

#### S&T Stakeholders Conference

#### WMD Terrorism Risk Assessment in DHS Science & Technology

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#### Why Risk Assessment in DHS?



#### DHS, HSC Guidance...

"...We need to adopt a risk-based approach in both our operations and our philosophy. Risk management is fundamental to managing the threat... The most effective way to apply risk-based approach is by using the trio of threat, vulnerability and consequence as a general model for assessing risk and deciding on protective measures we undertake." - Michael Chertoff, Secretary, DHS

"...the United States requires a continuous, formal process for conducting...assessments to guide prioritization of...investments in biodefense-related research, development, planning, and preparedness." - Biodefense for the 21<sup>st</sup> Century (HSPD-10)





#### DHS, HSC Guidance...(cont'd)

Required by HSPD-18: *Medical Countermeasures* against Weapons of Mass Destruction

§ 14 (c)

"The Secretary of Homeland Security shall develop a strategic, integrated all-CBRN risk assessment... Not later than June 1, 2008, the Secretary of Homeland Security shall submit a report to the President...which shall summarize key findings...and shall update those findings when appropriate, but not less frequently that every 2 years."





### iCBRNra Program Objectives

- 2 Key Deliverables:
  - First end-to-end quantitative Integrated Chemical, Biological, Radiological, and Nuclear Risk Assessment (iCBRNra) Report
  - WMD risk analysis toolset and platform for conducting tailored WMD assessments and risk mitigation strategy evaluation, with an initial focus on Medical Countermeasures.





#### First, some Bioterrorism...







- Use of these agents both for warfare and for terrorism<sup>1</sup>
- 400 BC Scythian archers developed a practice of dipping their arrows in manure, blood, and/or decomposing bodies
- 1346 Demonstrated success: Bubonic plague breaks out in Tartar camp during siege of Kaffa – Tartars began catapulting plague-infected dead bodies over the walls of Kaffa as part of the siege – resulting epidemic forced surrender. Some historians believe that this was the initial cause of the black death that spread across Europe killing 25 million people.



1. Arizona Department of Health Services, Division of Public Health Services http://www.azdhs.gov/index.htm



- 1495 Spanish infected French wine with the blood of leprosy patients
- 1600s Polish generals filled empty artillery shells with saliva from rabid dogs for use against enemies
- 1710 Russians used plague victims as weapons against Sweden in a similar fashion as the Tartars
- 1400s Pizarro gave smallpox-containing clothing to South American natives
- Same tactic used by the British in the French-and-Indian war, as well as by Kentucky governor Dr. Luke Blackburn during the American Civil War (smallpox and yellow fever)





- 1915 German-American physician in Washington D.C. produced large amounts of Anthrax and *Burkholderia mallei* (Glanders) that were inoculated into livestock headed for Allied forces in Europe – multiple reports of secondary human infections.
- 1918 Japanese miltary forms the infamous Unit 731. Experiments in Manchuria on prisoners of war continued through 1945 – mostly aerosolized Anthrax testing.
- 1931 During an investigation of Japanese seizure of Manchuria, Japan attempted to poison members of the League of Nations' investigatory committee by lacing fruit with cholera.





- 1939 Japanese poisoned Russian water at the Mongolian border with intestinal typhoid.
- 1941 Japanese military released an estimated 150 million plague-infected fleas from airplanes over villages in China and Manchuria.
- 1945 Japan stockpiled 400 kilograms of Anthrax for use in a special fragmentation bomb.
- In 1942 Prior to the battle of Stalingrad, several thousand Soviets and Germans contracted tularemia, with 70% contracting the pneumonic version, suggesting intentional release. Later learned that the Soviets had developed a tularemia weapon the prior year.





- 1940s British and Americans initiate their own offensive BW programs, fearing German and Japanese programs.
- 1942 U.S. begins offensive research into BW investigated Anthrax, botulinum toxin, Plague, Tularemia, Q fever, VEE, Brucella, and Staphylococcal enterotoxin B.
- 1950 U.S. BW program tests bioweapons disersal mechanisms by releasing a harmful but identifiable bacteria over San Francisco.
- 1966 Tested dissemination of a harmful bacteria by releasing it at a New York subway station, showing that the material spread all over the subway system due to train movement.





- 1969 President Richard Nixon stopped all offensive BW research and production by executive order. All stockpiles of offensive weapons were destroyed, and the programs converted to become strictly defensive in nature.
- 1972 U.S. and other countries sign the Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction.
- 1970s-90s Despite signing the treaty, Russian programs continued into the 90s





- 1975-1983 Soviet-backed forces in Laos and Afghanistan allegedly used T-2 mycotoxins against people and animals in what has been called "yellow rain" – this has been consistently denied, and the yellow spots observed were attributed to defecating bees.
- 1979 Outbreak of pulmonary Anthrax occurred in Sverdlovsk in the former Soviet Union. While the Soviets claimed infected meat was the cause, it is suspected that the infections were due to an accidental release of aerosolized Anthrax from Soviet Military Compound, a bioweapons facility. Final death toll estimated to be between 200 and 1000.





