

Translational Research Models to Evaluate the Pathogenesis of Inhaled Toxic Chemicals



Principal Investigator Dr. Vik Bebarta, MD
Professor, Emergency Medicine, Toxicology, Pharmacology

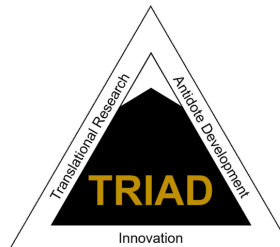
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University of Colorado
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CU Center for COMBAT Research



Vision - Save and improve lives on the battlefield and at home

Mission - We solve the U.S. military's toughest medical challenges by leading high-impact research, education, and innovation in collaboration with government, academic, and industry partners.

We turn military medical gains into better health care for all

We Help the DoD:

Execute collaborative research for definitive warfighter health solutions

Develop warfighter solutions to address DoD's highest-priority needs

Translational Research, Innovation, & Antidote Development

Research Priorities

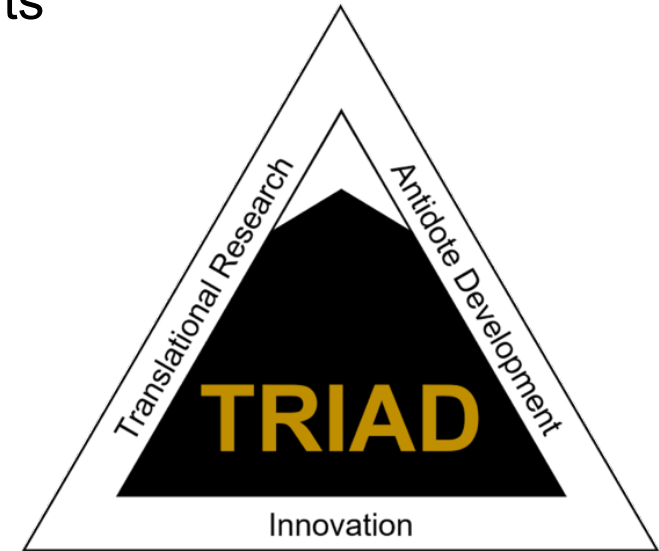
- Establish clinically relevant, preclinical, translational research models
- Innovative medical countermeasures against chemical agents
- Novel therapeutics for inhaled occupational exposures
- Pragmatic treatments for prehospital care

Current Funding

- National Institutes of Health
- Department of Defense
- United States Air Force
- United States Army

Mission

Bring lifesaving, innovative discoveries from the bench to the bedside

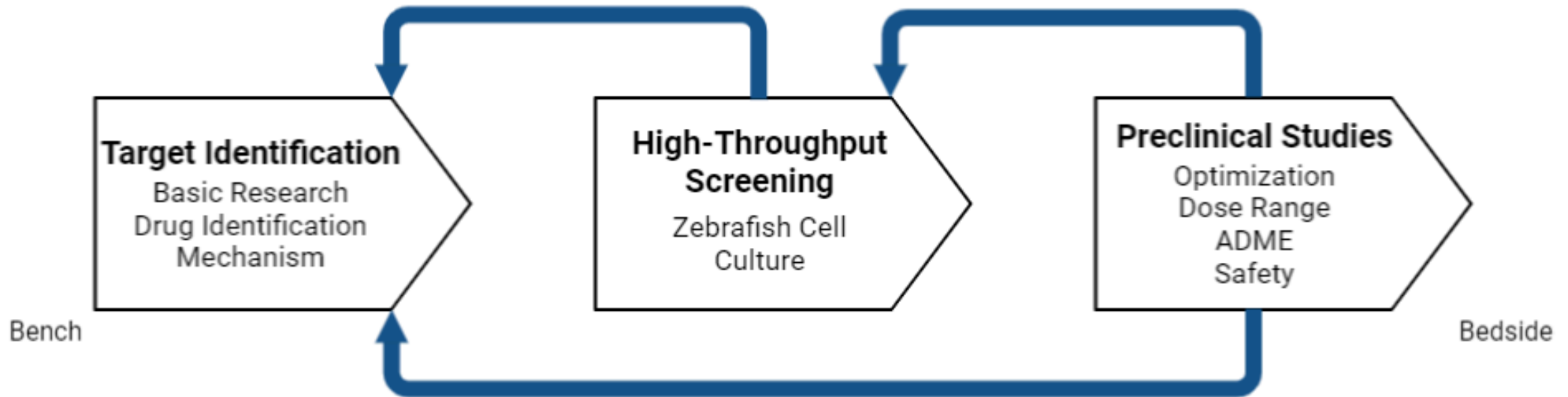


A pig is shown in profile, facing right, against a dark background. The pig is light-colored, possibly pink or white, and its features are clearly visible. The pig's head is in the foreground, and its body extends towards the left. The pig's ears are upright, and its snout is prominent. The pig's legs are visible, and it appears to be standing or walking. The pig is the central focus of the image, and its presence is likely related to the text about preclinical medical countermeasure drug development.

Swine for Preclinical Medical Countermeasure Drug Development

- Dose scaling, allometric, similar size, several studies
- **Similar anatomy/physiology** – cardiac, pulm, GI, oxidative stress, immune
- **Clinical** – Similar airway size, similar human devices
- **Experiment** – serial blood draws, large tissue samples
- **Current state** – medical countermeasures, ongoing and prior studies on SM for pulmonary, eye and skin – accepted by FDA

Countermeasure Pipeline



- Methyl Mercaptan
- Cyanide
- Hydrogen Sulfide

- Chlorine
- Sulfur Mustard

Methylmercaptan (Methanethiol aka)

- Industrial use
- Natural gas
- Jet fuel additive
- Noxious odor
- Symptoms of Exposures
 - Nasopharyngeal irritation
 - Bronchospasm
 - Pulmonary edema
 - Systemic injury
 - Death

