



# Toxicology:

---

**Common Pills,  
A Thing That Kills,  
& Cheap Thrills**



## CLAIRE EPPERSON, DO

Emergency Medicine

Medical Toxicology

Oklahoma City, Oklahoma



Oklahoma Center for Poison & Drug Information



Lindsey-epperson@ouhsc.edu



Lindseyepperson@gmail.com



**Oklahoma Osteopathic Association- August 12, 2022**

# Relevant Disclosure and Resolution

Under Accreditation Council for Continuing Medical Education guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

## **Claire Epperson, DO**

I have no relevant financial relationships or affiliations with commercial interests to disclose.



WE LOVE

DRUGS

**Common Pills** (acetaminophen)

**A Thing That Kills** (serotonin syndrome)

**Cheap Thrills** (street drugs)



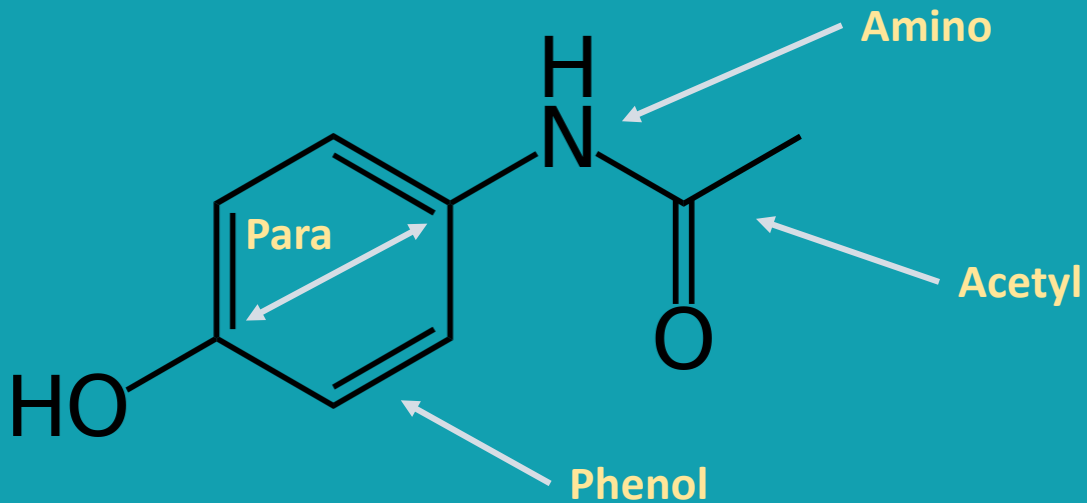
**Common Pills:**

---

**Acetaminophen**

# ACETAMINOPHEN

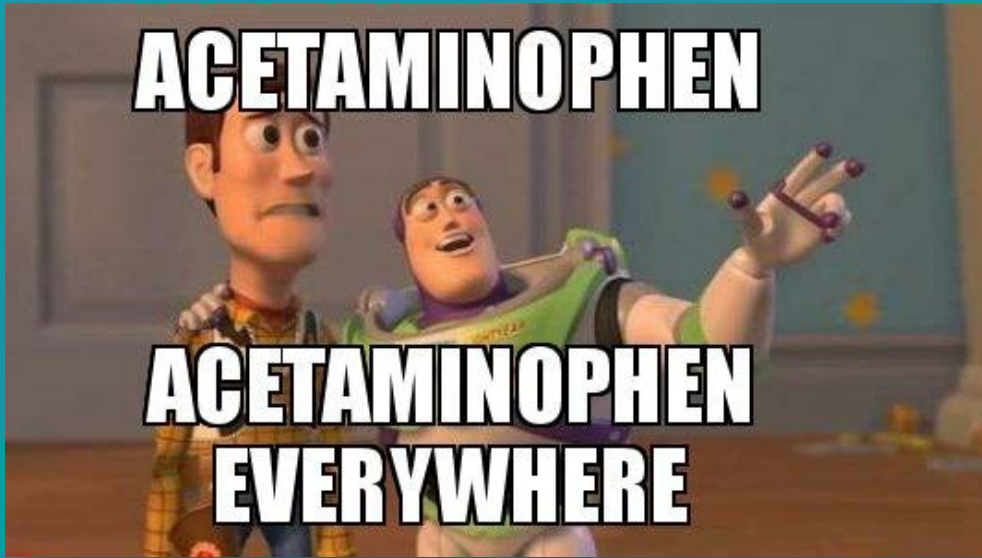
- N-acetyl-p-aminophenol

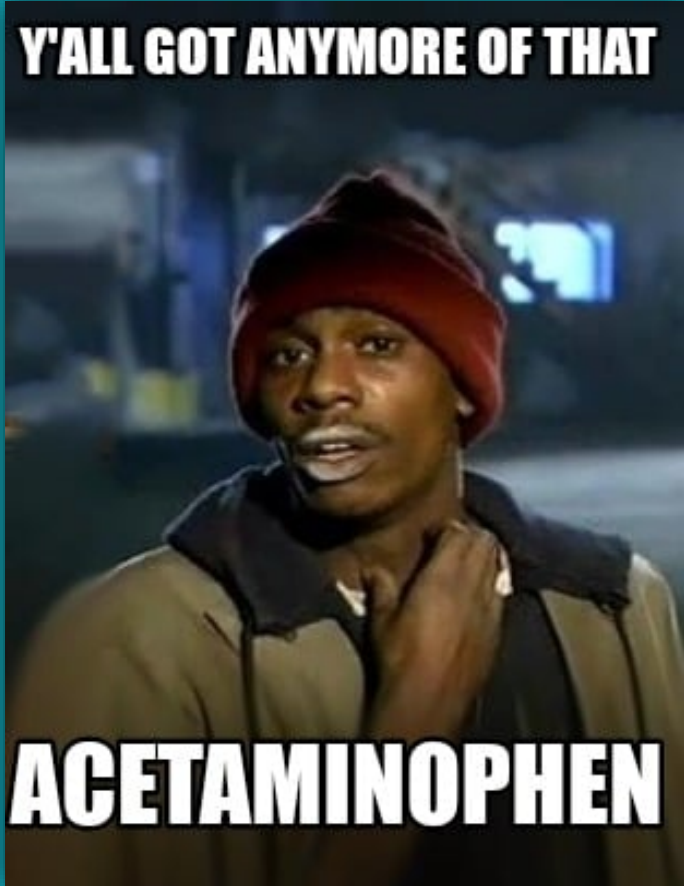


Howard Greller  
@heshiegreshie

Acetaminophen is like the golf of toxicology - simple to learn the basics, but you can spend a lifetime mastering the subtleties. [#FOAMtox](#)

3:09 PM · 6/5/19 · Twitter for iPhone

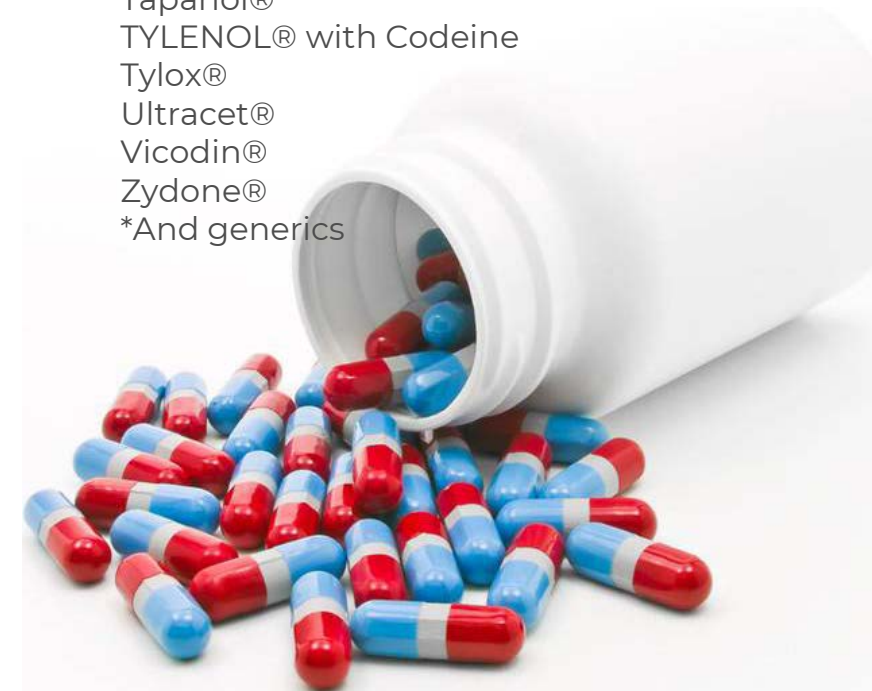




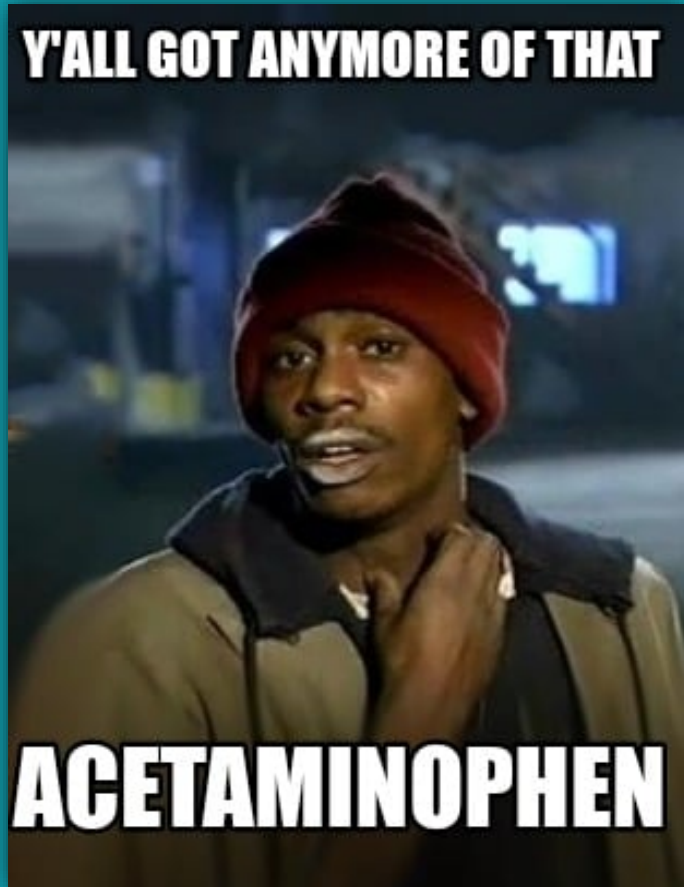
## Over-the-Counter Prescription

Actifed®  
Alka-Seltzer Plus®  
Cepacol®  
 Contac®  
Coricidin®  
DayQuil®  
Dimetapp®  
Dristan®  
Excedrin®  
Feverall®  
Formula 44®  
Goody's® Powders  
Liquiprin®  
Midol®  
Mucinex®  
NyQuil®  
Panadol®  
Robitussin®  
St Joseph® Aspirin-Free  
Singlet®  
Sinutab®  
Sudafed®  
Theraflu®  
Triaminic®  
TYLENOL® Products  
Vanquish®  
Vicks®  
\*And store brands

Butalbital  
Endocet®  
Fioricet®  
Hycotab®  
Hydrocet®  
Hydrocodone Bitartrate  
Lortab®  
MIDRIN®  
NORCO®  
Oxycodone  
Percocet®  
Phenaphen®  
ROXICET™  
Sedapap®  
Tapanol®  
TYLENOL® with Codeine  
Tylox®  
Ultracet®  
Vicodin®  
Zydone®  
\*And generics



