TOXICOLOGICAL CHEMISTRY OF CHEMICALS

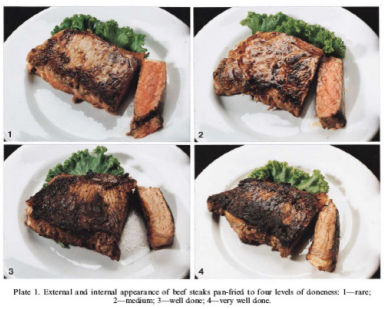


Plate 1. External and internal appearance of beef steaks pan-fried to four levels of doneness: 1—rare; 2—medium; 3—well done; 4—very well done.

Chapters 22-23, Manahan

The dangers of BBQ. Image available at
http://www.inklingmagazine.com/inkycircus/C29/29/P10/

1

Terminologies

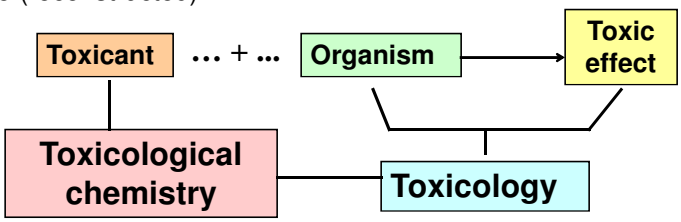
Toxicology (Chapter 22)

- The study of toxic substances or poisons

Toxicological chemistry (Chapter 23)

- Deals with the chemical nature and reactions of toxic substances

Figure 22.5 (reconstructed)



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Classification of exposures to toxicants

1) **Acute local** exposure
   - ❖ Brief exposure (sec to few hrs) that affects the exposed area (e.g. skin, eyes)

2) **Chronic local** exposure
   - ❖ Affects the same parts of the body as acute local exposure but the time span is longer (up to several yrs)

3) **Acute systemic** exposure
   - ❖ Brief exposure to toxicants that can enter the body (e.g. by inhalation) and affect organs that are remote from the entry site (e.g. the liver)

4) **Chronic systemic** exposure
   - ❖ Exposure occurs over a prolonged period; also affects organs remote from the entry site

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Major sites and routes of exposure

Major routes of accidental exposure by humans and other animals

- ➢ **Percutaneous (skin)**
  - ❖ Most likely for liquids, solutes in solution, and semisolids
- ➢ **Inhalation, respiration, pulmonary (lungs)**
  - ❖ Most likely for gases and very fine, respirable solids or liquids
- ➢ **Oral**
  - ❖ Most likely for solids

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Major sites and routes of exposure

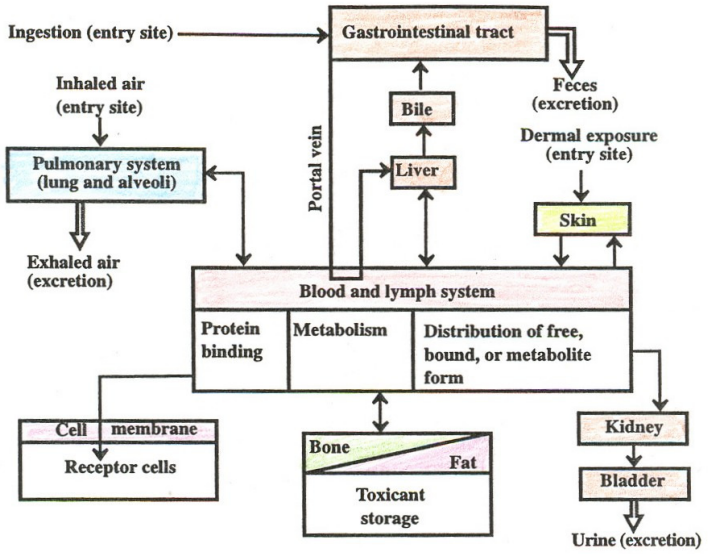

Figure 22.1. Major sites of exposure, metabolism, and storage, routes of distribution and elimination of toxic substances in the body.

