often used in the management of chronic seizure disorders and for bipolar disease as well as in the preventive management of migraine headaches. In which clinical circumstances has levocarnitine been proposed to manage overdoses of valproic acid?

Answer:

Levocarnitine has been proposed as part of the treatment regimen for patients with hyperammonemia, comatose patients and those with increasing blood levels (>400 mg/dl) (Sun C. Valproic acid. 2017 *Critical Decisions in Emerg Med*. 31(1):24)

Date:

4/13/2017

Question:

What is mephedrone?

Answer:

The cited reference notes “Mephedrone, 3-methoxy-2-(methylamino)-1-(4-methylphenyl)propan-1-one, is the alpha-methoxy-derivative of mephedrone (4-methyl-N-methyl cathinone). These authors point out “Whilst there are no published pharmacological studies of mephedrone, based on in vitro and in vivo studies of mephedrone, it can be anticipated that mephedrone inhibits the re-uptake of serotonin and dopamine in a dose-dependent manner

and has affinity for serotonin and dopamine membrane transporters and receptors (5-HT₂ and D₂ receptors), producing sympathomimetic effects similar to amphetamines.” (Roberts L et al. 11 analytically confirmed cases of mephedrone use among polydrug users. 2017 Clin Tox 55(3):181-186)

Date:

4/14/2017

Question:

What characterizes the clinical findings associated with tick paralysis?

Answer:

The cited reference notes “Tick paralysis, a uniquely tick-borne neurotoxic envenoming, is characterized by an ascending flaccid neuromuscular paralysis with sensory sparing and frequent cranial nerve involvement. Tick paralysis is caused by the dermal injection of salivary neurotoxins secreted primarily by gravid hard ticks (Acari: Ixodidae) while blood feeding, and often before ovipositing.” These authors also point out that tick paralysis “mimics polio and primarily afflicts children.” (Diaz JH. A comparative meta-analysis of tick paralysis in the United States and Australia. 2015 Clin Tox 53(9):874-883)

Date:

4/17/2017

Question:

What is the common name for the chemical 2-chlorovinylchloroarsine?

Answer:

2-chlorovinylchloroarsine is better known as Lewisite, a combination of acetylene and arsenic trichloride. Lewisite was originally developed as a chemical warfare agent and is a concern as a potential weapon that might be used by terrorists. The cited reference notes “Lewisite’s systemic toxicity and, presumably, its cutaneous and ocular irritability result primarily from its arsenic content.” (Vilensky JA and Redman K. British Anti-Lewisite (Dimercaprol: An amazing history. 2003 Ann Emerg Med 41:378-383)

Date:

4/18/2017

Question:

What is so-called “NSAID colopathy”?

Answer:

The cited reference notes “The term NSAID colopathy has been used for non-specific colonic injury seen at colonoscopy, ranging from erosions to ulcers, with or without strictures, which have been seen with NSAID (including low-dose aspirin) use. It does not have the protean manifestations of small bowel injury. The resolution of the findings with cessation of NSAID exposure has supported their etiological role, but proof with repeat challenge has not been clearly demonstrated in most cases. Diaphragm disease of the colon may be

considered diagnostic for NSAID-induced colon injury, although only a relatively small number of cases have been reported. Diclofenac-extended release formulations have been frequently implicated, supporting a role for high local drug concentrations due to its enterohepatic recirculation.” (Scheiman JM. NSAID-induced gastrointestinal injury: A focused update for clinicians. 2016 J Clin Gastroenterol 50:5–10)

Date:

4/19/2017

Question:

Hereditary angioedema may be clinically confused with severe drug related reactions in some circumstances. What is hereditary angioedema and what is the cause for hereditary angioedema?

Answer:

The cited reference notes: “Hereditary angioedema is a disabling and potentially fatal condition characterized by recurrent episodes of swelling without urticaria or pruritus. The condition is caused by deficiency (type I) or dysfunction (type II) of the C1 inhibitor protein, Patients have insufficient C1 inhibitor function to prevent bradykinin production by the contact system, leading to episodes of increased capillary hyper-permeability and swelling. These episodes manifest clinically as angioedema attacks.” (Longhurst H et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. 2017 NEJM 376(12): 1131-1140)

Date:

4/20/2017

Question:

What are the MRI findings consistent with severe methanol toxicity?

Answer:

The cited reference notes “Methanol directly affects the putamen of the basal ganglia. With severe intoxication, both hemorrhagic and non-hemorrhagic damage of the putamen occur commonly. This was described initially in 1953, and clinically results in a parkinsonian-like disorder such as dystonia, cog-wheeling, stooped posture, shuffling gait, and hypokinesia. The predilection for and mechanism of toxicity to the putamen are not understood. Cases of axonal polyneuropathy and anterior horn cell loss in association with chronic exposure have been reported. At CT and MRI, methanol toxicity results in putamen hemorrhage or necrosis and diffuse cerebral edema and petechial hemorrhages.” (Anderson JC. Et al. Basal ganglia: Anatomy, pathology and imaging characteristics. 2004 Curr Probl Diagn Radiol 33: 28-41)

Date:
4/21/2017

Question:
What is the LactMed database?

Answer:
The LactMed® database contains information on drugs and other chemicals to which breastfeeding mothers may be exposed. It includes information on the levels of such substances in breast milk and infant blood, and the possible adverse effects in the nursing infant. Suggested therapeutic alternatives to those drugs are provided, where appropriate. All data are derived from the scientific literature and fully referenced. A peer review panel reviews the data to assure scientific validity and currency. (<https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>; accessed March 2017)

Date:
4/24/2017

Question:
What is the Federal act that governs the speed of the regulatory review process for new therapeutic agents?

Answer:
The cited article notes: “Although the 21st Century Cures Act which was signed into law in December 2016, includes several reforms that are intended to further streamline FDA evaluations, the speed of the regulatory review process is directed by the Prescription Drug User Fee Act (PDUFA).” (Downing NS et al. Regulatory review of new therapeutic agents- FDA versus EMA, 2011-2015. 2017 NEJM, 376 (14): 1386-1387)

Date:
4/25/2017

Question:
A blue color tinge to the vision has been reported in conjunction with which drug sometimes prescribed for the treatment of erectile dysfunction?

