Chemical Segregation by Toxidrome for the Chemical Terrorism Risk Assessment

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Homeland Security

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For the best of reasons

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A **Toxidrome** is a constellation of toxic effects. Toxic syndromes comprise a set of clinical "fingerprints" for groups of toxicants.

A particular toxidrome may be identified with a clinical observations including vital signs, mental status, mucous membrane irritation, lung exam for wheezing or rales, skin for burns, moisture, and color. For CSAC purposes, the toxidromes include:

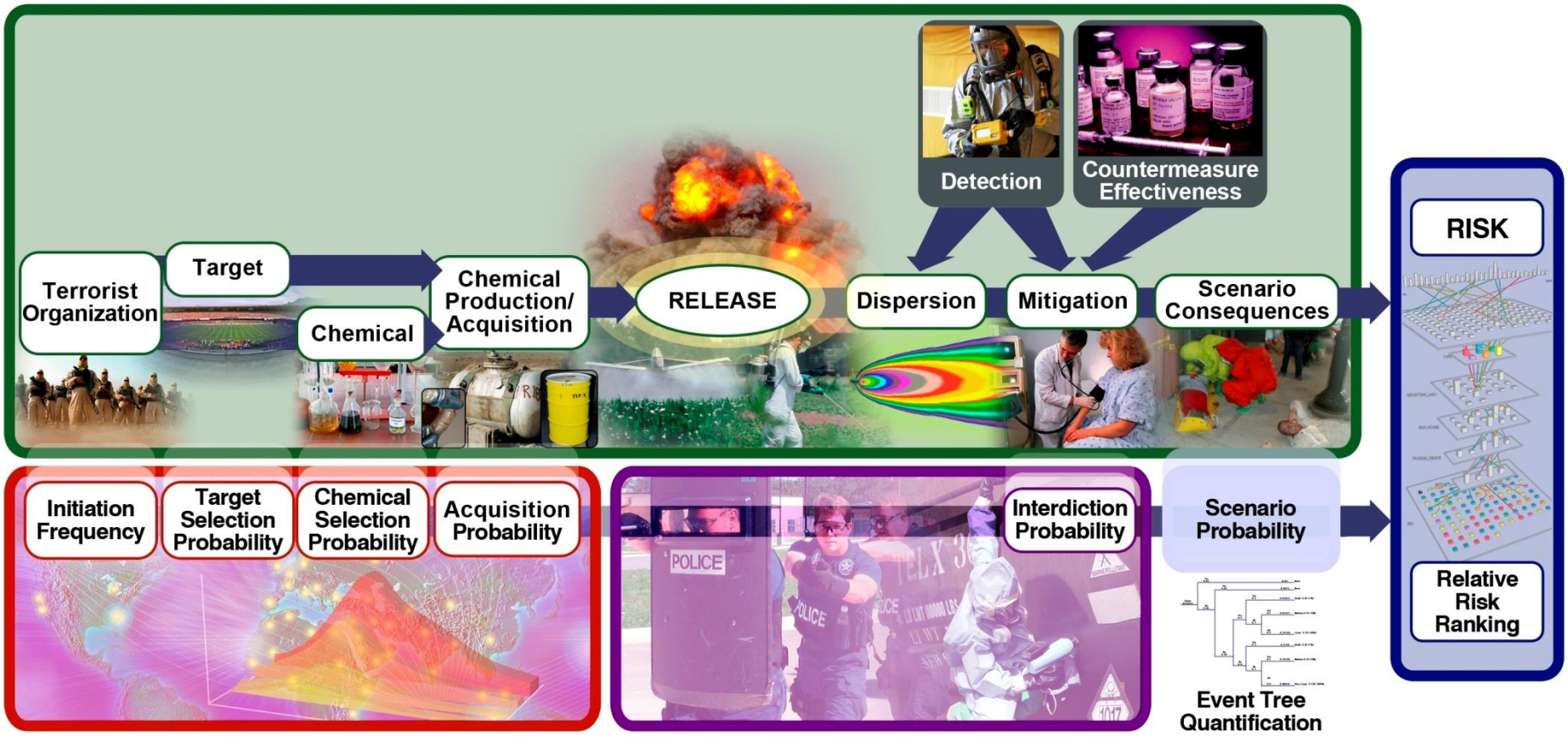
Anticoagulants	Opioids
Blood Agents	Hemolytic/Metabolic
Cholinergic CWA	Upper Pulmonary
Cholinergic Other	Lower Pulmonary
Convulsants	Vesicants

Why is segregation by Toxidrome necessary?