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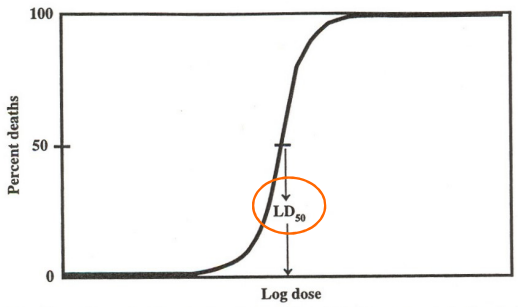
Dose-Response Relationships (Fig. 22.2)

Dose is the amount of toxicant to which an organism is exposed

→ Usually per unit body mass

Response is the effect of a toxicant to an organism



LD_{50} = dose that would kill 50% of the subjects

Figure 22.2. Illustration of a dose-response curve in which the response is the death of the organism. The cumulative percentage of deaths of organisms is plotted on the Y axis.

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Toxicity Ratings (Table 22.1, Modified)

Toxicity Rating	Approx. LD_{50}*	Ex. Substance
Supertoxic	< 5 mg/Kg	TCDD (Dioxin); Botulinus toxin
Extremely toxic	5 to 50 mg/Kg	TEPP+
Very toxic	50 to 500 mg/Kg	Parathion (pesticide)
Moderately toxic	500 to 5000 mg/Kg	Chlordane; Heptachlor
Slightly toxic	5000 to 15,000 mg/Kg	Ethanol
Practically nontoxic	> 15,000 mg/Kg	DEHP (a phthalate)

* Estimated lethal dose for humans in mg toxicant per Kg of body mass

+ Tetraethylpyrophosphate, a pesticide

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Chronic Responses to Toxicants

Teratogenesis (birth defects)

- Usually due to damage to embryotic or fetal cells

Mutagenesis (alteration of DNA to produce inheritable traits)

- Often cause birth defects as well

Carcinogenesis (uncontrolled replication and growth of the body's own [somatic] cells)

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Chronic Response to Toxicants (Cont.)

History of chemical carcinogenesis

1775 High incidence of **cancer of the scrotum** among chimney sweeps in London

- Exposure to soot and tar from the burning of coal
- Poor hygiene was key factor

~ 1900 Elevated incidence of **bladder cancer in dye workers** in Germany

- Exposure to chemicals extracted from tar; 2-naphthylamine

1915 & 1939 Observation of cancer from tobacco juice and smoke, resp.

1929 Observation of cancer from painting luminescent watch dials (oral exposure to radium)

1960 Observation of cancer from asbestos exposure

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Responses to Toxicants (Cont.)

Immune system response

Immune system acts as the body's natural defense against:

- **Xenobiotic** chemicals (foreign to a living organism)

  Ex. Infectious viruses or bacteria

- **Neoplastic cells** (rapidly proliferating; may give rise to cancerous cells)

1) **Immunosupression** = impairment of the body's natural defense mechanisms

2) Loss of ability to control **cell proliferation**
   - Results to leukemia or lymphoma

3) **Allergy** or **hypersensitivity**
   - Results from the immune system's overreaction to xenobiotic substances in a self-destructive manner

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ATSDR's Toxicological Profiles

Agency for Toxic Substances and Disease Registry

- Under the U.S. Dept. Health and Human Services
- A very useful source of information about the toxicological chemistry of various toxicants
- Table 23.1, p. 722

Below is a partial list

Table 23.1. Materials Listed by ATSDR[1]