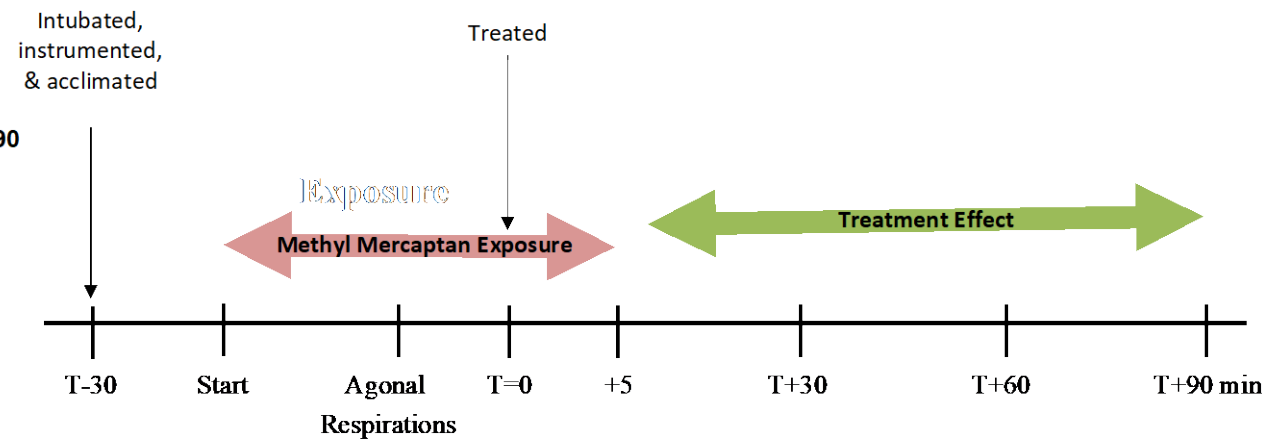
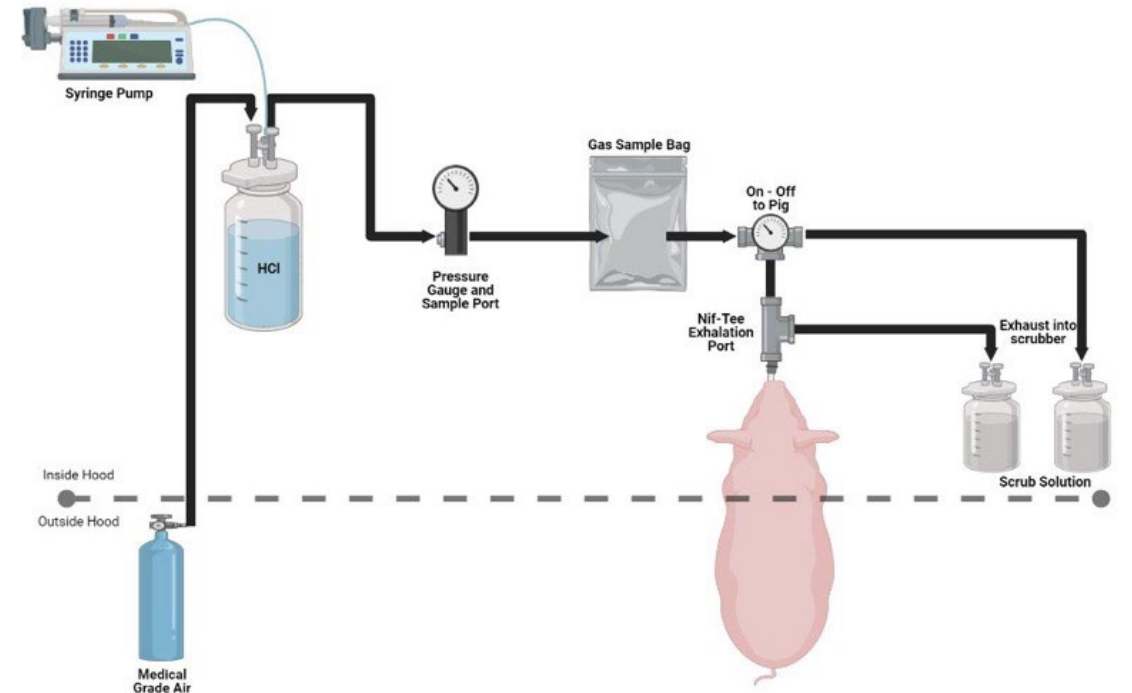
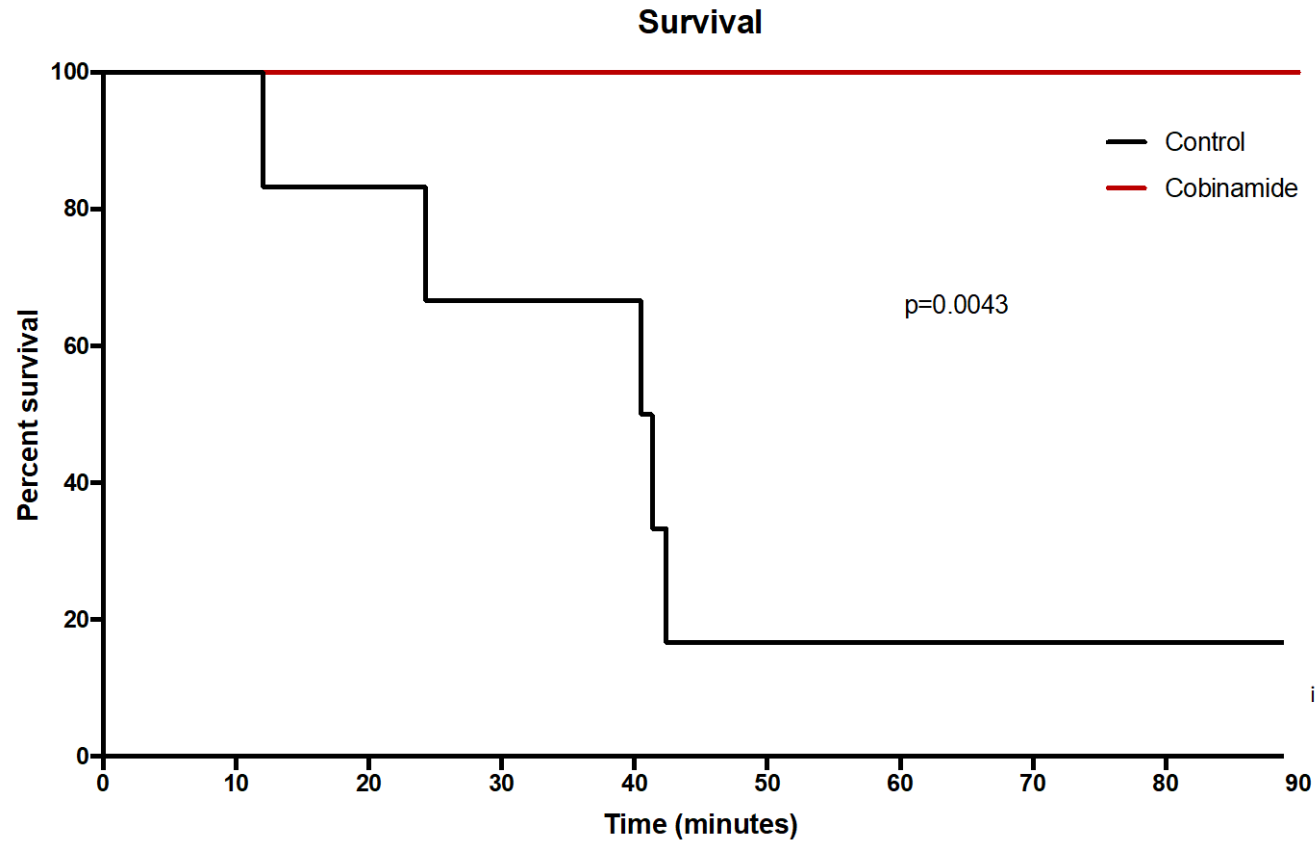