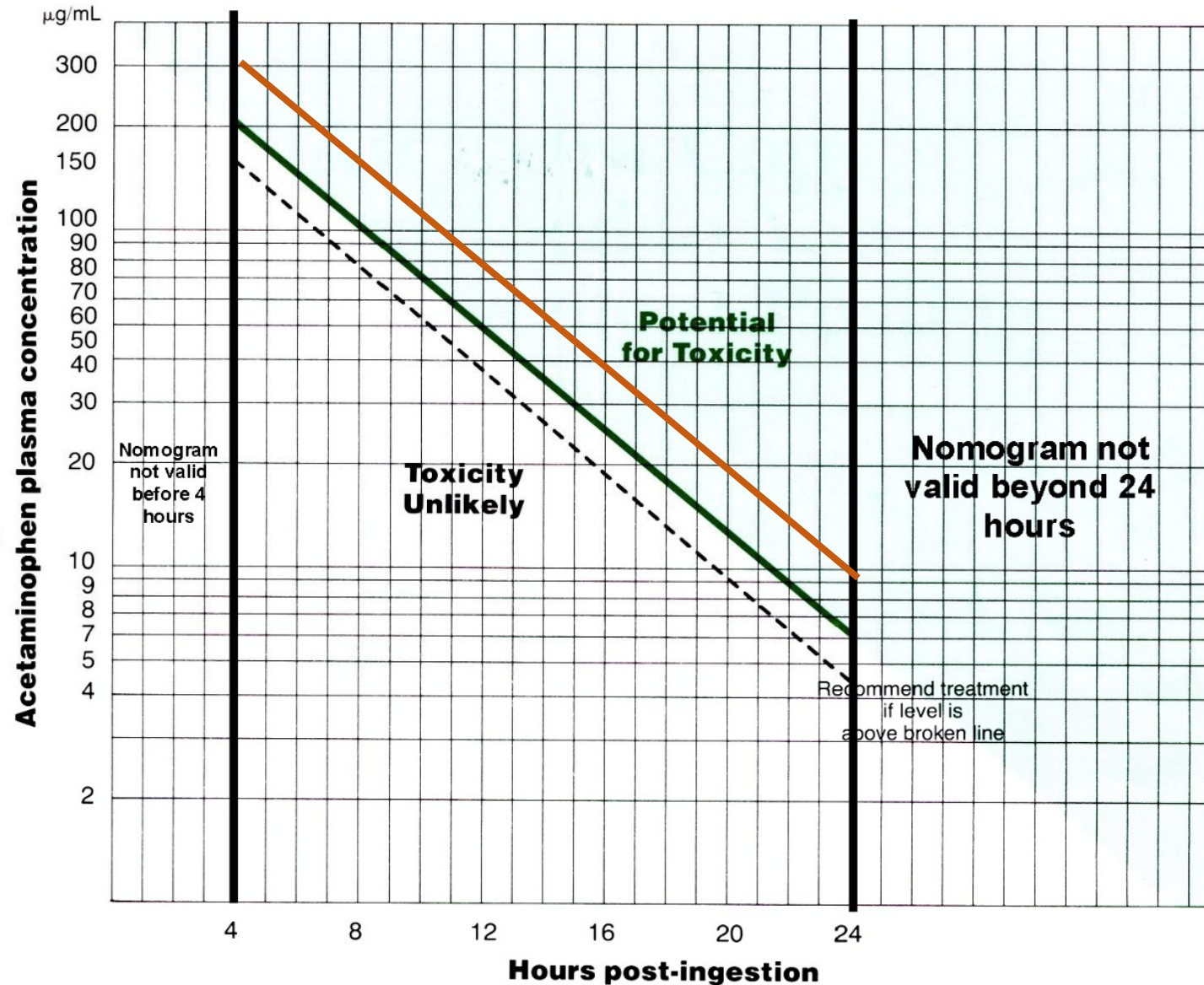




## Quick refresher:

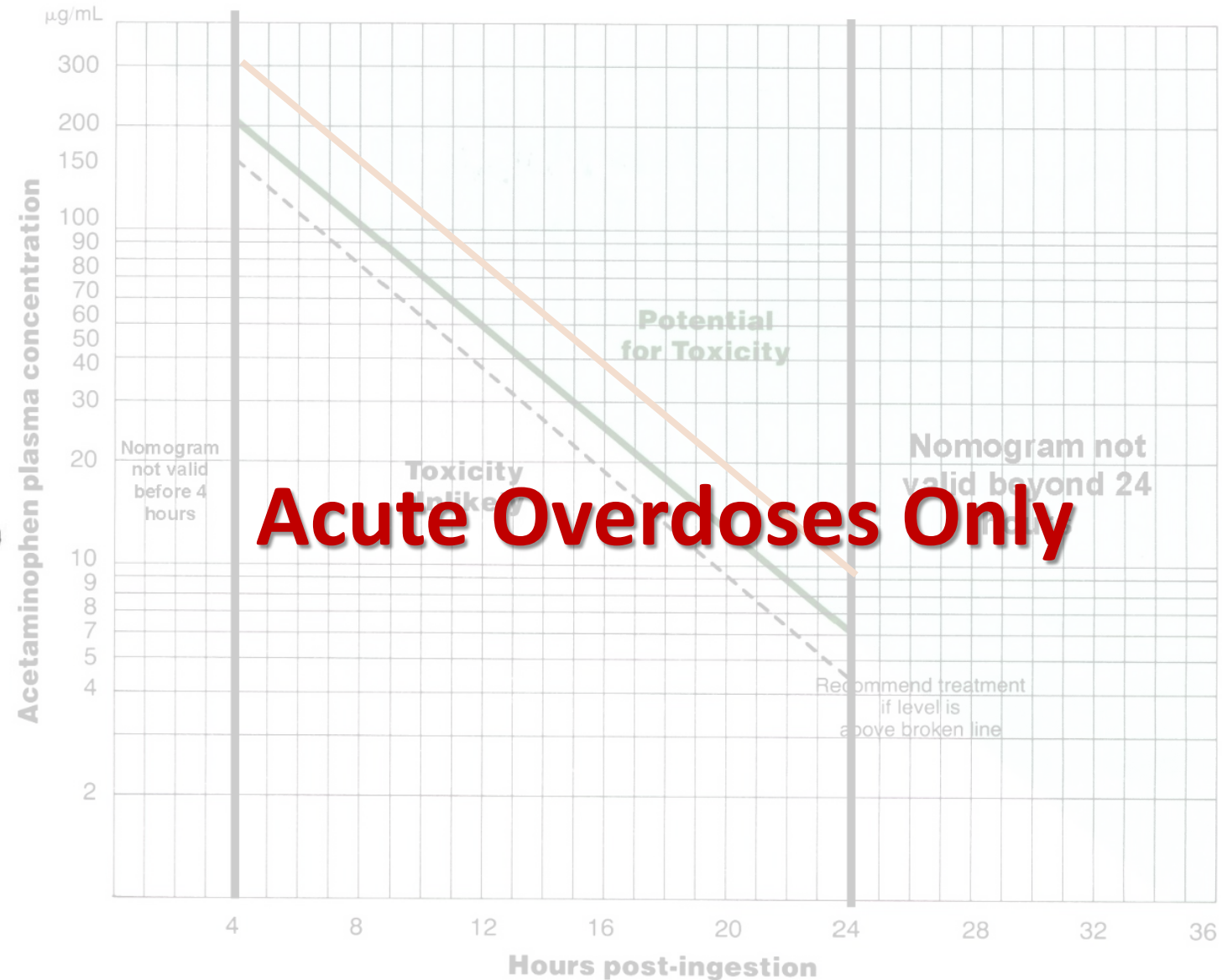
- **recommended max daily dose:**
  - **4g/day adults**
  - **75-90 mg/kg/day children**
- **Alcoholics may safely take APAP in therapeutic doses, but at increased risk for hepatotoxicity in OD.**
- **Repeated suprathreshold ingestion:**
- **>one ingestion during a period >8h resulting in cumulative dose >4g per 24 hours.**

# Rumack-Matthews Nomogram



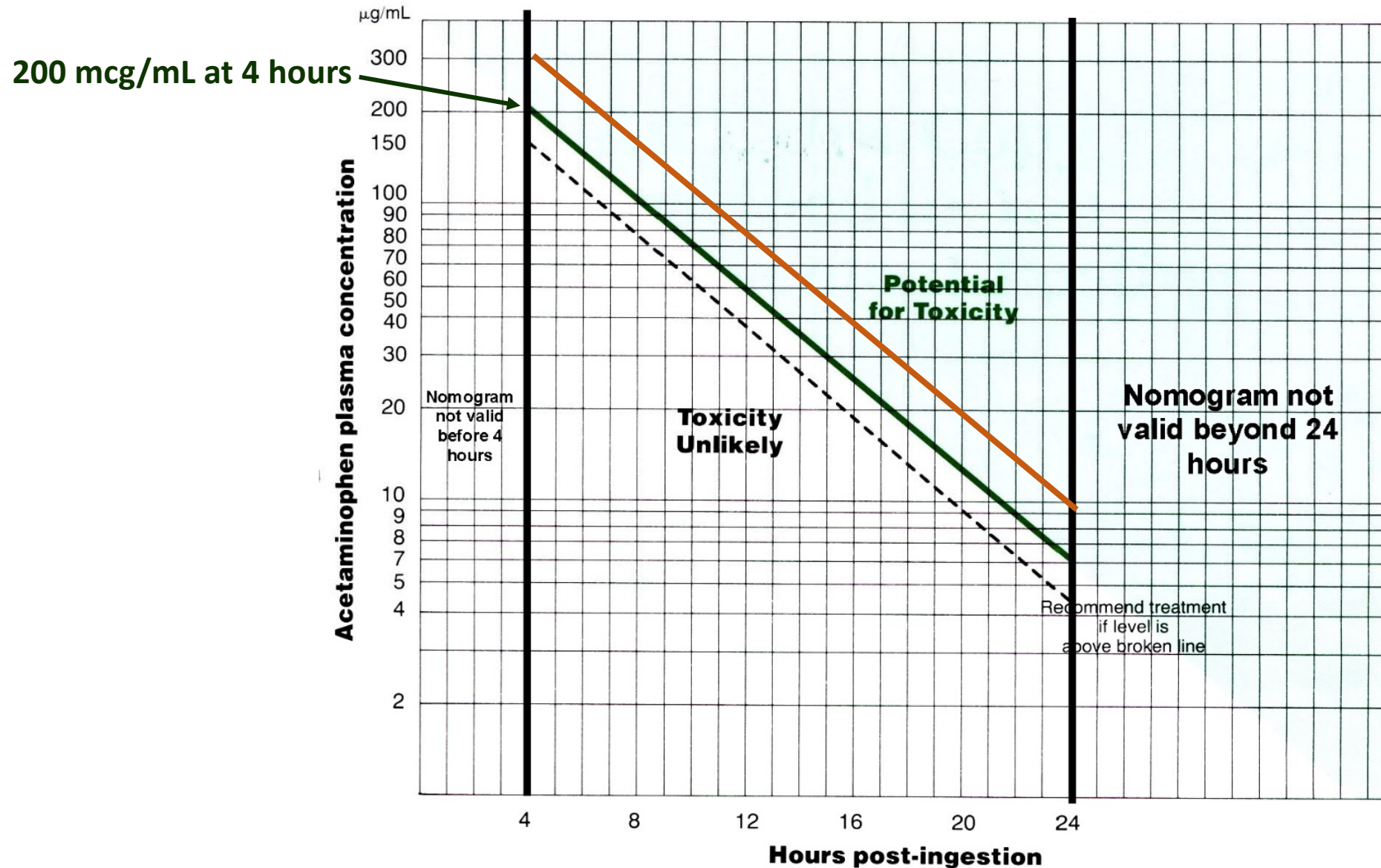
\*Adapted from Rumack and Matthew, *Pediatrics* 55:871-876, 1975.

# Rumack-Matthews Nomogram



\*Adapted from Rumack and Matthew, *Pediatrics* 55:871-876, 1975.