Acetone	1,2-Dibromoethane	Naphthalene
Acrolein	1,4-Dichlorobenzene	Nickel
Acrylonitrile	3,3'-Dichlorobenzidine	Nitrobenzene
Aldrin/Dieldrin	1,1-Dichloroethane	2-Nitrophenol/ 4-Nitrophenol
Alpha-,Beta-,Gamma- and Delta-Hexachloro-cyclohexane	1,2-Dichloroethane	Otto Fuels
	1,1-Dichloroethene	Pentachlorophenol
	1,2-Dichloroethene	Phenol
Aluminum	1,3-Dichloropropene	Plutonium
Ammonia	Diethyl Phthalate	Polybrominated Biphenyls
Arsenic	1,3-Dinitrobenzene/ 1,3,5-Trinitrobenzene	
Asbestos	Dinitrocresols	Polychlorinated Biphenyls
Automotive Gasoline	Dinitrophenols	
Barium	2,4-Dinitrotoluene/ 2,6-Dinitrotoluene	Polycyclic Aromatic Hydrocarbons (PAH's)
Benzene		
Benzidine	1,2-Diphenylhydrazine	Radon
Beryllium	Disulfoton	RDX
Bis(2-Chloroethyl) Ether	Endosulfan	Selenium
Boron	Endrin	Silver
Bromomethane	Ethylbenzene	Stoddard Solvent
1,3-Butadiene	Ethylene Glycol and Propylene Glycol	1,1,2,2-Tetrachloroethane
2-Butanone		Tetrachloroethylene
Cadmium		

Toxic Elements and Elemental Forms (Ch. 23)

Heavy metals

- Metallic elements that have relatively high density
- Mercury, lead, cadmium and arsenic (a semimetal) present the greatest environmental hazard - WHY?
  - Extensively used
  - Toxic
  - Widely distributed
- Ultimate sink for heavy metals are soils and sediments

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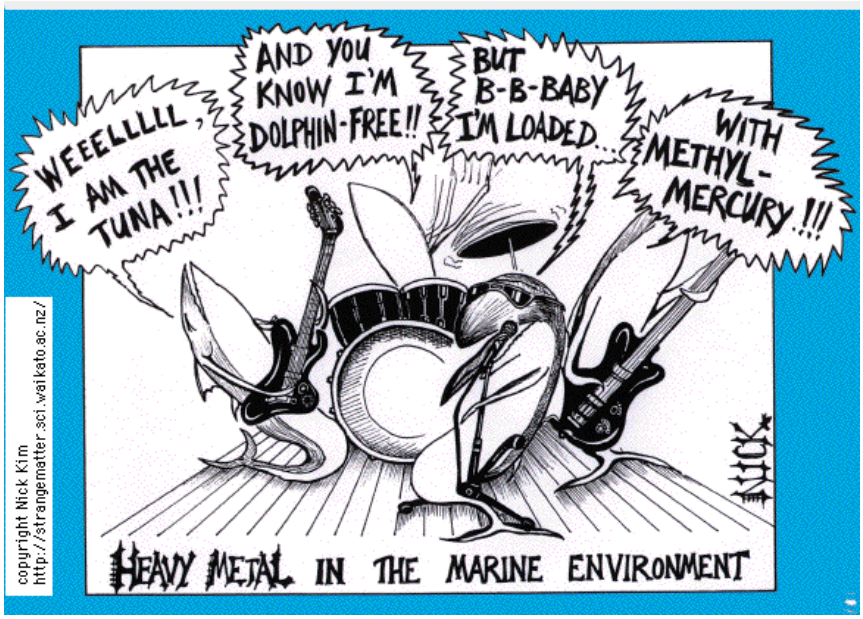

http://www.webelements.com

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Toxic Elements (Cont.)

Toxicity of the heavy metals

- Of the 4 heavy metals, only Hg is highly toxic in elemental form
  - Inhalation of Hg vapor from its liquid form
- All 4 are ***dangerous in the form***:
  - of their **cations** (e.g. from soluble forms of their compounds)
  - bonded to short chains of carbon atoms (i.e. **organometallic** form)

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Toxic Elements (Cont.)