Answer:
The cited reference reports: “A small percentage (3%) of patients treated with sildenafil in flexible-dose studies report transient visual adverse events described as a blue color tinge to vision.....” (Jagle H et al. Visual short-term effects of Viagra: double-blind study in healthy young subjects. 2004 Am J Ophthalmology 137(5): 842-849)

Date:
4/26/2017

Question:
What is the typical clinical progression of the phenytoin and fosphenytoin related “purple-glove syndrome”?

Answer:
Some authors have described “...three temporal stages of injury: initial painful blue-purple discoloration and edema around the IV catheter site, subsequent worsening of pain, edema, and discoloration with development of epidermal sloughing, ulceration, or bullae formation, and neuromuscular symptoms such as paresthesias or weakness and eventually resolution of edema and discoloration starting from the periphery of the injury and moving towards the site of catheter insertion. Timing of these stages appears quite variable, with initial discoloration occurring from minutes to days after phenytoin administration and tissue recovery spanning days to months.” (Garbovsky LA et al Purple glove syndrome after phenytoin or fosphenytoin administration: review of reported cases and recommendations for prevention. 2015 J Med Tox 11:445-459 and Bhattacharjee P et al. Early pathophysiologic changes in purple glove syndrome. 2004 J Cutan Pathol 31(7): 513-515)

Date:
4/27/2017

Question:
Most scorpions whose stings cause serious medical problems are members of the Buthidae family. This family includes scorpions from the genera leiurus, androctonus and buthus, tityus, centruroides, mesobuthus, and parabuthus. Each of these genera are indigenous to different geographic locations; North and Central America, Asia, North Africa, Near/Middle East and South America. Match the listed genera with the correct geographic location

Answer:
Leiurus: Near and Middle East, androctonus and buthus: North Africa, tityus: South America, centruroides: North and Central America, mesobuthus: Asia (especially India), and parabuthus in South Africa. (Isbister GK and Bawaskar HS. Scorpion envenomation 2014 NEJM 371:457-463)

Date:
4/28/2017

Question:
What are xenoestrogens?

Answer:
The cited reference notes, “Environmental, industrial, or naturally occurring chemicals that possess estrogenic and/or antiestrogenic activities are termed xenoestrogens and may interfere with endocrine systems. These xenoestrogens are therefore defined as endocrine-active or endocrine-disrupting compounds.” (Mueller SO. Xenoestrogens: mechanisms of action and detection methods. 2004 Anal Bioanal Chem 378:582-587)

Date:
5/1/2017

Question:

Collapsing focal segmental glomerulosclerosis is one cause for primary nephrotic syndrome. Which drugs have been implicated in causing this form of kidney disease?

Answer:

The cited article lists pamidronate, interferon and anabolic steroids as the drugs have been implicated in causing focal segmental glomerulosclerosis. (Sise ME et al. Case 12-2017: A 34 year old man with nephropathy. 2017 NEJM 376(16): 1575-1585)

Date:
5/2/2017

Question:

The use of cannabis and/or alcohol is usually discussed as increasing the risk for motor vehicle crash. What is the role of cannabis and alcohol in cycling related crash risk?

Answer:

One recent study found: "Approximately 15% of cyclists reported using cannabis just prior to the crash, and 14.5% reported using alcohol. Cannabis use identified by blood testing or self-report in the case period and by self-report in the control period yielded a crash risk of 2.38 (1.04–5.43); however, when self-report was used for both the case and control periods the estimate was 0.40 (0.12–1.27). Alcohol use, as measure either in blood or self-report, was associated with an odds ratio of 4.00 (95% CI: 1.64–9.78); results were similar when alcohol was measured by self-report only." (Asbridge M. et al. Cycling-related crash risk and the role of cannabis and alcohol: a case-crossover study. 2014 Preventive Med 66:80-86)

Date:
12:00:00 AM

Question:

What is chaparral and what toxicities have been associate with this substance?

Answer:

The cited reference notes: "Chaparral is an herbal preparation derived by grinding the leaves of the creosote bush (*Larrea tridentata*), an evergreen desert shrub. The ground leaves may be used for tea, placed in capsules, or formed into tablets. Chaparral has been recommended in nonscientific publications for use as an "antioxidant" or "free radical scavenger" to retard aging and to treat a variety of skin conditions (e.g., acne) and hepatitis. In addition, chaparral tea is used as a traditional American Indian medicine. The active ingredient in chaparral is a potent antioxidant, nordihydroguaiaretic acid (NDGA), which can act as a cyclooxygenase and lipoxygenase pathway inhibitor. Long-term studies in rats indicate that consumption of NDGA causes kidney cysts and mesenteric lymphadenopathy; however, there is no information on hepatotoxicity from animal

studies.” There have been a limited number of cases of hepatic toxicity reported in individuals ingesting chaparral. (Chaparral-induced toxic hepatitis—California and Texas, 1992 MMWR 41(43):812-814)

Date:

5/4/2017

Question:

What are the common pathogens found in so-called “raw milk” (milk that has not undergone pasteurization to kills disease-causing pathogens)

Answer:

Listeria, E. Coli, Salmonella and campylobacter are the most common pathogens found in raw milk. (<https://www.cdc.gov/foodsafety/rawmilk/raw-milk-index.html>; accessed, April 2017)

Date:

5/5/2017

Question:

Under the Controlled Substances Act, what are the factors used to determine into which schedule a drug or substance should be placed or whether a substance should be decontrolled or rescheduled?

Answer:

These factors are listed in Section 201 (c), [21 U.S.C. § 811 (c)] of the CSA as follows:(1) Its actual or relative potential for abuse. (2) Scientific evidence of its pharmacological effect, if known. (3) The state of current scientific knowledge regarding the drug or other substance. (4) Its history and current pattern of abuse. (5) The scope, duration, and significance of abuse. (6) What, if any, risk there is to the public health. (7) Its psychic or physiological dependence liability. (8) Whether the substance is an immediate precursor of a substance already controlled under this subchapter. (<https://www.dea.gov/druginfo/csa.shtml>; accessed- April 2017)

Date:

5/8/2017

Question:

Which serious cutaneous disease resulted from the use of contaminated shaving brushes during the First World War and into the 1920s?