- 1991 Iraq (signatory to the Bioweapons convention), admits research into offensive use of Anthrax, and a number of other agents.
- 1970s Leftist group "Weather Underground" attempts to blackmail a homosexual Army officer at Ft.
  Detrick, Maryland, to obtain organisms to be used in contaminating U.S. water supplies.
- 1972 Right-wing group "Order of the Rising Sun" dedicated to creating a new master race, was found in possession of 30 to 40 kilograms of typhoid bacteria cultures to be used to contaminate water supplies of major midwestern cities.





- 1975 Symbionese Liberation Army found in possession of bioweapons manuals.
- 1978 Bulgarian exile was stabbed in the leg using an umbrella that injected a tiny pellet containing the toxin Ricin, killing him several days later.
- 1980 "Red Army Faction" facility in Paris contained large quantities of botulinum toxin.
- 1983 FBI arrests two brothers in the Northeastern U.S. for being in possession of an ounce of nearly pure Ricin.





- 1995 Two men convicted under the Biological Anti-Terrorism Act of 1989 for Ricin production. Men were part of the "Minnesota Patriots Council" and planned to poison federal agents by coating doorknobs with Ricin.
- 1984 Followers of Bhagwan Shree Rajneesh contaminated a number of salad bars in Oregon with Salmonella, intending to effect the outcome of a local election. Over 750 cases of salmonellosis were determined to be caused by t his act. Strain of Salmonella obtained by mail order from the American Type Culture Collection (ATCC).





- 1995 Following Aum Shinrikyo's sarin gas attack in the Tokyo subway, it was discovered that developed and attempted to use biological agents such as Anthrax, Q Fever, Ebola, and botulinum toxin on at least ten other occasions.
- 1995 Larry Wayne Harris arrested for illegally obtaining Plague (again from ATCC). CDC establishes rigorous guidelines for shipment of specific pathogens that could be used in bioterrorism.
- October 2001 Anthrax letters...





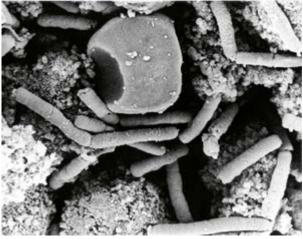






### Overview of Important Bioterrorism Agents: Anthrax

- Bacillus anthracis (Bacteria)
- Inhalation, Ingestion, Cutaneous
- Inhalational form near 100% mortality if untreated prior to symptom appearance
- Forms a durable spore that is extremely stable under a range of conditions



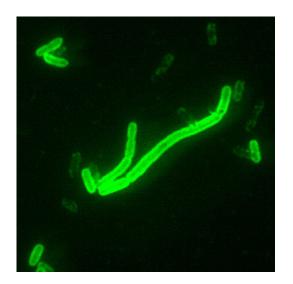




ICDRINITA Risk Assessment

#### Overview of Important Bioterrorism Agents: Plague

- Yersinis pestis (Bacteria)
- Infection from flea bites, inhalation, ingestion?
- Pneumonic form is transmissible
- Untreated mortality rates between 50% and 90%





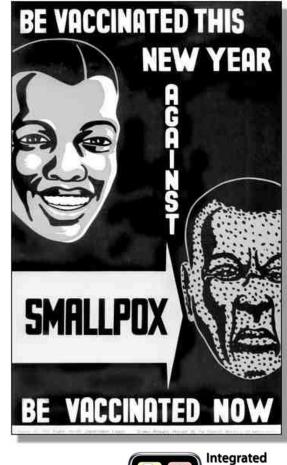
ICBRNra Risk Assessment

### Overview of Important Bioterrorism Agents: Smallpox

- Variola major (Virus)
- Infection via inhalation
- Highly contagious (transmissible)
- Responsible for 300 to 500 million deaths in the 20<sup>th</sup> century
- Eradicated in 1977
  - Effective vaccine
- Cultures exist at CDC and VECTOR
- 30% mortality rate



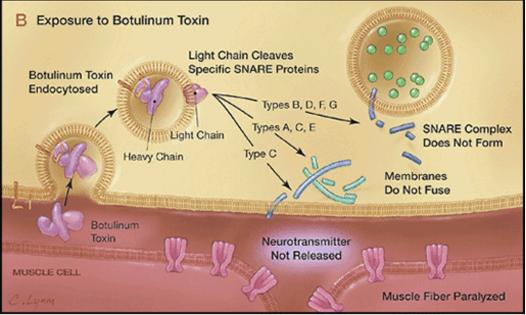




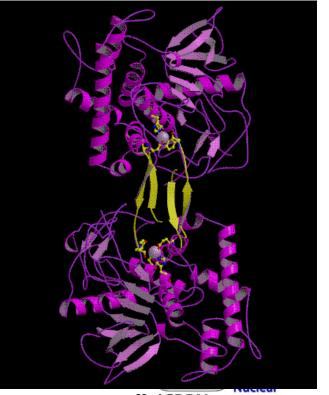


#### Overview of Important Bioterrorism Agents: Botulinum toxin

- From the bacteria Clostridium botulinum
- Neurotoxin blocks the neuromuscular junction
- Countermeasures:
  - Antitoxin
  - Respirator support