# Rumack-Matthews Nomogram

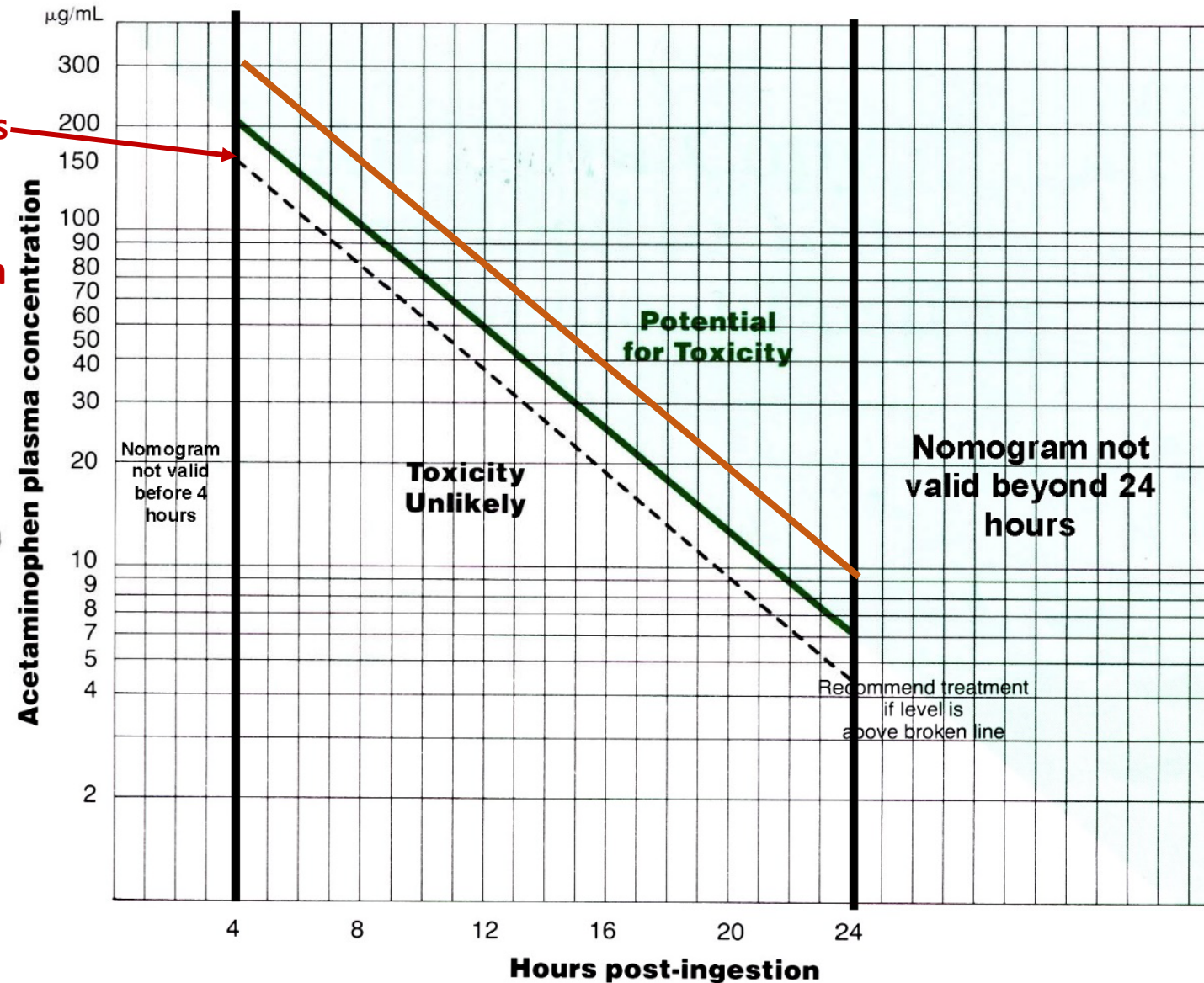


\*Adapted from Rumack and Matthew, *Pediatrics* 55:871-876, 1975.

# Rumack-Matthews Nomogram

150 mcg/mL at 4 hours

Treatment Line  
Has 25% Safety Margin



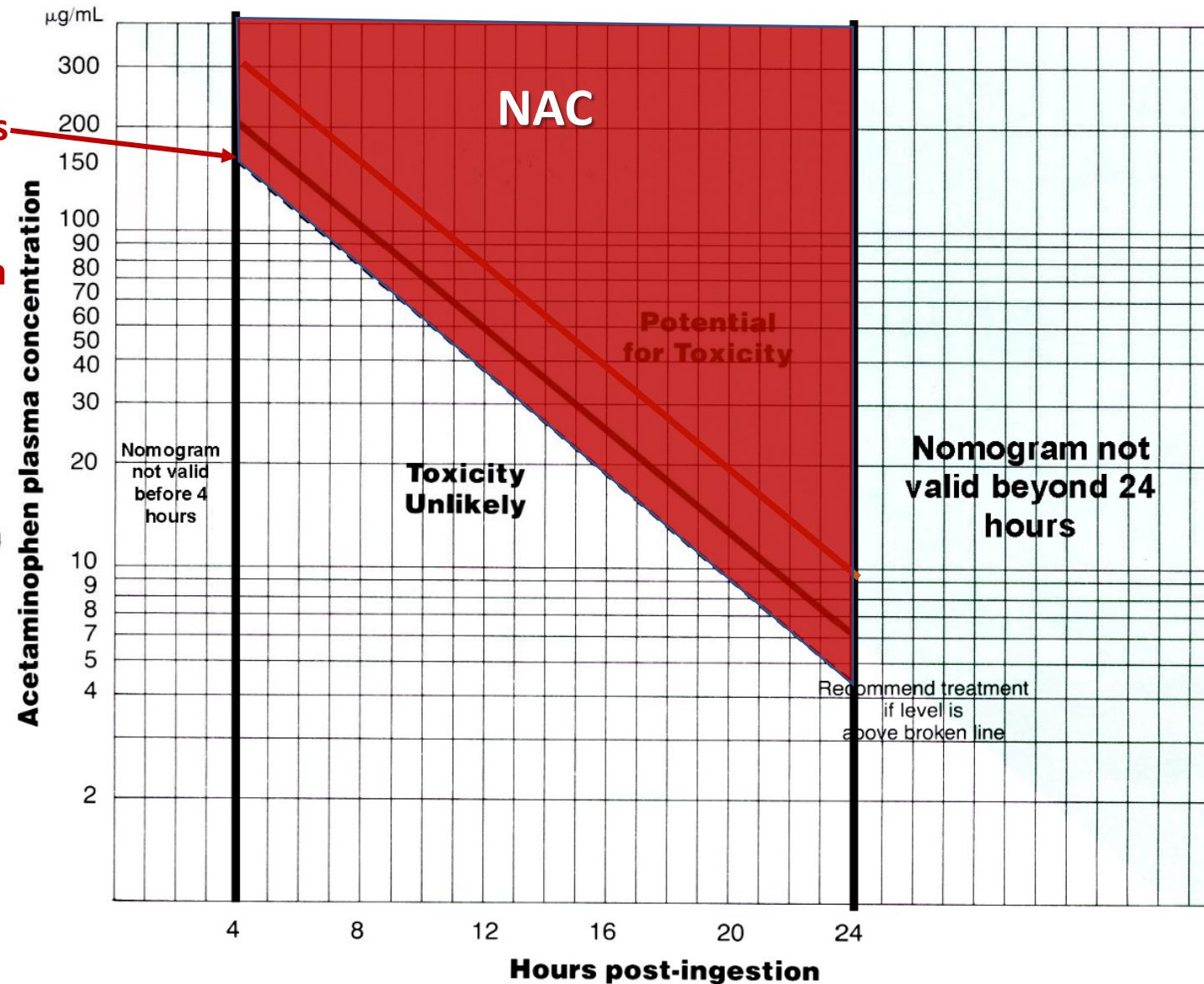
\*Adapted from Rumack and Matthew, *Pediatrics* 55:871-876, 1975.

# Rumack-Matthews Nomogram

150 mcg/mL at 4 hours

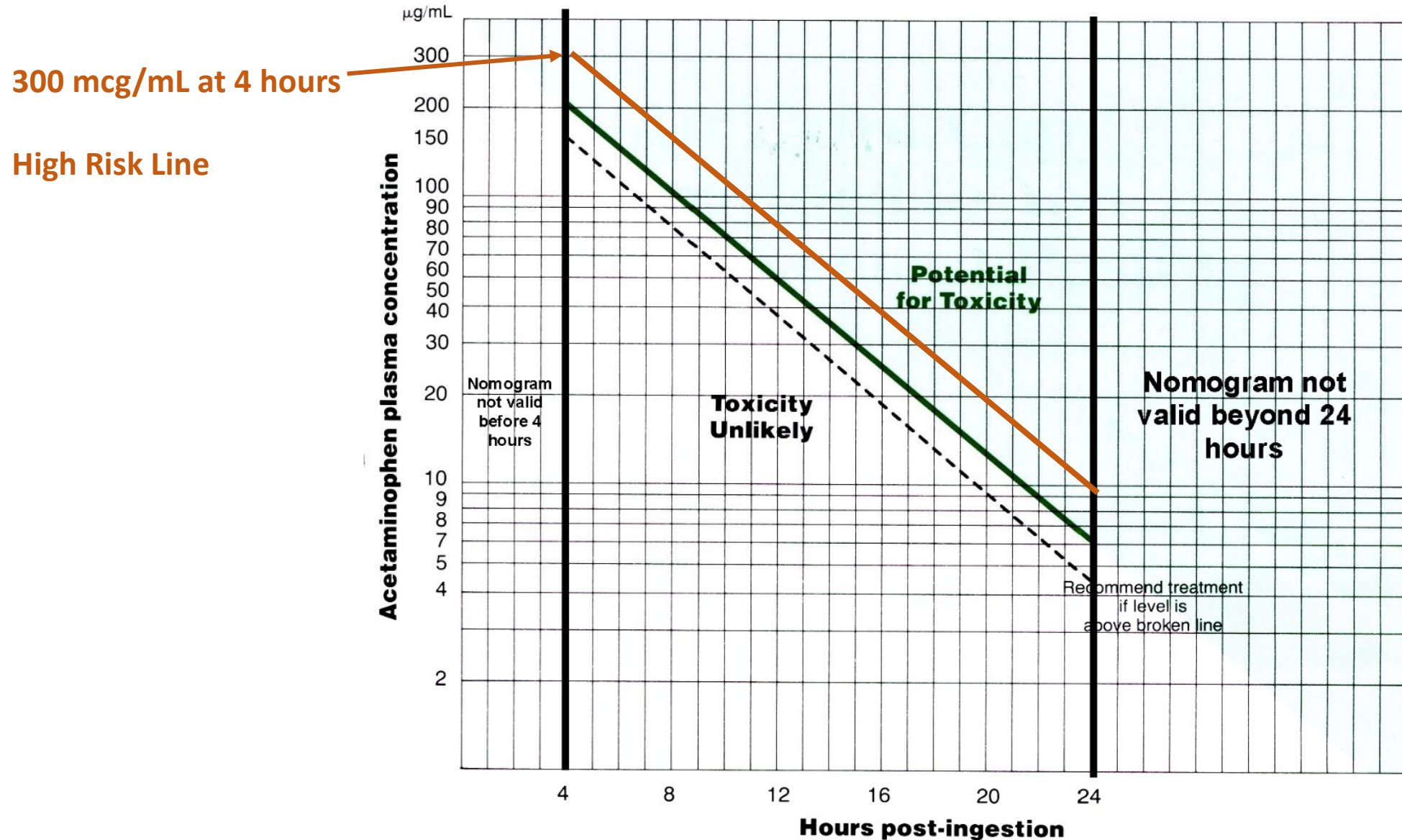
Treatment Line  
Has 25% Safety Margin

NAC recommended if level  
above this line



\*Adapted from Rumack and Matthew, *Pediatrics* 55:871-876, 1975.