Answer:

Cutaneous anthrax resulted from the use of contaminated shaving brushes during the 1920s. The cited reference notes, “...the source material origin of shaving brushes had changed during the war (WWI). Cheap brushes of imported horsehair were being made to look like the preferred badger-hair brushes. Unfortunately, some of the these brushes were not effectively disinfected and brought with them a nasty stowaway, *Bacillus anthracis*.” (Szablewski CM et al. Anthrax cases associate with animal-hair shaving brushes. 2017 Emerg Inf Dis 23(5): 806-808)

Date:

5/9/2017

Question:

Hydroxychloroquine is commonly used in the treatment of a variety of rheumatologic diseases including lupus, and rheumatoid arthritis as well as for the treatment of certain malignancies (e.g. non-small cell lung cancer). What is the time course for the development of retinal toxicity in relation to the use of this drug?

Answer:

The listed article notes: "The risk of hydroxychloroquine mediated retinal toxicity is relatively low within the first 5-10 years of therapy when used at daily doses that do not exceed 5mg/kg, typically 200-400mg daily". However when used at very high doses (e.g. 1000 mg per day), "hydroxychloroquine can initiate the development of retinal toxicity within 1-2 years". (Leung LB et al. Rapid onset of retinal toxicity from high dose hydroxychloroquine given for cancer therapy. 2015 Am J Ophthalmol 160(4):799-805)

Date:

5/10/2017

Question:

Pulmonary toxicity is the most important dose limiting side effect of the chemotherapeutic agent bleomycin. What is the most common clinical presentation for patients with bleomycin pulmonary toxicity (BPT)?

Answer:

The cited reference notes "Patients with BPT usually present with nonproductive cough, exertional dyspnea, and occasionally fever, and the radiologic findings show bilateral infiltrates." Sleijfer S. Bleomycin-induced pneumonitis. 2001 Chest 120: 617-624 and Hauges HS et al. Pulmonary and cardiovascular toxicity in long-term testicular cancer survivors. 2015 Urol Onc 33(9): 339-406.

Date:

5/11/2017

Question:

What is endosulfan and what is the primary toxicity of this compound

Answer:

The cited reference notes: "Endosulfan is a restricted-use pesticide (EPA class I) (a chlorinated hydrocarbon) that is particularly effective against aphids, fruit worms, beetles, leafhoppers, moth larvae, and white flies on a wide variety of crops. It is not approved for residential use. It is sold as a mixture of two different forms of the same chemical (referred to as α - and β -endosulfan). It is a cream-to-brown-colored solid that may appear crystalline or in flakes. It has a distinct odor similar to turpentine. The use of endosulfan is being restricted to certain crops and is scheduled to be canceled for all uses by 2016." The primary toxicity is neurological with seizures being a prominent effect. Poor coordination, imbalance, difficulty breathing, gagging, vomiting,

diarrhea, agitation, and loss of consciousness have also been reported.
(<https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=609&tid=113>; accessed April 2017)

Date:
5/12/2017

Question:
What is “bear spray”?

Answer:
“Bear spray is a non-lethal bear deterrent designed to stop aggressive behavior in bears. Its use can reduce human injuries caused by bears and the number of bears killed by people in self-defense. Bear spray uses a fine cloud of Capsicum derivatives to temporarily reduce a bear's ability to breath, see, and smell, giving you time to leave the area.” <https://www.nps.gov/yell/learn/nature/bearspray.htm>; accessed March 2017 and Gervais, J. A. ; Luukinen, B.; Buhl, K.; Stone, D. 2008. Capsaicin Technical Fact Sheet; National Pesticide Information Center, Oregon State University Extension Services. <http://npic.orst.edu/factsheets/archive/Capsaicintech.html>; accessed April 2017)

Date:
5/15/2017

Question:
What is the historical significance of the drug aminorex?

Answer:
The cited reference notes: “In 1967, only 2 years after the introduction of the anorexigen drug aminorex on the market in Switzerland, West Germany and Austria, an epidemic of pulmonary arterial hypertension (PAH) was observed. During this period, nearly 60% of the diagnosed patients had a history of aminorex intake that allowed us to recognize the temporal and geographical relationships between the use of the drug and PAH development. Furthermore, this epidemic significantly decreased 2 years after the withdrawal of aminorex. These patients were found to have precapillary PH with typical plexiform arteriopathy upon histological examination and a severe prognosis: 10 years after the epidemic, half of the patients died, usually of right heart failure.” (Montani D. et al. Drug-induced pulmonary arterial hypertension: a recent outbreak. 2013 Eur Resp Rev 22:244-250)

Date:
12:00:00 AM

Question:
What is the current status for use of the drug Rohypnol® in the United States?

Answer:

Rohypnol® (flunitrazepam) produces sedative-hypnotic, anti anxiety and muscle relaxant effects. This drug has never been approved for medical use in the United States by the FDA. Outside the U.S., Rohypnol® is commonly prescribed to treat insomnia. Rohypnol is also referred to as a “date rape” drug. Rohypnol® is a Schedule IV substance under the Controlled Substances Act and is not approved for manufacture, sale, use or importation into the U.S. Rohypnol® is smuggled into the US from other countries including Mexico. (https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf; accessed May 2017)

Date:

5/17/2017

Question:

What are the potential advantages of buprenorphine as compared with morphine treatment of neonatal abstinence syndrome?

Answer:

One recent study reported: “Among infants with the neonatal abstinence syndrome, treatment with sublingual buprenorphine resulted in a shorter duration of treatment and shorter length of hospital stay than treatment with oral morphine, with similar rates of adverse events.” (Kraft WK. Buprenorphine for the treatment of the neonatal abstinence syndrome. 2017 NEJM published online May 4, 2017, (DOI: 10.1056/NEJMoa1614835)

Date:

5/18/2017

Question:

What is the current usage level of illicit drugs by American youth?

Answer:

The cited reference notes “Youth are especially vulnerable to drug abuse. According to NIDA, young Americans engaged in extraordinary levels of illicit drug use in the last third of the twentieth century. Today, about 47% of young people have used an illicit drug by the time they leave high school and about 16 percent of eighth, tenth, and twelfth graders are current (within the past month) users.