JAMA. 2001;285:1059-1070. C American Medical Association



<sup>23</sup> iCBRNra Risk Assessment

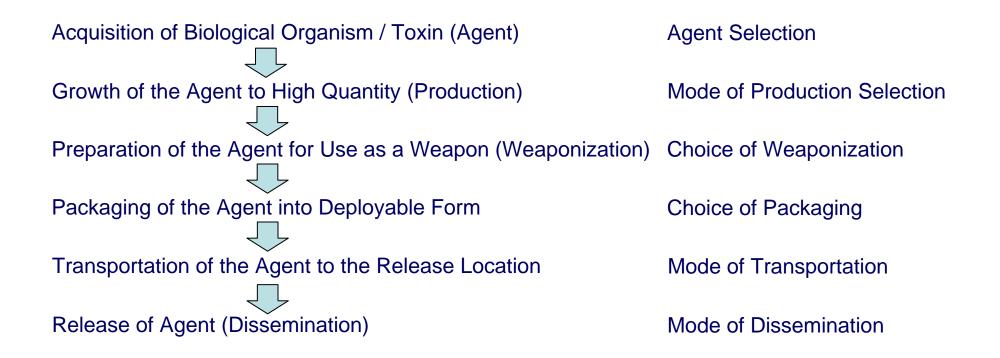
### Group Exercise

- Okay so how do the "good guys" go about cracking the problem for a 21<sup>st</sup> century adversary? An important first step to being able to prevent or mitigate effects of bioterrorism is understanding what the critical steps are in the event from planning to execution.
- What do you think are the required steps that a potential bioterrorist must take to successfully conduct a bioterrorism attack?





#### Possible Steps an Adversary Might Take:



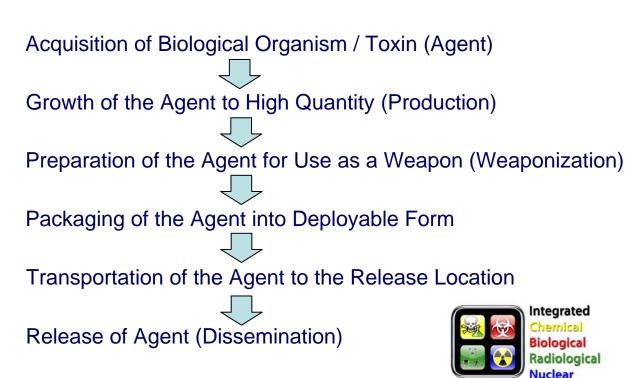




## Homeland Security Issues: Identifying the Threat



Is BOTOX a threat?



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ra Risk Assessment



# Homeland Security Issues: Identifying the Threat



- Most common cosmetic procedure in the United States (as of 2006)
- Uses expanding to treat disorders such as excessive salivation and excessive underarm sweating
- Given what we learned about botulinum toxin, what is the threat of BOTOX being used as a bioterrorism weapon?





## Homeland Security Issues: Identifying the Threat



What information do we need to know?





## How much toxin is in a typical box or injection of BOTOX?

#### BOTOX COSMETIC

(Botulinum Toxin Type A) Purified Neurotoxin Complex

> Manufactured by: Allergan Pharmaceuticals Ireland A subsidiary of: Allergan. Inc. 2525 Dupont Dr. Irvine. California 92612

#### DESCRIPTION

BOTOX- COSMETIC (Botulinum Toxin Type A) Purified Neurotoxin Complex is a sterile, vacuumdried purified botulinum toxin type A, produced from fermentation of Hall strain *Clostridium botulinum* type A grown in a medium containing casein hydrolysate, glucose and yeast extract. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing (themas descent) of the complex is dissolved in sterile sodium chloride solution containing (themas descent) of the complex is dissolved in sterile filling and vacuum terming.

One that of BOTOX- COSMETIC corresponds to the calculated median intraperitoneal lethal are (CD<sub>w</sub>) in mice. The method utilized for performing the assay is specific to Allergan's product BOTOX- COSMETIC. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD<sub>w</sub> assays, Units of biological activity of **BOTOX-** COSMETIC council to ecompared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. In addition, differences in species sensitivities to different botulinum neurotoxin serotypes precludes extrapolation of animal-dose activity relationships to human dose estimates. The specific activity of **BOTOX-** COSMETIC is approximately 20 units/nanogram of neurotoxin protein complex.

Each vial of **BOTOX**: **COSMETIC** contains 100 Units (U) of *Clostridium betulinum* type A neuror of complex 0.5 milligrams of Albumin Human, and 0.9 milligrams of sodium chloride in a tentie, vacuum-dhed non-without a preservative.

#### CLINICAL PHARMACOLOGY

BOTOX- COSMETIC blocks neuromuscular transmission by binding to acceptor siles on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acety/choline. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acety/choline from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, BOTOX- COSMETIC produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by BOTOX- COSMETIC.

