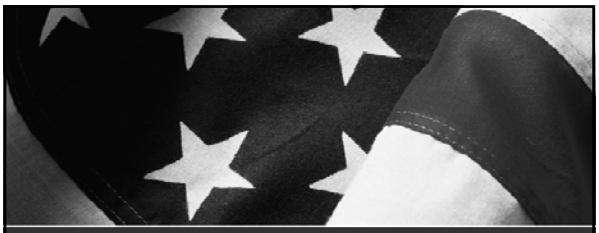


Chemical Agents of Opportunity for Terrorism: TICs & TIMs

Section 12
Terrorism by Fear and Uncertainty:
Delayed Toxic Syndromes

Training Support Package

Learning Objectives

- Recognize that exposure to some chemical agents results in delayed onset of symptoms.
- Describe chemical agents that may cause delayed toxic syndromes.
- Describe toxidromes caused by chemicals with delayed-onset syndromes

Anticipating the Unthinkable: Delayed Toxic Syndromes

- Choice of a toxin with delayed onset?
  - Allows time to escape
    - Complicates diagnosis and response
  - Potential for a large number of victims
  - May overwhelm health care system / "medically unexplainable symptoms"
  - Good at inducing terror
- Delayed onset may mimic some biological agents
  - Anthrax, smallpox

Thallium salts

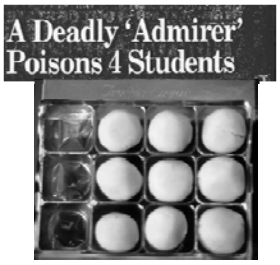
- Qualities for unintentional and malicious use
  - Tasteless and odorless
  - Salts are water-soluble
  - Rapidly absorbed (oral, inhalation, dermal)
  - Not detected on routine toxicological screening
  - Highly toxic and easily concealable
  - Lethal dose ~10-20 mg/kg (about 1 gram in an adult)
  - Inexpensive (~$1-2 per gram)

Thallium Poisoning

- Classic Triad:
  - Gastrointestinal distress (N/ V/ D) within a few hours, mild
  - Painful polyneuropathy (severe pain in the extremities)
    - About 24 hours after exposure, dose dependent
  - Hair loss; usually 2(+) weeks after exposure
  - Other: constipation, hypertension, EKG changes
- Diagnostic testing
  - Abdominal x-rays may show metal
  - Blood thallium > 100 µg/L, urine thallium greater than 200 µg/L considered toxic

Thallium-Tainted Marzipan

- Four young adults in NYC share premium marzipan candies recieved by mail from an “unknown admirer”
- The next day they developed diarrhea, vomiting, abdominal cramps and constipation



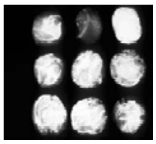
J Toxicol Clin Toxicol. 1994;32:723-30.

Thallium-Tainted Marzipan (cont.)

- After 2 days the two who ate most (a whole candy each) developed pain in the palms and soles worse with touch
  - Hypertension in and EKG changes in two
  - Three of 4 developed alopecia (hair loss)

Thallium Poisoning

- X-rays of the candies showed abnormal radioopacity
- Lethal dose of thallium in each candy
  - Lab confirmed that each candy contained 810 to 1090 mg thallium




Arrest in Tainted-Candy Mystery

Jilted admirer, Filip Semey, arrested in Belgium

Malicious Thallium Poisoning
Other cases

- 1971: Graham Frederick Young kills two co-workers
  - Liked to poison people
- 1988: George Trepal kills Peggy Carr
  - Tainted Coca-Cola; 7 others poisoned, 2 became ill
  - Kids playing loud music, and dogs chasing his cats
- 1988 and 1995: Iraqi dissidents poisoned
  - 1988: Abdullah Rahim Sharif Ali killed
  - 1995: Maj Safa al-Battat; presumably recovered
- 1997: Kurds poisoned by Iranian agents
  - 60 sickened; presence of thallium confirmed

Poisoned Mother, Daughter Leave Hospital

Monday, March 19, 2007

LOS ANGELES — Two American women poisoned by thallium during a trip to Russia left the hospital Monday.

Dr. Marina Kovalevsky, 49, and her daughter, Yana, 26, were discharged from Cedars-Sinai Medical Center after their thallium levels decreased with treatment, their doctor, Shrinath Barathan, said in a statement.

"Both Dr. Kovalevsky and her daughter have improved, but continue to exhibit symptoms, which will be managed at home," Barathan said.

The women became ill late last month and were hospitalized in Moscow before being flown home. Tests later confirmed they were poisoned by thallium, but they believe it was accidental.