(https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf; accessed May 2017)

Date:

5/19/2017

Question:

The following street names refer to which synthetic narcotic: Amidone, Chocolate Chip Cookies, Fizzies, Maria, Pastora, Salvia, Street and Wafer?

Answer:

Amidone, Chocolate Chip Cookies, Fizzies, Maria, Pastora, Salvia, Street and Wafer all refer to the drug methadone. (https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf; accessed May 2017)

Date:

5/22/2017

Question:

Which flowering evergreen shrub that is abused for its stimulant effects is known by the following street names: Abyssinian Tea, African Salad, and Oat?

Answer:

Abyssinian Tea, African Salad, and Oat all refer to khat. The cited reference notes: "Khat is a flowering evergreen shrub. Khat that is sold and abused is usually just the leaves, twigs, and shoots of the Khat shrub. Khat is typically chewed like tobacco, then retained in the cheek and chewed intermittently to release the active drug, which produces a stimulant-like effect. Dried Khat leaves can be made into tea or a chewable paste, and Khat can also be smoked and even sprinkled on food." (https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf; accessed may 2017)

Date:

5/23/2017

Question:

Tramadol has been marketed in the United States for more than 29 years to treat mild-to-moderate pain. What are the two mechanisms by which this drug produces analgesia?

Answer:

The cited reference notes that tramadol "...has minimal affinity for the mu-opioid receptor and inhibits the reuptake of serotonin and norepinephrine. The active hepatic metabolite, o-desmethyltramadol or M1, is an opioid agonist with high relative intrinsic efficacy and moderate affinity for the mu-opioid receptor." (Babalonis S et al. Abuse liability and reinforcing efficacy of oral tramadol in humans. 2013 Drug Alc Dep 129:116-124)

Date:

5/24/2017

Question:

Is the American Conference of Governmental Industrial Hygienists (ACGIH) a U.S. governmental agency?

Answer:

No. ACGIH® is a 501(c)(3) charitable scientific organization that advances occupational and environmental health. (<http://www.acgih.org/about-us/about-acgih>; accessed May 2017)

Date:

5/25/2017

Question:

What are the potential cabin air hazards on commercial airliners?

Answer:

The potential cabin air hazards on commercial airliners include “Ventilation hazards (including carbon monoxide, ozone, and carbon dioxide levels); Transmission of communicable diseases from sick passengers; Cabin altitude and pressurization changes; Air contamination events, when cabin air becomes contaminated with breakdown products from heated engine oil or hydraulic fluid; pesticide exposures on certain flights.” (<https://www.cdc.gov/niosh/topics/aircrew/cabinairquality.html>; accessed April 2017)

Date:

5/26/2017

Question:

The diagnosis of cyanide toxicity is generally a clinical one as blood cyanide levels are rarely if ever available quickly. Which readily available laboratory test may be helpful in the diagnosis cyanide toxicity in victims of smoke inhalation specifically?

Answer:

The cited article notes: “Although blood cyanide concentration can be measured, it is not of use for diagnosis in the acute setting as few laboratories perform the assay and results cannot be obtained rapidly. Diagnosis is therefore clinical; however, plasma lactate has been found to correlate with the severity of cyanide toxicity due to lactic acidosis from the prevailing anaerobic metabolism. In victims of smoke inhalation with burns <15% total body surface area (TBSA), a plasma lactate level >10 mmol/L (90 mg/dL) has been found to be a sensitive indicator of cyanide toxicity suggesting blood cyanide levels >40 mmol/L (1.0 mg/L).” (MacLennan L and Moiemann N. Management of cyanide toxicity in patients with burns. 2015 Burns 41:18-24)

Date:

5/29/2017

Question:

On January 5, 2005, in Graniteville, South Carolina, a train crash caused the release of what chemical that killed 9 people and injured more than 250?

Answer:

On January 5, 2005, in Graniteville, South Carolina, a train crash cause the release of 90 tons of chlorine gas killing 9 people and injured more than 250. (MMWR, January 28, 2005 / 54(03); 64-67)

Date:

5/30/2017

Question:

With regard to carcinogenicity how does IARC classify radiofrequency electromagnetic fields?

Answer:

The WHO/International Agency for Research on Cancer (IARC) has classified radiofrequency electromagnetic fields as possibly carcinogenic to humans (Group 2B), based on an increased risk for glioma, a malignant type of brain cancer, associated with wireless phone use. (http://www.iarc.fr/en/media-centre/pr/2011/pdfs/pr208_E.pdf; accessed May 2017)

Date:

5/31/2017

Question:

What are the most common adverse effects of the topically applied (applied directly to the eye) aminoglycosides tobramycin and gentamicin?

Answer:

Superficial punctate lesions on the cornea are the most common findings in patients receiving topical aminoglycosides. Corneal ulceration and conjunctival pseudomembranes may occur but are rare. (Fraunfelder FW. Corneal toxicity from topical ocular and systemic medications. 2006 Cornea 25:1133-1138)

Date:

6/1/2017

Question:

What is 2,3 benzofuran?

Answer:

2,3-Benzofuran is a colorless, sweet-smelling, oily liquid made by processing coal into coal oil. It may also be formed during other uses of coal or oil. 2,3-Benzofuran is not used for any commercial purposes, but the part of the coal oil that contains 2,3-benzofuran is made into a plastic called coumarone-indene resin. This resin resists corrosion and is used to make paints and varnishes. The resin also provides water resistance and is used in coatings on paper products and fabrics. It is used as an adhesive in food containers and some asphalt floor tiles. The resin has been approved for use in food packages and as a coating on citrus fruits. We do not know how often the resin is used or whether any 2,3-benzofuran in the coating or packaging gets into the food. Exposure to 2,3 benzofurans has been implicated in the development of hepatic and renal injury in some experimental animal models. (<https://www.atsdr.cdc.gov/toxprofiles/tp25-c2.pdf>; accessed May 2017)

Date:

6/2/2017

Question:

What are the anthracycline chemotherapeutic agents and what is the primary toxicity that is dose limiting for these agents?

Answer:

The four most common anthracyclines are doxorubicin, daunorubicin, epirubicin and idarubicin. Doxorubicin and daunorubicin were the first to be used in clinical practice. Cardiotoxicity is the primary dose limiting toxicity for these agents.