Mechanism of their toxicity

- A result of the strong affinity of metal cations for sulfur
  - ***Sulfhydryl groups***, - **S-H**, in many enzymes easily react with ingested heavy metal cations
  - Can deactivate the enzyme => affects metabolic processes

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Toxic Elements (Cont.)

Drill: Write the balanced chemical reactions that correspond to the reaction of an Hg^{2+} ion (a) with H_2S and (b) with R-SH to produce hydrogen ions and an organometallic product.

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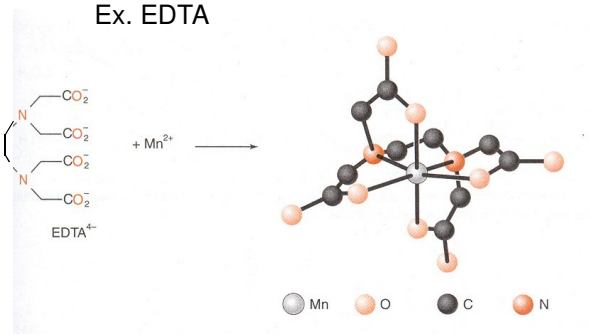
Toxic Elements (Cont.)

Treatment of heavy metal poisoning

Chelation therapy

- Utilizes a chelating agent that binds strongly to the metal cation

Ex. EDTA



13-1 Metal-Chelate Complexes 259

Figure 13-1 EDTA forms strong 1:1 complexes with most metal ions, binding through four oxygen and two nitrogen atoms. The six-coordinate geometry of Mn^{2+}-EDTA found in the compound $KMnEDTA \cdot 2H_2O$ was deduced from X-ray crystallography. [J. Stein, J. P. Fackler, Jr., G. J. McClune, J. A. Fee, and L. T. Chan, "Reactions of Mn-EDTA and MnCyDTA Complexes with O_2^-. X-Ray Structure of $KMnEDTA \cdot 2H_2O$," *Inorg. Chem.* **1979,** *18,* 3511.

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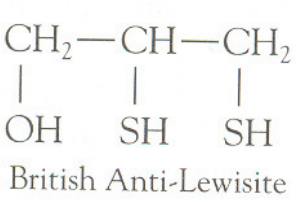
Source: Harris (6th ed., p. 259)

Toxic Elements (Cont.)

Treatment of heavy metal poisoning (Cont.)

Medicinal treatment

- Administers a compound that binds to the metal more strongly than does the enzyme. Ex. BAL



British Anti-Lewisite

Source: Baird, p. 383

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Toxic heavy metals (Cont.)

1) Mercury

Mode of entry:

- Elemental Hg through inhalation
- Carried by the bloodstream to the brain

Effect:

- Hg disrupts metabolic processes in the brain (i.e. a *neurotoxin*), causing:
  - Tremor
  - Psychopathological symptoms: *insomnia, depression, irritability*
- Hg^{2+} (from Hg compounds) damages the kidney

NOTE: Organomercury compounds are the most toxic form of Hg

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Mercury is the only common metal liquid at ordinary temperatures. Mercury is sometimes called ***quicksilver***. It rarely occurs free in nature and is found mainly in cinnabar ore (HgS) in Spain and Italy. It is a heavy, silvery-white liquid metal. It alloys easily with many metals, such as gold, silver, and tin. These alloys are called amalgams. Its ease in amalgamating with gold is made use of in the recovery of gold from its ores.

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http://www.webelements.com

Toxic heavy metals (Cont.)

Mercury (Cont.)