LaPorte, Texas Dupont 2014 – several deaths

Raised the awareness for methylmercaptan as a threat

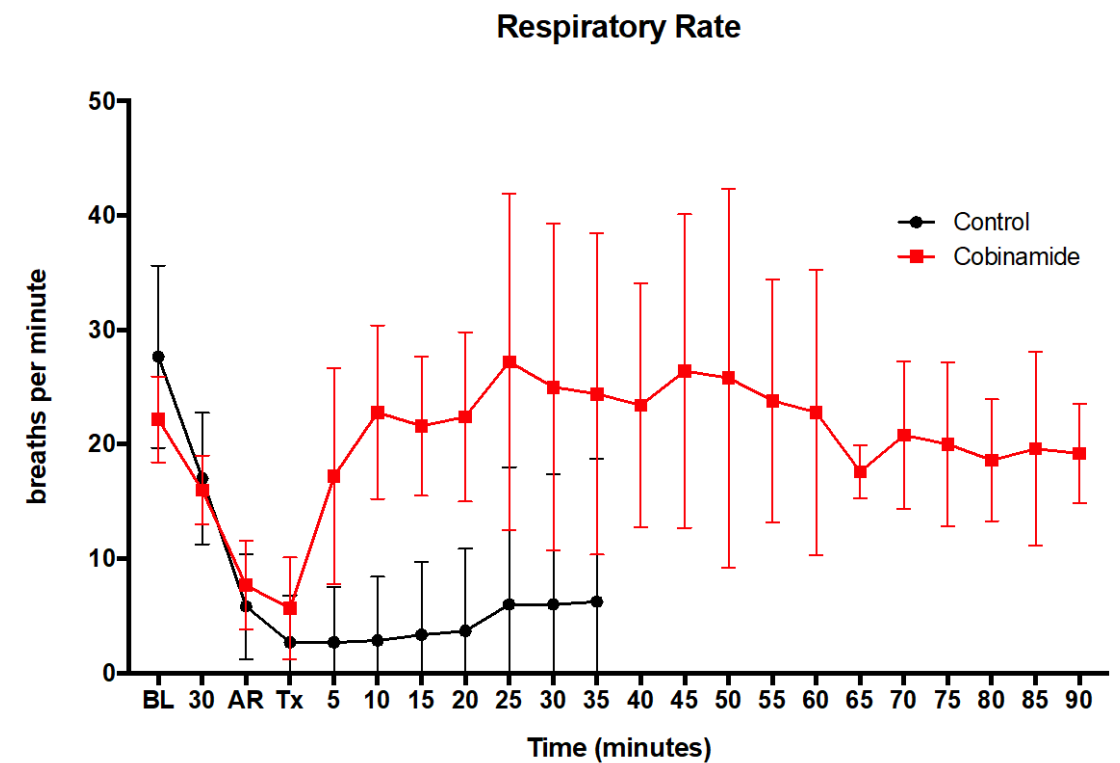
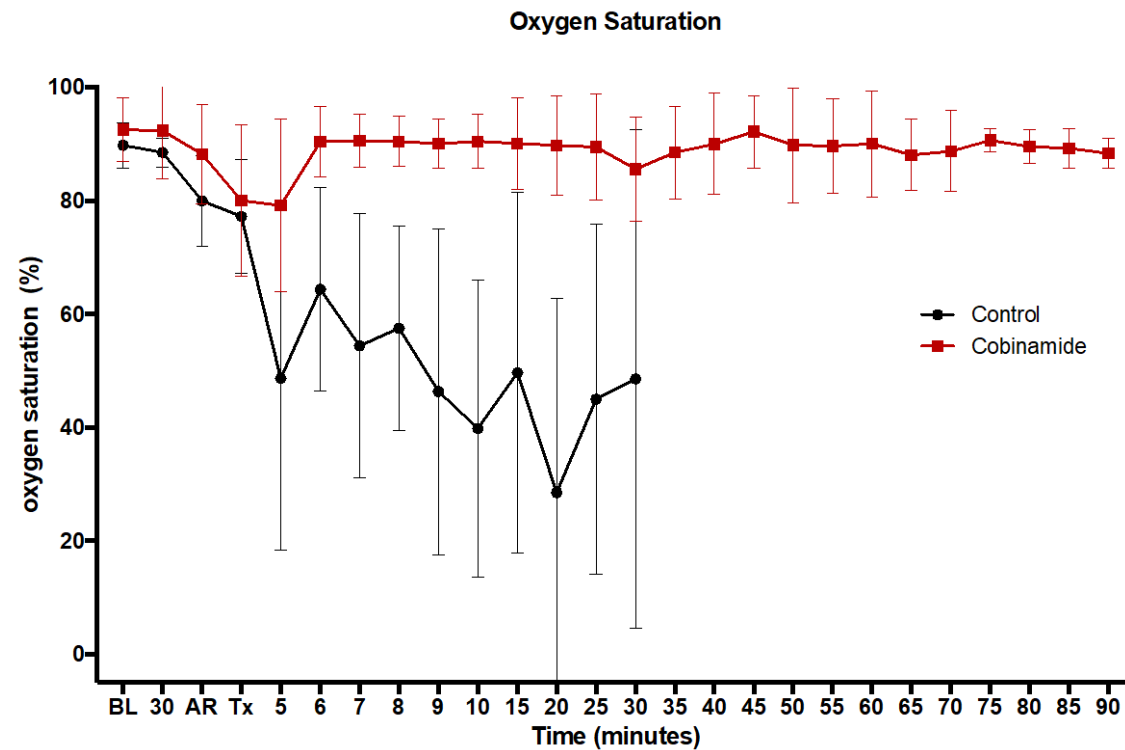


Cobinamide as a Treatment for Methyl Mercaptan



This work was supported by NIEHS-CounterACT grant # U54ES027698

Cobinamide as a Treatment to Methyl Mercaptan Exposure



Hendry-Hofer TB, Ng PC, McGrath AM, Soules K, Mukai DS, Chan A, Maddry JK, White CW, Lee J, Mahon SB, Brenner M, Boss GR, Bebartva VS. Intramuscular cobinamide as an antidote to methyl mercaptan poisoning. *Inhal Toxicol.* 2021 Jan;33(1):25-32. doi: 10.1080/08958378.2020.1866123. Epub 2020 Dec 26. PMID: 33356664; PMCID: PMC8063453.

Hydrogen Sulfide

- Industrial use
- Oil and gas refining
- Sewer gas
- Volcanoes
- Noxious odor

Symptoms of Exposures

- Shortness of breath
- Apnea
- Knock down
- Long-term neurologic effects
- Death