It was not immediately clear how they came into contact with thallium. The powdered or crystallized form is said to be a tool of choice for Russian assassins but has many everyday

www.foxnews.com/

Treatment

- Multi-dose activated charcoal
  - Prevents absorption
  - Enterohepatic circulation
- Prussian Blue (Radiogardase)
  - Prevents absorption from GI tract
  - Undefined efficacy
- Unclear role for chelators once thallium is absorbed

Three forms of Mercury

Elemental (Hg^0; quicksilver)	Liquid: essentially nontoxic by ingestion Vapor: brain and lung toxicity
Inorganic salt (Hg^{2+})	Typically rapid onset of GI effects when ingested
Organic (Methyl-Hg)	Aryl (cyclic): behave like inorganic Alkyl (short-chain): methylmercury, ethylmercury, dimethylmercury

Organomercurials

- Uses:
  - Bactericidal, fungicides, paper manufacture, laboratory standard
- Generally well absorbed by all routes

Dimethymercury
Properties

- Colorless, dense, volatile liquid
- Readily absorbed through the skin
- Rapidly penetrates latex gloves
- Lethal dose approx 400 mg (5 mg/kg)
- 10 grams = $183.80


14 The Dartmouth Wednesday, June 11, 1997

Chemist dies after toxin penetrates gloves

CHEMIST KAREN E. WETTERHAHN was accidentally poisoned by her own lab.

Dimethylmercury Toxicity
Dr. Karen Wetterhahn

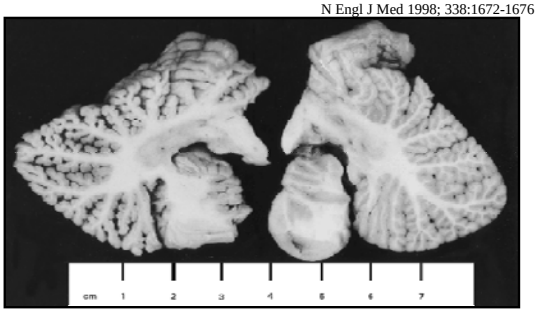
- Day 0 : Spills few drops on latex-gloved hand
  - Initially asymptomatic and continued normal activities. She delivered a paper at an overseas conference 3 months later.
- Day 154: Onset of symptoms
  - Balance, gait and speech problems
- Day 159: Admitted to hospital; symptoms progress
  - Paresthesias; visual field changes; bilateral high-pitched tinnitus; deterioration of speech, hearing, gait, mental status
- Day 176: Persistent vegetative state
- Day 298: Dies

Dimethylmercury Toxicity
Dr. Karen Wetterhahn

- Initial blood mercury level:
  - 4,000 mcg/L
  - nl 1-5 mcg/L; toxic > 200
- Chelated with DMSA
- Exchange transfusion
- No other Hg source identified

http://www.dartmouth.edu/~toxmetal/TXQAcr.shtml

N Engl J Med 1998; 338:1672-1676



Dr Wetterhahn's Cerebellum

Age-Matched Woman

Methylmercury Poisoning
Iraq, 1971-1972

- Wheat crop failure in 1970
- Sept to Nov, 1971 govt distrib mercury treated crops
  - 73,201 metric tons wheat
  - 22,262 tons barley seed
- Seed intended for planting
  - Methylmercury added to grain seeds as an antifungal
  - Warning in English
  - Shipment received after planting
- Grain used to make flour rather than plant it
  - MeHg content 9.1 mg/kg (range 4.8 -14.6)

Methylmercury Poisoning
Iraq, 1971-1972

- Mean exposure period was 32 days.
- ~40,000 exposed over several months
  - Est. total MeHg dose was 80 to 250 mg.
- 6530 hospital admissions / 459 hospital deaths
- Latency to onset of ≈ 2 to 6 weeks
- Initial lack of symptoms among animals fed grain may have instilled false sense of security that it was safe to eat

Methylmercury Poisoning
Clinical Findings in Adults

- Numbness around the mouth and in a stocking-glove distribution
- Classic Triad
  - Ataxia - slight unsteadiness to inability to walk
  - Visual changes ranging from blurred or decreased vision to blindness
  - Dysarthria - Slurring of speech
- Mental deterioration
- Severity of signs and symptoms are dose-dependent
  - Mild/moderate symptoms: 2.4 mg/kg
  - Severe symptoms: 3.6 mg/kg