The cited reference notes "The exact mechanism of anthracycline-induced cardiotoxicity remains unclear, though it is likely to be multifactorial. Until recently, the most widely accepted hypothesis was that anthracyclines interfered with redox cycling, resulting in DNA damage due to reactive oxygen species (ROS) production. More recently, topoisomerase 2 has been suggested to be the main mediator of cardiotoxicity, though other mechanisms contribute. (McGowan JV et al. Anthracycline chemotherapy and cardiotoxicity. 2017 Cardiovasc Drugs 31:63-75

Date:

6/5/2017

Question:

A report documents a patient has been taking a rhubarb and cascara compound as a laxative for a period of 5 years. On colonoscopy the entire colon appears black and dark brown. What is the basis for this abnormal coloration of the colon?

Answer:

This abnormal coloration of the colon is known as melanosis coli. The cited reference notes "the active ingredient in these substances (rhubarb and cascara) is anthraquinone, which causes injury to the colonic epithelial cells, resulting in the production of lipofuscin, the dark pigment seen in melanosis coli. The condition is benign and reversible." (Kew ST and Chakravarthi S. Melanosis coli. 2013 NEJM 368:24)

Date:

6/6/2017

Question:

While the use of activated charcoal in poisoning and overdose cases is usually safe, it is not without potential risks. What is the most widely cited concern associated with the use of single dose activated charcoal?

Answer:

According to the cited reference, pulmonary aspiration is "the most widely cited concern associated with the use of single dose activated charcoal". (Juurlink DN, Activated charcoal for acute overdose: a reappraisal. 2015 Br J Clin Pharmacol 81(3): 482-487)

Date:

6/7/2017

Question:

What are the systemic effects that have been attributed to envenomation by the brown recluse spider?

Answer:

The cited reference notes "Envenomation effects vary depending on the amount of venom injected, anatomic location of the bite, the inclusion of gastric contents within the bite, host susceptibility, and concomitant illness." These authors further point out that "Twenty-four to 72 hours after envenomation, a morbilliform rash, fever, chills, nausea, vomiting, malaise, arthralgia, and myalgia may occur. Hemolytic anemia, leukocytosis, and thrombocytopenia are characteristic hematologic abnormalities. Very rarely, disseminated intravascular coagulation occurs." Finally the cited article reports: "Systemic effects are more common in children and may be severe." (Sams HH et al. Nineteen documents cases of *Loxosceles reclusa* envenomation. 2001 J Am Acad Dermatol 44:603-8.)

Date:

6/8/2017

Question:

What is so called "bee venom therapy"?

Answer:

The cited reference notes: "Bee venom therapy (BVT), in which bee venom is used for medicinal purposes, is available worldwide, but is primarily utilized in Asia, Eastern Europe, and South America. The diverse therapeutic applications of BVT include various musculoskeletal conditions, such as arthritis and rheumatism, chronic recalcitrant neuralgia, arthralgia, and immune-related diseases. BVT is also used to de-sensitize patients to bee stings and thus inhibit allergic reactions. (Park JH et al. Risk associated with bee venom therapy: A systematic review and meta-analysis. 2015 PLoS One 10(5): e0126971. doi:10.1371/journal.pone.0126971

Date:

6/9/2017

Question:

The cited reference notes "Acrylonitrile (AN) is an important industrial chemical used in the manufacture of acrylic and modacrylic fibers, resins, plastics, elastomers, adiponitrile, and nitrile rubber for various consumer goods. The primary routes of potential human industrial exposures to AN are inhalation and dermal contact." What are the potential sources for nonindustrial AN exposures?

Answer:

The cited article reports “Potential nonindustrial AN exposures arise from the burning of biomass (eg, wild fires and fuel wood) and as a component of tobacco smoke.” (Marsh GM and Zimmerman SD. Mortality among chemical plant workers exposed to acrylonitrile. 2015 JOEM 57(2): 134-145)

Date:

6/12/2017

Question:

Despite some warnings to the contrary, lithium is often used a treatment for bipolar disorder in females of child bearing age. During the first trimester of pregnancy, maternal use of lithium is associated with an increased risk in which category of fetal malformations?

Answer:

Maternal use of lithium is associated with an increased risk of cardiac malformations, including Ebstein’s anomaly. However, the cited study of more than 1,300,000 pregnancies reported approximately “1 additional case [of cardiac malformations] per 100 live births when there was exposure early in pregnancy and that this association is dose dependent. (Patorno E et al. Lithium use in pregnancy and the risk of cardiac malformations. 2017 NEJM 376(23):2245-2254)

Date:

6/13/2017

Question:

What is favism?

Answer:

The cited reference notes “Reduced concentrations of G6PD render erythrocytes susceptible to hemolysis under oxidative conditions induced by oxidant drugs, infection, or ingestion of fava beans. The latter is known as favism.” These authors also note “Favism is characterized by acute hemolysis, hemoglobinuria, anemia, and jaundice. Headache, nausea, back pain, chills, and fever may be present. Although elevated methemoglobin (metHb) levels have been observed during the hemolytic crisis of favic patients textbooks and recent review articles do not mention symptomatic methemoglobinemia as a clinical feature. (Schuurman M et al. Severe hemolysis and methemoglobinemia following fava beans ingestion in glucose-6-phosphatase dehydrogenase deficiency—case report and literature review. 2009 Eur J Pediatr 168:779-782)

Date:

6/14/2017

Question:

The reference cited below notes “Despite the unusually beneficial effects of clozapine, its use is limited due to potentially severe or even life-threatening adverse effects, including agranulocytosis, hepatitis, ileus, epileptic seizures, and cardiovascular effects.” What are the adverse cardiovascular effects associated with clozapine?

Answer:

The cited reference notes “Among adverse cardiovascular effects, clozapine has been associated with tachycardia (in at least 10 % of clozapine- treated patients), hypertension or hypotension, syncope, and electrocardiographic (ECG) abnormalities (at an incidence of at least 1 %). Other severe adverse cardiac effects include rare but potentially life-threatening early myocarditis and later cardiomyopathy. (Curto M et al. Systematic review of clozapine cardiotoxicity. 2016 Curr Psychiatry Reports 18(7): 68-86)

Date:

6/15/2017

Question:

What is the AIHA?