World » Foiled plot to blow up plane, unleash gas revealed in Australia

Live TV

U.S. Edition +



Foiled plot to blow up plane, unleash gas revealed in Australia

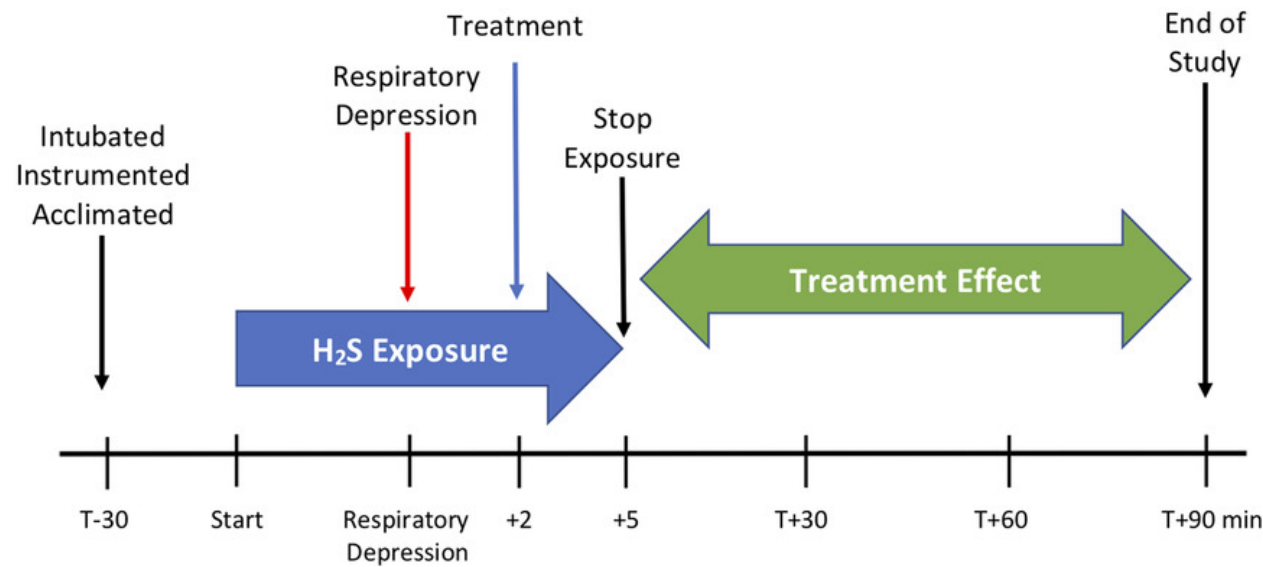
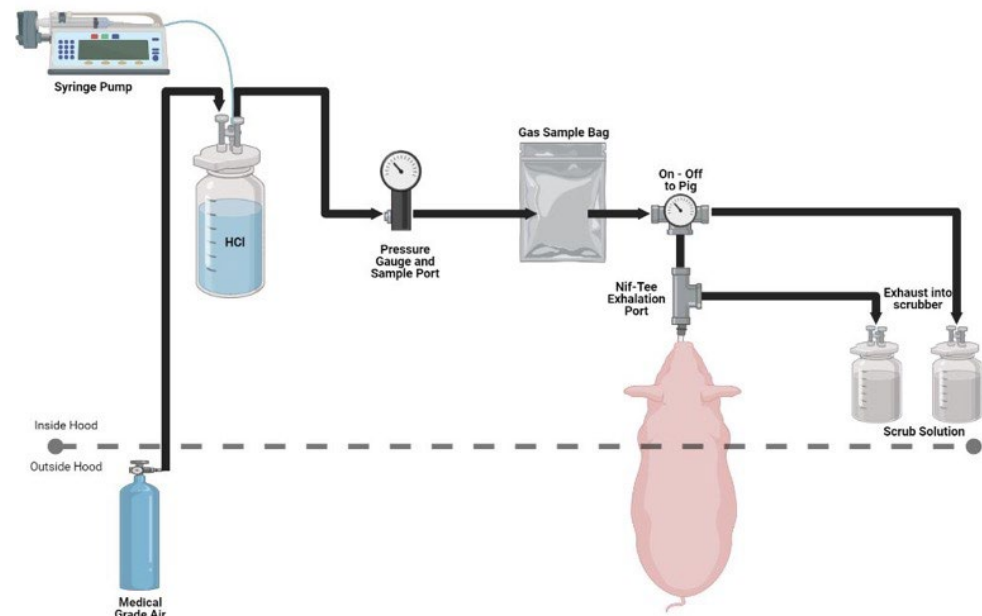
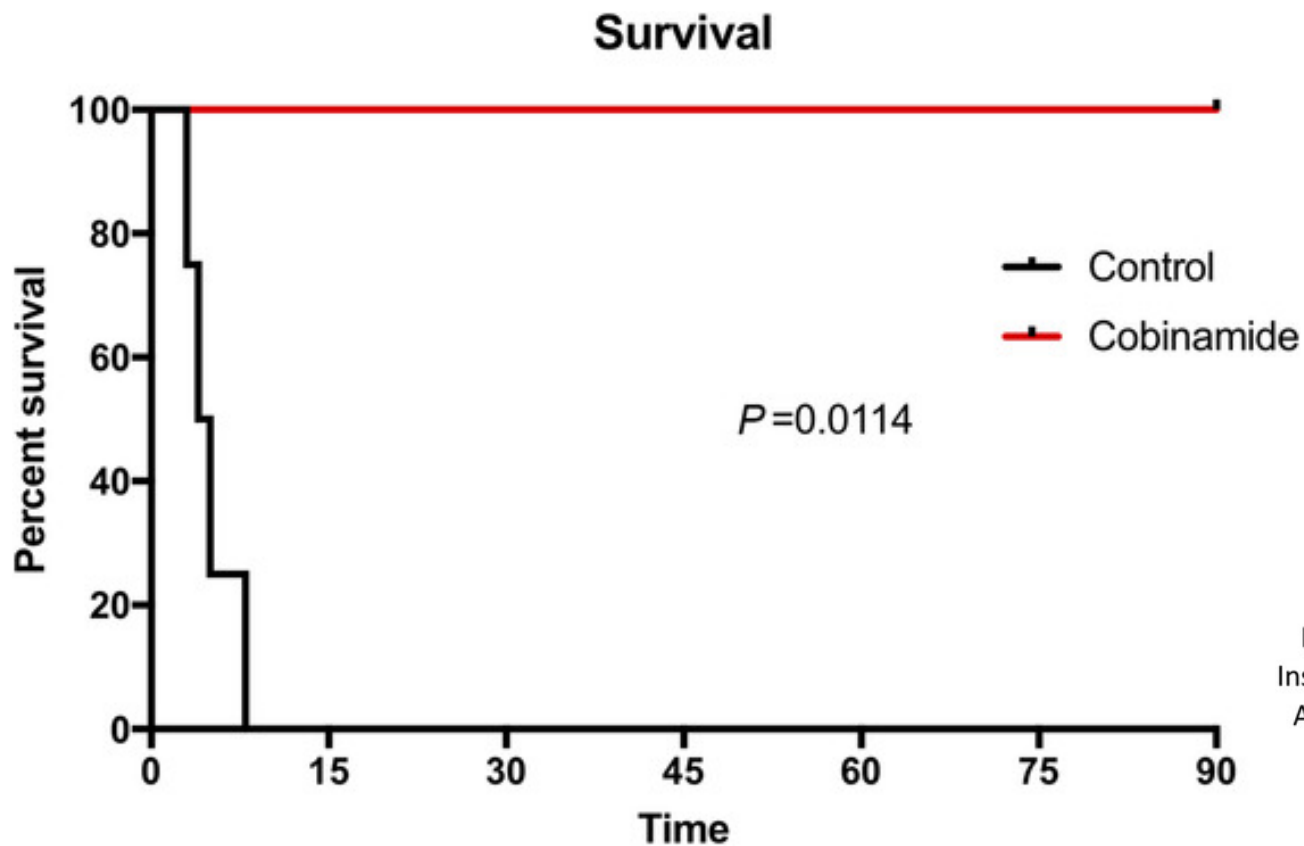


By **Euan McKirdy** and Karen Smith, CNN

Updated 1:39 AM ET, Sat August 5, 2017



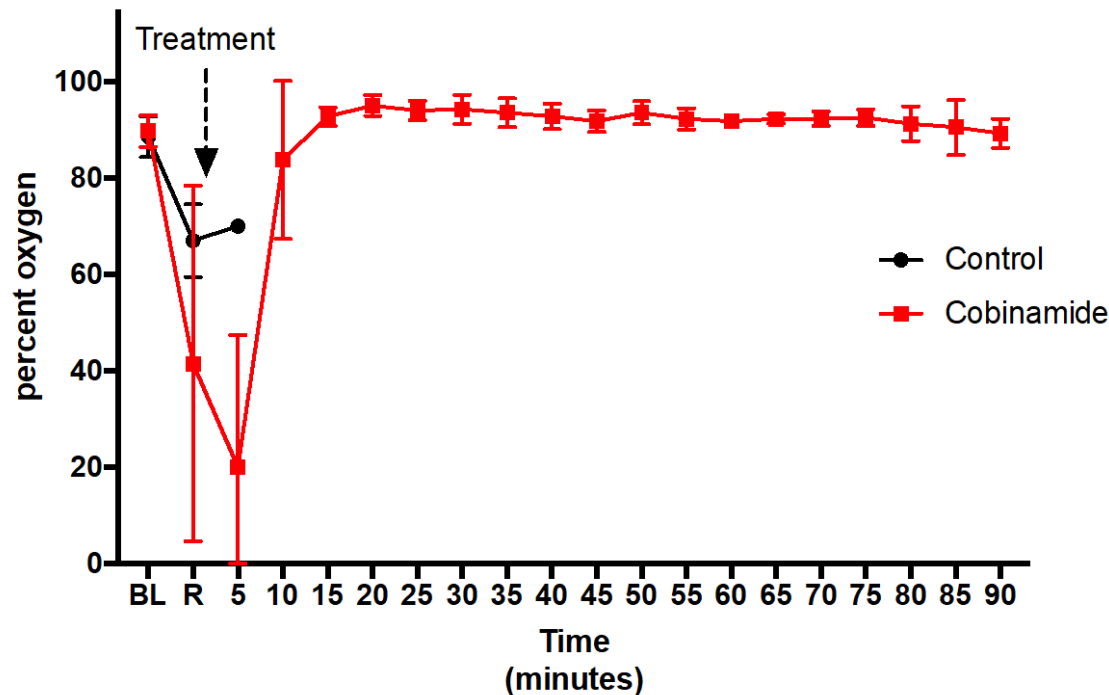
Cobinamide as a Treatment for Hydrogen Sulfide



