



United States Army Medical Research Institute of Chemical Defense

The Nation's Center of Excellence for Medical Chemical Defense

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A Medical Response Model for Mass-Casualty Intentional Food-Contamination Scenarios: Appreciating Dose, Toxicity, and Treatment Efficacy

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Disclaimers

Opinions, interpretations, conclusions, and recommendations are those of the author(s) and are not necessarily endorsed by the U.S. Army.

This research complied with the Animal Welfare Act and implementing Animal Welfare Regulations and adhered to the principles noted in *The Guide for the Care and Use of Laboratory Animals*.

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United States Food Contamination

Year	Contaminant	Vehicle	# Affected	# Deaths	Days to ID	States
1985	Listeria	Cheese	142	48		1
1985	Salmonella	Milk	5770	5		6
1993	E. coli	Beef	708	4		4
1994	Salmonella	Ice Cream	593	0		41
1997	Hepatitis A	Strawberries	153	0		1
1999	Salmonella	Juice	400	1		15
2003	Hepatitis A	Onions	935	3	14+	2
2006	E. coli	Spinach	238	5		25
2007	Salmonella	Pot Pies	401	3	150+	35
2007	Salmonella	Peanut Butter	715	0	65+	47
2008	Salmonella	Peppers	1500	2	112	43
2009	Salmonella	Peanut Butter	714	9		46
2010	Salmonella	Eggs	1939	0		14
2011	Listeria	Cantaloupe	147	33	32	28
2015	Salmonella	Cucumbers	558	3	10+	33

Intentional Poisoning

1984: members of a religious cult poisoned 10 Oregon salad bars with Salmonella (751 cases)

- 183 days to identify source
- Over one year to gather physical evidence and convict

2003: Supermarket employee adulterated 200 pounds of beef with insecticide (92 cases)

2016: Michigan man sprays supermarket salad bars and produce with rat poison

2016: Pesticide-poisoned sweets kill more than 30 people in Pakistan



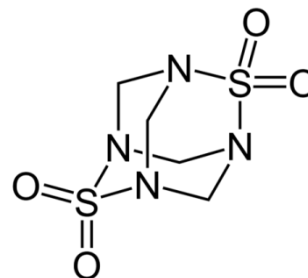
Intentional Poisoning

Tetramethylenedisulfotetramine (tetramine; TETS; *GABA antagonist*) has produced thousands of casualties

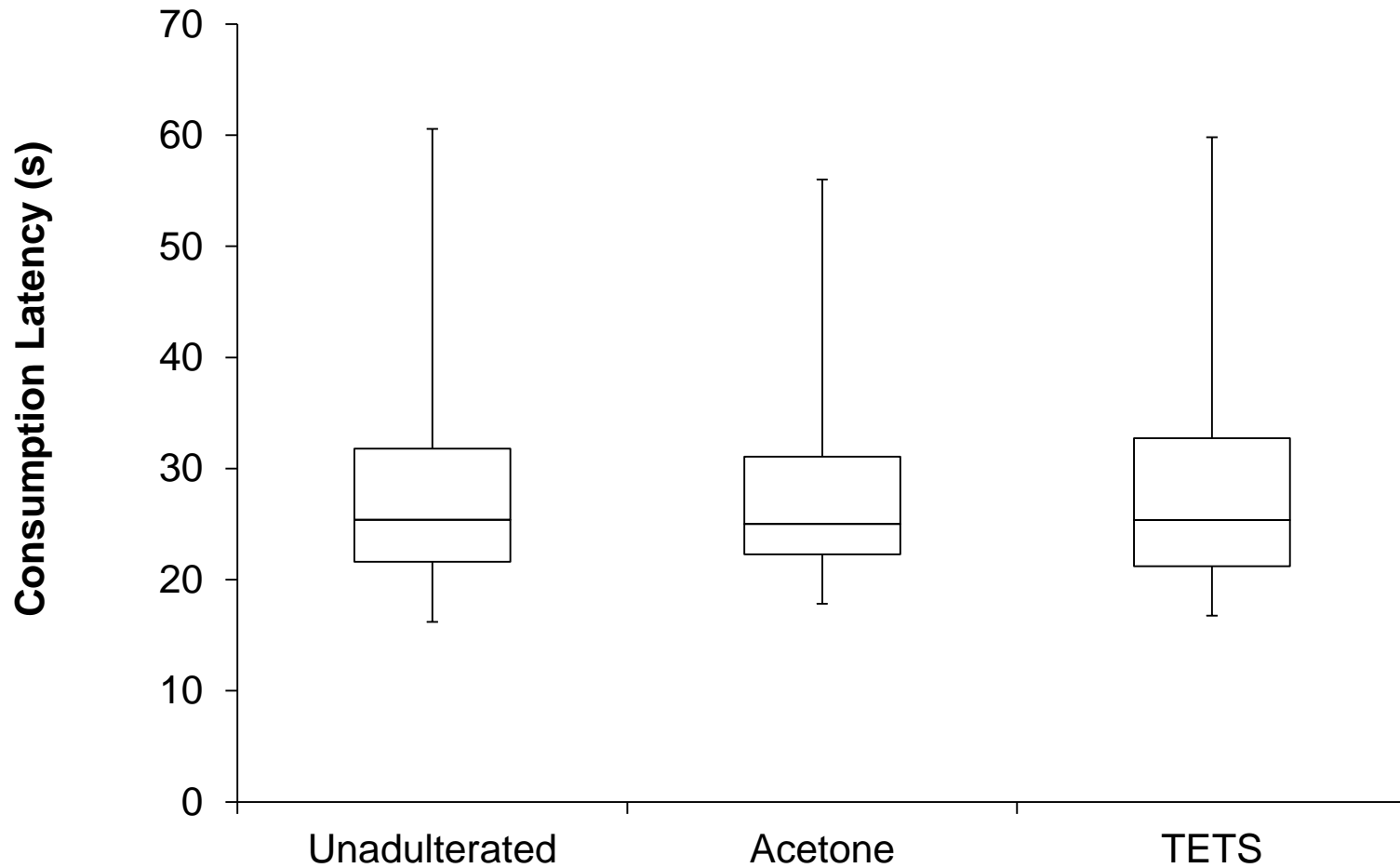
- 14,000+ people poisoned
- 900+ deaths (many children)
- Homicidal; schools, weddings, restaurants, street vendors

Chemical Properties:

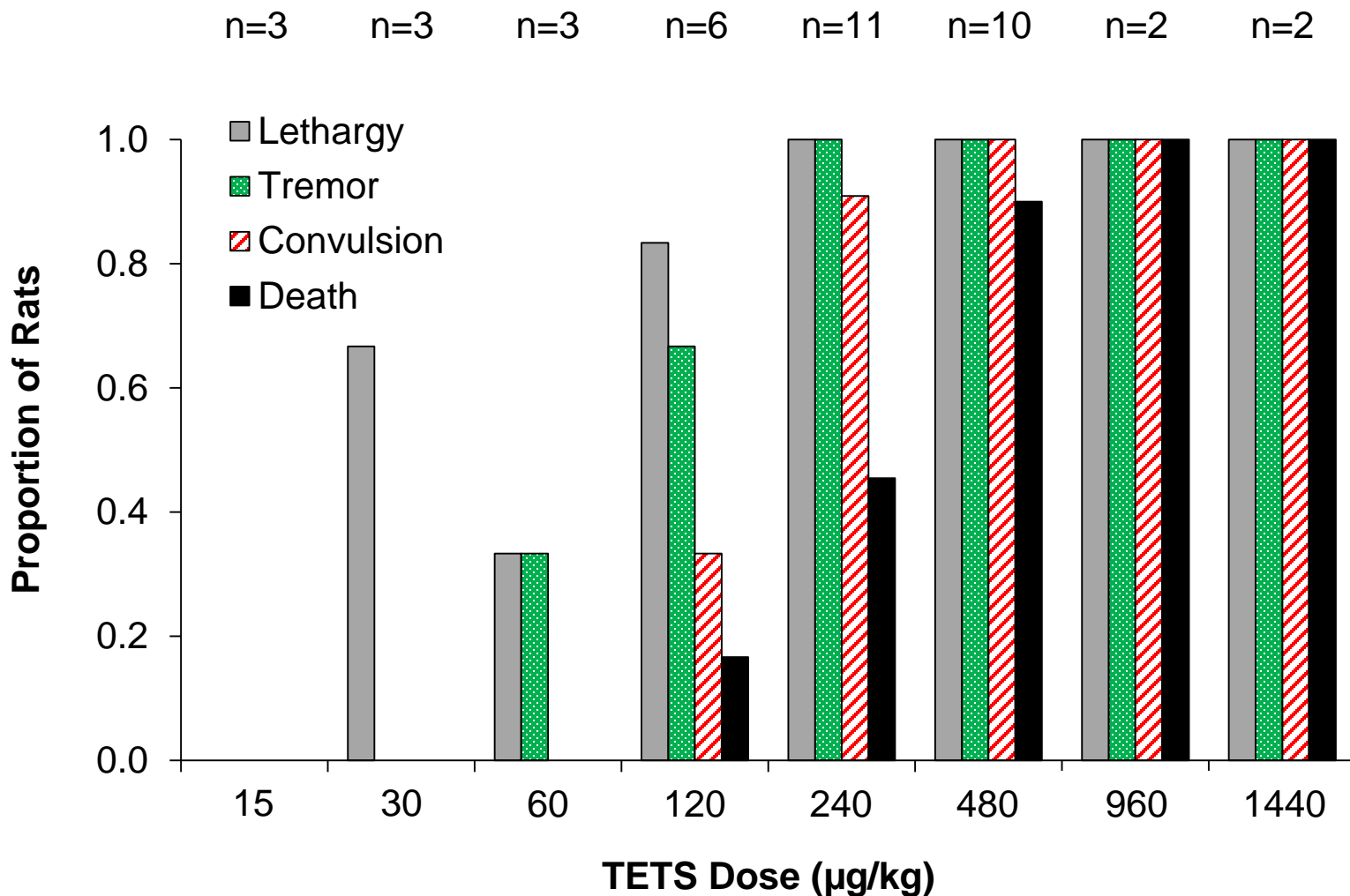
- Easily synthesized
- Tasteless, odorless
- Stable in water 6+ months
- Environmentally persistent
- Can remain in the body 6+ months