#### TABLE 1.

Investigator's Assessment of Glabellar Line Severity at Maximum Frown – Responder Rates (% and Number of Subjects with Severity of None or Mild)

DAY	BOTOX* COSMETIC	Placebo	DIFFERENCE	
7	74%	6%	68%	
	299/405	8/132	(62, 74)	
30 <sup>b</sup>	80%	3%	77%	
	325/405	4/132	(72, 82)	
60	70%	2%	69%	
	283/403	2/130	(64, 74)	
90	48%	2%	45%	
	192/403	3/128	(40, 51)	
120	25%	2%	24%	
	102/403	2/128	(19, 29)	

\* Day 30: Co-Primary Efficacy Time point, P<0.001</p>

#### TABLE 2.

Subject's Assessment of Change in Appearance of Glabellar Lines – Responder Bates ( Number of Subjects with at Least Moderate Improvement)

DAY	POTO		
	OUSMETIC	Placebo	DIFFERENCE
7	82%	9%	73%
	334/405	12/132	(68, 80)
30*	89%	7%	83%
	362/405	9/132	(77, 88)
60	82%	4%	78%
	330/403	5/130	(73, 83)
90	63%	3%	60%
	254/403	4/128	(54, 66)
120	39%	1%	38%
	157/403	1/128	(33, 43)

95% confidence intervals are shown in parentheses
Day 30: Co-Primary Efficacy Type point, P<0.001</li>

In the subset of patients with resting severity scores of moderate or severe, the investigator assessment of a resting severity of mild or none at day 30 was also achieved by more BOTOX-COSMETIC treated patients (74%, 1197/161) than placebo treated patients (20%, 10/49).

Analysis of the limited number of patients 65 years or older suggested lower treatment-associated response compared to patients less than 65 years of age. (Table 3). Each vial of BOTOX contains 100 "units" of BOTOX

Each injection is diluted such that it contains 20 "units"

Here, a "unit" is defined as the amount of toxin required to kill 50% of a population of mice that are exposed to that amount  $(LD_{50})$ .





# How much BOTOX would it take to kill a person?

#### Median lethal dose (LD50)

Botulinum toxin's median lethal dose (LD50) has been determined across several animal species, but not in humans. A unit of BTX-A usually is defined in terms of its biologic potency. One mouse unit (MU) of BTX-A equals the LD50 for a 20-g Swiss-Webster mouse. Yet BTX-A sensitivity varies among different species. LD50 in monkeys has been determined as 39 U/kg. Based on these findings from primate studies, human LD50 is estimated at approximately 3000 U for a 70-kg adult. Typical doses for larger muscle groups range from 60-400 total units given in a single treatment; however, because of inadequate understanding of the complete dose response curve in humans, a relative ceiling dose of 360 U, given no sooner than 12 weeks apart, is recommended.

- 3000 "units" is the estimated (extrapolated) human LD<sub>50</sub>.
- So how many vials/boxes of BOTOX would a bad guy need to get to come up with an LD<sub>50</sub> of botulinum toxin.





### **BOTOX Summary**

- 100 "units" in each BOTOX vial
- Human LD<sub>50</sub> = 3000 "units"
- Would need 30 vials of BOTOX to have a 50% chance of killing one person!
  - How much is on-hand at any given time in a physician's office?
- To conduct an attack where an adversary wanted to have a 50% chance of killing 100 people, would require 3000 vials of BOTOX!!
- Are there other issues/challenges for the adversary?
  - Yes storage and stability
    - Refrigeration
    - Decay over time
    - Contaminants and denaturants
- In this case, our example shows that this is clearly not a *significant* threat, or at minimum, we'd have the possibility of being alerted to the fact that there were large amounts of BOTOX missing in advance of an attack.
- But this exercise does highlight the fact that the research required to investigate feasibility of attacks is readily available on the internet.





## Challenges for Homeland Security

- Unlike radiological and nuclear threats, bioterrorism is not a materials problem.
- Dual use BOTOX, for example.
- Recurring theme "untreated mortality rates" in the descriptions of the agents. Were treatment available to exposed individuals, many lives can be saved. This implies a logistical challenge for bioterrorism response.
  - Attacks expected to be covert
  - May be some time before event is known (people start showing up in ERs?)
  - Fixed time to mobilize and deliver countermeasures
  - This delay determines what our treatment effectiveness will be.
- Huge threat space any biological pathogen that can cause disease could potentially be used by a terrorist – how do we prioritize what we need to defend against with so many potential threats? – RISK ASSESSMENT!





### A multi-criteria decision analysis (MCDA) example

- MCDA: Multiple Criteria Decision Analysis
  - Example:
    - Goal: Purchase a car
      - Objectives:
        - Good Fuel Economy
        - Color
        - Horsepower
        - Interior Options
        - Warranty/Service





### A multi-criteria decision analysis (MCDA) example

- MCDA: Multiple Criteria Decision Analysis
  - Example:
    - Goal: Purchase a car

#### Objectives:

- Good Fuel Economy 10%
- **Color** 10%
- Horsepower 50%
- Interior Options 10%
- Warranty/Service 20%





# Two Quantitative Approaches: MCDA and PRA

- MCDA: Multiple Criteria Decision Analysis
  - Example:
    - Goal: Purchase a car
      - Alternatives:
        - Chevrolet Suburban
        - Honda Civic
        - Toyota Prius
        - Cadillac Escalade
        - Ford Pinto





# Two Quantitative Approaches: MCDA and PRA

- MCDA: Multiple Criteria Decision Analysis
  - Example:
    - Goal: Purchase a car

	Fuel Econ (0.1)	Color (0.1)	Horsepwr (0.5)	Interior (0.1)	Warranty (0.2)
Chevrolet Surburban	0	3	3	2	2
Honda Civic	3	2	1	2	3
Toyota Prius	4	2	1	2	2
Cadillac Escalade	0	3	3	2	3
Ford Pinto	1	4	0	0	0





# Two Quantitative Approaches: MCDA and PRA

- MCDA: Multiple Criteria Decision Analysis
  - Example:
    - Goal: Purchase a car