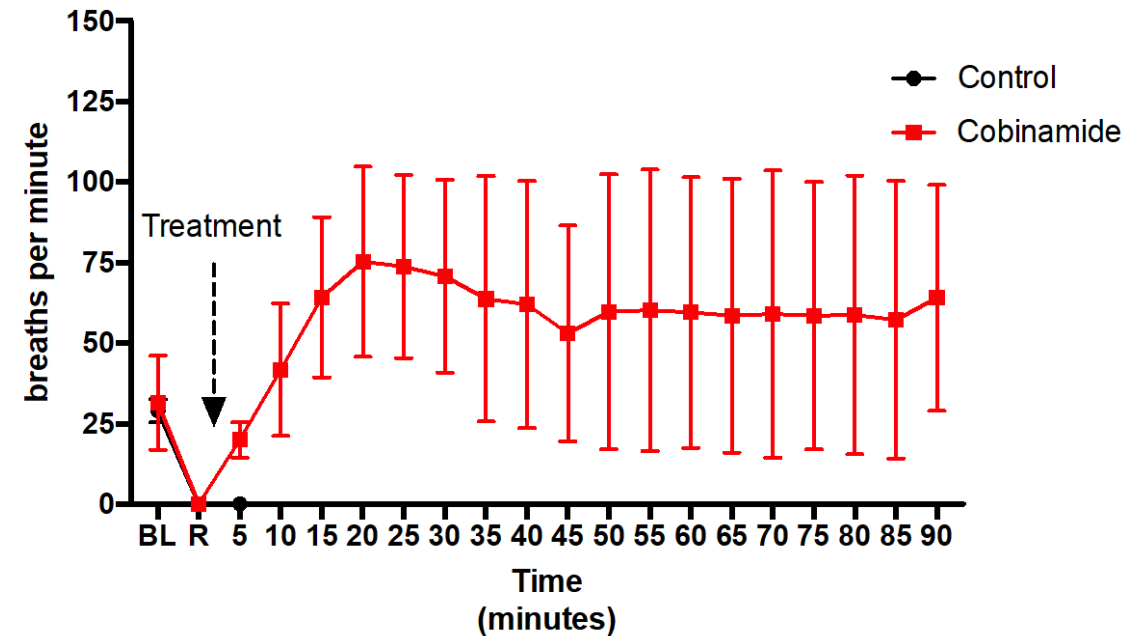
This work was supported by NINDS-CounterACT grant # 5 U01 NS087964-04.

Cobinamide as a Treatment to Hydrogen Sulfide Exposure

Oxygen Saturation



Respiratory Rate



Ng PC, Hendry-Hofer TB, Garrett N, Brenner M, Mahon SB, Maddry JK, Haouzi P, Boss GR, Gibbons TF, Araña AA, Bebartha VS. Intramuscular cobinamide versus saline for treatment of severe hydrogen sulfide toxicity in swine. *Clin Toxicol (Phila)*. 2019 Mar;57(3):189-196. doi: 10.1080/15563650.2018.1504955. Epub 2018 Nov 15. PMID: 30430872; PMCID: PMC6540978.

A photograph of a pig in a wire cage, serving as the background for the slide. The pig is white and pink, looking towards the camera. The cage floor is made of yellow plastic mesh. The background is dark and out of focus.

Long-Term Survival Models

- Off gassing
- Recover from anesthesia
- Veterinary observation and care
- Husbandry and housing
- Clinical monitoring
- Blood sampling
- Long-term outcomes

Chlorine Attacks in Iraq

Jan 28 2007 – Ramadi – killed 16

Feb 20 – N. Bagdad – 150 injured, 9 died

Feb 21 – S. Bagdad – 55 injured, 2 died

Apr 6 – Ramadi – 27 died

Several more explosions – > 9 events

Dump truck detonated

Large chlorine tank detonated

Chlorine truck detonated

Clinical Symptoms

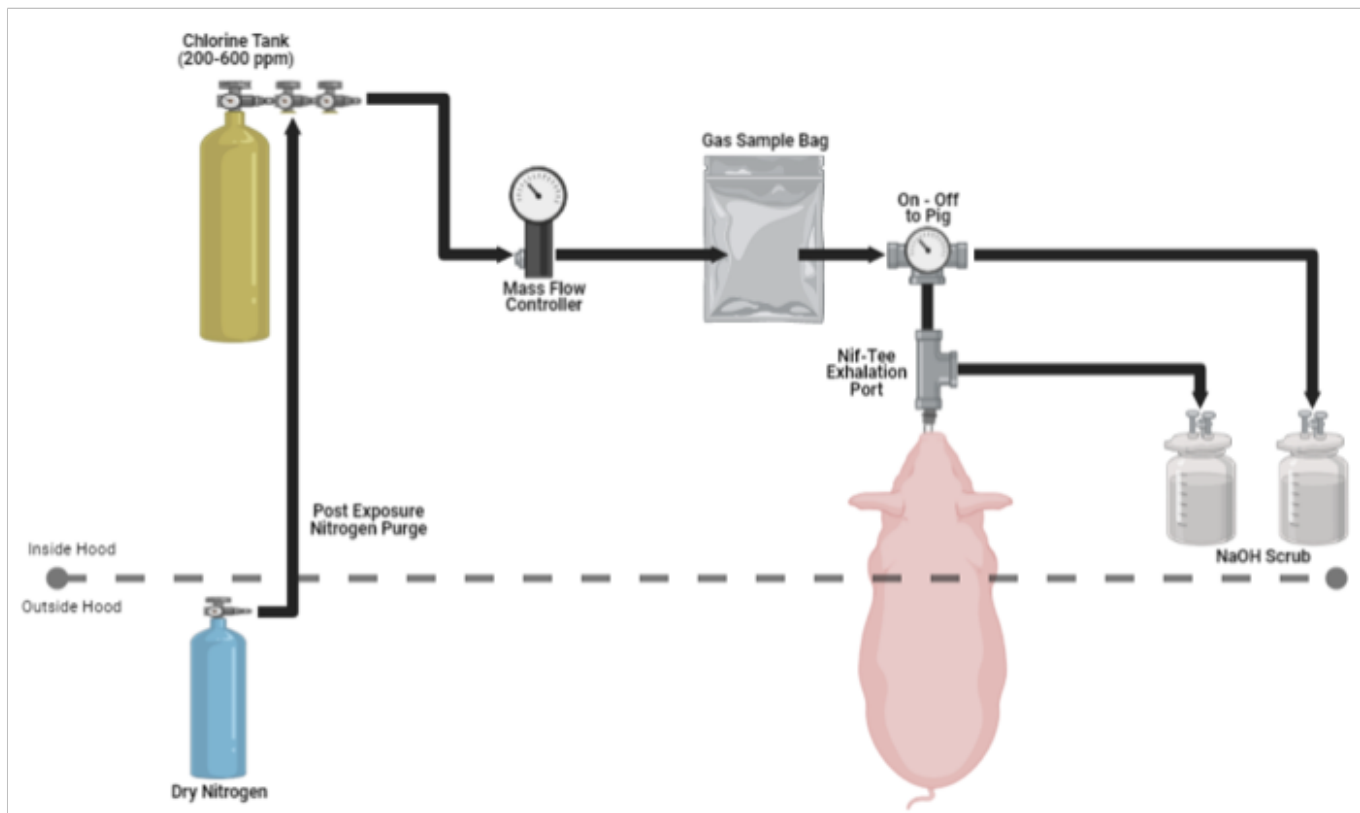
Immediate effects

- Burning of eyes, nose, throat
- Cough, wheezing
- Upper airway edema

Delayed effects

- Bronchospasm
- Pulmonary edema
- ALI and ARDS (rare)