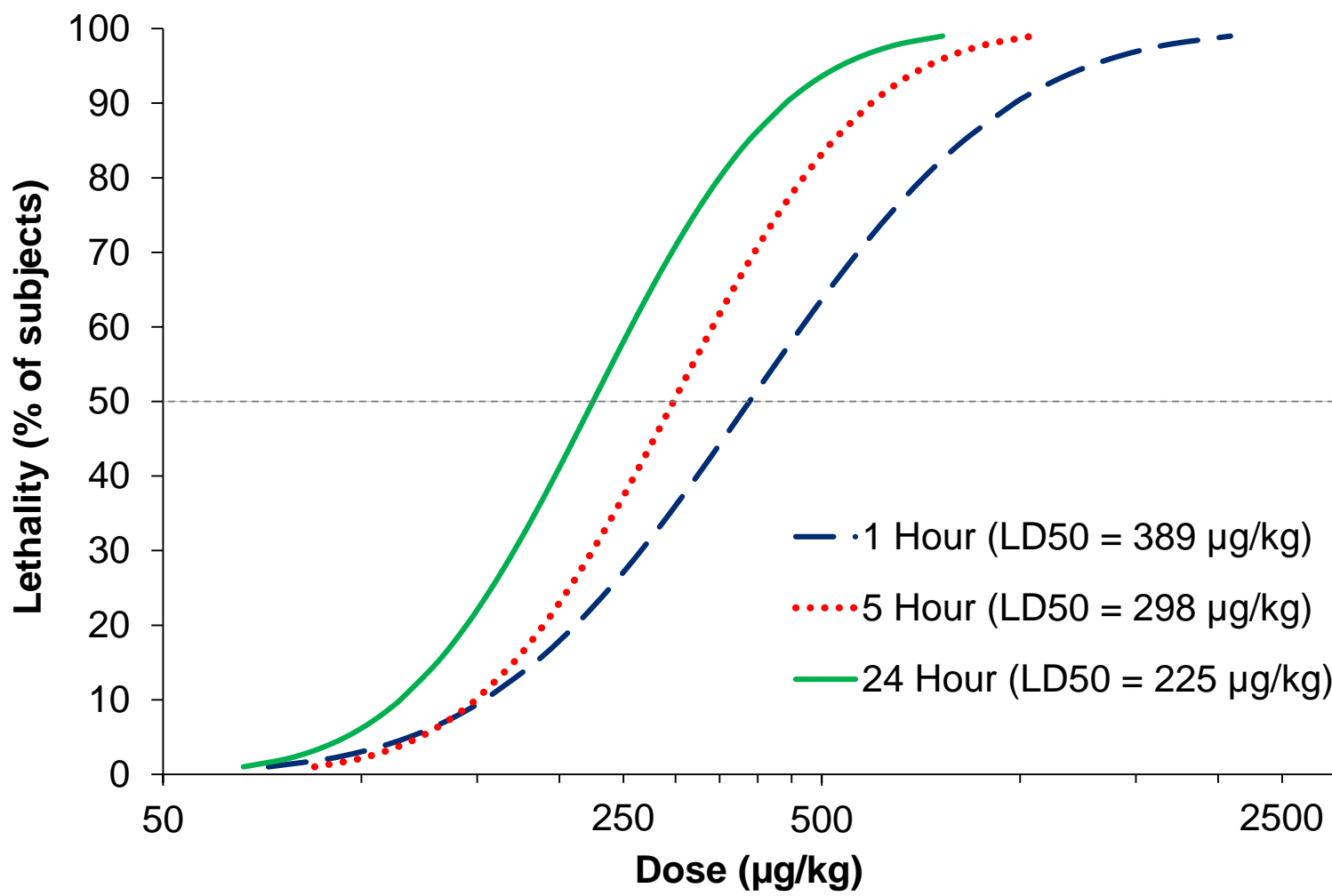
Voluntary Consumption



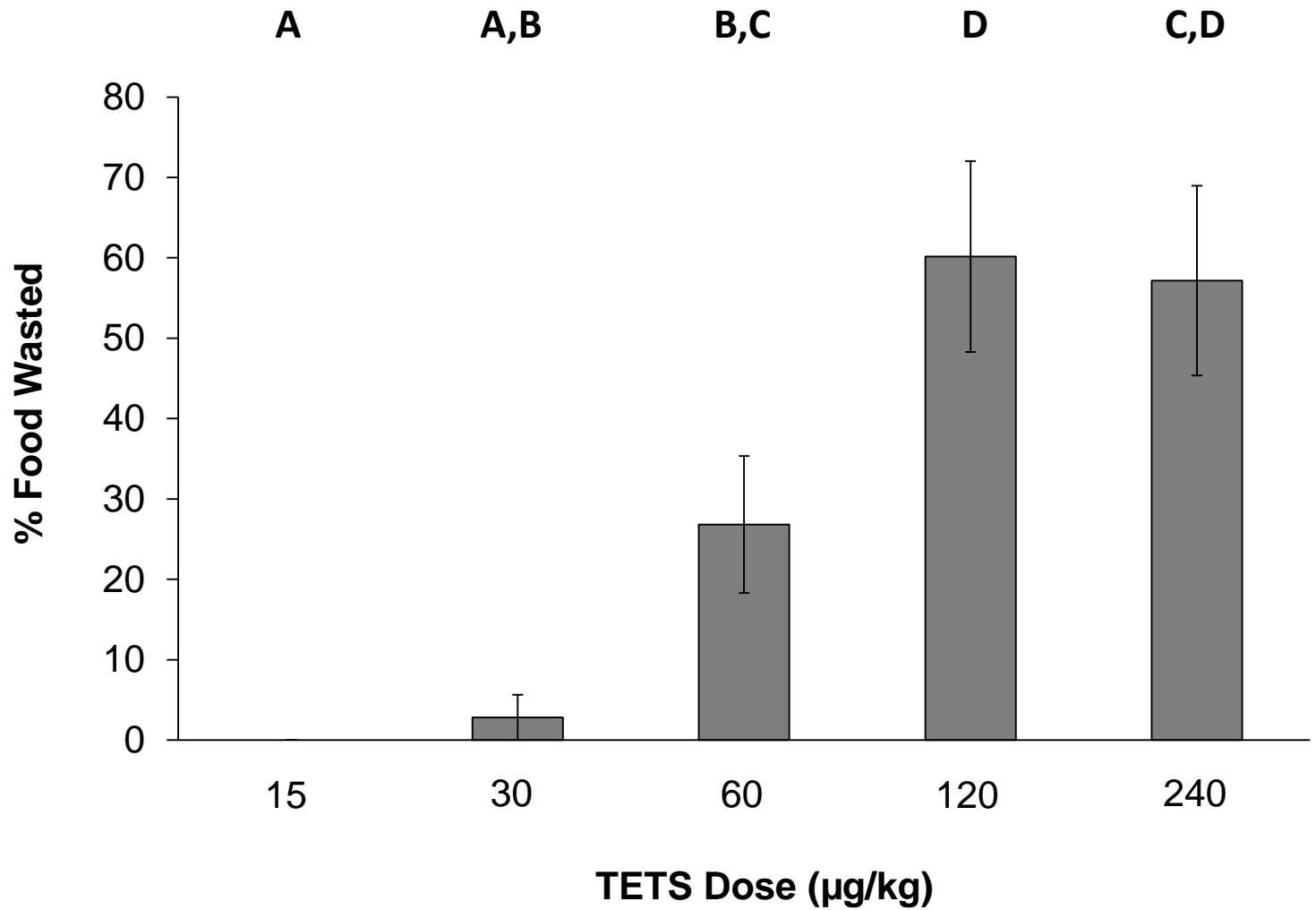
TETS Toxic Signs



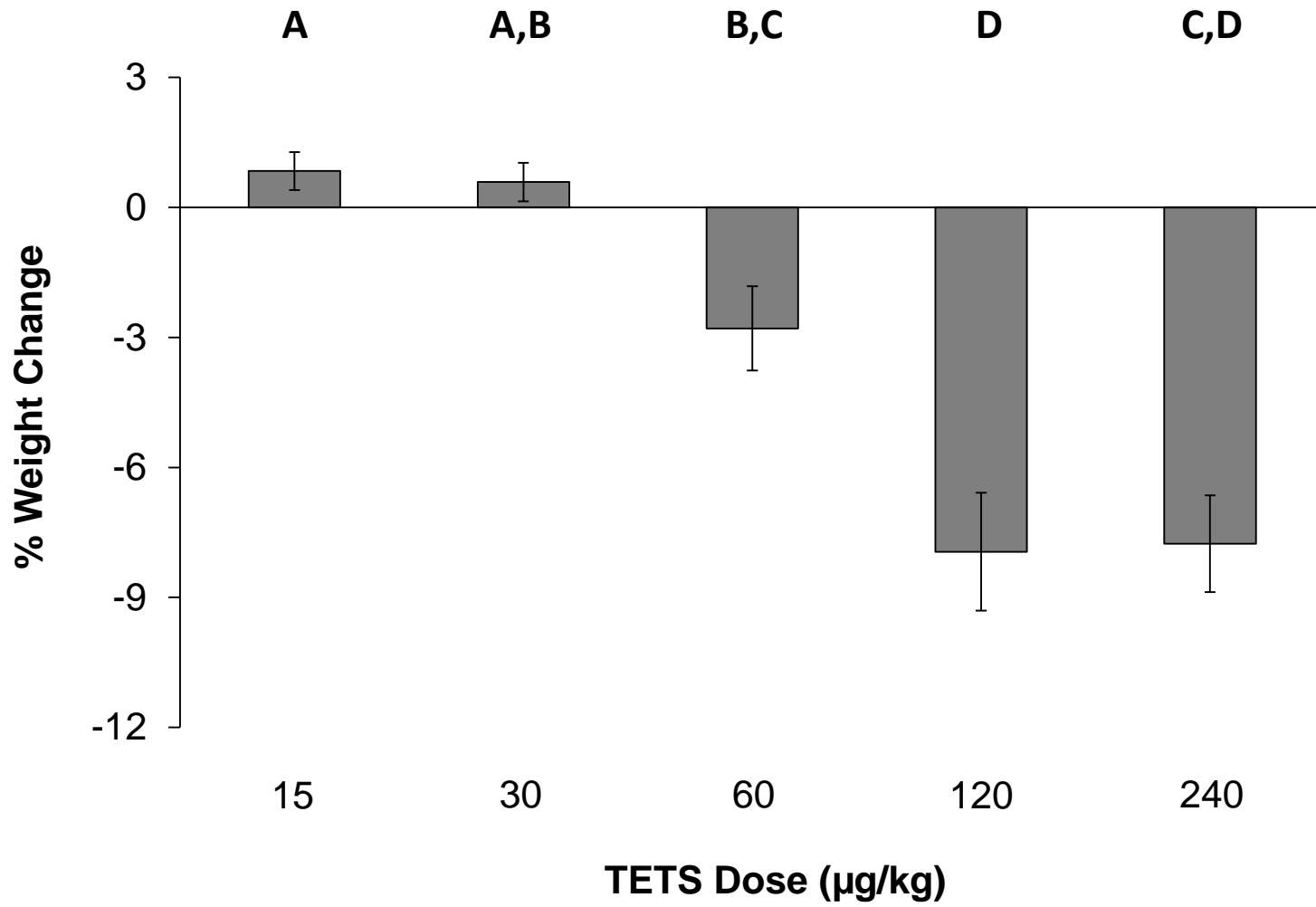
TETS Median Lethal Dose (LD₅₀)



Post-Exposure Food Wastage



Post-Exposure Weight Change



Behavioral Intoxication

Onset

- How rapid do toxic signs occur?
 - In what order do they occur?
- When does it become apparent that treatment is needed?

Severity

- Can a victim seek medical attention?
 - Drive? Make a phone call? Yell for help?
- How long left untreated do permanent behavioral impairments occur?
Death?

Duration

- How long does intoxication last left untreated or when treated?
- Are there any long-term impairments?