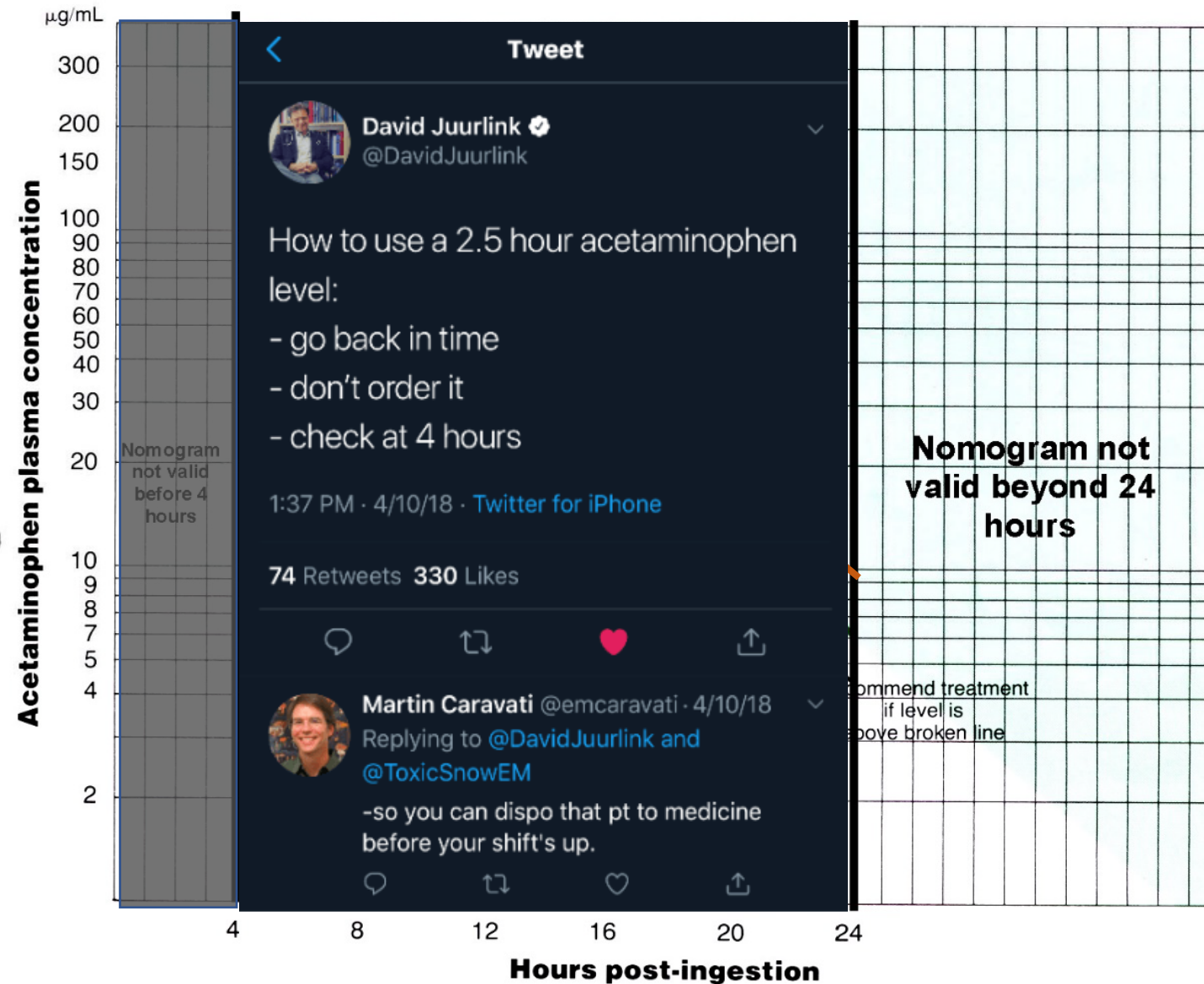
# Rumack-Matthews Nomogram



\*Adapted from Rumack and Matthew, *Pediatrics* 55:871-876, 1975.

# Rumack-Matthews Nomogram

REMEMBER...  
Nomogram not  
valid before 4 hours

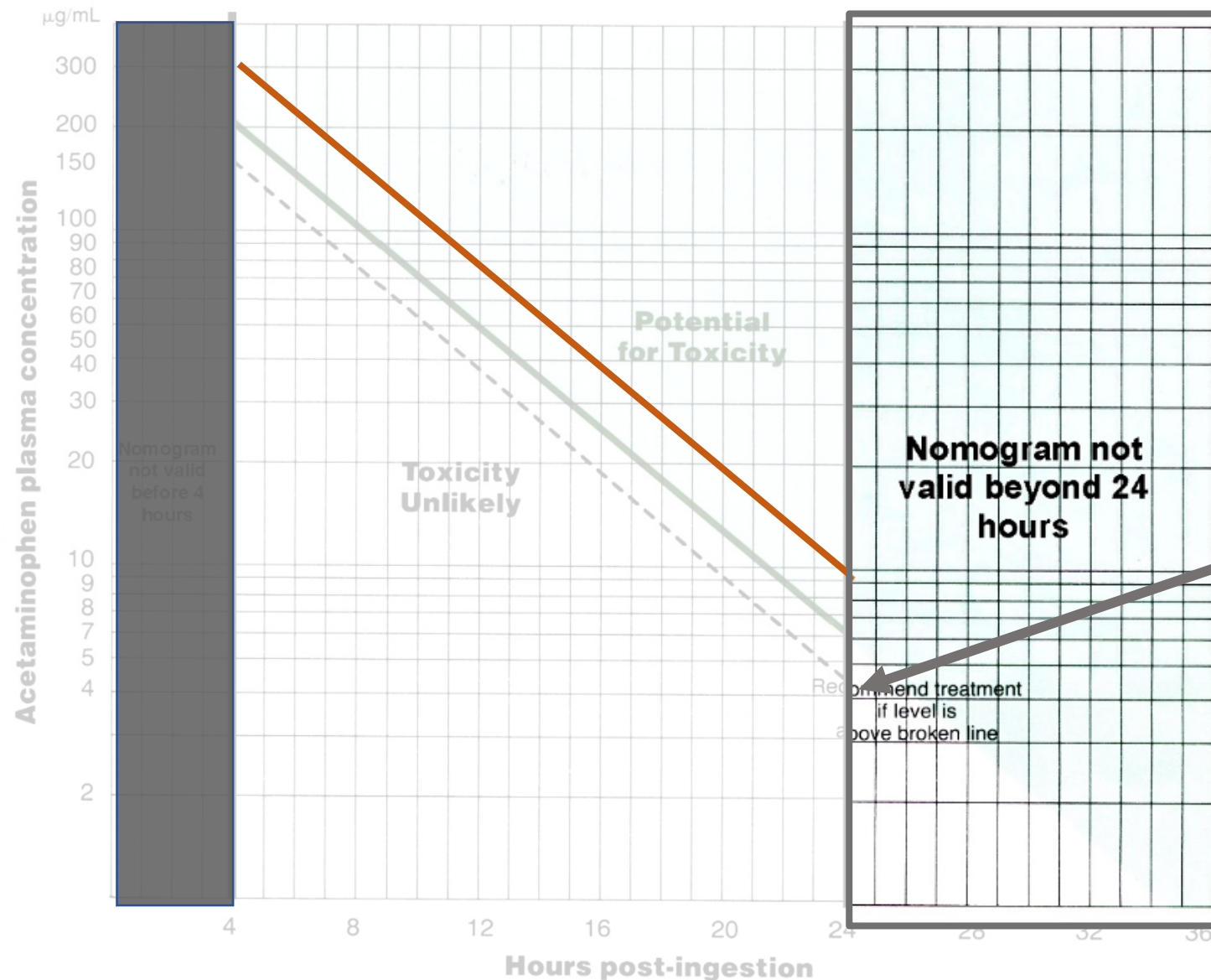


\*Adapted from Rumack and Matthew, *Pediatrics* 55:871-876, 1975.