Spontaneously Breathing Inhaled Chlorine Model



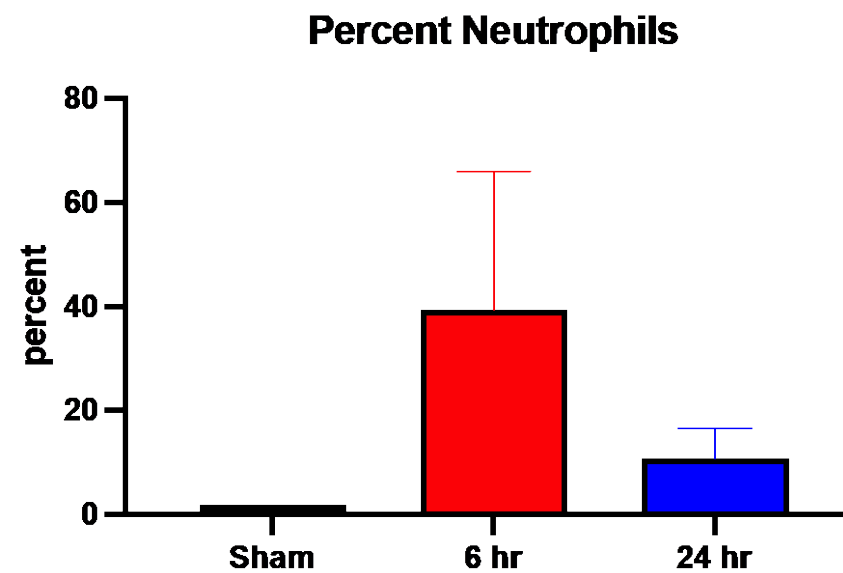
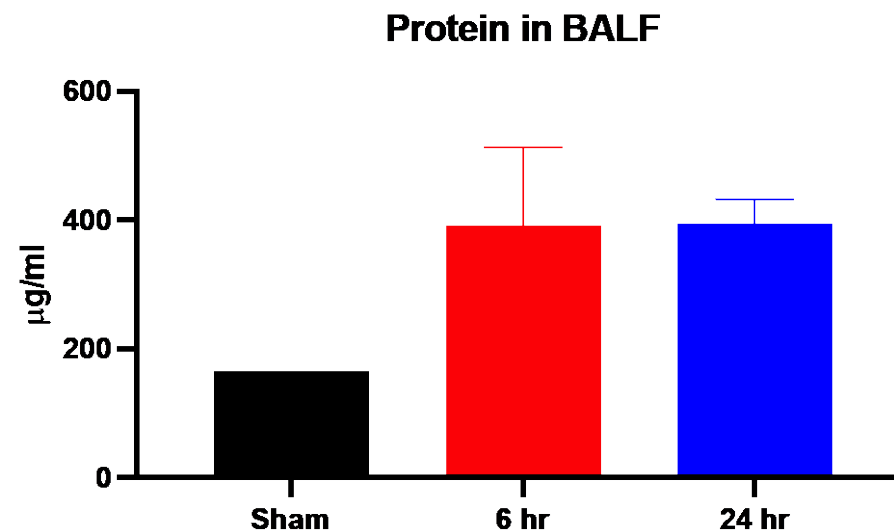
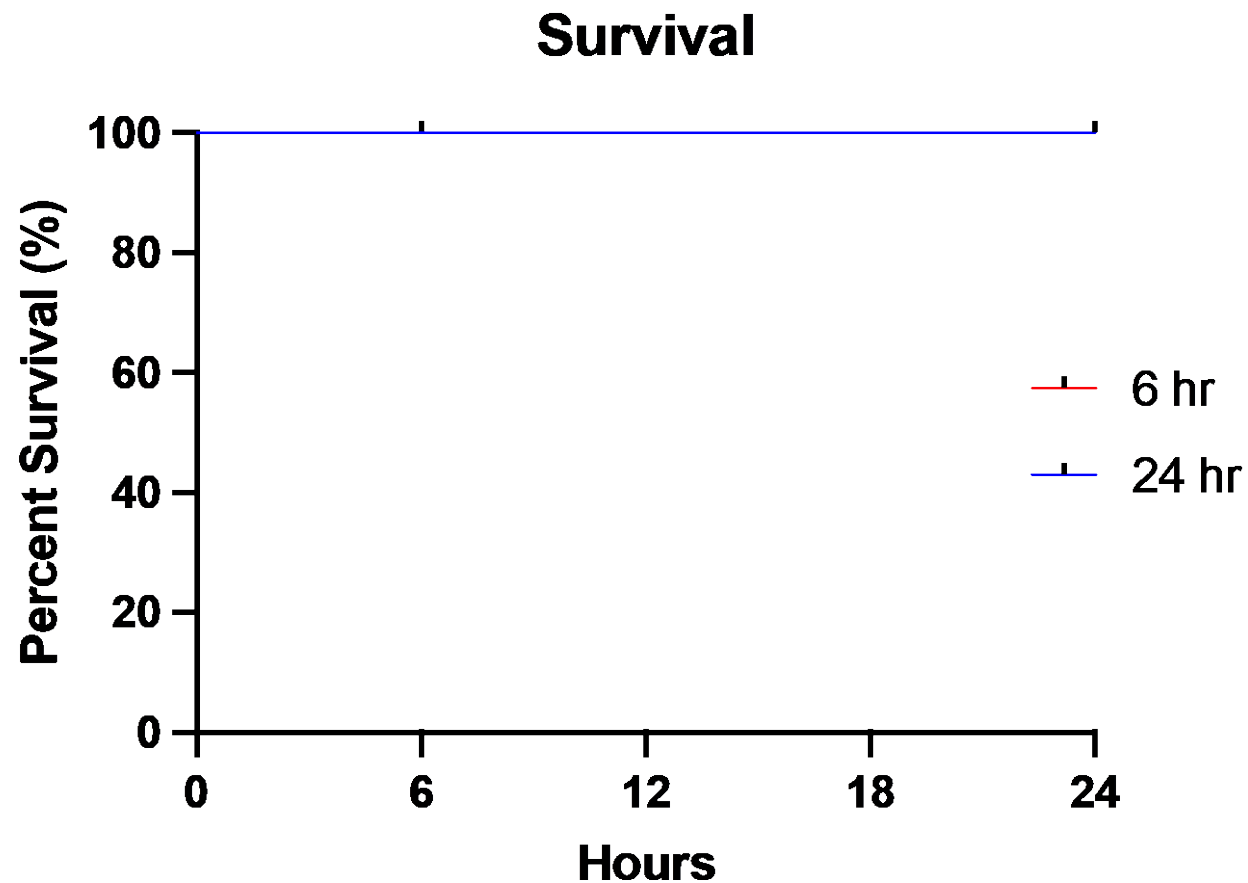
- Spontaneously breathing
- Pulsed exposure
- Sublethal
- Recovered and monitored post exposure
- Clinical symptoms and survival monitored for up to 24 hours