Cue Lights

Cue Lights

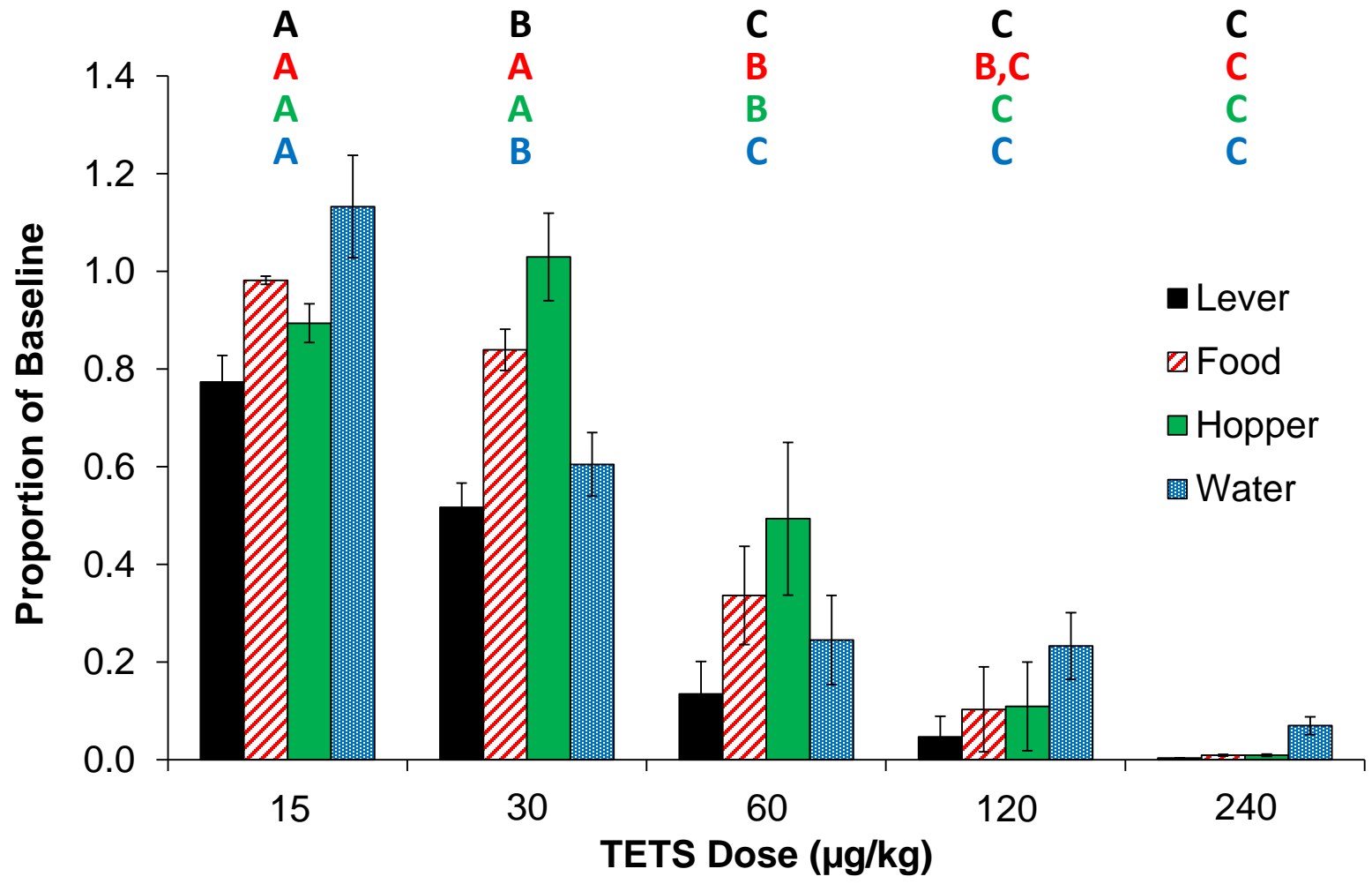
Left Lever

Right Lever

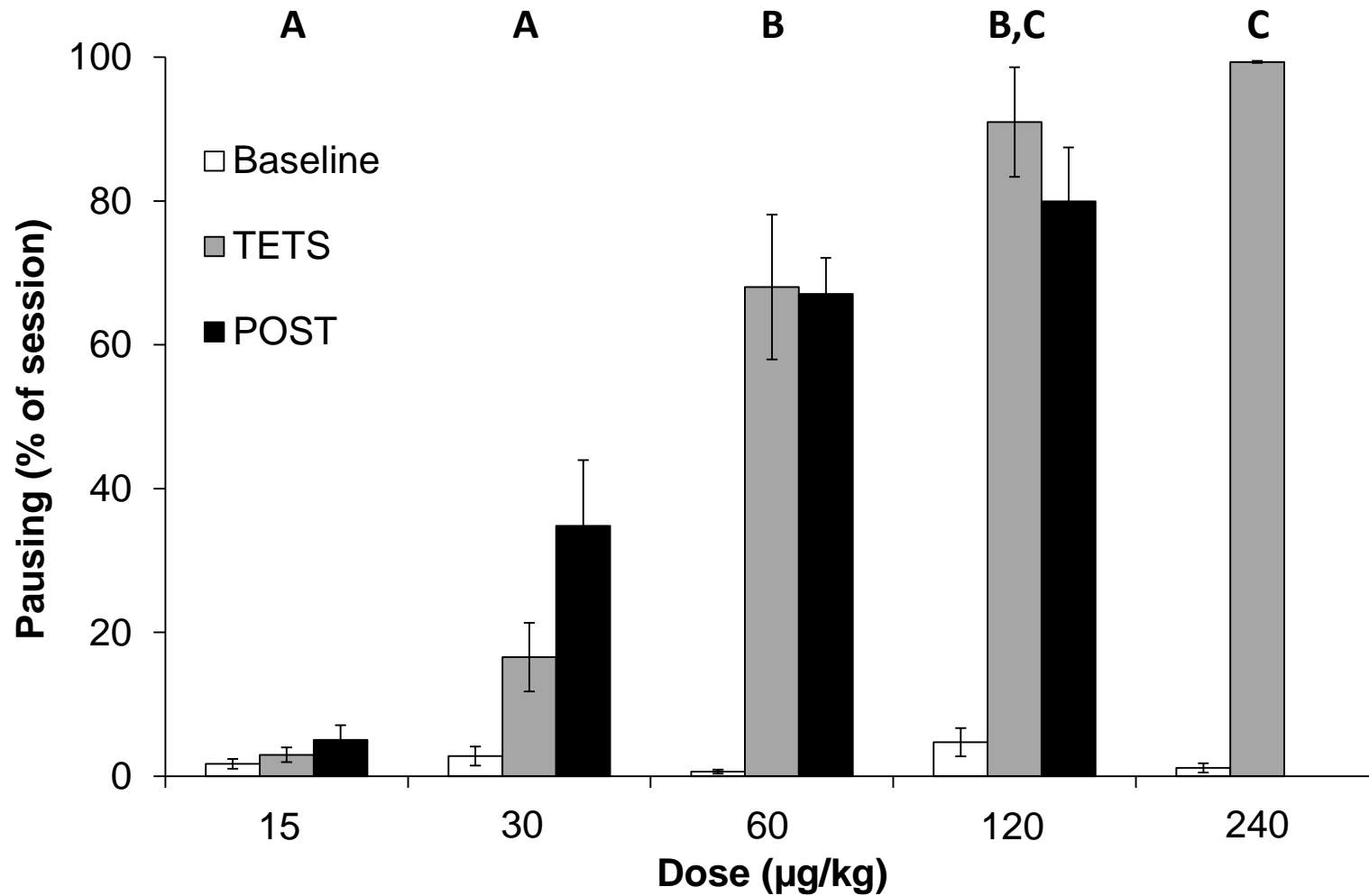
Food Hopper

Water Dipper

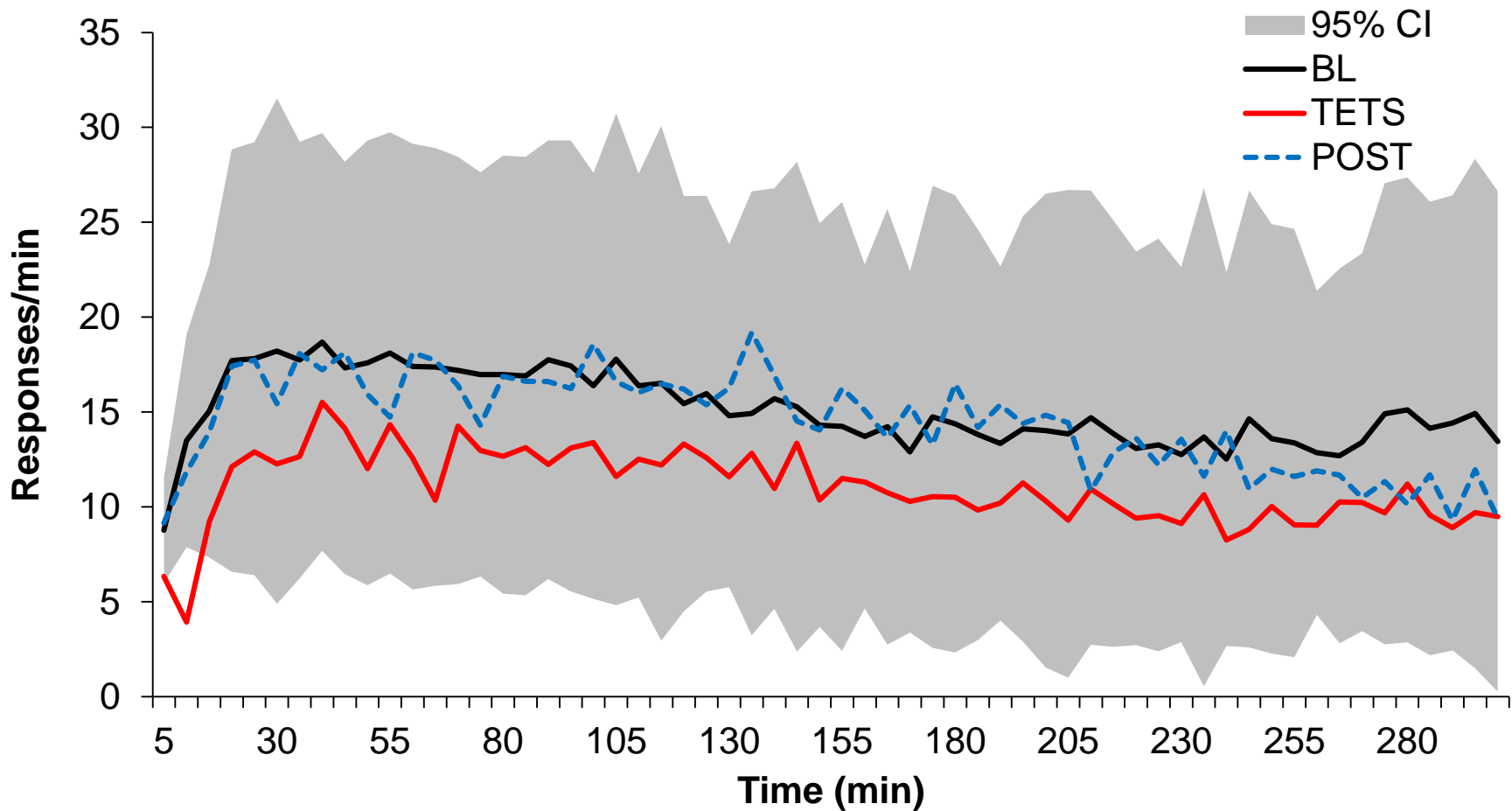
TETS Behavioral Effects



TETS Pausing

