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Risk, Toxicology and Human Health

Chapter 11

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Risk

- Risk is the possibility of suffering harm from a hazard that can cause injury, disease, economic loss, or environmental damage
- Probability is used to describe the likeliness of a specific risk occurring within a population
- Risk = exposure x harm
- Probability of having an accident on the way to school = # accidents/# miles traveled
- # miles traveled = all trips X length of trip = all cars that traveled between those two points x miles traveled

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Risk Assessment

- Identifying a real or potential hazard
- Determining the probability of its occurrence
- Assessing the severity of its health, environmental, economic, and social impact

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- **The RAND study, commissioned by the National Institutes of Health and released today, reviewed recent evidence on the risks and benefits of ephedra and ephedrine. The study found limited evidence of an effect of ephedra on short-term weight loss, and minimal evidence of an effect on performance enhancement in certain physical activities. It also concluded that ephedra is associated with higher risks of mild to moderate side effects such as heart palpitations, psychiatric and upper gastrointestinal effects, and symptoms of autonomic hyperactivity such as tremor and insomnia, especially when it is taken with other stimulants. The study reviewed over 16,000 adverse events reported after ephedra use and found about 20 "sentinel events" including heart attack, stroke, and death that occurred in the absence of other contributing factors.**

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Assessing Risk of Taking Ephedra

- **Weight Loss**

1. **What is the evidence for efficacy of ephedra-containing dietary supplement products in weight loss, over a sustained period of time?**
2. **Can efficacy for weight loss be attributed to ephedra alone, or ephedra in combination with other ingredients (e.g., caffeine)?**
3. **Does ephedra have additive effects with other agents?**
4. **What dosage levels of ephedra are necessary to achieve weight loss?**

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- **Athletic Performance**

1. **What is the evidence for efficacy of ephedra-containing dietary supplement products in terms of energy enhancement and enhancement of athletic performance, over a sustained period of time?**
2. **Can efficacy for energy enhancement and enhancement of athletic performance be attributed to ephedra alone, or ephedra in combination with other ingredients (e.g., caffeine) that produce energy enhancement and/or enhancement of athletic performance?**
3. **Does ephedra have additive effects with other agents?**
4. **What dosage levels of ephedra are necessary to achieve energy enhancement and enhancement of**

athletic performance?

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- **Safety Assessment**

1. **Does use of ephedra-containing dietary supplement products over a sustained period of time increase the risk of cardiovascular disease (CVD) or other serious and life-threatening events in specific populations?**
2. **What populations are at risk of CVD and other life-threatening events through use of ephedra over a sustained period of time?**
3. **Can the risk for adverse events in these populations be attributed to ephedra alone, or in combination with other ingredients (e.g., caffeine)?**
4. **Does ephedra have additive effects with other agents?**

8 Safety (cont.)

1. What dosage levels of ephedra produce risk of CVD or other life-threatening events?
2. Do ephedra-containing dietary supplement products alter physiologic markers of cardiovascular function?
3. What are the metabolic actions of ephedra, so as to explain its beneficial and adverse effects?

9 Evidence

- **identified 52 controlled clinical trials of ephedrine or herbal ephedra for weight loss or athletic performance in humans.**
- **FDA reported over 1,000 adverse event reports (AERs) related to herbal ephedra and 125 AERs related to ephedrine.**
- **identified 70 case reports in the literature and received a disk of 15,951 reports containing 18,502 cases from Metabolife, a manufacturer of ephedra products.**

10 Adverse Event Reports Criteria

1. **Documentation of an adverse event that met our selection criteria.**
2. **Documentation that the person having the adverse event took an ephedra-containing supplement or ephedrine within 24 hours prior to the event (for cases of death, myocardial infarction, stroke, or seizure).**
3. **Documentation that alternative explanations for the adverse event were investigated and were excluded with reasonable certainty.**

11 Did ephedra contribute to weight loss?

- Adding caffeine to ephedrine modestly increases the amount of weight loss. There is no evidence that the effect of ephedra-containing dietary supplements with herbs containing caffeine differs from that of ephedrine plus caffeine: Both result in weight loss that is approximately two pounds per month greater than that with placebo, for up to four to six months.

12 Does ephedra improve athletic performance?

- The data support a modest effect of ephedrine plus caffeine on very short-term athletic performance. No studies have assessed the sustained use of ephedrine on performance over time. The only study that assessed the additive effects of these agents reported that ephedrine must be supplemented with caffeine to affect athletic performance.