	Fuel Econ (0.1)	Color (0.1)	Horsepwr (0.5)	Interior (0.1)	Warranty (0.2)
Chevrolet Surburban	0	0.3	1.5	0.2	0.4
Honda Civic	0.3	0.2	0.5	0.2	0.6
Toyota Prius	0.4	0.2	0.5	0.2	0.4
Cadillac Escalade	0	0.3	1.5	0.2	0.6
Ford Pinto	0.1	0.4	0	0	0





# Two Quantitative Approaches: MCDA and PRA

- MCDA: Multiple Criteria Decision Analysis
  - Example:
    - Goal: Purchase a car

	Fuel Econ (0.1)	Color (0.1)	Horsepwr (0.5)	Interior (0.1)	Warranty (0.2)	Scores:
Chevrolet Surburban	0.0	0.3	1.5	0.2	0.4	2.40
Honda Civic	0.3	0.2	0.5	0.2	0.6	1.80
Toyota Prius	0.4	0.2	0.5	0.2	0.4	1.70
Cadillac Escalade	0.0	0.3	1.5	0.2	0.6	2.60
Ford Pinto	0.1	0.4	0.0	0.0	0.0	0.50





# Two Quantitative Approaches: MCDA and PRA

- MCDA: Multiple Criteria Decision Analysis
  - Example:
    - Goal: Purchase a car

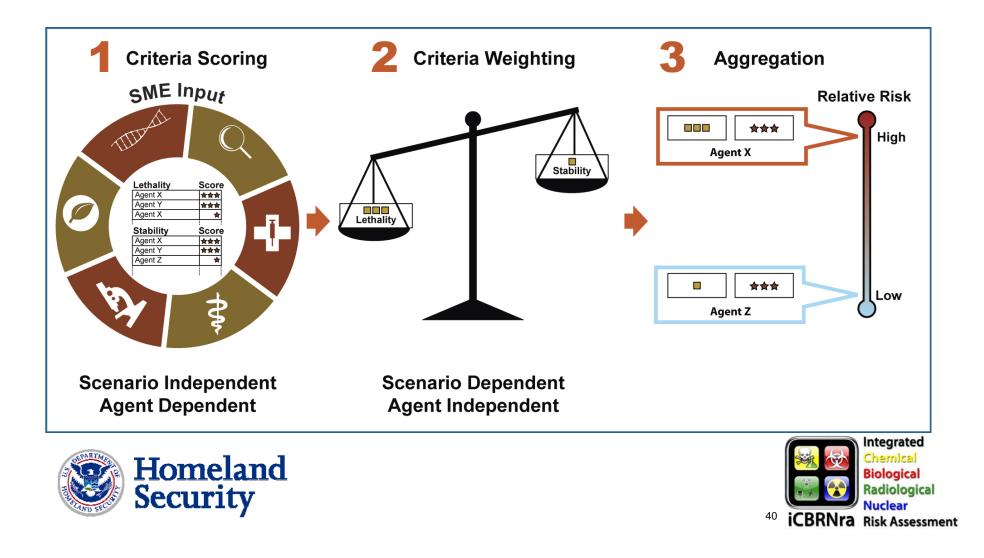
	Fuel Econ (0.1)	Color (0.1)	Horsepwr (0.5)	Interior (0.1)	Warranty (0.2)	Scores:
Chevrolet Surburban	0.0	0.3	1.5	0.2	0.4	2.40
Honda Civic	0.3	0.2	0.5	0.2	0.6	1.80
Toyota Prius	0.4	0.2	0.5	0.2	0.4	1.70
Cadillac Escalade	0.0	0.3	1.5	0.2	0.6	2.60
Ford Pinto	0.1	0.4	0.0	0.0	0.0	0.50

	Fuel Econ (0.1)	Color (0.1)	Horsepwr (0.5)	Interior (0.1)	Warranty (0.2)
Chevrolet Surburban	0	3	3	2	2
Honda Civic	3	2	1	2	3
Toyota Prius	4	2	1	2	2
Cadillac Escalade	0	3	3	2	3
Ford Pinto	1	4	0	0	0

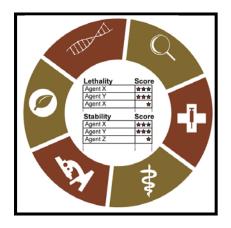




## Multi-Attribute Risk Analysis (MARA) for Bioterrorism



#### Step 1: SMEs Score Agents Against Criteria



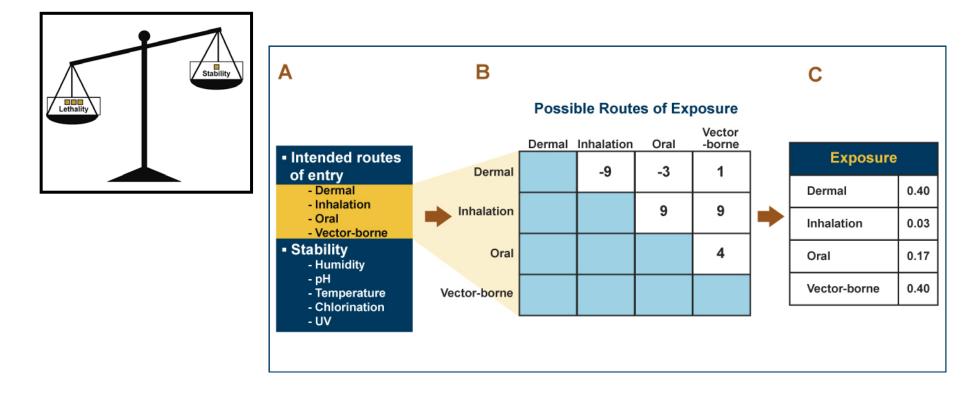
These criteria include:

- Transmissibility
- Morbidity
- Mortality
- Medical Countermeasures
- Detection/Diagnostic Capabilities
- Availability





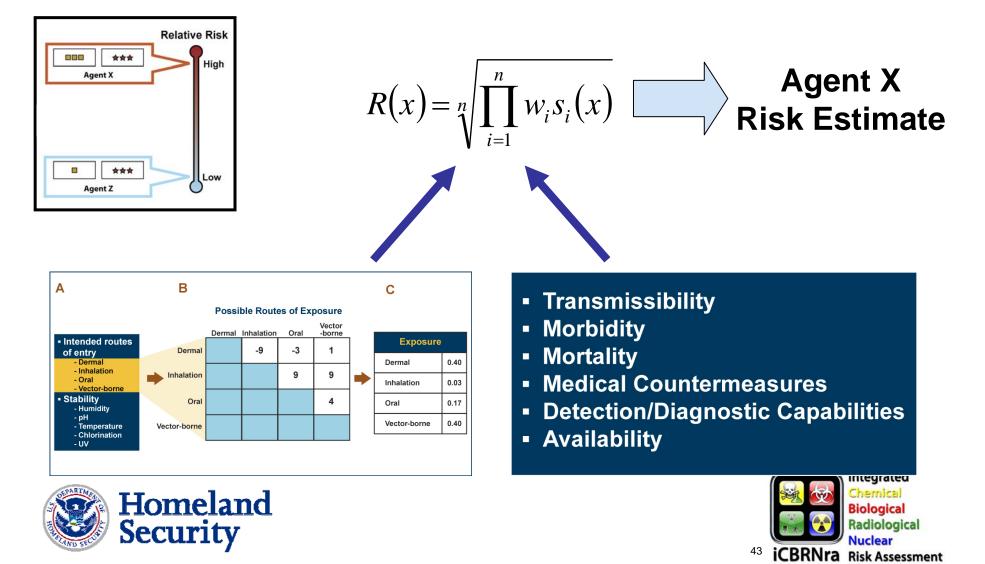
## Step 2: SMEs Determine the Relative Importance of the Criteria







### Step 3: Analysts Aggregate the Weights and Scores to Produce Risk Estimates



## Formal Risk Analysis...





## What is Risk?

"The potential for realization of unwanted, adverse consequences to human life, health, property, or the environment; estimation of risk is usually based on the expected value of the conditional probability of the event occurring times the consequence of the event given that it has occurred." (Society for Risk Analysis)

Risk = f(p, C)





# Risk Assessment for common events is 'easy'

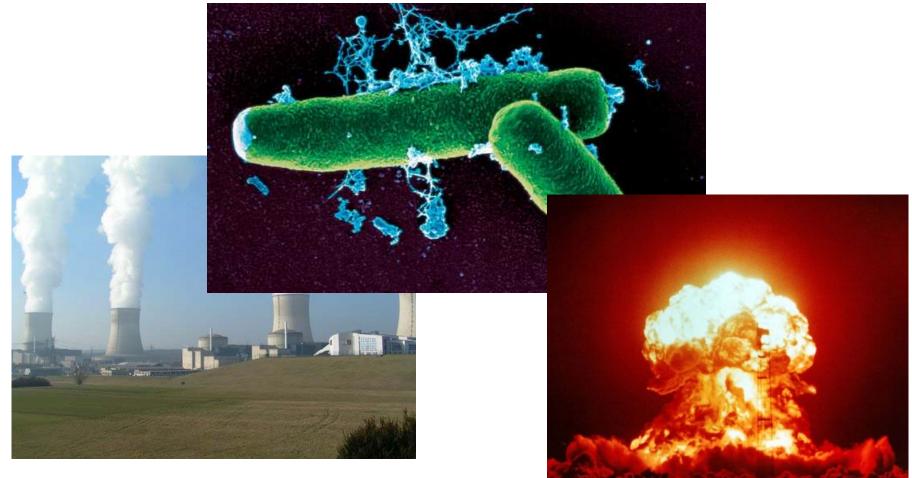
Total Traffic Crashes In the United States	2005	2004	2003	2002	2001	2000	1999	1998	1997
Fatal Vehicle Crashes	39,189	38,444	38,477	38,491	38,862	37,526	37,140	37,107	37,324
Fatality Totals:									
Drivers	27,472	28,871	26,779	26,659	25,869	25,567	25,257	24,743	24,667
Passengers	10,036	10,355	10,458	10,604	10,469	10,695	10,521	10,530	10,944
Other	86	78	104	112	102	86	97	109	114
Sub-total	37,594	37,304	37,341	37,375	36,440	36,348	35,875	35,382	35,725
Non-Motorists Killed									
Pedestrians	4,881	4,675	4,774	4,851	4,901	4,763	4,939	5,228	5,321
Bicyclists	784	727	629	665	732	693	754	760	814
Other	184	130	140	114	123	141	149	131	153
Total Killed	43,443	42,836	42,884	43,005	42,196	41,945	41,717	41,501	42,013