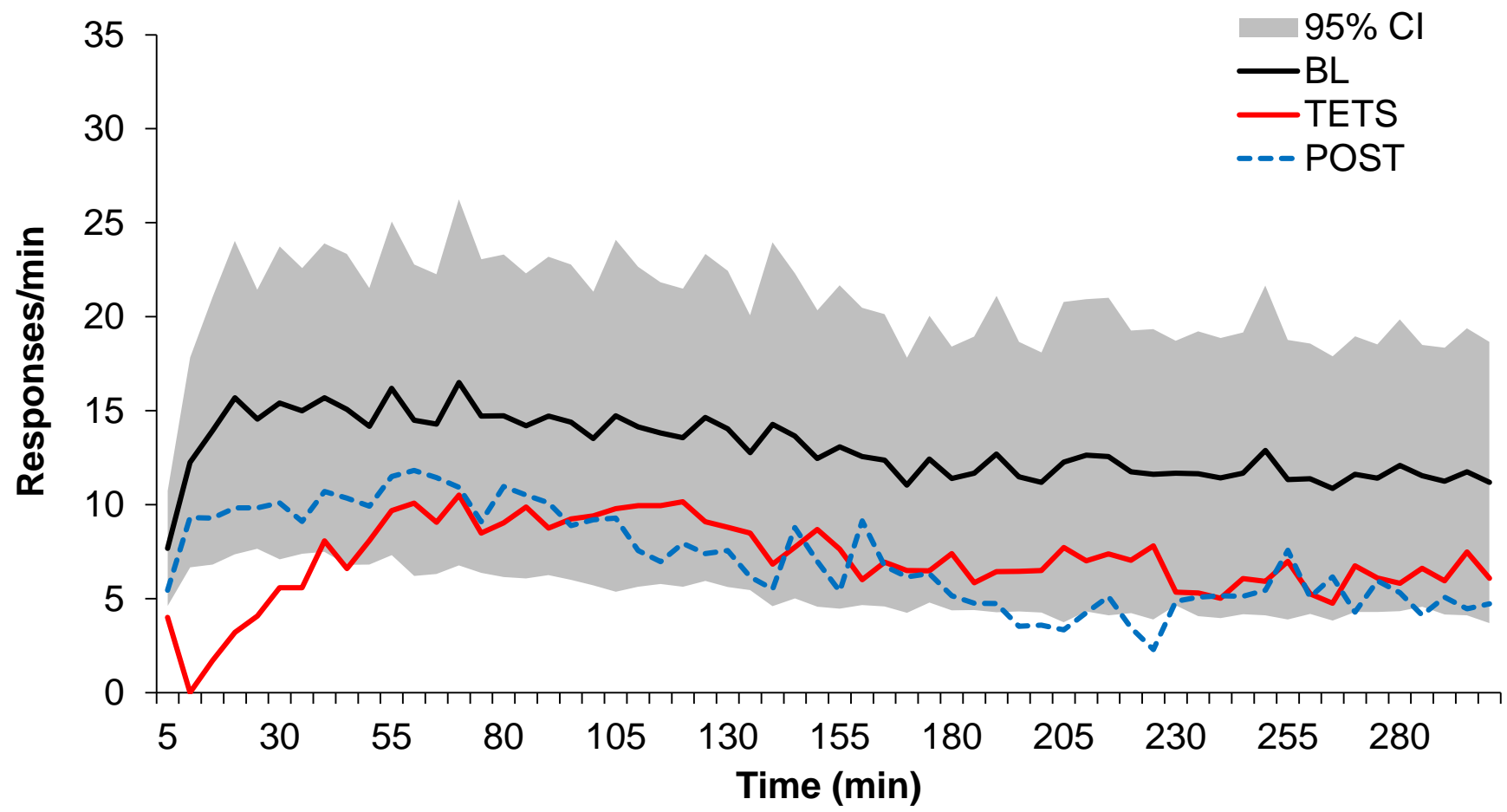


Real-Time Behavioral Analysis



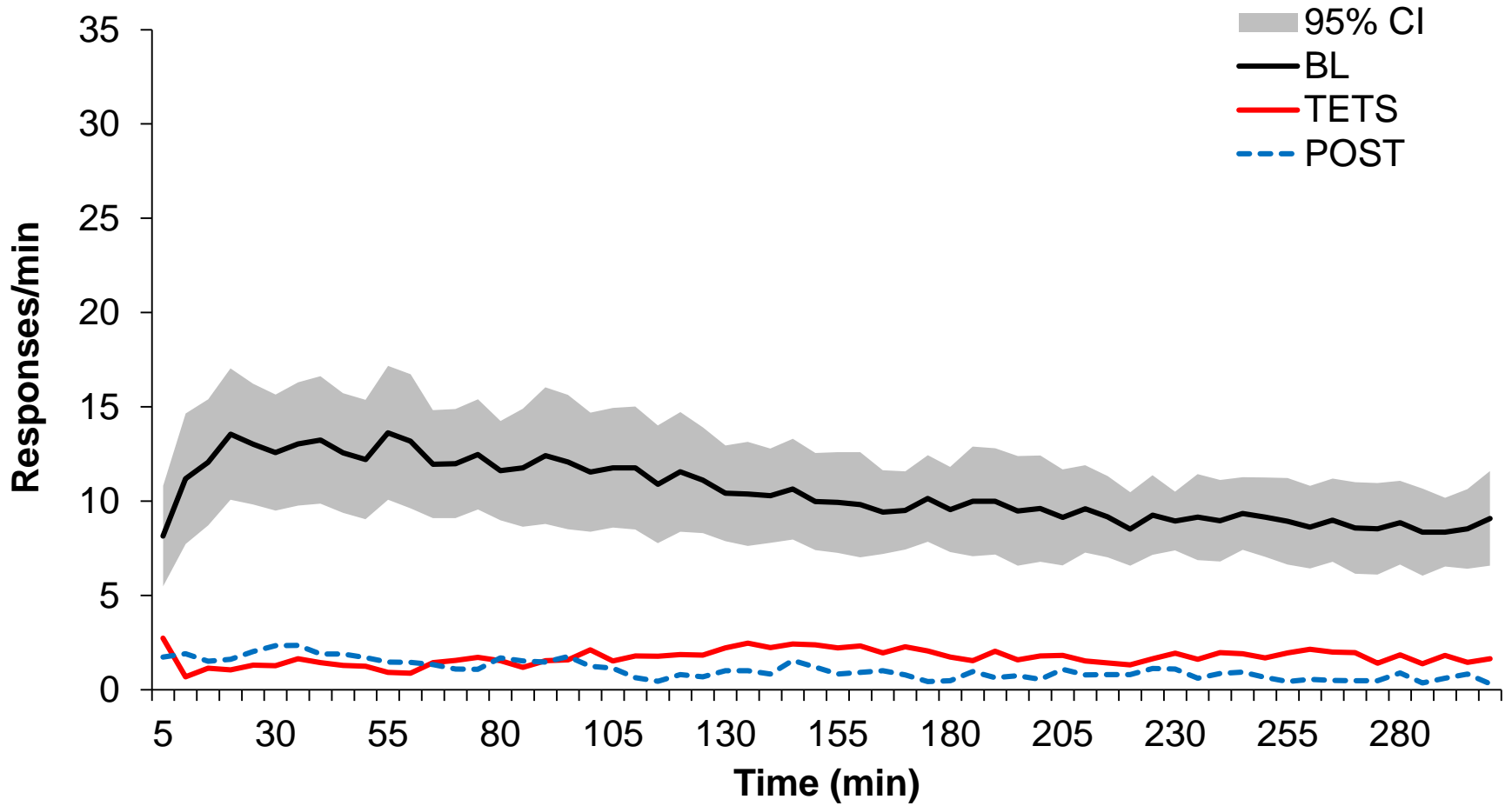
15 µg/kg

Real-Time Behavioral Analysis



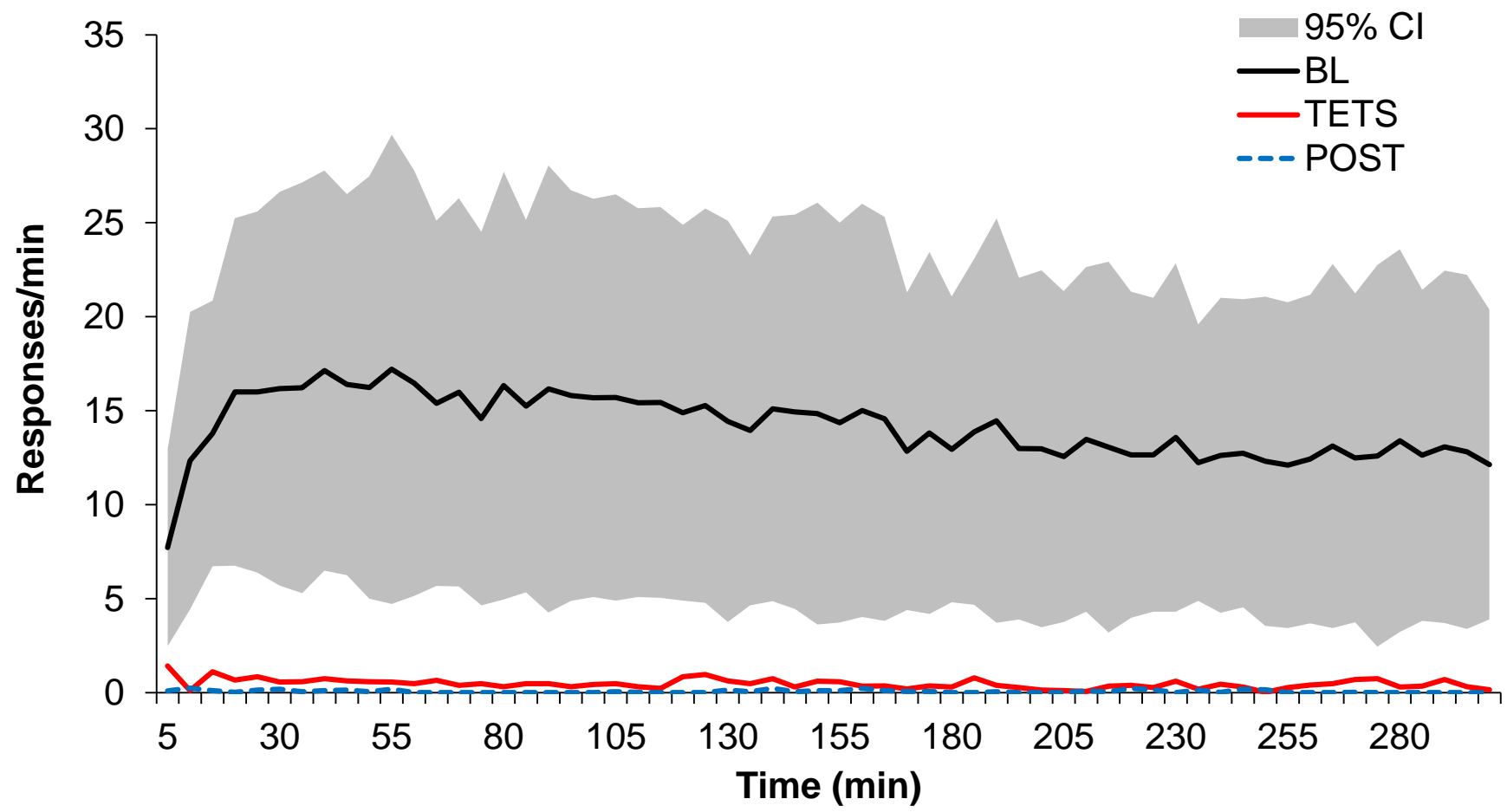
30 µg/kg

Real-Time Behavioral Analysis