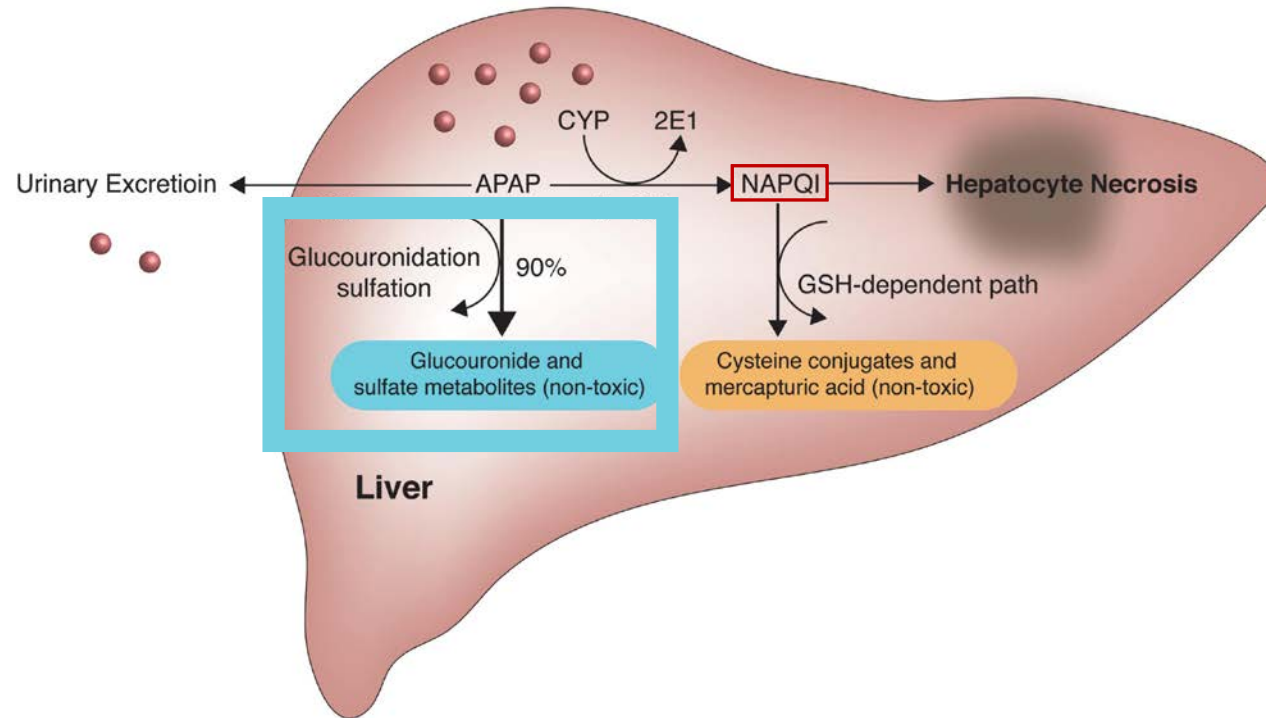
# Rumack-Matthews Nomogram

REMEMBER...  
Nomogram not  
valid before 4 hours



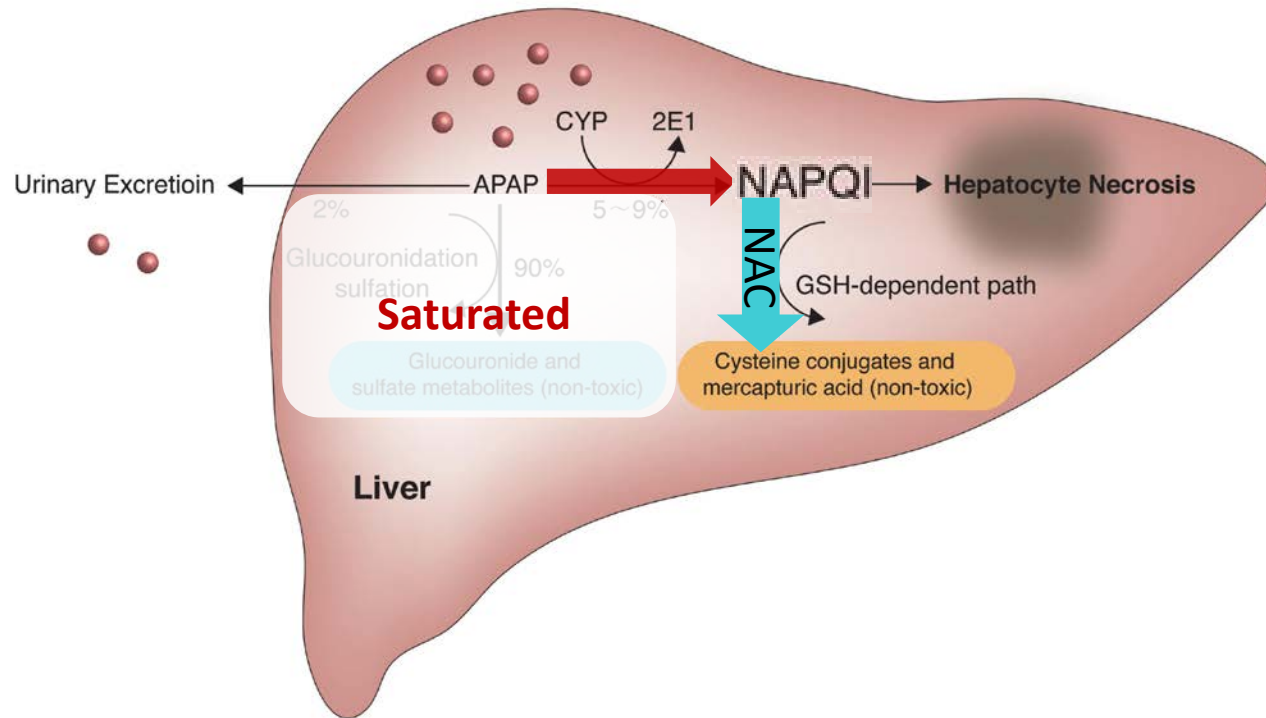
Nor valid after 24h  
(~4 mcg/mL at 24h)

# Normal Metabolism



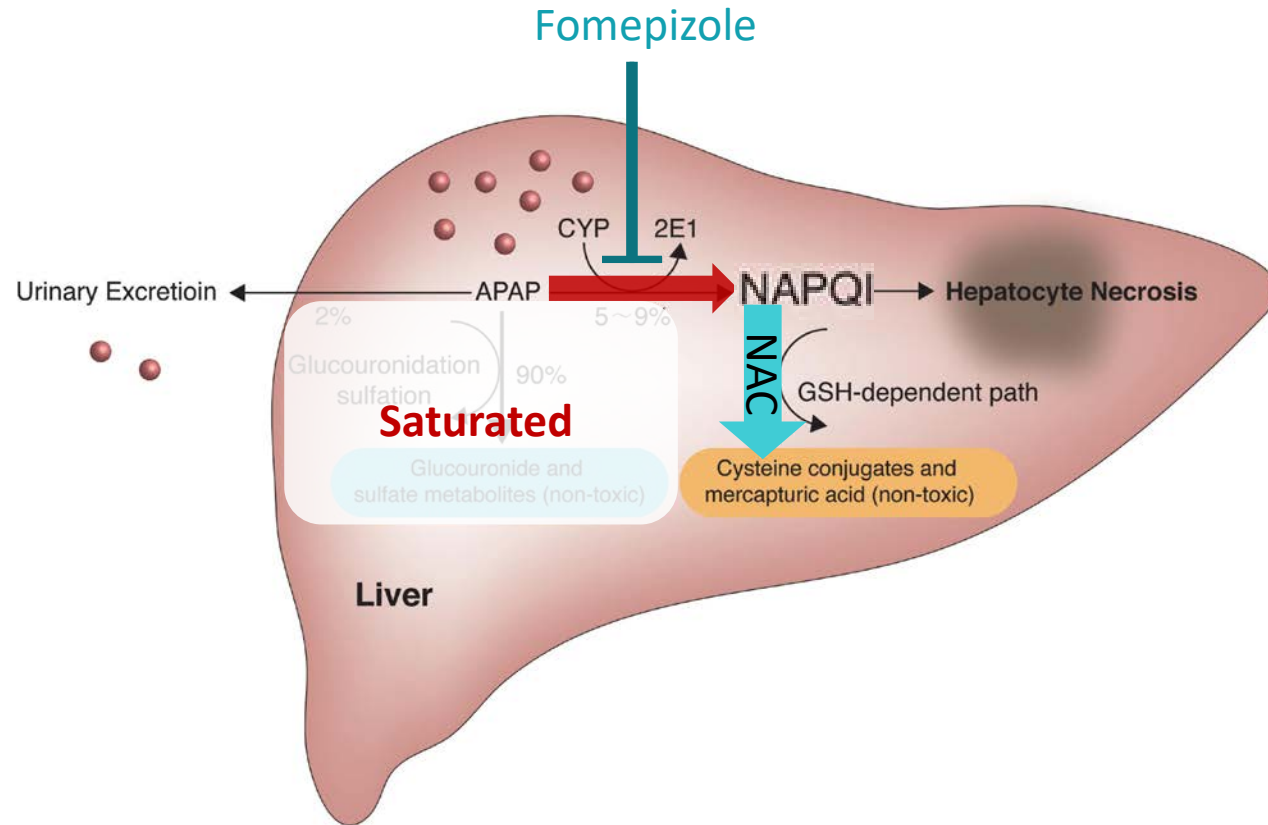
- 90% glucuronidation & sulfation
- Only 5-9% converted by CYP2E1 to NAPQI

# Overdose



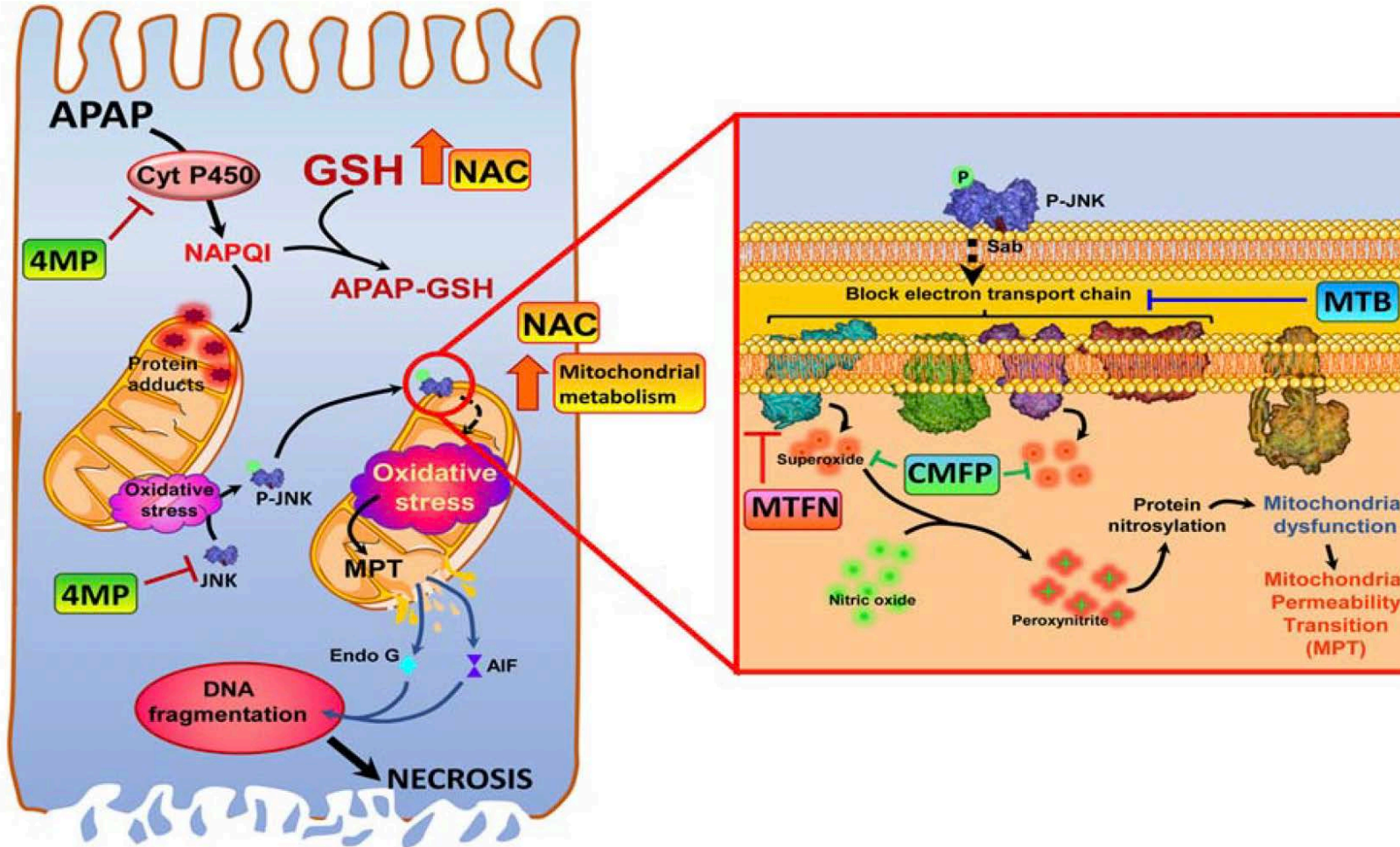
- Glucuronidation & sulfation saturated
- more APAP is converted to NAPQI by CYP2E1

# Overdose



- Glucuronidation & sulfation saturated
- more APAP is converted to NAPQI by CYP2E1

# Fomepizole in Treatment of APAP toxicity



Fomepizole does *not* replace NAC.

When weighing risks vs benefits, risk of harm appears low, and amelioration of toxicity in late-presenting cases appears promising in addition to NAC.

Many case reports.  
Need more trials.

# Literature on fomepizole for APAP

Check for updates

Article

## 4-Methylpyrazole protects against acetaminophen hepatotoxicity in mice and in primary human hepatocytes

JY Akakpo<sup>1</sup>, A Ramachandran<sup>1</sup>, SE Kandel<sup>1</sup>, HM Ni<sup>1</sup>, SC Kumer<sup>2</sup>, BH Rumack<sup>3</sup> and H Jaeschke<sup>1</sup>

H E T

Human and Experimental Toxicology  
2018, Vol. 37(12) 1310–1322  
© The Author(s) 2018  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/0960327118774902  
journals.sagepub.com/home/het  
SAGE

## 4-Methylpyrazole Blocks Acetaminophen Hepatotoxicity in the Rat

From the Departments of Emergency Medicine, Pharmacology, and Toxicology, Albany Medical College, Albany, New York

Received for publication: November 23, 2016; revision received April 16, 2017; accepted for publication June 10, 2017.

Presented at the Society for Academic Emergency Medicine Annual Meeting, San Francisco, May 1993.

Supported in part by NIAAA AG14894 Grant AA-07243 and AA-08230 (BPH).

Richard J. Brown, MD, BS, FACEP  
Russell F. Macken, PhD  
Rose Letour, BS  
Nancy Nuccio-Robak, RN, MPH  
Robert H. Swensky, MD  
James A. DeVecchio, MD  
Brian J. Zink, MD

**Study objective:** To determine whether 4-methylpyrazole inhibits the hepatotoxic effects of acetaminophen in a rat model.