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Department of Medicine



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Chlorine Inhalation Model





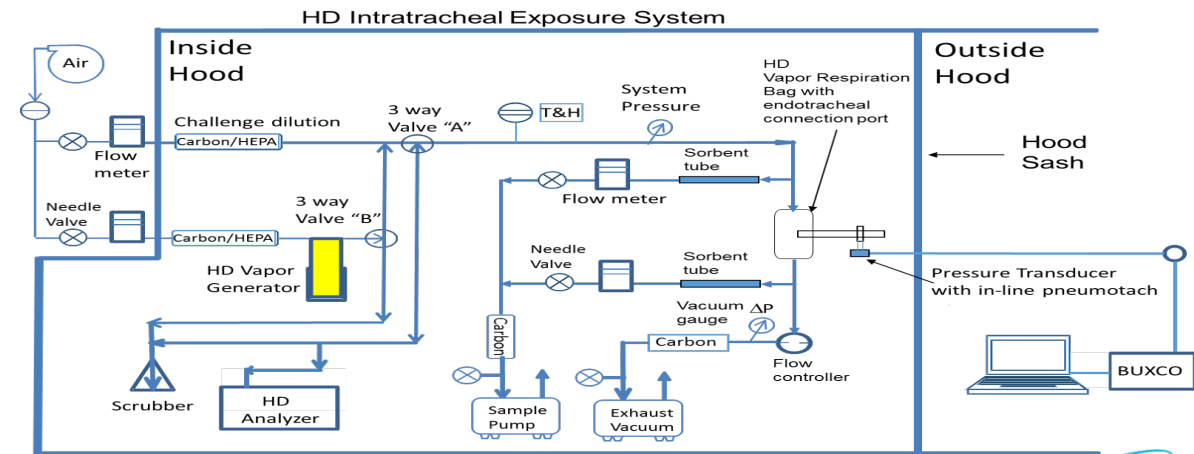
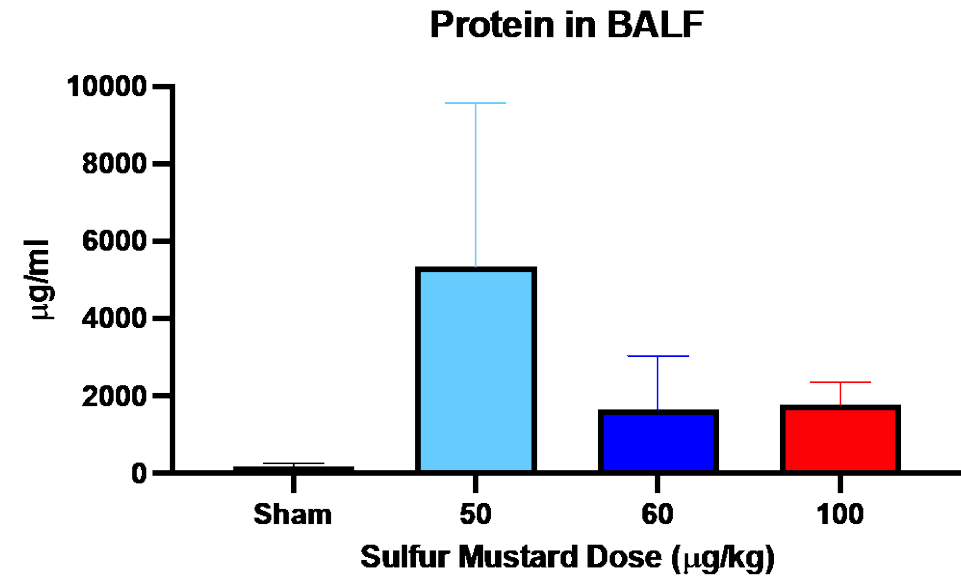
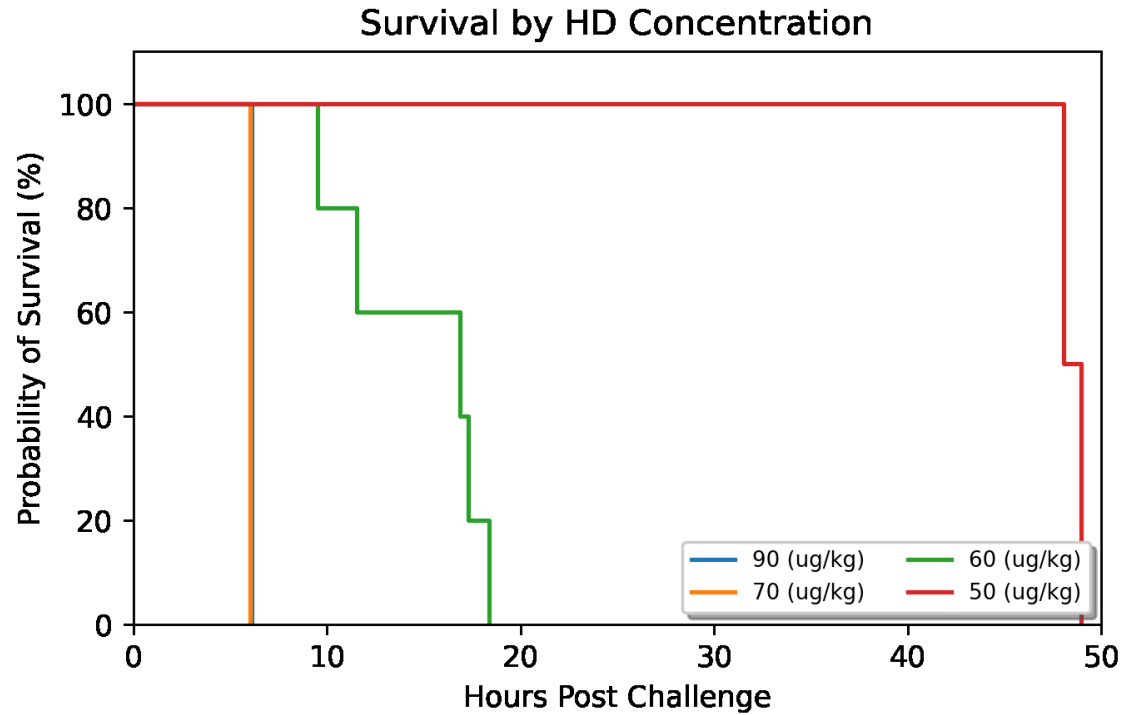
Sulfur Mustard Gas

- Chemical warfare agent
- Yellow-brown vapor
- Yellow liquid or solid
- Odorless or onion/garlic smell

Symptoms of Exposure

- Blistering of skin, eyes
- Difficulty Breathing
- Respiratory failure
- Airway obstruction
- Death

Sulfur Mustard Inhalation Model



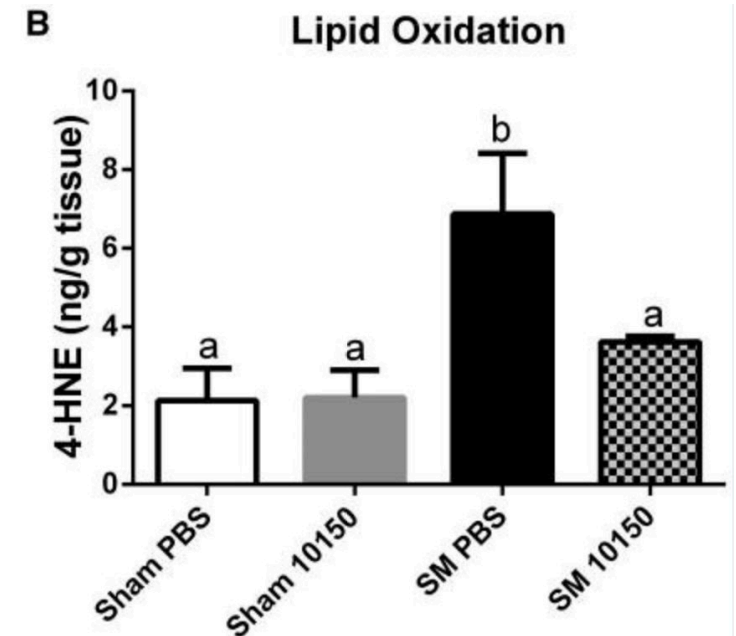
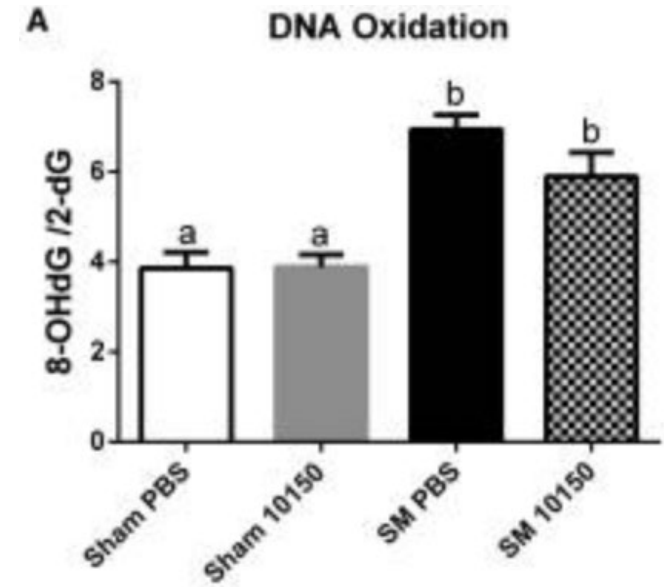
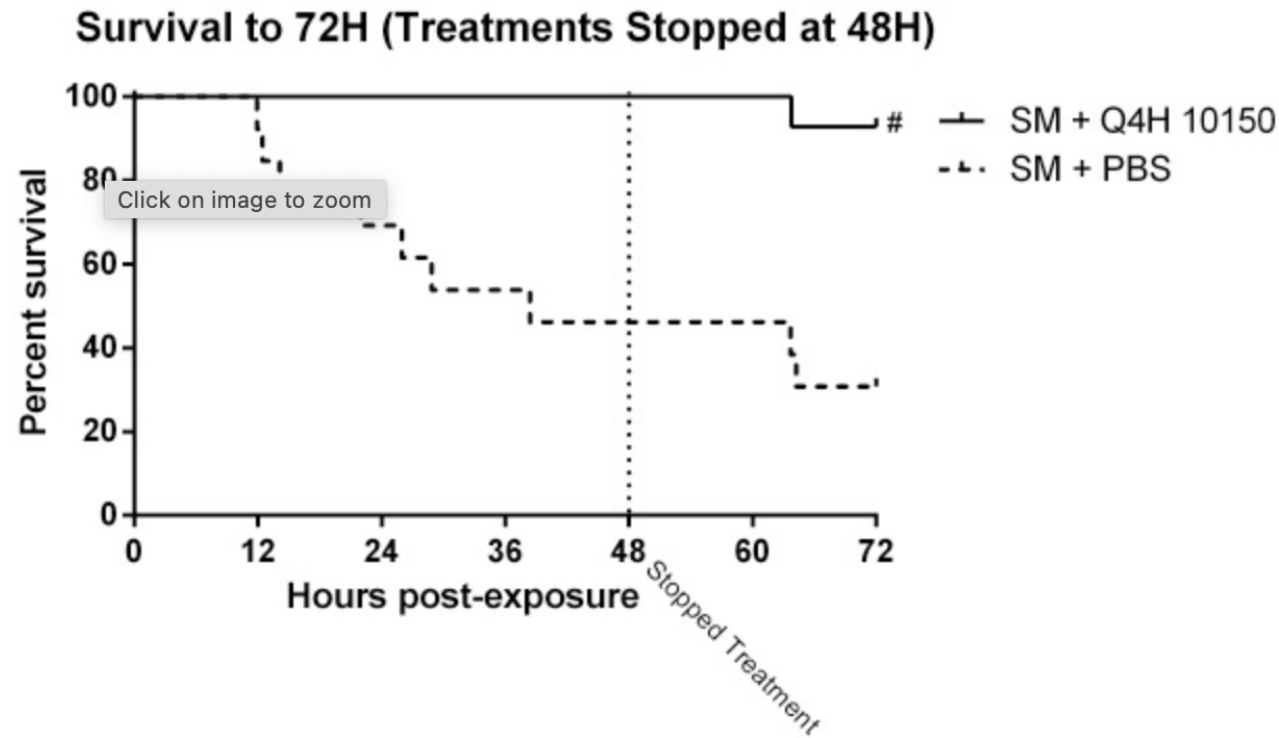
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This work is supported by NIEHS-CounterACT 5U01ES029430