HSPD-22 Paragraph (14) requires that an over-arching Chemical Terrorism Risk Assessment (CTRA) be conducted biennially, and that all federal agencies consider the CTRA for Domestic Chemical Terrorism purposes

Based on a Danish study of 100K chemicals, about 25% have harmful health effects, so of more than 60M chemicals in the CAS registry there may be more than 15M chemicals that may be used in a chemical attack.

Critical Factors and Inputs for CTRA



Why is segregation by Toxidrome necessary?

By itself, no characteristic of a chemical is adequate for identifying and segregating chemicals for medical mitigation after a chemical mass casualty event.

- Chemical Class
- Mechanism
- Toxicity
- Target Organ
- Route of Exposure
- Physical Properties
- Human Health Effects

Clinical presentation may not accurately represent mechanisms and may require refinement. Some chemicals will be elusive to categorize and may be treated individually

Although segregation by Toxidrome has limitations it provides adequate life saving treatment for victims of mass casualty exposures. Use of toxidromes as a diagnostic tool is fundamental to effective medical response

Why is Segregation into Toxidromes Necessary?

An Ideal Classification System would be a component of a care management scheme and allow treatment to be developed for **each chemical** based on its physical properties, mechanism of action, route of entry, toxicity, target organ, and other human health effects.

• Impossible because for a majority of the hazardous chemicals complete experimental and clinical information doesn't exist. Only hypothetical, anecdotal , or high level chemical event information exists that may not lead to compound identification.

• Impractical because in a chemical event dose may be unknown, or the signs and symptoms may be from a combination of chemicals.

• Unnecessary because treatments don't vary appreciably for similar compounds.

Chemical List

- **Chemical Terrorism Risk Assessment (CTRA) lists 130 chemicals including CWA, TIC/TIM, Herbicides, Pesticides, Pharmaceuticals, and low molecular weight toxins**.

- DHS 6 CFR Part 27: “Appendix to Chemical Facility Anti-Terrorism Standards” lists 325 Chemicals that, “if released, stolen or diverted have the potential to create significant human life and/or health consequences.”

- DOT 49 CFR 172.101 "Hazardous Materials Table" identifies materials that are forbidden in transportation. The chemicals include explosives; flammable, non-flammable, and poison gases; flammable liquids, flammable solids, air and water reactive chemicals, oxidizers, organic peroxides, and corrosives.

Toxidromes and Chemicals

Anticoagulant
Brodifacoum
Bromodialone
Diphacinone

Blood
Acrylonitrile
Aniline
Cyanogen chloride
Hydrogen cyanide
Hydrogen sulfide
Isobutyronitrile
Methanethiol
Methyl acrylonitrile
Methylthiocyanate
Pentacarbonyliron
Potassium cyanide
Proprionitrile
Sodium azide
Sodium fluoroacetate

Cholinergic (CWA)
Chlorosarin
Chlorosoman
Cyclosarin (GF)
Sarin (GB)
Soman (GD)
Tabun (GA)
R-VX
VX

Cholinergic (Other)
Chlorfenvinphos
Chlorpyrifos
Dicrotophos
Disulfoton
Methamidophos
Parathion
Phorate
Phosphamidon
Sulfotep
Tetraetylpyrophosphate
Aldicarb
Methomyl
Anatoxin
4-Aminopyridine

Convulsant
Picrotoxin
Strychnine
Tetramethylene disulfotetramine (TETS)

Hemolytic/Metabolic
Arsenic trioxide
Arsine
BZ (3-quinuclidinyl benzilate)
Carbon disulfide
Dimethyl mercury
Mercuric chloride
Osmium tetroxide
Tetraethyllead
Tetramethyllead
Thallium sulfate

Opioid
Carfentanil (synthetic)
2,3-diacetylmorphine (semi-synthetic)
Fentanyl (synthetic)

Toxidromes and Chemicals

Pulmonary (Upper)

Acrolein
Allyl alcohol
Ammonia solutions
Ammonium metavanadate
Anhydrous ammonia
Arsenic trichloride
Boron Trifluoride
Boron Trifluoride and its common 50% industrial formulation with methyl ether
Boron trichloride
Bromomethane
Chloroacetone
Bis(2-chloromethyl) ether
Chloromethyl methyl ether
Chlorosulfonic acid
Cyclohexylamine
Diborane
Diphenylchloroarsine (DA)
Diphenylcyanoarsine (DC)
Disulfur dichloride
(continues in next column)