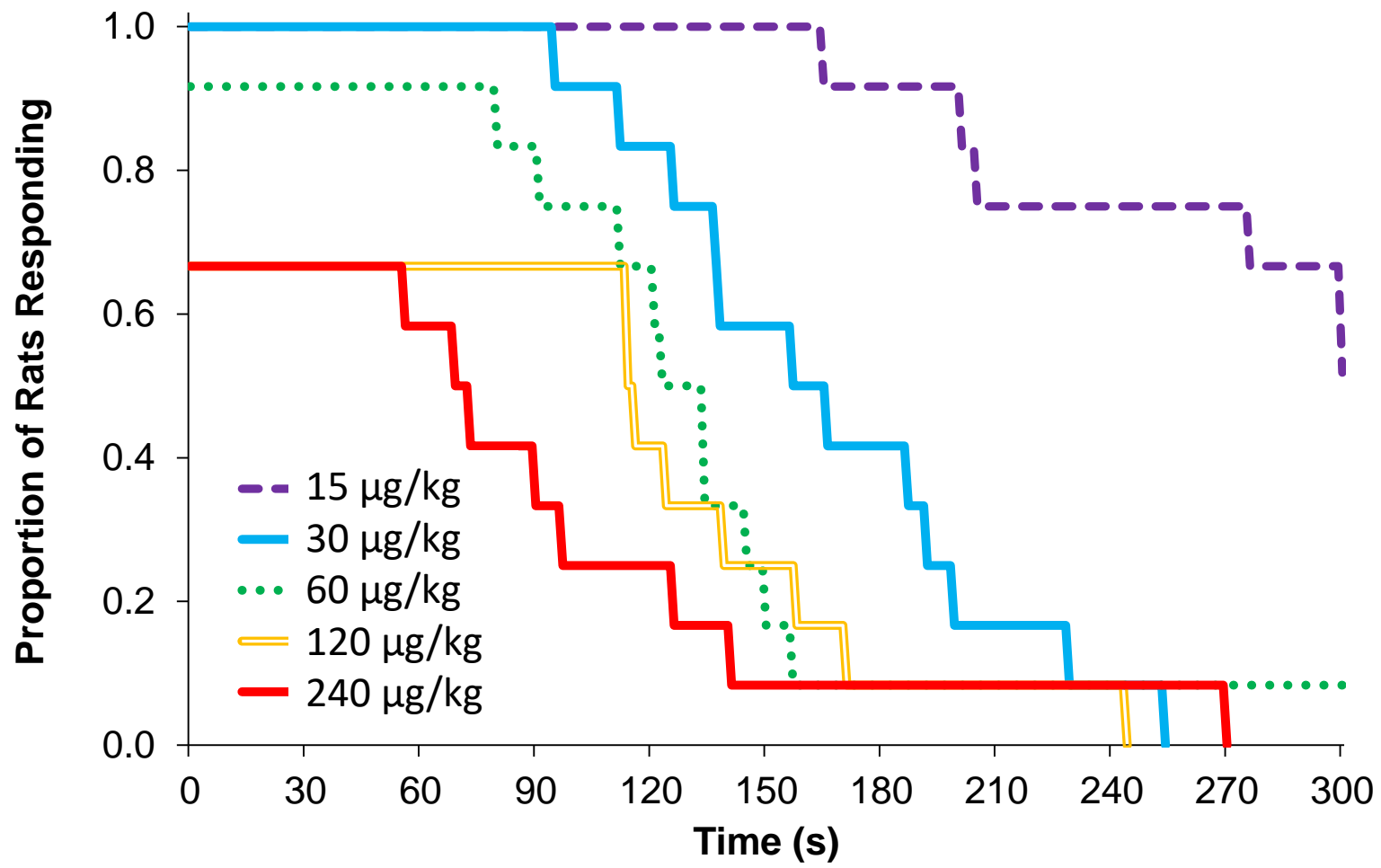
60 µg/kg

Real-Time Behavioral Analysis



120 µg/kg

TETS Intoxication Onset



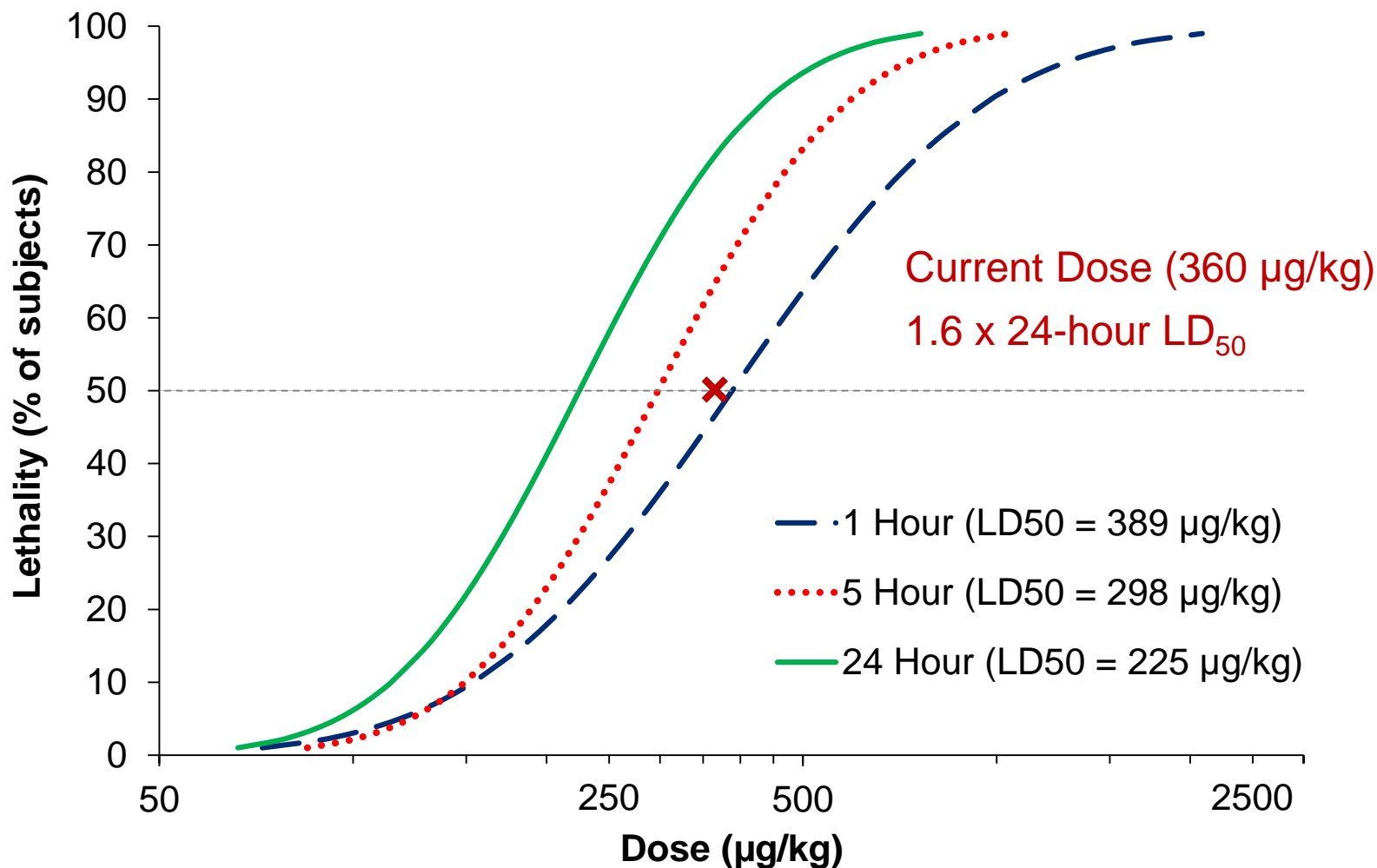
TETS Treatments

- TETS intoxication will likely be treated as either status epilepticus [induced by an unknown substance] or organophosphate/pesticide poisoning
- There is currently no standard treatment for TETS poisoning in the United States
- Commonly reported intervention in China:
 - Gastric lavage
 - high-volume or charcoal-filter hemoperfusion