13 Is ephedra safe for use?

- **The clinical trials enrolled only enough patients to detect a serious adverse event rate of at least 1.0 per 1,000. A causal relationship between ephedra or ephedrine use and these events cannot be assumed or proven.**
- **Evidence from controlled trials was sufficient to conclude that the use of ephedrine and/or the use of ephedra-containing dietary supplements or ephedrine plus caffeine is associated with two to three times the risk of nausea, vomiting, psychiatric symptoms such as anxiety and change in mood, autonomic hyperactivity, and palpitations.**

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- **The majority of case reports are insufficiently documented to make an informed judgment about a relationship between the use of ephedrine or ephedra-containing dietary supplements and the adverse event in question. For prior consumption of ephedra-containing products, we identified two deaths, three myocardial infarctions, nine cerebrovascular accidents, three seizures, and five psychiatric cases as sentinel events; for prior consumption of ephedrine, we identified three deaths, two myocardial infarctions, two cerebrovascular accidents, one seizure, and three psychiatric cases as sentinel events**.

15 Safety (cont)

- We identified 43 additional cases as possible sentinel events with prior ephedra consumption and seven additional cases as possible sentinel events for prior ephedrine consumption. About half the sentinel events occurred in persons aged 30 years or younger. Classification as a sentinel event does not imply a proven cause and effect relationship.

16 Major Types of Hazards

- Cultural hazards: unsafe working conditions, smoking, poor diet, drugs, driving…..
- Chemical hazards: air borne, water, soil, & food
- Physical hazards: ionizing radiation, fire, earthquake, volcanic eruption…
- Biological hazards: pathogens, pollen & other allergens, animals – “dangerous” bees, snakes, bears, …

17 8 Major Causes of Death in US

18 Factors in Environmental Toxicity

- Toxicity measures how harmful a substance is
- Factors related to the toxic agent
- Factors related to exposure
- Factors related to organism

19 Factors related to Toxic Agent

- **Chemical composition and reactivity**
- **Physical characteristics (solubility, state)**
- **Presence of impurities or contaminants**
- **Stability and storage characteristics of toxic agent**
- **Availability of vehicle (solvent) to carry agent**
- **Movement of agent through environment and into cells**

20 ☐ Factors related to Exposure

- **Dose: concentration and volume of exposure**
- **Route, rate, and site of exposure**
- **Duration and frequency of exposure**
- **Time of exposure (time of day, season, year)**

21 ☐ Factors Related to Organism

- **Resistance to uptake, storage, or cell permeability of agent**
- **Ability to metabolize, inactivate, sequester, or eliminate agent**
- **Tendency to activate or alter nontoxic substances so they become toxic**
- **Concurrent infections or physical or chemical stress**
- **Species and genetic characteristics**
- **Nutritional status of subject**
- **Age, sex, body weight, immunological status, and maturity**
- **Response: acute or chronic**

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24 ☐ Bioaccumulation and Biomagnification

- **Bioaccumulation: the selective absorption and storage of a molecule**
- **Biomagnification: toxic burden of a large number of organisms at lower trophic levels is accumulated and concentrated by a predator in a higher trophic level**

25 ☐ Bioaccumulation and Biomagnification

26 ☐ Solubility, Persistence, Chemical Interactions

- **Oil or water soluble (w reference to cell storage and function and env storage)**
- **Persistence: how long molecule remains intact (DDT doesn't degrade rapidly; some herbicides do)**
- **Additive: sum is greater than individual parts**
- **Antagonistic: interfere w effects or stimulate breakdown of another chemical**
- **Synergistic: one substance exacerbates the effects of another**
- **(asbestos increases lung cancer rates 20x' if also smoke, 400x increase in lung cancer)**

27 ☐ Minimizing Toxic Effects, Metabolic degradation and Excretion

- **Dose and length of time: 100 cups coffee, 100 aspirin, 22 lbs. spinach are all lethal doses, but not over a lifetime**
- **Enzymes in liver (doesn't always detox), breathe out CO_2, HCN, & ketones, salts in sweat, kidneys, some in feces**
- **Tissues w high cell-replacement rates are more likely to develop cancers**

28 ☐ The dose makes the poison. Paracelus

- **What is safe? Do you choose most sensitive person? "normal" sensitivity?**
- **Organic/natural vs synthetic: moot**
- **LD50 lethal dose for 50% of population**
- **Poison lethal for 50% of population at 50 mg/kg**

- **Toxicity varies As is poison; 50 mg/kg lethal; lower chronic doses are also lethal but response time is different**

29 Hypothetical Dose Response Curve

30 Determining Toxicity

- Case reports: physician reports; adverse effects, accidental poisonings, drug od, homicides, suicide attempts…..
- Epidemiological studies: comparison of groups exposed to possible harmful agent and a similar population not exposed to agent
- In both sources, too few people have been exposed to high enough levels of agents to detect differences, hard to isolate effect of agent from others exposed to in lifetime, new chemicals or technologies not around long enough to be tested