Ethyldichloroarsine (ED)
Ethylenediamine
Formaldehyde
Hydrogen bromide
Hydrogen chloride
Hydrochloric acid
Hydrogen fluoride
Hydrofluoric acid
Isopropylchloroformate
Nitric acid
Nitric oxide
Oleum
Phosphorous trichloride
Phosphoryl trichloride
Propyleneimine
Sulfur dioxide, anhydrous
Sulfur tetrafluoride
Sulfur trioxide
Titanium tetrachloride
Vanadium pentoxide

Vesicant,

"Delayed" onset
Nitrogen mustard (HN-3)
Sulfur mustard

"Rapid" onset
Lewisite
Phosgene oxime

Pulmonary (Lower)

"Mid" onset
Adamsite
Benzenethiol
Bromine
Bromopropyne
2-Butanone peroxide
Chloropicrin
Chlorine
Chlorine dioxide
Chloroform
α, α-Dimethylbenzyl hydroperoxide
Dimethyl sulfate
Epichlorohydrin
Ethylchloroacetate
Fluorine
Hexachlorocyclopentadiene
Hydrazine
Hydrogen selenide
Methyl hydrazine
Perfluoroisobutene
Perchloromethyl mercaptan
Phosphine
Methyl isocyanate
Phosgene

Anticoagulants Toxidrome

Inhibits vitamin K dependent synthesis of biologically active forms of the calcium-dependent clotting factors.

Toxidrome	Toxicant Examples	Medical Mitigation
Bleeding. For example, hematomas after minor trauma, nosebleeds, GI bleeding, hematuria, and intracranial hemorrage. Elevated PT and INR (International Normalized Ratio)	Brodificoum Diphacinone Bromodialone	Vitamin K Activated charcoal by mouth or NG tube if patient is unconscious

Blood Toxidrome

Cyanide has a high affinity for certain sulfur and metallic complexes, particularly those containing the trivalent form of iron. The cyanide ion binds with iron in the cytochrome oxidase complex and prevents intracellular oxygen utilization leading to anaerobic cell metabolism and metabolic acidosis. Poisonings by may be treated essentially the same as poisoning by cyanide salts.

Medical Endpoints	Toxicant Examples	Medical Mitigation
Acute onset Flushing of the skin, weakness Nausea, anxiety, difficulty breathing Moderate to severe Convulsions Respiratory distress	Cyanides Nitriles Pentacarbonyl iron Sodium azide	Oxygen Cyanide antidote kits Mechanical ventilation

Cholinergic Toxidrome

Acetylcholine is the principal neurotransmitter in all autonomic ganglia. Cholinergic chemicals prolong acetylcholine's stimulative effects by prohibiting it from being metabolized by acetylcholinesterase. G agents are considered separately from pesticides in terms of time to symptom onset and other timing considerations.

Medical Endpoints	Toxicant Examples	Medical Mitigation
Blurred vision Miosis Chest tightness and dyspnea Muscular spasm Nausea Rhinorrhea Lacrimation Salivation	Sarin (GB) Soman (GD) Cyclosarin (GF) Tabun (GA) VX Organophosphorus Pesticides Carbamate Pesticides	Atropine sulfate 2-PAM Benzodiazepines Supportive cardio and pulmonary care

Convulsants Toxidrome

GABA inhibitors are chemicals that block the activity of γ-aminobutyric acid, the major inhibitory neurotransmitter in the mammalian central nervous system. Signs and symptoms include central nervous system excitation and seizures. Death is caused by convulsive interference with pulmonary function and by depression of respiratory center activity.

Medical Endpoints	Toxicant Examples	Medical Mitigation
Convulsions Muscle rigidity	Picrotoxin Hydrazine Strychnine TETS GABA antagonists	Activated charcoal by mouth or NG tube Diazepam Phenobarbitol Lorazepam Cardiopulmonary support

Hemolytic/Metabolic Toxidrome

The heavy metals and some other compounds are systemic poisonings that impair metabolic mechanisms in an array of enzymes, and produce multisystem effects. Toxicants interfere with metabolic-biochemical reactions that are necessary to maintain life . These include glycolysis, anaerobic respiration, Krebs cycle, oxidative phosphorylation, ß-oxidation, gluco-neogenesis, CoA-reductase pathway, heme synthesis, and the Urea cycle.