Uses:

- Elemental mercury in thermometers and barometers
- Gaseous Hg is used in fluorescent light bulbs and advertising signs
- Mercury is also the basis of dental amalgams and preparations

Sources of Hg contamination:

- Burning of coal and fuel oil (electric utilities; other industries)

  Contains low levels of Hg
- Incineration of municipal waste that contain Hg

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INCIDENTS: SAN JUAN, CHOROPAMA AND MAGDALENA, PERU - MERCURY SPILL OF 2 JUNE 2000

On 2 June, 151 kilograms of liquid mercury was spilled from a truck delivering mercury mined as a by-product of gold at Yanacocha, to a warehouse in Lima, to be sold to a vendor. The mercury was spilled along the main highway from Cajamarca to the coast, including in the communities of San Juan, Choropampa, and Magdalena. Almost 300 people were found to have suffered some degree of mercury poisoning. Minera Yanacocha is owned by Newmont Mining Corporation of Denver, Colorado; Minera Buenaventura of Peru, and the International Finance Corporation (IFC). It is the largest gold mine in Latin America in the province of Cajamarca in Northern Peru.

http://www.mineralresourcesforum.org/incidents/Cajamarca/

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Toxic Heavy Metals (Cont.)

2) Lead

- Only a problem in soluble form, **Pb^{2+}** (or the less stable Pb^{4+})

Mode of entry:

- Ingestion of Pb^{2+} contaminated water and food

Effects:

- Pb^{2+} can inhibit the synthesis of hemoglobin
- Adverse effect on the central and peripheral nervous systems and the kidneys
- Interferes with the normal development of children's brains
  - Behavioral effects, including lack of attentiveness
  - Possibly low IQ

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Lead (Cont.)

http://www.espimetals.com/

Lead is a bluish-white lustrous metal. It is very soft, highly malleable, ductile, and a relatively poor conductor of electricity. Alloys include pewter and solder. Tetraethyl lead ($PbEt_4$) is still used in some grades of petrol (gasoline) but is being phased out on environmental grounds.

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Lead (Cont.)

Uses:

- Pb metal and its oxide are used in storage batteries, cable covers, plumbing, ammunition (lead shots)
- Used extensively in paints (yellow $PbCrO_4$)
  - Pre-1978 homes used lead-based paints
- Solder
- Historical: Pb was used by the Romans for plumbing (Some historians hypothesize that the decline of the Roman empire is attributed to lead in wine [from Pb-coated containers] and the water supply!)

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Lead (Cont.)

Sources of Pb contamination in the environment:

- Vehicle emissions (in many countries)
  The U.S., Canada and Europe use unleaded gasoline
- Leaching from landfills (discarded batteries and other Pb-containing products)

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Toxic Elements (Cont.)

3. Cadmium

Cadmium is a soft, bluish-white metal and is easily cut with a knife. It is similar in many respects to zinc. Cadmium and its compounds are highly toxic.

Image available at www.webelements.com

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Cadmium (Cont.)

Mode of entry:

- Mostly through ingestion of contaminated food (as Cd^{2+})
  - Highest levels in seafood and organ meats

Effects:

- Cd is acutely toxic (lethal dose ~ 1 g)
  - Low levels of Cd (as Cd^{2+}) is complexed by a sulfur-rich protein and is eliminated by urination
- Kidney disease may result from chronic exposure to high levels of Cd
  - Excess Cd (not complexed by proteins) is stored in the liver and kidneys

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Cadmium (Cont.)

Uses:

- Rechargeable batteries (Nicad)
- Cd compounds used as a pigment
  - CdS and CdSe color plastics

Also used in paints*

Also used in TV screens

* Van Gogh's "Sunflower" was painted with CdS pigment (Baird, C. "Environmental Chemistry, 2nd ed.)

Sources environmental contamination:

- Metal smelters (In nature Cd occurs with Zn, Pb and Cu)
- Coal burning
- Incineration of waste that contains Cd - plastics, batteries, etc.

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Toxic Elements (Cont.)

4) Arsenic

Historical perspective:

- Arsenic compounds (e.g. As_2O_3) used in murder and suicide from Roman times to Middle Ages

Elemental arsenic occurs in two solid modifications: **yellow**, and grey or **metallic**. The element is a steel grey, very brittle, crystalline, semimetallic solid. It tarnishes in air, and when heated rapidly oxidises to ***arsenous oxide*** which has a garlic odour. Arsenic and its compounds are **poisonous** as any reader of "who-done-it" books knows.