31 Laboratory Testing

- Modeling (PETA pleasers) based on past animal studies; can use bacteria (prokaryotes, we're eukaryotes); cell/tissue cultures; chicken egg membranes; animal studies; human studies
- Animal: matched genetically, exposed to same conditions; use high dosages to reduce the number of test animals required and obtain results quickly
- Costs $2million/substance and takes 2-5 years
- High dose extrapolated to low dose and low dose to humans

32 Dose Response Models

- Nonthreshold dose-response models assume that any amount of substance will be harmful; more is more harmful (carcinogens, teratogens)
- Threshold dose-response models establish a threshold up to which there is no observable harmful effect and after which more is more harmful (up to response, body compensates)

33 Dose Response Models

34 Chemical Hazards

- Toxic chemicals: substances at LD50 (at given concentrations???)
- Hazardous chemicals: flammable or explosive, irritating or damaging to tissues, asphyxiants, or allergens
- Mutagens: cause random mutations in DNA; autonomic or germ cell mutations
- Teratogens: cause birth defects to embryo-PCBs, thalidomide, steroids
- Carcinogens: cause or promote growth of malignant tumors

35 Factors contributing to development of cancer

- Cigarette smoke 30-40% of cancers
- Diet 20-30%
- Occupational exposure 5-15%
- Environmental pollutants 1-10%
- Inherited genetic factors and some viruses 10-20%
- 10-40 years elapse between exposure and development of cancer

36 Effects of Chemical, Physical, and Biological Agents on an Organism

- Chromosomal damage at the molecular level
- Tissue irritations or damage
- Organs
- Systems: immune, nervous, or endocrine

37 Compromising Immune System

- Agents that can affect immune system: viruses (HIV), ionizing radiation, malnutrition, synthetic chemicals
- With compromised immune system, body vulnerable to allergens, infectious bacteria, viruses, fungi, and protozoans

38 Chemicals that Effect Nervous System

- Neurotoxins: chlorinated hydrocarbons (DT, PCBs, dioxins),
- Organophosphate pesticides
- Formaldehyde
- Various compounds of arsenic, mercury, lead, and cadmium
- Industrial solvents tricholorethylene (TCE), toluene, and xylene

39 Effects on Endocrine System

- Hormones regulate growth and development and to some extent behavior
- Some pesticides and synthetic chemicals have shapes similar to natural hormones and disrupt the endocrine system if they occupy receptor sites:HAA hormonally active agents
- Synthetic hormones are fat soluble and may biomagnify
- Precautionary principle: great scientific uncertainty and a reasonable suspicion of harm

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41 Precautionary Approach

- Prevent pollution
- Few chemicals have or will be tested for toxicity or mutagenic capability
- The cost would be prohibitive and the time would be lengthy, to the point of being moot (exposure and interactions over a life time of individuals)

42 Transmissible and Nontransmissible Diseases

- Nontransmissible diseases: not caused by living organism and cannot spread from one affected organism to another organism (some genetic disorders, cardiovascular disease, cancers, diabetes, asthma, emphysema, malnutrition)
- Transmissible diseases: caused by pathogen in host organism which may be spread to other organisms

43 Pathogens

- Bacteria, fungi, viruses, protozoans
- Infectious diseases cause 25% of all deaths globally (mostly in undeveloped countries)
- 7 deadliest diseases: acute respiratory infections, acquired immune deficiency syndrome, diarrheal diseases, tuberculosis, malaria, hepatitis B, and measles

44 Epidemiological Transition

- When countries move from undeveloped to developed status, the main causes of death move from transmissible to nontransmissible diseases

45 Viral Diseases

- Influenza, Ebola, West Nile virus, rabies, AIDS
- Mutate w or ahead of host organism
- Vaccinations target specific viruses, but the viruses mutate ahead of vaccine development and production – influenza vaccines effective for that strain
- Viruses can mutate and move to new host organisms (bird flu to humans)
- Some vaccines highly effective: smallpox, polio, rabies, measles, hepatitis B

46 Bacterial Diseases

- Stapholoccocus, sepsis, strepoloccocus, tuberculosis
- Transformation, transduction, & conjugation all ways of bacterial mutation
- Easily outpace antibiotics and host immune systems
- Just as easily prevented – washing and not sharing food and drink

47 STD:sexually transmitted diseases

- 23% of Americans have an STD
- Some are gifts that keep giving: AIDS, Herpes
- Old timers, syphilis, gonorrhea, Clamidia still around and itching
- May cause sterility, cancers, death
- AIDS 40 million people have HIV; decimating African populations 20% of adults have HIV