**Design and type of participants:** A nonblinded experiment using male Sprague-Dawley rats.

**Interventions:** Animals were divided into four groups. Groups 1 through 3 received 2,000 mg/kg acetaminophen by gavage; group 4 acted as a control. At four or eight hours, group 2 received 400 mg/kg 4-methylpyrazole; group 3 received 50 mg/kg 4-methylpyrazole. Blood samples were taken for measurements of serum AST and ALT levels. Livers were removed for microscopic examination and grading of necrosis.

**Results:** Lower AST and ALT levels were obtained for both the 400 mg/kg ( $P < .01$ ) and 50 mg/kg ( $P < .05$ ) doses of 4-methylpyrazole administered four hours after acetaminophen.

## Delayed Treatment With 4-Methylpyrazole Protects Against Acetaminophen Hepatotoxicity in Mice by Inhibition of c-Jun n-Terminal Kinase

Jephte Y. Akakpo,\* Anup Ramachandran,\* Luqi Duan,\* Matthew A. Schaich,† Matthew W. Jaeschke,\* Bret D. Freudenthal,† Wen-Xing Ding,\* Barry H. Rumack,‡ and Hartmut Jaeschke\*<sup>1</sup>

ORIGINAL ARTICLE

## The Effect of 4-Methylpyrazole on Oxidative Metabolism of Acetaminophen in Human Volunteers

A. Min Kang<sup>1,2</sup>, Angela Padilla-Jones<sup>2</sup>, Erik S. Fisher<sup>2</sup>, Jephthe Y. Akakpo<sup>3</sup>, Hartmut Jaeschke<sup>3</sup>, Richard D. Gerkin<sup>2</sup>, Steven C. Curry<sup>1,2</sup>

### Use of fomepizole as an adjunct in the treatment of acetaminophen overdose: a case series

Garrett Rampon<sup>a,b</sup>, Haley Wartman<sup>a</sup>, Stephen Osmon<sup>a,b,c</sup> and Anthony Scalzo<sup>a,b,d</sup>

### Case Report

## A Case Report of Massive Acetaminophen Poisoning Treated with a Novel “Triple Therapy”: N-Acetylcysteine, 4-Methylpyrazole, and Hemodialysis

Emily A. Kiernan,<sup>1</sup> Julie A. Fritzges,<sup>1</sup> Kathryn A. Henry,<sup>1</sup> and Kenneth D. Katz<sup>1,2</sup>

LETTER TO THE EDITOR

### Fomepizole as an adjunctive treatment in severe acetaminophen ingestions: a case series

American Journal of Emergency Medicine 38 (2020) 402.e5–402.e7



Contents lists available at ScienceDirect  
American Journal of Emergency Medicine  
journal homepage: www.elsevier.com/locate/ajem

### Use of fomepizole, n-acetylcysteine, and hemodialysis for massive acetaminophen overdose

Jordan A. Woolum<sup>a,\*</sup>, William B. Hays<sup>a</sup>, Kripa H. Patel<sup>b</sup>

14889

American Journal of Emergency Medicine 38 (2020) 410.e5–410.e6



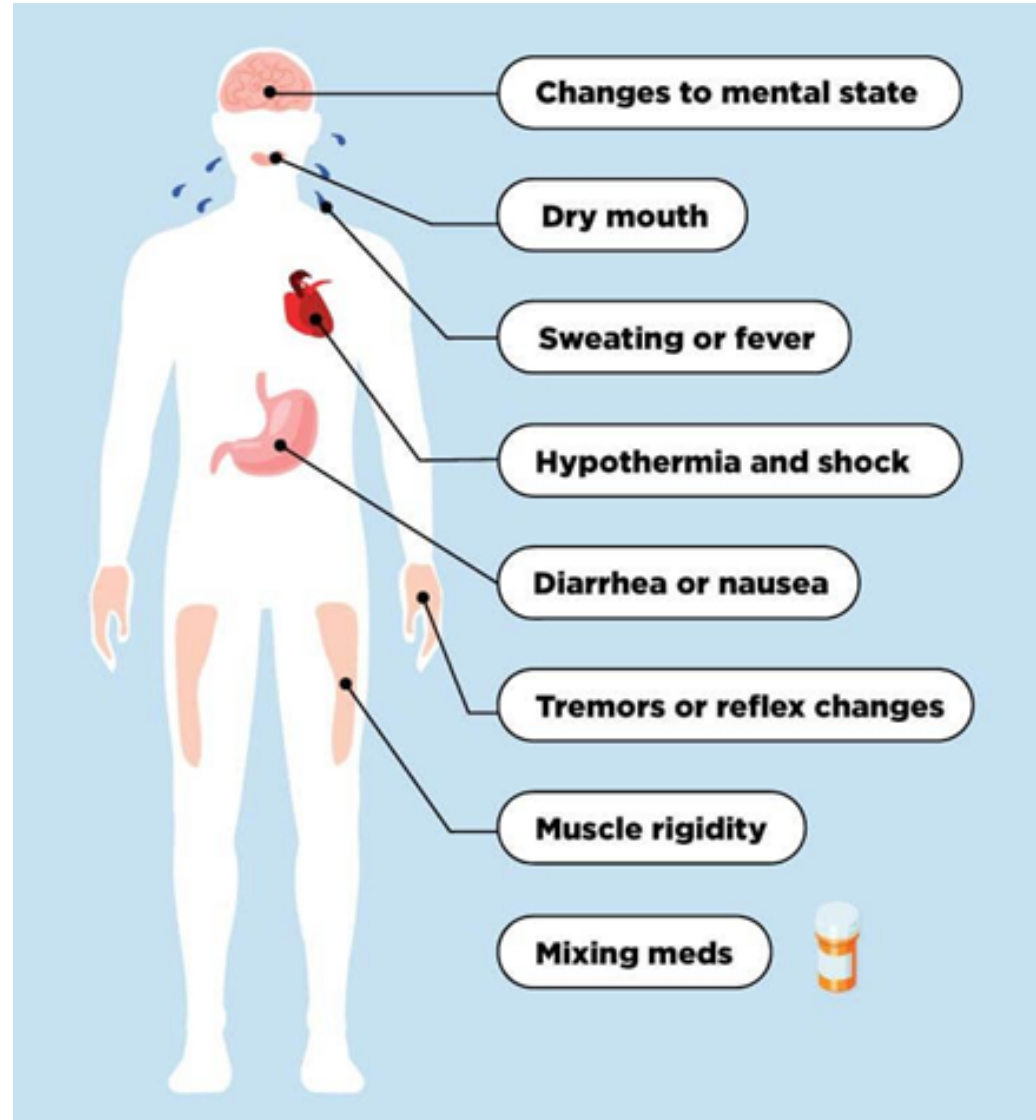
Contents lists available at ScienceDirect  
American Journal of Emergency Medicine  
journal homepage: www.elsevier.com/locate/ajem

### Fomepizole as an Adjunctive Treatment in Severe Acetaminophen Toxicity

Kartik R. Shah<sup>a,\*</sup>, Michael C. Beuhler<sup>b</sup>

# A Thing That Kills

(Serotonin syndrome)



## Opioid Toxidrome

- Signs: **CNS Depression**, Miosis, Respiratory Depression
  - Some agents have “other” effects:
  - Tramadol is serotonergic
  - Propoxyphene causes dysrhythmias
  - Cutting agents can alter presentations
- Drug Examples: Heroin, Fentanyl(s), U-47700MT45, Hydrocodone & Oxycodone

Pupils

## Sedative Hypnotic Toxidrome

- Signs: **CNS Depression**, Respiratory Depression. Additional symptoms may vary a lot
- Drug Examples: Benzodiazepines, Barbiturates, Ethanol, Many Anti-Psychotics and Anti-Depressants, The “Z” Sleeping Agents, Muscle Relaxants, GHB

## Sympathomimetic Toxidrome

- Signs: Think  $\alpha$  &  $\beta$  agonism: CV-  $\uparrow$ HR,  $\uparrow$ BP. Neuro- **Hyperactive**, Agitated, Delirium. Skin – Diaphoresis  
Pupils - Dilated
- Drug Examples: Amphetamines, Methamphetamine, Many Novel Psychoactive agents, Cocaine, Synthetic Cathinones (Bath Salts), Synthetic Cannabinoids

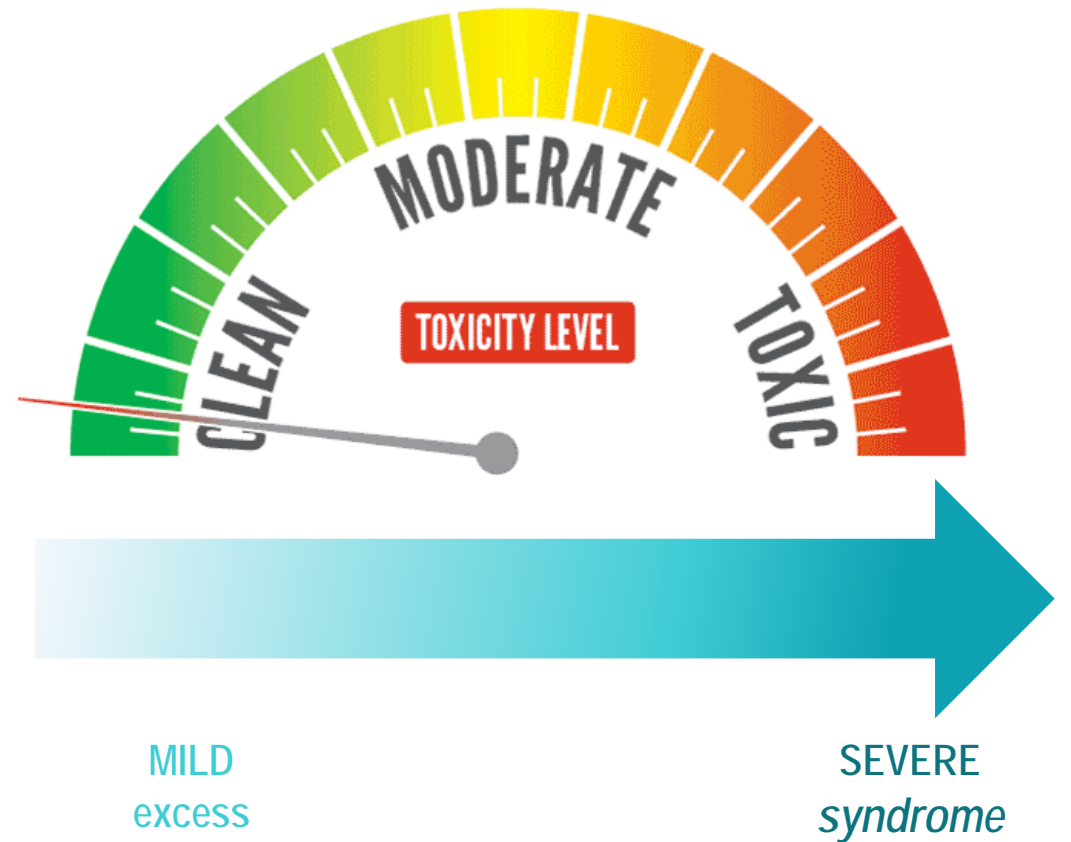
Reflexes

## Serotonergic Toxidrome

- Signs: **Hyperreflexia**, Clonus, **Tremor**, **Tachycardia**, Diaphoresis, Diarrhea, Agitation
- Drug Examples: MDMA (Ecstasy) & many other similar drugs, Cough & Cold meds, BOMEs, SSRIs & SNRIs, Tramadol, Meperidine, Dextromethorphan, MAOIs



# Serotonin Toxicity Exists along a spectrum



# Hunter Criteria

## Serotonin Toxicity

*Diagnosis*

Is Patient currently on serotonergic agent?

No

Not serotonin syndrome

Yes

Is at least 1 of the following 5 conditions present?