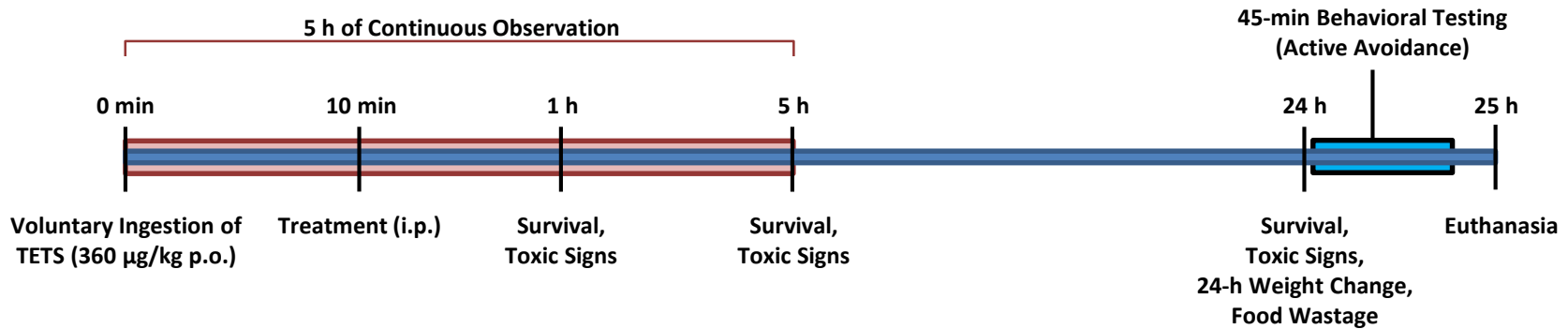
Author	Year	Species	TETS	Drugs	Doses	Safety Data	Behavior Data
Shakarjian	2012	Mouse	400 µg/kg	DZP	2	No	No
				KET	2		
				MK801	2		
Vito	2014	Mouse	150 µg/kg	DZP	1	Yes	No
				DZP + TUPS	1		
Bruun	2015	Mouse	150 µg/kg	DZP	2	No	Wire Hang
				ALLO	2		
				DZP + ALLO	2		
Flannery	2015	Mouse	150 µg/kg	DZP	1	Yes	Multiple
Shakarjian	2015	Mouse	400 µg/kg	DZP	6	No	No
				MK801	5		
				DZP + MK801	8		

Author	Year	Species	TETS	Drugs	Doses	Behavioral Safety Data	Behavioral Efficacy Data
Myers	Ongoing	Rat	360 µg/kg	DZP	3	Yes	Yes
				MDZ	3		
				LZP	3		
				KET	3		
				PhB	3		
				PeB	3		
				ALLO	3		
				DEX	3		
				ETOH	3		
				Combo 1	*		
				Combo 2	*		
				Combo 3	*		

TETS Median Lethal Dose (LD₅₀)