Catalytic Antioxidant Rescue of Sulfur Mustard Toxicity

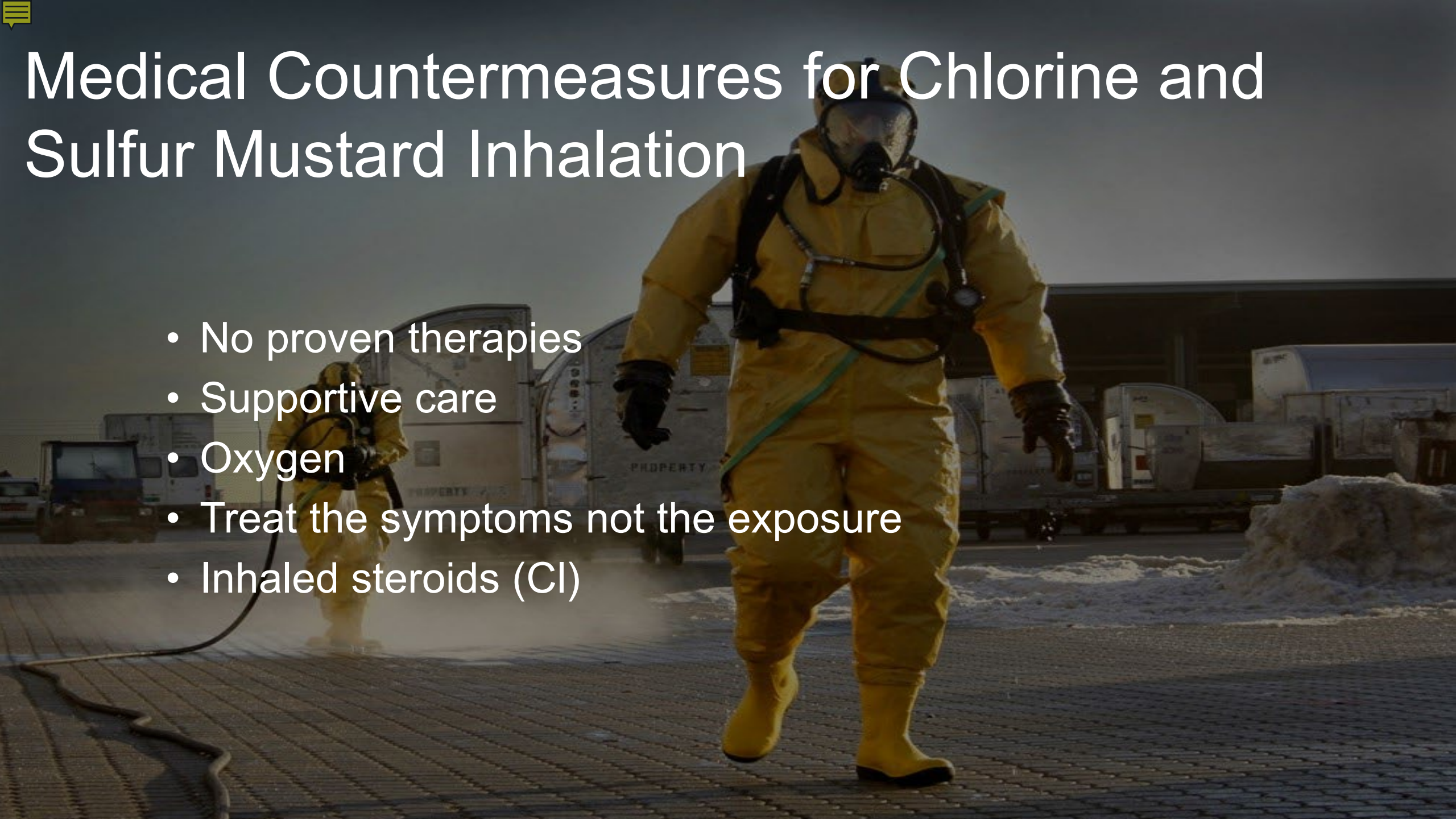


McElroy CS, Min E, Huang J, Loader JE, Hendry-Hofer TB, Garlick RB, Rioux JS, Veress LA, Smith R, Osborne C, Anderson DR, Holmes WW, Paradiso DC, White CW, Day BJ. From the Cover: Catalytic Antioxidant Rescue of Inhaled Sulfur Mustard Toxicity. *Toxicol Sci.* 2016 Dec;154(2):341-353. doi: 10.1093/toxsci/kfw170. Epub 2016 Sep 7. PMID: 27605419; PMCID: PMC5139068.



Medical Countermeasures for Chlorine and Sulfur Mustard Inhalation

- No proven therapies
- Supportive care
- Oxygen
- Treat the symptoms not the exposure
- Inhaled steroids (CI)





Common Mechanisms of Injury Across Chemical Threat Agents

- Apnea
- Oxidative Stress
- Pulmonary edema and vascular permeability
- Inflammation

Potential Therapeutics

- Respiratory stimulants
- Antioxidants
- Fibrinolytics
- Binding agents

Future Research Needs

Long term complications

- Restrictive airway disease, asthma, BO, fibrosis
- Cancers
- Other?
- Common mechanism/treatments

Clinically relevant translational research models provide us with the tools to better understand the mechanisms of toxicity and better target therapeutics

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