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Arsenic (Cont.)

Mode of entry:

- Mostly through ingestion of contaminated water
- As_2O_3 can be absorbed through the lungs and intestines

Effects:

- A known **carcinogen**
- Acute dose can be lethal
  - Causes gastrointestinal damage – severe *vomiting*; *diarrhea*
- Coagulates proteins and complexes with coenzymes
- Inhibits production of ATP

Note: As (III) is more toxic than As (V) – presumably due to stronger binding with S-containing proteins

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Arsenic (Cont.)

Uses:

- Pesticides (compounds of As) – prior to use of organic pesticides
- Hardening and improving the sphericity of shots
- Doping agent in solid-state devices such as transistors

Sources of environmental contamination:

- From the continued use of its compounds as pesticide
- Unintended release during mining and smelting of gold, copper and other metals
- Leaching from gold mines

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Toxic Inorganic Compounds

Gases:

- Carbon monoxide, CO
- Sulfur dioxide, SO_2
- Nitrogen oxides, NO_x ($x = 1, 2$)
- Hydrogen halides, HX (X = F or Cl)
- Hydrogen cyanide, HCN
- Hydrogen sulfide, H_2S

Solids:

- Silica and silicate materials (**asbestos**)
- Cyanide salts

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Toxic Inorganic Compounds – *Cont.*

1) Carbon monoxide, CO

Major source: Incomplete combustion of carbon-containing fuel

Effects of exposure:

- Binds strongly to hemoglobin, thus preventing it from carrying O_2 to body tissues
- Symptoms of exposure varies depending on level of exposure

ppm CO	Symptoms
100 ppm	Dizziness, headache, weariness
250 ppm	Loss of consciousness
1000 ppm	Death

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Toxic Inorganic Compounds – *Cont.*

2) Sulfur dioxide, SO_2, and 3) Nitrogen oxides, NO_x

Major sources:

- **NO_x**: Burning of fuel at very high T (e.g. in the internal combustion engine)
- **SO_2**: Burning of coal

Effects of exposure:

- Irritates the respiratory tract, skin, eyes and mucous membranes. *WHY?*
- Both dissolve in water to produce acids (SO_2 -> sulfuric; NO_x -> nitric)
  - Same reason why they cause ***acid rain***

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Toxic Inorganic Compounds – *Cont.*

4) Hydrogen halides, HF and HCl

Uses of HF: Fabrication of electronic components; Etching glass; Manufacture of semiconductors

Effects of exposure to HF: Extreme irritation of exposed area, causing ulcers in affected areas of the upper respiratory tract

- Also causes lesions that heal poorly upon contact

Uses of HCl: Manufacture of phosphoric acid, ammonium chloride, fertilizers, dyes, and artificial silk and pigments for paints; Used as a lab reagent, and as a metal treating agent

Effects of exposure to HCl: HCl is less toxic than HF

- Causes spasms of the larynx
- High levels cause pulmonary edema or even death

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Toxic Inorganic Compounds – *Cont.*

5) Hydrogen cyanide, HCN

Uses: HCN is used as a fumigant insecticide and as rodenticide

Effects of exposure:

- A rapidly acting poison (also its cyanide salts)
  - Binds strongly to Fe^{3+} in the enzyme ferricytochrome oxidase
  - Prevents utilization of O_2 in cells, thus stopping metabolic processes

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Toxic Inorganic Compounds – *Cont.*

6) Hydrogen sulfide, H_2S (Rotten egg smell)

Uses:

- Production of sulfur (one of the most commercially important elements)

Occurrence:

- H_2S occurs naturally in crude petroleum, natural gas, volcanic gases, and hot springs

Effects of exposure:

- Very toxic; Kills faster than HCN
- Deadly level: 1000 ppm (due to asphyxiation from respiratory system paralysis)

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