Methylmercury Poisoning
Developmental Toxicity

- Crosses placenta and accumulates in child
- Transmitted mother to child via breast milk
- Severe developmental delay / Cerebral-palsy-like syndrome
- Mother may have minimal or no symptoms

Organomercurials – Potential Advantages in Toxic Terrorism

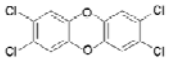
- Toxic to humans in small amounts
- Symptoms occur days to weeks after ingestion, depending on the dose
- Highly fetotoxic, cross the placenta most readily of all forms of mercury, enter breast milk
- Enter the body via ingestion of contaminated foodstuffs, inhalation and dermal exposure

Seveso, Italy
July 10,1976

www.chm.bris.ac.uk

Unintentional Dioxin Release
Seveso, Italy

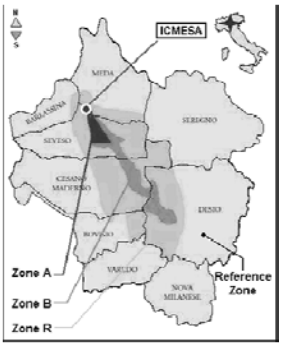
- ICMESA chemical plant
  - Synthesis of trichlorophenol from trichlorobenzene
- Reaction goes out of control
  - Temp up to 250ºC and pressure up to 4 atm
- Safety valve ruptures
  - > 1500 kg vented directly into the atmosphere
  - 2 to 34 kg 2,3,7,8-tetrachlorodibenzo-r -dioxin
- Mayor notified the next day



Unintentional Dioxin Release
Immediate Events

- Some residents with HA, nausea, eye irritation
- Plants turn yellow; rabbits and chickens die
- Day 6: 14 children to hospital “chemical burns”
- Day 10: Confirmed that dioxin was released
- Day 16-23: Zone A evacuated

Chloracne, Seveso, Italy



Seveso Chemical Plume

Zone	Size*	Pop.
A	0.3	804
B	1.0	5941
R	5.5	38,624
Ref	28.8	182,843

***Size in square miles**

Seveso, Italy: The Aftermath

- Zone A cleaned and soil removed
- Thousands of soil and blood samples collected
- Surveillance Programs
  - Liver enzyme induction, lipid metabolism, congenital malformation, immunosuppression, chloracne (193 cases)
  - 20 years later TCDD blood levels still high
  - Increased female:male birth ratio

Unintentional Dioxin Release
Controversial human effects

- Many of the reported relationships between dioxin exposure and human toxicity have come under epidemiologic scrutiny
- Carcinogenicity???
  - Known carcinogen in mice and rats
  - In humans reported association with some cancers such as Non-Hodgkin's Lymphoma and soft tissue sarcomas but causation has not been established
- Undisputed link between dioxin exposure and chloracne

The Poisoned Candidate
Victor Yushchenko, Ukraine

- Was well until 9/5/04 when he developed severe headache and stomach pains within hours after eating dinner
  - 3 weeks later developed chloracne
- Extremely high serum level of TCDD (100,000 ppt)
- Only other higher level found in Austrian secretary who had serum level of 144,000 ppt and severe generalized chloracne (body burden 1.6 mg TCDD)

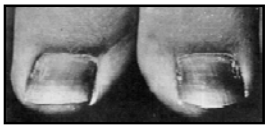
Intentional Dioxin Use
Victor Yushchenko, Ukraine

http://img.dailymail.co.uk

"Yusho" Poisoning
Japan, 1968

- Kanemi rice oil contaminated with Kanechlor 400
  - Mixture of polychlorinated biphenyls (PCB) & polychlorinated dibenzofurans (PCDF)
- 1788 certified exposures by end of 1982
- Subacute symptoms: acne-like eruptions
- Growth retardation in school children one year later
  - Triglyceride, immune & endocrine disturbances
- PCDF may have played the greater role

Yusho Effects



Chlorinated hydrocarbon
Dioxin, PCB

- Intentional mass exposure to dioxin or PCBs would be difficult to detect, induce wide-spread fear, and tax our resources for decades at an enormous cost

Audience Response

Why would a delayed-onset toxin be desirable as a terrorist weapon?

1. Victim can leave the immediate area
2. Large number of victims in a small area
3. Unrecognizable symptomology
4. Easier to produce than acute toxins

Why would a delayed-onset toxin be desriable as a terrorist weapon?

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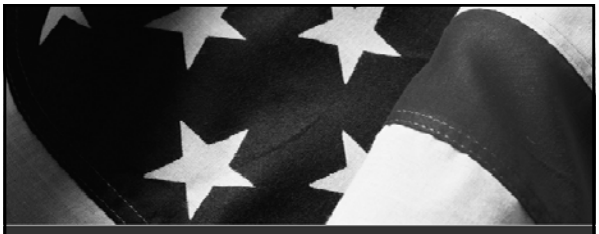
5.
6.
7.
8.
9.
10.