Answer:

AIHA is the American Industrial Hygiene Association. According to the organization website, “AIHA is a nonprofit organization devoted to achieving and maintaining the highest professional standards for its members. More than half of the nearly 8,500 members are certified industrial hygienists (CIHs), and many hold other professional designations. AIHA administers comprehensive education programs that keep occupational and environmental health and safety (OEHS) professionals current in the field of industrial hygiene. AIHA is one of the largest international associations serving OEHS professionals practicing industrial hygiene and is a resource for those in large corporations, small businesses and who work independently as consultants.” (<https://www.aiha.org/about-aiha/Pages/default.aspx>; accessed May 2017)

Date:

6/16/2017

Question:

What are the unique aspects of norbormide rat poison?

Answer:

According to the cited reference, “Norbormide was introduced in 1964 by McNeil Laboratories Inc., as a toxicant selective for the rat species. Norbormide is a unique vasoactive substance endowed with species and tissue specific, endothelium independent, vasoconstrictor activity that is restricted to the peripheral arteries of rats.” (Bova S et al. Norbormide: a calcium entry blocker with selective vasoconstrictor activity in rat peripheral arteries. 2001 Cardiovascular Drug Reviews 19(3): 226-233)

Date:

6/19/2017

Question:

What are the usual clinical manifestations of hyper-magnesemia?

Answer:

The cited reference points out that the clinical manifestations of hyper-magnesemia are “concentration dependent” and that “They range from mild nausea and vomiting to absence of deep tendon reflexes. At higher levels, paralysis of voluntary muscles can occur. This could result in respiratory compromise by affecting diaphragmatic muscles... Higher levels cause conduction defects and hypotension” (Kala J and Abudayyeh A. Magnesium: An overlooked electrolyte. 2017 J Emerg Med 52(5): 741-743)

Date:

6/20/2017

Question:

Nephrolithiasis is a known complication associated with treatment of HIV using the protease inhibitor indinavir sulfate. What unique factor often makes the diagnosis of nephrolithiasis secondary to Indinavir difficult?

Answer:

The cited reference notes: “The detection of Indinavir [related stones] itself poses another challenge as no single imaging modality proves superior in definitively diagnosing indinavir stones. One study found that no abdominal imaging study is diagnostic, intravenous pyelogram detects less than 8% of indinavir stones, renal ultrasounds demonstrated obstruction in 82% of cases, and CT imaging revealed obstruction with no stones in over 50% of the cases.” (Huynh J et al. Indinavir-induced nephrolithiasis three and one half years after cessation of Indinavir therapy. 2011 Int Urol Nephrol 43:571-573 and Nadler RB, et al. The etiology of urolithiasis in HIV infected patients. 2003 Am Urolog Assoc 169:475–477).

Date:

6/21/2017

Question:

Can buprenorphine be used as an effective modality for the treatment of neonatal abstinence syndrome?

Answer:

A recently published article described a double blind, double dummy clinical trial of 63 infants who were exposed to opioids in utero. The authors of this study reported “The median duration of treatment was significantly shorter with buprenorphine than with morphine (15 days vs. 28 days), as was the median length of hospital stay (21 days vs. 33 days) ($P < 0.001$ for both comparisons). Adjunctive phenobarbital was administered in 5 of 33 infants (15%) in the buprenorphine group and in 7 of 30 infants (23%) in the morphine group ($P = 0.36$). Rates of adverse events were similar in the two groups.” (Kraft WK et al. Buprenorphine for the treatment of the neonatal abstinence syndrome. 2017 NEJM 376(24):2341-2348)

Date:

6/22/2017

Question:

Which anti-arrhythmic drug has been associated with a so-called “pancerebellar syndrome” associated with “nystagmus, dysmetria, titubation, and ataxia of gait and stance”?

Answer:

The cited reference notes: “Amiodarone appears to be associated with cerebellar toxicity. A pan-cerebellar syndrome with nystagmus, dysmetria, titubation, and ataxia of gait and stance occurred. Symptoms tended to resolve gradually over the course of weeks after drug withdrawal. There was a strong dose-dependent effect.” (Van Gaalen J et al. Drug-induced cerebellar ataxia: a systematic review. 2014 CNS Drugs 28:1139-1153)

Date:

6/23/2017

Question:

What is methyl ethyl ketone? By what other name is this chemical known?

Answer:

The cited reference notes: “2-Butanone, also known as methyl ethyl ketone (MEK), is a colorless liquid with a sweet, but sharp odor. 2-Butanone is manufactured in large amounts for use in paints, glues, and other finishes because it rapidly evaporates and will dissolve many substances. It will quickly evaporate into the air. 2-Butanone is often found dissolved in water or as a gas in the air. 2-Butanone is also a natural product made by some trees and is found in some fruits and vegetables. The exhausts of cars and trucks release 2-butanone into the air. 2-Butanone is usually found in the air, water, and soil of landfills and hazardous waste sites.” “Clinical reports and animal studies have clearly shown that exposure to 2-butanone alone causes minimal chronic neurological or hepatic deficits, if any. It does potentiate both the neurotoxicity of n-hexane and methyl-n-butyl ketone and the hepatotoxicity of carbon tetrachloride and chloroform”.

(<https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=343&tid=60>; accessed May 2017)

Date:

6/26/2017

Question:

What percentage of drug-induced cases of torsade de pointes are associated with previously unrecognized long QT syndrome?

Answer:

The cited reference notes “.....previously unrecognized long QT syndrome, of any subtype, can be identified in 5 to 20% of patients with drug induced torsade de pointes.” (Roden DM. Long-QT Syndrome. 2008 NEJM 358:169-176)

Date:

6/27/2017

Question:

What are the mechanisms of action of triptan drugs used in the treatment of migraine headaches?

Answer:

The listed reference states “Triptans are serotonin agonists with high affinity for 5-HT_{1B} and 5-HT_{1D} receptors. Triptans were originally thought to provide relief from migraine by causing cranial vasoconstriction, most likely through action at postsynaptic 5-HT_{1B} receptors on smooth muscle cells of blood vessels. It is now theorized that triptan also block the release of vasoactive peptide from the perivascular trigeminal neurons through their action at presynaptic 5-HT_{1D} receptors on nerve terminals. In addition, triptans bind to presynaptic 5-HT_{1D} receptors in the dorsal horn, and this binding is thought to block the release of neurotransmitters that activate second order neurons ascending to the thalamus. Triptans may also facilitate descending pain inhibitory systems.” (Loder E. Triptan therapy in migraine. 2010 NEJM 363:63-70)

Date:

6/28/2017

Question:

What is lycoperdonosis?