Toxidrome	Toxicant Examples	Medical Mitigation
Vomiting, diarrhea Difficulty to severe breathing Chest pain Nervous system disorder Long term systemic effects	Arsenic trioxide Arsine BZ Carbon disulfide Dimethyl mercury Mercuric chloride Osmium tetroxide Organolead compounds Thallium sulfate	Chelating agents Activated carbon by mouth or nasogastric tube Diuretics

Opioids Toxidrome

Natural and synthetic opioid receptor agonists, their effect is to depress the central nervous system.

Toxidrome	Toxicant Examples	Medical Mitigation
Decreased blood pressure Decreased heart rate Decreased body temperature Analgesia Induces sleep Miosis Slow and shallow breathing Pulmonary edema Nausea and vomiting	Diacetylmorphine (heroin) Fentanyl Carfentanil	Cardiopulmonary support Naloxone by IV, IM, SC or ET tube

Upper Pulmonary Toxidrome

Upper pulmonary agents include gases, aerosols, and particulates that are readily soluble in water or react with it to form a corrosive environment, or react directly with the linings of the nose, throat, and airways of the upper pulmonary system. These chemicals are almost completely removed by solution and react at the surfaces of the respiratory tract, and thus are very efficiently scrubbed by the upper respiratory tract

Toxidrome	Toxicant Examples	Medical Mitigation
Non-debilitating to debilitating cough Bronchospasm Dyspnea Drooling and dysphagia Nasal and tracheal irritation URT infection Upper respiratory edema Lacrimation and blurred vision Chemical skin irritation, itching, and burns	Acids and bases Organohalides Metal and metalloid halides Acrolein, allyl alcohol, and formaldehyde Vanadium pentoxide and ammonium metavanadate	Oxygen Mechanical Ventilator Bronchodilators, Albuterol and Ipitropium Bromide Eye irrigation

Lower Pulmonary Toxidrome

Chemicals include relatively water insoluble gases, aerosols, and particulates up to about 5 um. Toxicity mechanisms include direct damage to tissues from hydrolysis products, inactivation of key enzymes by reaction with biological functional groups, reaction with alveolar surfactants, and organ toxicity from chemicals that may successfully cross the alveolar-capillary boundary. The chemicals are further segregated into long (30 minutes to 24 hours) and short onset (3 to 180 minutes).

Toxidrome	Toxicant Examples	Medical Mitigation
Cough Bronchospasm Dyspnea Drooling and dysphagia Nasal and tracheal irritation RT infection and edema **Life threatening to fatal Pulmonary Edema** Lacrimation and blurred vision Chemical skin irritation and burns	Arsine Carbon disulfide Chloropicrin Chlorine Dimethyl sulfate Hydrazine Hydrogen selenide Methyl Isocyanate Perfluoroisobutene Phosgene	Oxygen Mechanical Ventilator Bronchodilators, Albuterol and Ipitropium Bromide Eye irrigation

Comments regarding pulmonary agents

The distinctive feature of upper pulmonary injury is the rapid onset of easily identifiable effects. Those symptoms motivate the victims to leave the area and reduce their exposure.

Lower pulmonary agents have poorer warning properties so victims are not motivated to leave the area and avoid a higher exposure dose. Some lower pulmonary agents may cause a delayed onset of pulmonary edema that is a direct result of cellular damage.

Some pulmonary agents are both upper and lower. Chlorine is a good example; lower doses cause mostly upper pulmonary effects and higher doses cause both.

Lower pulmonary agents that inhibit oxygen usage may cause rapid effects to oxygen sensitive organs, notably the brain and heart. Victims may quickly become unconscious and suffer from seizures, cardiac dysrhythmias or cardio-respiratory arrest aside from pulmonary irritation, but pulmonary edema is rare even in lower dose exposures

Vesicant Toxidrome

Chemicals that cause moderate to debilitating eye, skin, and mucosal pain but don't necessarily result in death.

Toxidrome	Toxicant	Medical Mitigation
Erythemia Vesicles, bullae, blistering Necrosis Eyelid swelling, corneal damage, blindness Debilitating pain Shortness of breath, tachypnea, hemoptysis, pulmonary edema Cardiovascular-cardiovascular arrest Nervous system-convulsions and coma	**Slow onset:** Sulfur mustard Nitrogen mustard **Rapid onset:** Lewisite (L) Phosgene oxime (CX)	Clothing and skin decontamination Eye irrigation Analgesics Oxygen Respiratory support Bronchodilators Debridement

Conclusion

Although Toxidrome Classification has limitations it provides adequate life saving treatment for victims of mass casualty exposures. Use of toxidromes as a diagnostic tool is fundamental to effective medical response.

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Questions?