- 1 Spontaneous clonus
- 2 Inducible clonus & Agitation or diaphoresis
- 3 Ocular clonus & Agitation or diaphoresis
- 4 Inducible clonus or ocular clonus & Hypertonia + hyperthermia
- 5 Tremor & Hyperreflexia

No

Not serotonin syndrome

Yes

Serotonin syndrome

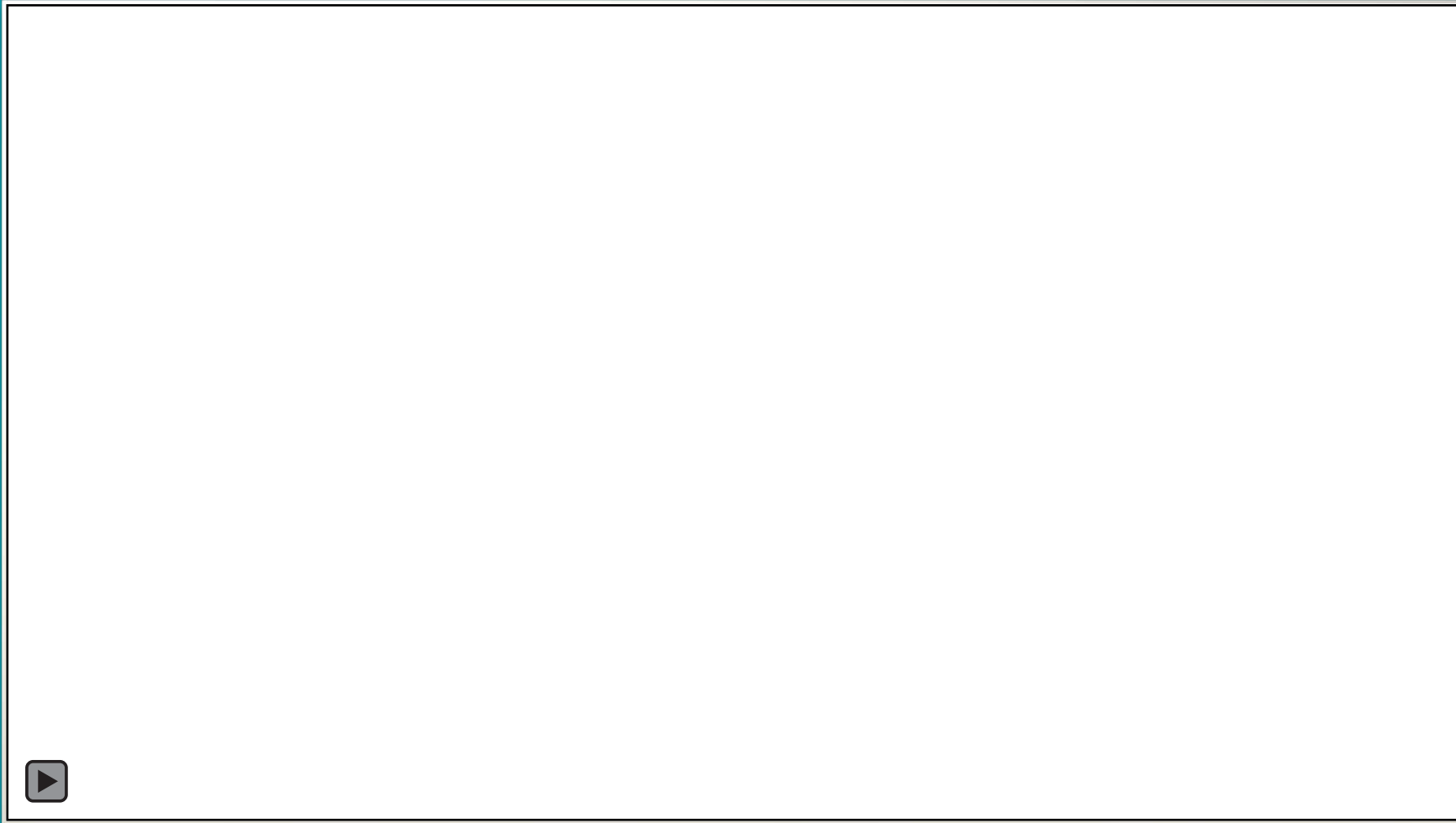
# Inducible Ankle Clonus

## Serotonin Toxicity



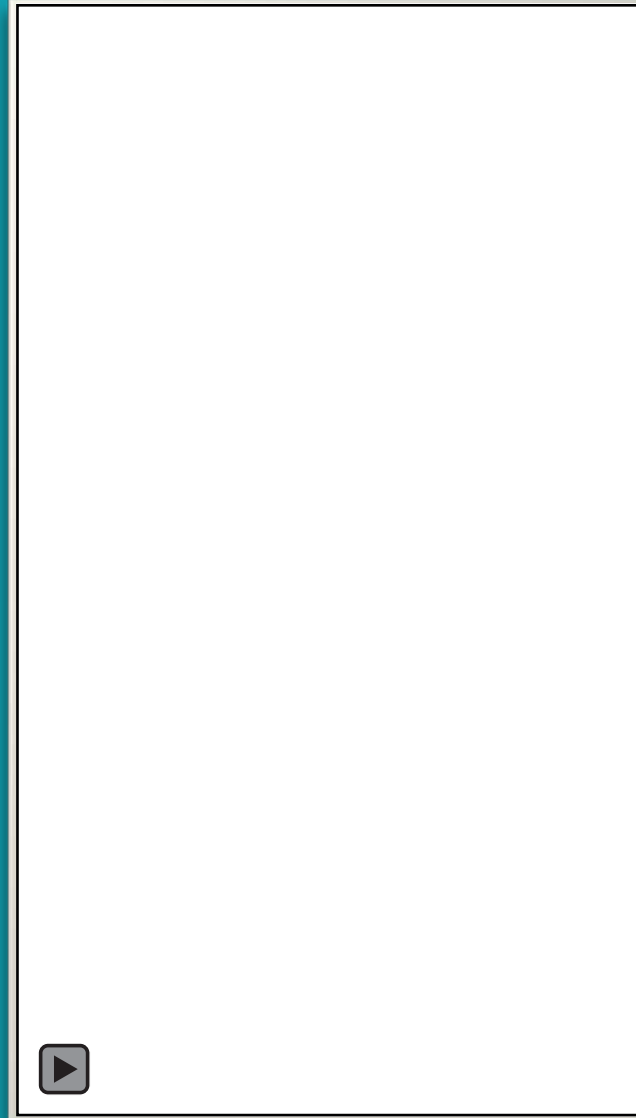
# Spontaneous Clonus

## Serotonin Toxicity



# Spontaneous Clonus

## Serotonin Toxicity



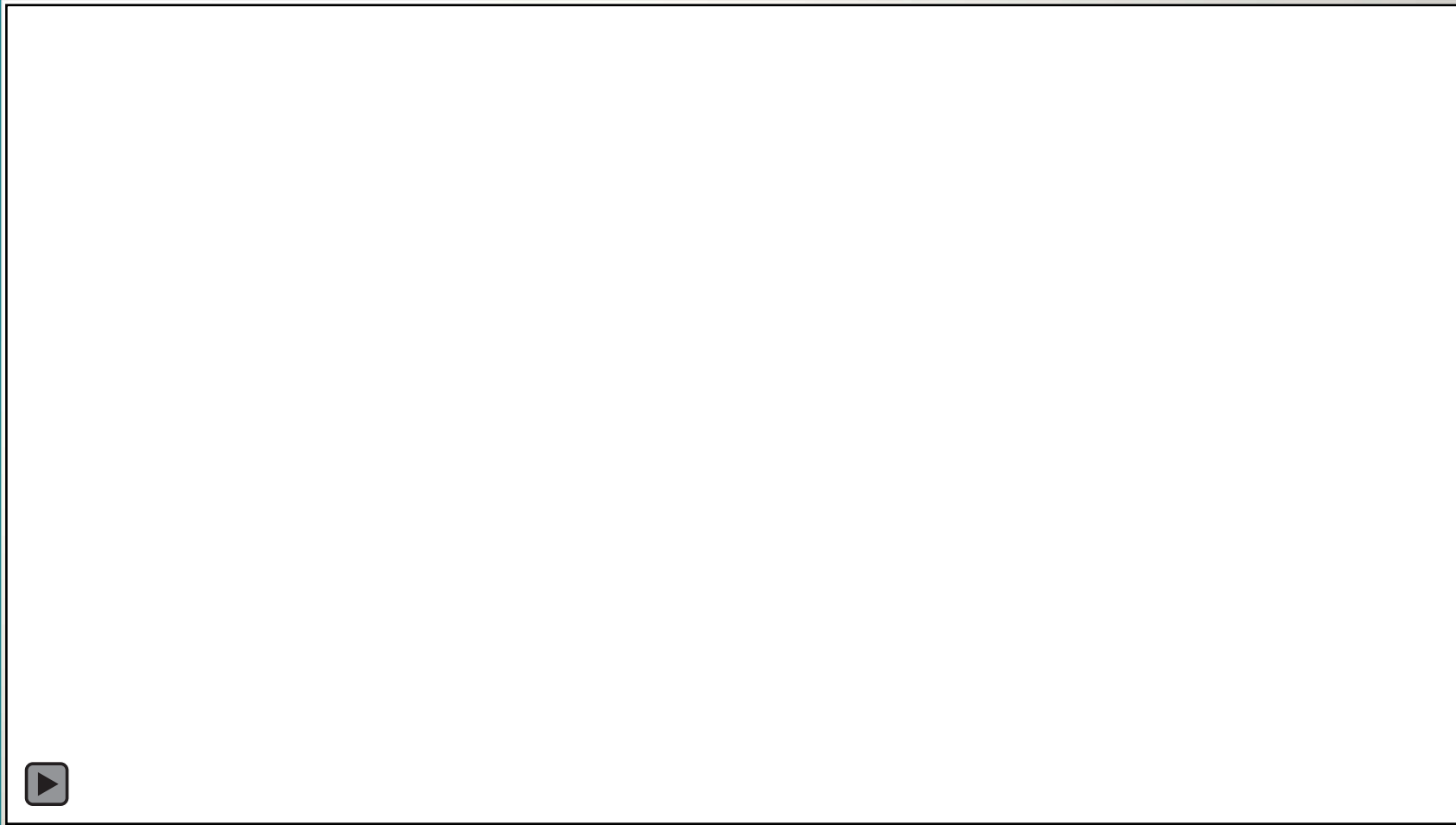
# Ocular Clonus

## Serotonin Toxicity



# Ocular Clonus

## Serotonin Toxicity



# Serotonin Toxicity

## Treatment

- Supportive care
- BENZOS for agitation, tremor, clonus, tachycardia, HTN.
- Cyproheptadine- anti-serotonergic antihistamine (12mg PO, initial dose for adults)
- Severe effects such as rigidity, hyperthermia, SZ:
  - Intubation
  - Aggressive sedation and cooling
  - Possibly neuromuscular blockade