Forewarned Is Forearmed

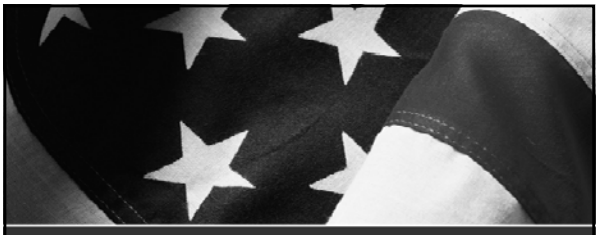
- Given a new willingness by terrorists in the 21st Century to use previously unthinkable means to meet their ends, we must prepare:
  - Limit access to highly toxic agents
  - Protections of food and water supplies, toxic substances in industrial plants and in transport
- Raise awareness of potential clinical effects to:
  - Hasten recognition
  - Limit exposure
  - Speed response

Lessons Learned

- Highly toxic substances are currently readily available whose onset of toxicity is delayed
- Toxins with delayed effects can be used to affect large numbers of people before it is discovered
- The delay in onset of toxicity aids a would-be terrorist in avoidance of detection and escape
- Widespread exposure and uncertainty re: long-term effects maximizes the fear factor – serves the purpose of the terrorist
- Even less toxic compounds which are biopersistent and whose detection is delayed have enormous potential to cause fear and overwhelm health care resources



Questions?

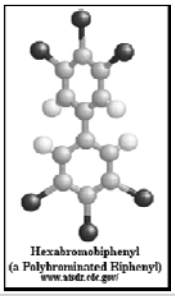


Supplemental Slides

Polybrominated Biphenyl (PBB) Exposure through Contaminated Food

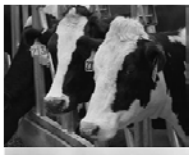
Michigan (1973)

- Chemical plant packaged FireMaster flame retardant (PBB) and NutriMaster (MgO dairy cattle feed supplement) in similar brown paper bags due to a shortage of pre-printed bags.
- Ten to twenty 50lb bags of PBB were included in a truckload of NutriMaster sent to a cattle feed mill during the summer of 1973.
- PBB contaminated cattle feed was sold to dairy farms throughout the state



Polybrominated Biphenyl (PBB) Exposure through Contaminated Food

- Weight loss, decreased milk production, and nonspecific illness noted among dairy herds in Fall 1973, Spring 1974
- After months of analysis, PBB detected in feed in April, 1974.
- Quarantine of dairy herds and other farm animals started in May, 1974.
- By 1975, 500 farms quarantined:
  - 30,000 cattle
  - 4500 swine
  - 1500 sheep,
  - 1.5 million chickens destroyed and buried.

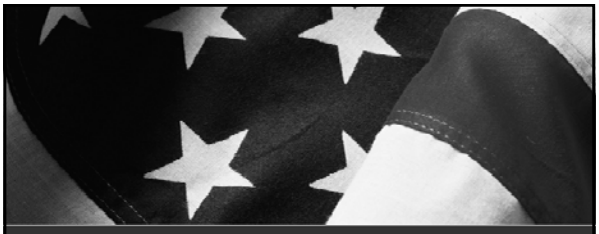


Polybrominated Biphenyl (PBB) Exposure through Contaminated Food

- Widespread, low level human exposure to PBB occurred throughout Michigan. E.g. 51 of 53 (96%) of random breast milk samples in 1976 had detectable levels.
- Exposure most intense among dairy farm families, and persons obtaining dairy foods directly from quarantined farms.
- High dose animal studies revealed PBB could cause multisystemic effects, including liver neoplasms
- Between 1976 - 1979, state and federal agencies assembled a cohort of ≈ 4000 people, mainly farm families, to study long-term human health effects.

Polybrominated Biphenyl (PBB) Exposure through Contaminated Food

- PBB is highly lipophilic and extremely persistent; Body burden T1/2 estimated to be 10.8 years
- Serum PBB acceptable biomarker of body burden
- Initial cohort findings found no relationship between serum levels and symptoms (highest symptom prevalence occurred in subjects with lowest serum PBB) [Landrigan et al, 1979]
- No relationship between serum PBB and lymphocyte number or function [Landrigan et al, 1979]
- A 1998 study raised concern of possible carcinogenesis; this has not been confirmed



Questions?