48 Distribution of AIDS Globally

49 AIDS Interactions

50 Infectious Disease Transmission Facilitated by Global Change

- Globalization
- Migration to urban areas
- Deforestation and migration into new areas
- Hunger and malnutrition
- Increased rice cultivation (water breeding insects)
- Global warming
- High winds/hurricanes and flooding
- Accidental introduction of insect vectors
- bioterrorism

51 ☐ Global Tuberculosis Epidemic

- Under reported; highly infectious; 1 in 3 infected
- Screening best prevention
- Drug resistant forms due to incomplete treatment
- Urbanization, poverty and AIDS contributing factors to spread of TB

52 ☐ Global Occurrence of Tuberculosis

53 ☐ Malaria

- Caused by protozoan Plasmodium transmitted by mosquitoes
- Mosquitoes bite infected person then transmit through biting another person
- Symptoms: fever/chills, anemia, enlarged spleen, severe abdominal pain/ headaches, extreme weakness, compromised immune system
- From Anopheles into bloodstream to liver, multiply, move into bloodstream continue to multiply
- DDT in 1950s and 60s reduced; mosquitoes resistant to DDT, malaria back

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55 ☐ Global Incidence of Malaria

56 ☐ Preventing Malaria

- Get rid of standing water: move the water, soak up the water
- Mosquito nets in windows and doors
- Cultivate mosquito feeding fish
- Increased health (vit A and zinc)
- education

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59 ☐ Risk Analysis

- Identifying hazards and evaluating associated risks (assessment)
- Ranking risks (comparative risk analysis)
- Determining options and making decisions about reducing / eliminating risks
- Informing decision makers and the public about risks (risk communication)

60 ☐ High Risk Health Problems

Scientists Citizens

1 ☐

- Indoor air pollution
- Outdoor air pollution
- Worker exposure to chemicals
- Pollutants in drinking water
- Pesticide residues on food
- Toxic chemicals in consumer products

- Global climate change
- Stratospheric ozone depletion
- Wildlife habitat alter/destruct
- Species extinction/ loss biodiversity

2
- Hazardous waste sites
- Industrial water pollution
- Occupational exposure to chemical
- Oil spills
- Stratospheric ozone depletion
- Nuclear power plant accidents
- Industrial accidents w pollutants
- Radioactive wastes
- Air pollution from factories
- Leaking underground tanks

61 ☐ Medium Risk Ecological Problems

Scientists Citizens

1
- Acid deposition
- Pesticides
- Airborne toxic chemicals
- Toxic chemicals, nutrients, and sediment in surface waters

2
- Coastal water contamination
- Solid waste and litter
- Pesticide risks to farm workers
- Water pollution from sewage plants

62 ☐ Low Risk Ecological Problems

Scientists Citizens

1
- Oil spills
- Groundwater pollution
- Radioactive isotopes
- Acid runoff to surface waters
- Thermal pollution

2
- Air pollution from vehicles
- Pesticide residues in foods
- Global climate change
- Drinking water contamination

63 ☐ Risk Reduction

- Not smoke
- Avoid excess sunlight
- Not drink or not more than 2/day
- Reduce consumption of cholesterol and sat fats
- Eat variety fruits/veg
- Exercise regularly
- Lose excess weight
- Drive safely in safe vehicle

64 ☐

65 ☐ Technical Reliability

- System reliability (%) =
- technology reliability x human reliability
- Humans err
- Chernobyl; Challenger; Love Canal; 3 mile island

66 ☐

67 ☐ Limitations of Risk Analysis

- Quality of data/ models
- Short term vs long term risks
- Who profits
- Acceptable risk or least damage
- Who should do risk analysis
- Who profits
- Cumulative effects of various risks together or individually assessed
- How widespread; what is acceptable
- Workers vs general public

68 ☐ Perception, Reporting, and Assessment of Risks

- Motorcycling 1:50 die
- Smoking 1:300 by age 65
- Hang gliding 1:1250
- Driving 1:3000 no seatbelt 1:6000 w seatbelt
- Airplane crash 1:1 million
- Lightning: 1:4 million
- Train crash 1:20 million
- Snakebite 1:36 million
- Shark attack 1:300 million
- Trichloroethylene in drinking water 1: 2 billion

69 ☐ Perception of Risks on Personal Level

- Familiar vs unfamiliar
- Voluntary vs involuntary
- Publicity
- Unfair distribution- NIMBY not in my backyard
- Lack of information or involvement in decision making
- No alternatives pursued