Car accidents (2005): 43,443 deaths, 2.9 million injuries, 40% of accidents involve alcohol



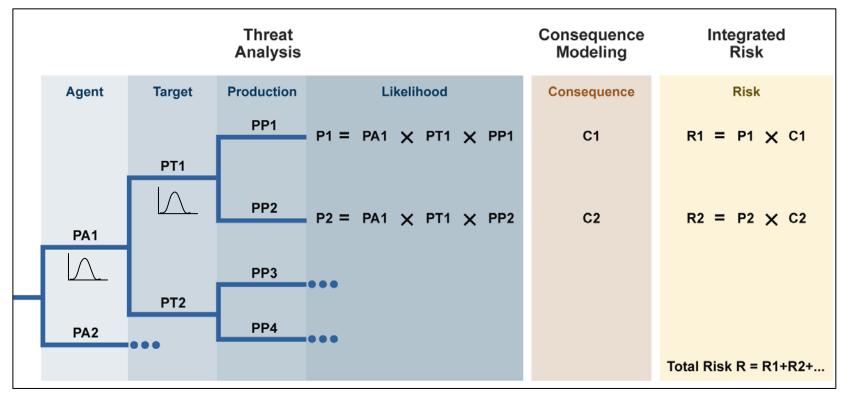


## Risk Assessment for rare (data-poor) events is **hard**





#### A Simple (Binary) Event Tree



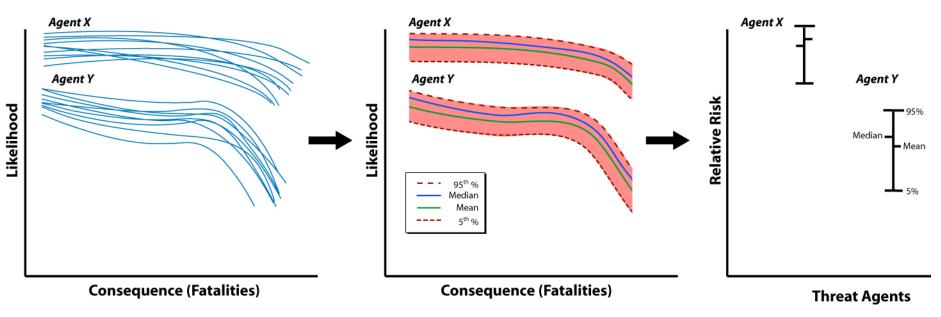


**Security** 

- Ability to adjust parameters to address different questions
- Ability to query system at consequence level of interest

## Summarizing the Risk Curves

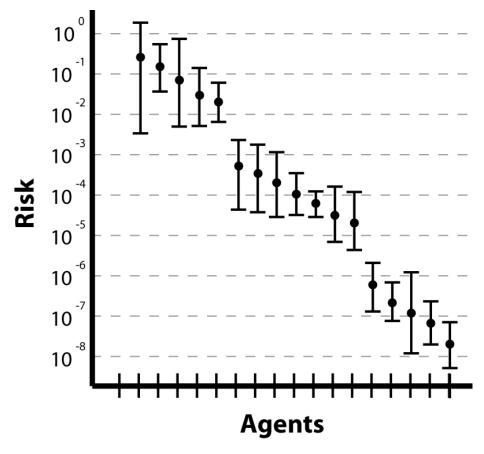
#### **Risk Curves**







In the Bioterrorism and Chemical Terrorism Risk Assessments, Agents Were Evaluated by Comparing Relative Risk







## Summarizing Probabilistic Risk Analysis

- Useful for comparing risks against one another
- Consistent method for aggregating risk from a sequence of events
- Provides decision-makers with the opportunity to ask the 'what-if' questions. Can determine what the impacts of potential risk mitigation strategies will be.
- Potential Criticisms:
  - We cannot accurately estimate probabilities (more on this later)
  - May miss the 'creative' new threat