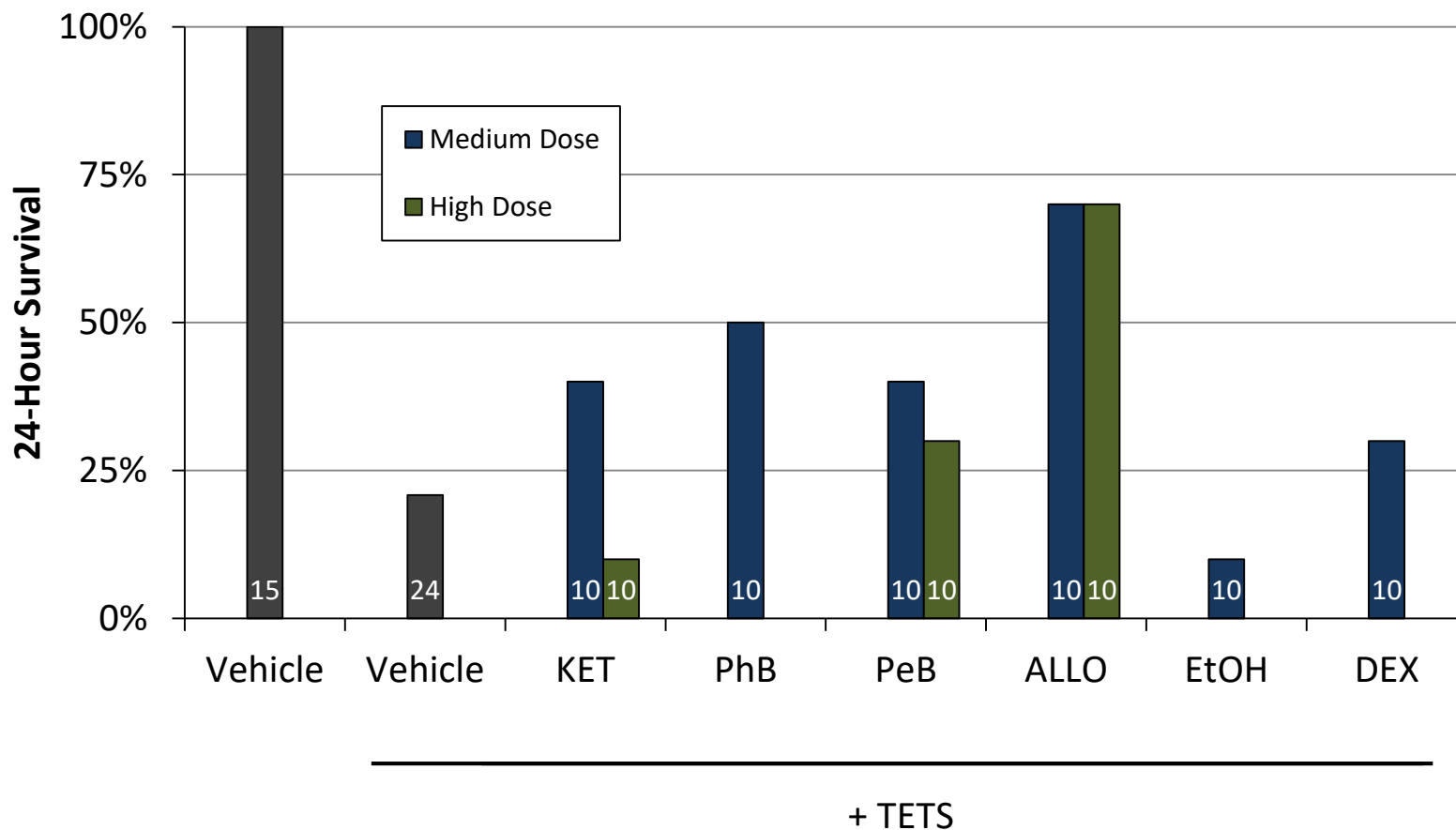


TETS Drug Therapies

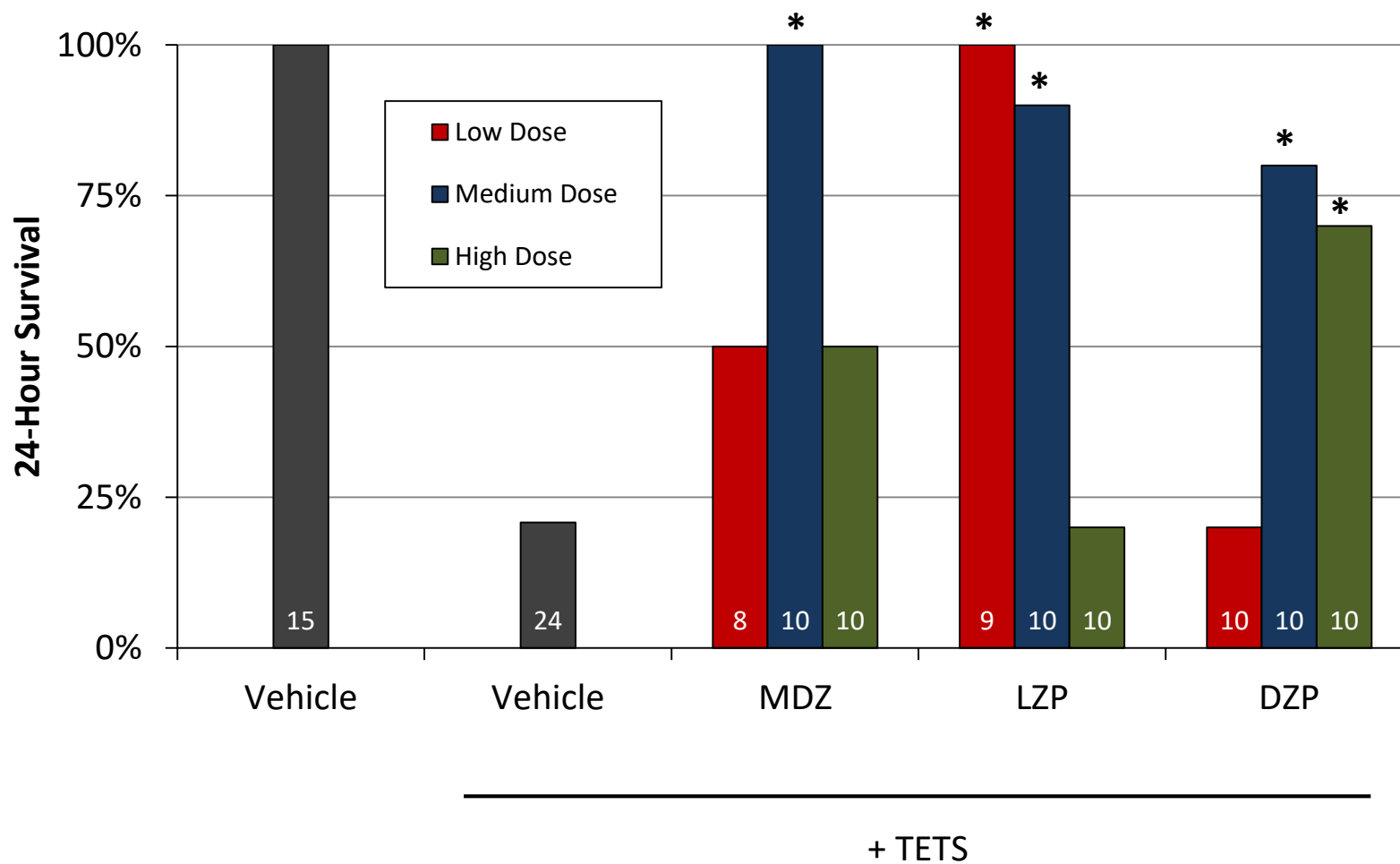


Drug	Low Dose	Med Dose	High Dose
Sub Midazolam (MDZ)	12.5	25	50
• 1 Lorazepam (LZP)	12.5	25	50
• 3 Diazepam (DZP)	6.25	12.5	25
• 1 Ketamine (KET)	37.5	75	150
• 1 Phenobarbital (PhB)	25	50	100
1 Pentobarbital (PeB)	12.5	25	50
Allopregnanolone (ALLO)	10	20	60
Ethanol (EtOH)	1.25	2.5	5
Dexmedetomidine (DEX)	0.25	0.5	1

24-Hour Survival



24-Hour Survival

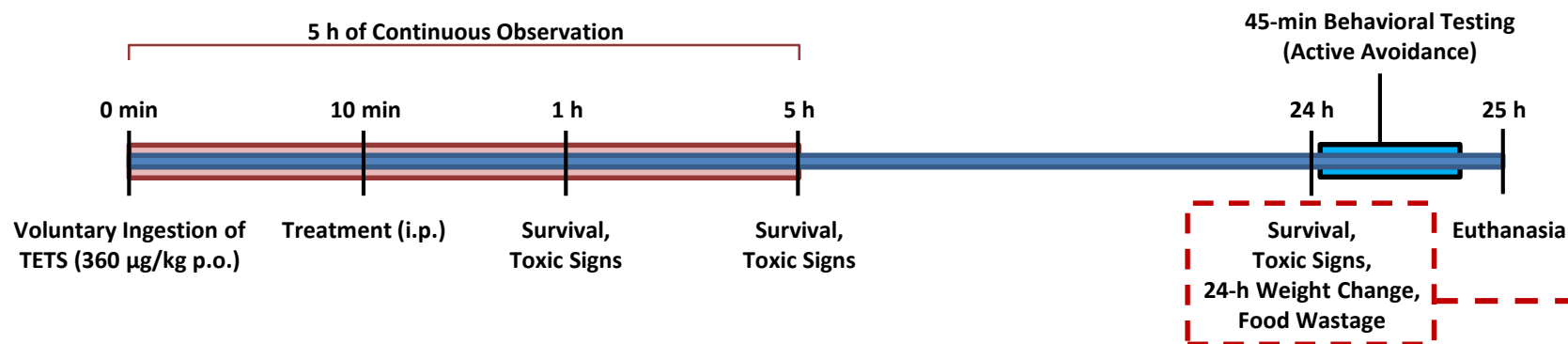


Combinatorial Drug Therapies

Treatments will be down-selected for combinatorial treatments based on:

- Efficacy
- Safety
- Mechanism of action
- Potential synergy

Three combinations of 2-3 drugs each will be assessed



Organoleptics

- Realistic models of consumption (both food and drink) need to consider whether the contaminant can be detected
- Detection will vary across sensory modalities
 - Taste, smell, sight
- Detection will vary depending on the item contaminated
 - Strong masking odor/taste?
 - Liquid vs. Solid
 - Fatty vs. Lean
- How does detection vary across a contaminants concentration?
 - Detection vs. Harmful

Cyanide

- A readily available laboratory and industrial reagent
 - 1.84 billion pounds of HCN generated in 2004
- Incredibly rapid metabolic poison with high solubility

Infamous Chicago Tylenol murders:

- 7 people killed after consuming potassium-cyanide tainted capsules
- Led to two notable safety improvements:
 - Foil seal
 - “Caplet”



Cyanide Dosing



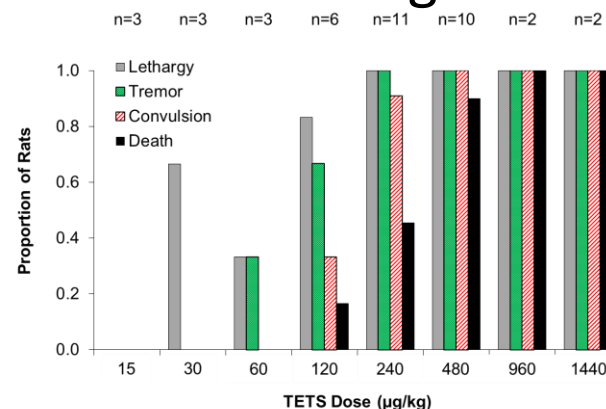
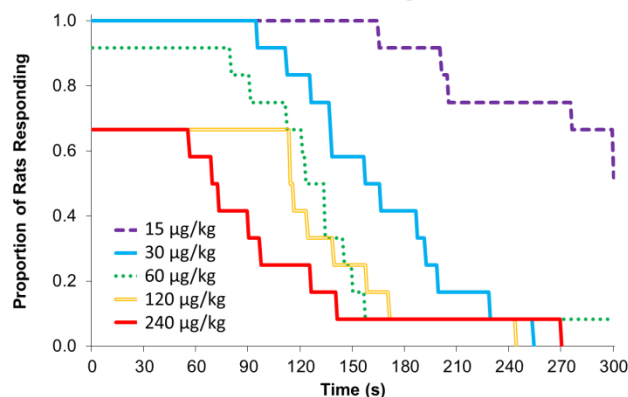
Different Approaches:

- Fruit Loop
 - Cyanide solubility required the use of water as the solvent
- Peanut Butter/Cookie Dough/Flour Dough
 - Using peanut butter was difficult and the food size was too large
- Pill/Tablet
 - Two different sizes attempted, with a variety of substrates
- Water/Assisted Drinking
 - ~75 uL of cyanide solution placed into the mouth of a rat
 - No excess solution leftover
 - No gavage stress
 - No accidental dosing into the lungs



Voluntary Consumption Model

- Mimics real-world consumption of TETS (and other poisons)
- Able to be embedded into other experimental procedures
 - Treatments can occur pre- and post-exposure
 - Different behavioral assessments may be used
 - Long-term recovery can easily be assessed
- Behavioral assessments are sensitive across multiple measures, including doses with no overt toxic signs





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Thank You

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