Answer:

The cited reference notes, “Lycoperdon is the genus of fungi to which most puffballs belong”. These authors further note, “Lycoperdonosis is the respiratory disease caused by inhalation of large quantities of spores from the mature mushroom, commonly termed puffball.” (Strand RD et al. Lycoperdonosis, 1967 NEJM 277(2):89-91)

Date:

6/29/2017

Question:

What is the chemical denoted by the formula N₃Na?

Answer:

N₃Na is the chemical formula for sodium azide.

(https://pubchem.ncbi.nlm.nih.gov/compound/sodium_azide#section=RTECS-Number; accessed June 2017)

Date:

6/30/2017

Question:

The co-ingestion of drugs in which class may potentiate the adverse effects of the drug loperamide?

Answer:

According to the cited reference. "Loperamide is actively removed from the central nervous system by p-glycoprotein, a membrane transporter at the blood brain barrier, and therefore ingestion of P-glycoprotein inhibitors (e.g. amiodarone, macrolide antibiotics, ketoconazole, quinidine and verapamil) potentiates euphoria or anti-withdrawal effects." These authors also note "Further potentiation can be achieved with drugs that inhibit hepatic metabolism of the drug." (Bellew S and Barrett TW. Loperamide will stop you up but it can also bring you down. 2017 Ann Emerg Med 69(6):786-791)

Date:

7/3/2017

Question:

The reference cited below notes "Over the past decade, artemisinin-based combination therapies (ACTs) have been deployed as first- and second- line treatments for uncomplicated malaria across malaria-endemic regions. Since 2001, this deployment has included the delivery of over 500 million treatments of artemether-lumefantrine (AL), making it one of the most widely prescribed drugs worldwide". What neurologic toxicity is of most concern in patients receiving ACTs?

Answer:

Neuroauditory toxicity is the neurologic toxicity of most concern in patients receiving ACTs. (Ramos-martin V et al. Review Article: Neuroauditory toxicity of artemisinin combination therapies—Have safety concerns been addressed? 2014 Am J Trop Hyg 91(1):62-73)

Date:

7/4/2017

Question:

Saw palmetto extracts are widely used as self-treatment for a variety of symptoms due to benign prostatic hyperplasia in men. What are the adverse effects associated with the use of saw palmetto?

Answer:

The cited reference reports a randomized trial of 369 men taking various doses of saw palmetto extract over 18 months. The authors report "There were no statistically significant differences between the groups in the rates of serious or non-serious adverse events, changes in vital signs, digital prostate examination findings or study withdrawal rates. Overall, there were no significant intergroup differences in laboratory test abnormalities, while differences in individual laboratory tests were rare and small in magnitude. No evidence of significant

dose-response phenomena was identified. (Avins AL et al. Safety and toxicity of saw palmetto in the CAMUS trial. 2013 J Urol 189:1415-1420)

Date:

7/5/2017

Question:

What are the so-called PAMORA agents?

Answer:

The cited reference notes “Peripherally acting μ -opioid receptor antagonist” agents (PAMORA’s) are newer agents that specifically block the peripheral effects of opioids on μ -opioid receptors in the enteric nervous system to treat OIC (opioid induced constipation). It has been suggested that up to 50% of patients with OIC may benefit from treatment with a PAMORA, however, PAMORA resistant constipation may be found in patients with other etiologies which may include medications, advanced age, immobility or advanced illness. Currently two agents are FDA-approved for the treatment of opioid-induced constipation. Naloxegol (Movantik®) was approved in 2014 for the treatment of opioid-induced constipation in adult patients with chronic non-malignant pain. Methylnaltrexone (Relistor®) was initially approved in 2008 for the treatment of opioid-induced constipation in adult patients with advanced illness who are receiving palliative care, when response to laxative therapy was not sufficient, and expanded in 2014 to include the treatment of opioid-induced constipation in adult patients with chronic, non-malignant pain. The use of PAMORAs are being incorporated within guidelines for management of constipation in patients receiving opioids.” (Frydrych V.

<https://medicaid.utah.gov/pharmacy/ptcommittee/files/Criteria%20Review%20Documents/2015/2015.12%20PAMORA%20Drug%20Class%20Review.pdf>; accessed June 2017)

Date:

7/6/2017

Question:

Polonium-210 was used as a homicidal agent in the well-publicized case of Alexander Litvinenko. Which decay related particle is emitted by Polonium-210 and is responsible for the adverse effects of this isotope?

Answer:

The cited reference notes “Polonium-210 is a naturally occurring radioactive element that was discovered in 1898 by Marie Curie. It decays to stable lead-206 by emitting one alpha particle, with occasional excitation in the nucleus and emission of 803 keV gamma rays.” (Nathwani AC et al. Polonium-210 poisoning: a first-hand account. 2016 The Lancet 388:1075-1080)

Date:

7/7/2017

Question:

What is the risk of future opioid misuse, after high school, in those high school students with legitimate opioid use before high school graduation?

Answer:

The cited reference analyzed data from the Monitoring the Future Study and reports “Legitimate opioid use before high school graduation is independently associated with a 33% increase in the risk of future opioid misuse after high school. This association is concentrated among individuals who have little to no history of drug use and, as well, strong disapproval of illegal drug use at baseline.” These authors concluded “Use of prescribed opioids before the 12th grade is independently associated with future opioid misuse among patients with little drug experience and who disapprove of illegal drug use. Clinic-based education and prevention efforts have substantial potential to reduce future opioid misuse among these individuals, who begin opioid use with strong attitudes against illegal drug use. (Miech R et al. Prescription opioids in adolescence and future opioid misuse. 2015 Pediatrics 136 (5):e1169-e1177)

Date:

7/10/2017

Question:

The combination of 5-hydroxytryptamine (5-HT₃) receptor antagonist and dexamethasone is often recommended for the treatment of vomiting related to cancer chemotherapy. What other common complication occurs in this setting and is most often due to dexamethasone?