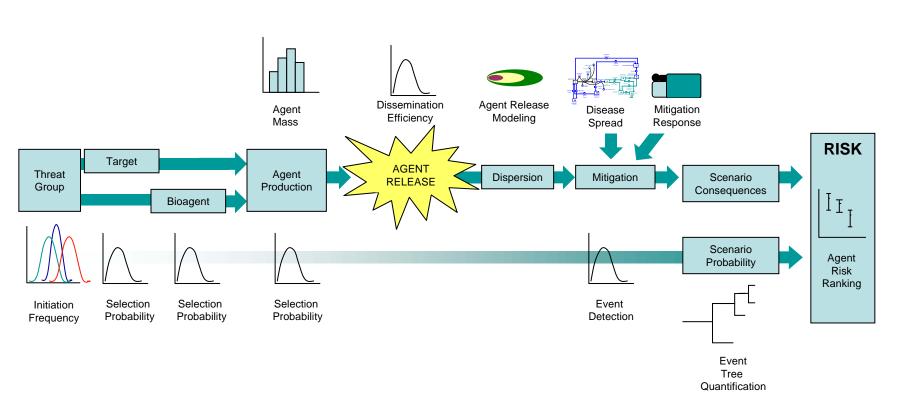


## Components of the DHS iCBRNra



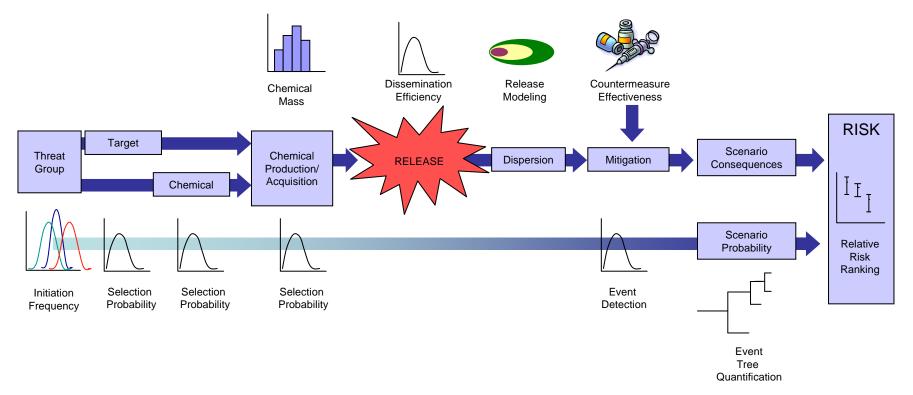


## iCBRNra Components: Bioterrorism Risk Assessment (BTRA)



- Required by HSPD-10; first assessment delivered to White House Homeland Security Council (HSC) in January, 2006. Updated assessments are due every two years.
- 2008 update scheduled for delivery 31 January 2008 many significant expansions and improvements.

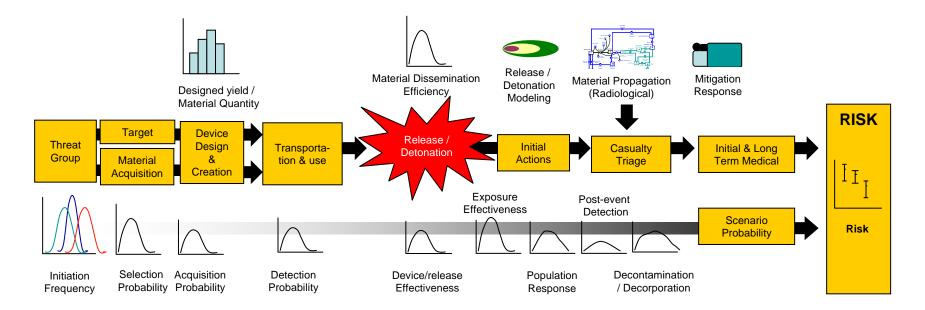
## iCBRNra Components: Chemical Terrorism Risk Assessment (CTRA)



- 60 chemicals screened from an initial list of over 10,000
- Analogous process and approach to that of the BTRA.



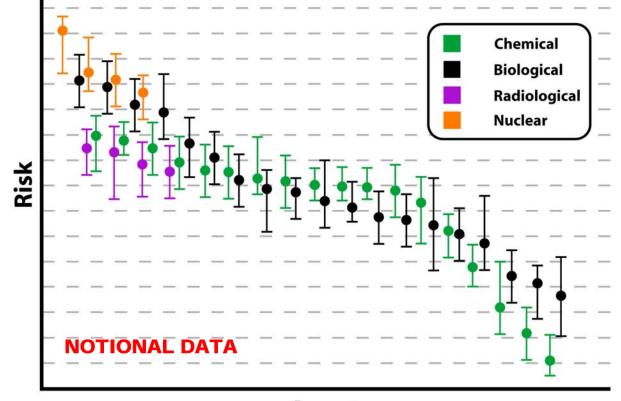
#### iCBRNra Components: Radiological / Nuclear Terrorism Risk Assessment (RNTRA)



- "R": 10 radioisotopes considered in RDDs, REDs, and food/water contamination
- "N": INDs with various designs and yields ranging from 0.1 to 100kT
- Analogous process and approach to that of the BTRA and CTRA.

## A dynamic tool, not just a snapshot of risk

<u>Step 1: Risk Assessment.</u> Integrated CBRN Assessments will Allow for Direct Comparisons Across WMD Threat Areas

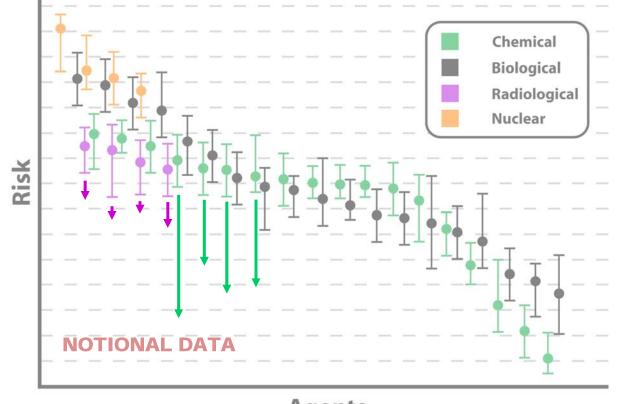


Agents





<u>Step 2: Risk Management Recommendations.</u> Integrated CBRN Assessments will Allow for MCM Strategy Evaluation Across WMD Threat Areas



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# Homeland Security