Answer:

The cited reference notes “The use of dexamethasone may reduce the delayed symptoms, but this benefit may be balanced by adverse effects, one of which is hiccup. The incidence of hiccups varies from 3% to 61% in cancer patients using dexamethasone based antiemetics for the prophylaxis of cisplatin-induced [as well as other chemotherapy induced] nausea/vomiting.” These authors further comment: “Although the mechanism is not known, it has been proposed that corticosteroids reduce the synaptic transmission threshold in the midbrain and directly stimulate the hiccup reflex arc.” (Liaw CC et al. Cisplatin-Related Hiccups: Male predominance, induction by dexamethasone, and protection against nausea and vomiting. 2005 J Pain Symptom Management. 30(4):359-366)

Date:

7/11/2017

Question:

What are the details of the classification system often used for endoscopic grading of esophageal injury secondary to caustic ingestion?

Answer:

Grade 0: No detectable mucosal change; Grade 1: erythema of mucosa; Grade 2: Erythema, sloughing, ulceration and non-circumferential exudates; Grade 3 Deep mucosal ulceration and circumferential mucosal sloughing; Grade 4 Eschar, full thickness changes and perforation. (Riffat F and Cheng A. Pediatric caustic ingestion: 50 consecutive cases and a review of the literature. 2009 Disease of the Esophagus 22:89-94)

Date:

7/12/2017

Question:

Many commercial mixtures containing which chemicals are known in the U.S. by the trade name Aroclor?

Answer:

Many commercial PCB mixtures are known in the U.S. by the trade name Aroclor. Polychlorinated biphenyls are mixtures of up to 209 individual chlorinated compounds (known as congeners). There are no known natural sources of PCBs. PCBs are either oily liquids or solids that are colorless to light yellow. Some PCBs can exist as a vapor in air. PCBs have no known smell or taste. PCBs have been used as coolants and lubricants in transformers, capacitors, and other electrical equipment because they don't burn easily and are good insulators. The manufacture of PCBs was stopped in the U.S. in 1977 because of evidence they build up in the environment and can cause harmful health effects. Products made before 1977 that may contain PCBs include old fluorescent lighting fixtures and electrical devices containing PCB capacitors, and old microscope and hydraulic oils. (<https://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=26>; accessed June 2017)

Date:

7/13/2017

Question:

The neurotoxicity associated with the chemical n-hexane were first observed in workers in which industry?

Answer:

The cited reference notes: "The neurotoxicity of n-hexane was first observed in the shoe industries of Japan and Italy in the 1960s and early 1970s. A number of epidemiological studies were initiated in response to outbreaks of apparent peripheral neuropathy in shoe workers." These authors go on to point out "One of the first large epidemiological investigations carried out was a case series of 93 cases of peripheral neuropathy in workers exposed to n-hexane from glues and solvents used in sandal manufacture. After several cases of advanced quadriplegia were noted in the Fukaya district, Mie prefecture, Japan, an epidemiological investigation was carried out." (<https://www.atsdr.cdc.gov/toxprofiles/tp113-c2.pdf>; accessed July 2017)

Date:

7/14/2017

Question:

How might intra-operative carbon monoxide exposure occur during general endotracheal anesthesia?

Answer:

The cited reference reports, “Exposure to carbon monoxide during general anesthesia may result from volatile anesthetic degradation by carbon dioxide absorbents and rebreathing of endogenously produced CO. Although adherence to the Anesthesia Patient Safety Foundation guidelines reduces the risk of CO poisoning, patients may still experience subtoxic CO exposure during low-flow anesthesia. The consequences of such exposures are relatively unknown.” (Levy RJ. Anesthesia-related carbon monoxide exposure: Toxicity and potential therapy. 2016 Anesth Analg 123:670-681)

Date:

12:00:00 AM

Question:

The combination of 5-hydroxytryptamine (5-HT₃) receptor antagonist and dexamethasone is often recommended for the treatment of vomiting related to cancer chemotherapy. What other common complication occurs in this setting and is most often due to dexamethasone?

Answer:

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Date:

7/18/2017

Question:

What are the details of the classification system often used for endoscopic grading of esophageal injury secondary to caustic ingestion?

Answer:

Grade 0: No detectable mucosal change; Grade 1: erythema of mucosa; Grade 2: Erythema, sloughing, ulceration and non-circumferential exudates; Grade 3 Deep mucosal ulceration and circumferential mucosal sloughing; Grade 4 Eschar, full thickness changes and perforation. (Riffat F and Cheng A. Pediatric caustic ingestion: 50 consecutive cases and a review of the literature. 2009 Disease of the Esophagus 22:89-94)

Date:

7/19/2017

Question:

Many commercial mixtures containing which chemicals are known in the U.S. by the trade name Aroclor?

Answer:

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Date:

7/20/2017

Question:

The neurotoxicity associated with the chemical n-hexane were first observed in workers in which industry?

Answer:

The cited reference notes: "The neurotoxicity of n-hexane was first observed in the shoe industries of Japan and Italy in the 1960s and early 1970s. A number of epidemiological studies were initiated in response to outbreaks of apparent peripheral neuropathy in shoe workers." These authors go on to point out "One of the first large epidemiological investigations carried out was a case series of 93 cases of peripheral neuropathy in workers exposed to n-hexane from glues and solvents used in sandal manufacture. After several cases of advanced quadriplegia were noted in the Fukaya district, Mie prefecture, Japan, an epidemiological investigation was carried out." (<https://www.atsdr.cdc.gov/toxprofiles/tp113-c2.pdf>; accessed July 2017)

Date:

7/21/2017

Question:

How might intra-operative carbon monoxide exposure occur during general endotracheal anesthesia?

Answer:

The cited reference reports, "Exposure to carbon monoxide during general anesthesia may result from volatile anesthetic degradation by carbon dioxide absorbents and rebreathing of endogenously produced CO. Although adherence to the Anesthesia Patient Safety Foundation guidelines reduces the risk of CO poisoning, patients may still experience subtoxic CO exposure during low-flow anesthesia. The consequences of such exposures are relatively unknown." (Levy RJ. Anesthesia-related carbon monoxide exposure: Toxicity and potential therapy. 2016 Anesth Analg 123:670-681)