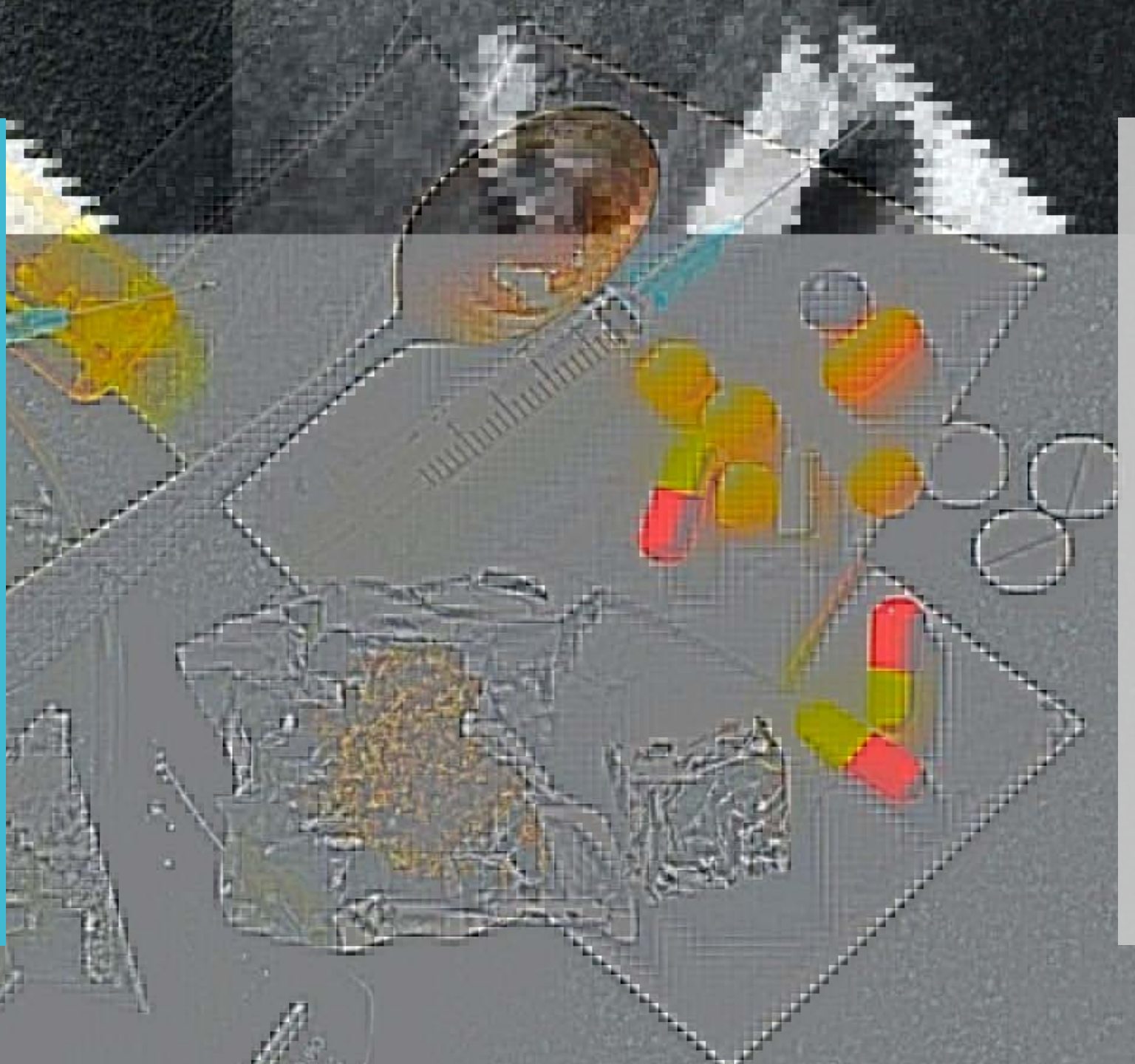
I ❤️  
**BENZOS**



**ANTI-HISTAMINE for ALLERGIC REACTIONS Like Itchy EYES, runny NOSTRIL, SNEEZING, HIVES, and FOR FASTER WEIGHT GAIN**



# Cheap Thrills



# GoodRx

Find the lowest local prices  
on your prescriptions



# Pricing



## streetRx latest street prices for illicit and prescription drugs

### Okc, Oklahoma

**\$80** methamphetamine (powder/crystal), 1g rock/crystal  
 Jul 28 2022 Rate: \$ \$ \$ \$ \$

### Woodward, Oklahoma

**\$15** escitalopram pill, 10mg pill  
 Aug 3 2022 Rate: \$ \$ \$ \$ \$

### Tulsa, Oklahoma

**\$15** generic Klonopin, 0.5mg pill Reasonable  
 Aug 1 2022

#### Prices for Norco — USA

Include products with the same active ingredient

**\$6** Norco, 10mg/325mg pill  
 Mar 21 2021 Newport Beach, California Rate: \$ \$ \$ \$ \$

**\$9** Norco, 10mg/325mg pill  
 Mar 14 2021 Manteca, California Rate: \$ \$ \$ \$ \$

**\$7.50** Norco, 10mg/325mg pill  
 Mar 13 2021 Jacksonville, Texas Reasonable \$ \$ \$ \$ \$

**\$5** Norco, 10mg/325mg pill  
 Mar 10 2021 Santa Rosa, California Reasonable \$ \$ \$ \$ \$

**\$10** Norco, 5mg/325mg pill  
 Mar 9 2021 Illinois Cheap \$ \$ \$ \$ \$

**\$4.50** Norco, 10mg/325mg pill  
 Mar 9 2021 Michigan Not Bad \$ \$ \$ \$ \$

#### Prices for , heroin, heroin (black tar), heroin (chunk), heroin (cut with fentanyl), heroin (powder), ... — USA

Include products with the same active ingredient


**\$150** heroin (black tar), 8-ball (1/8oz) tar  
 Mar 14 2021 Salt lake City, Utah Rate: \$ \$ \$ \$ \$

**\$20** heroin (cut with fentanyl), 1g powder  
 Mar 14 2021 Massachusetts Cheap \$ \$ \$ \$ \$



**"WASPING" A DANGEROUS NEW DRUG TREND**



Three clear plastic vials with black caps are lined up on a dark surface. The vial on the left contains a white powder. The middle vial contains a small amount of clear crystals. The vial on the right is empty. Each vial has a white label with black text.

HEROIN

FENTANYL

CARFENTANYL

# Heroin



**Quarter** 1//4<sup>th</sup> or 0.25g

**Teener** 1//16<sup>th</sup> of an ounce, or ~ 1.75g

**8-ball** (2 teeners = 14 quarters)  
1//8<sup>th</sup> of ounce, or 3.5g

Prices for , heroin, heroin (black tar), heroin (chunk), heroin (cut with fentanyl), heroin (powder), ... — USA

Include products with the same active ingredient

**\$150** heroin (black tar), 8-ball (1/8oz) tar Rate:  
Mar 14 Salt lake City, Utah \$ \$ \$ \$ \$  
2021

**\$20** heroin (cut with fentanyl), 1g powder Cheap  
Mar 14 Massachusetts \$ \$ \$ \$ \$  
2021

# Heroin- routes of abuse

Oral

Intranasal

Intravenous

Subcutaneous - "skin popping"

Intramuscular - "muscle popping" or "muscling"

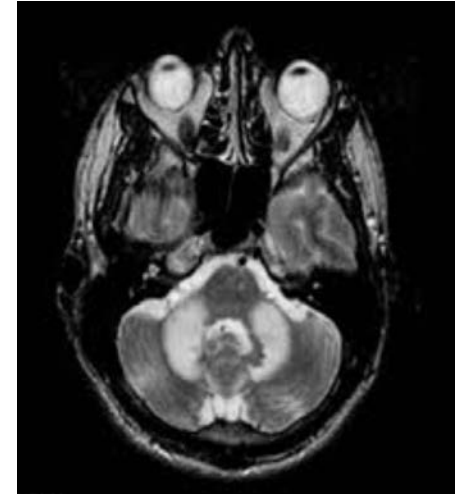


# Chasing the Dragon

Inhaled white pyrolysate [vapour] generated by heating heroin on aluminum foil

Produces heroin pharmacokinetics similar to IV

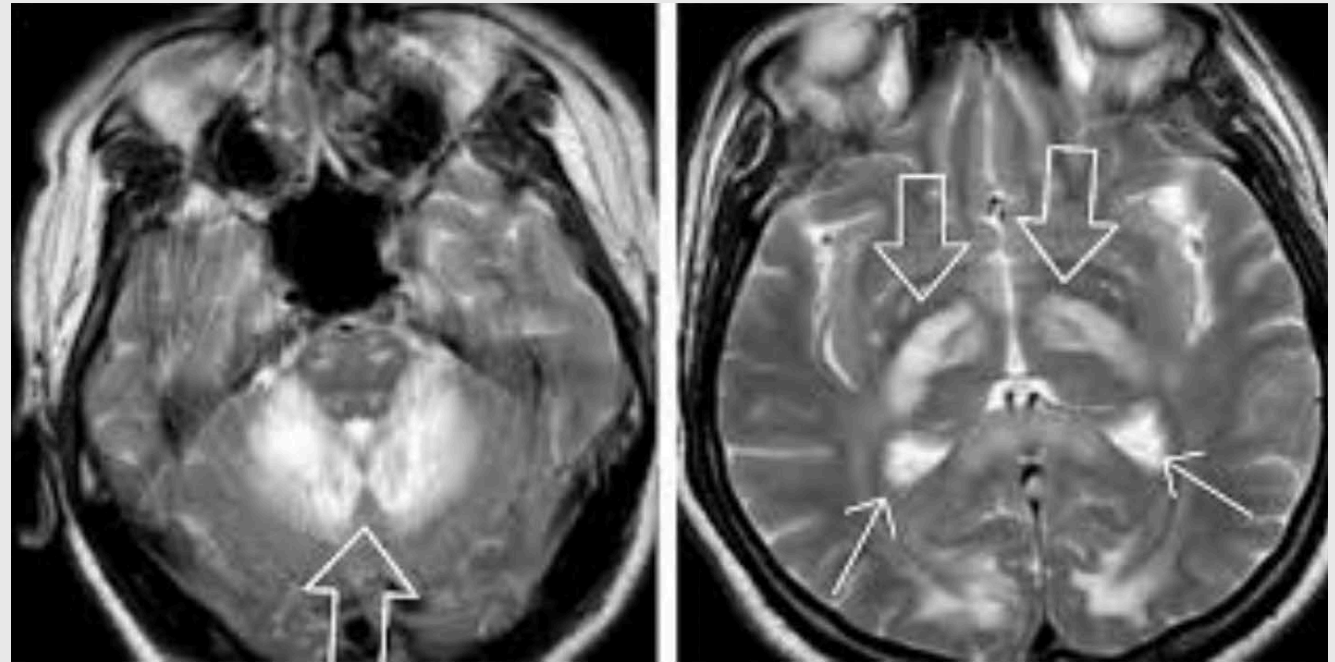
Trying to avoid injection drug use for infection risks





# Spongiform Leukoencephalopathy

- 1980s, Netherlands
- 47 cases “chasing the dragon”
- 23% died within 2 weeks of use
- Bradykinesia, ataxia, abulia, speech abnormalities
- Half-recovered, others progressed to spastic paraparesis, pseudobulbar palsy, hypotonia
- Symmetric cerebellar and cerebral white matter destruction
- Supportive care





# Cocaine Adulteration



Annals of Emergency Medicine

Volume 22, Issue 9, September 1993, Pages 1485-1487



Case report

## Phenytoin toxicity from smoking crack cocaine adulterated with phenytoin

MD Alan A Katz <sup>\*</sup>, MD Robert S Hoffman <sup>†</sup>, MD Robert A Silverman <sup>\*</sup> 

[Show more](#) 

[+](#) Add to Mendeley  [Share](#)  [Cite](#)

[https://doi.org/10.1016/S0196-0644\(05\)82002-5](https://doi.org/10.1016/S0196-0644(05)82002-5)

[Get rights and content](#)

Drugs of abuse often are adulterated with agents designed to lower cost or alter the intoxication. Recently, we began to hear of the intentional addition of phenytoin to crack cocaine. We report the cases of five patients with measurable phenytoin levels attributable to smoking crack cocaine adulterated with phenytoin. Three of these patients presented with signs, symptoms, and phenytoin levels consistent with phenytoin toxicity. Clinicians should be aware of this practice when faced with cocaine users with altered mental status, ataxia, or nystagmus.

## Levamisole-adulterated cocaine: Two fatal case reports and evaluation of possible cocaine toxicity potentiation

Francesca Indorato <sup>1</sup>, Guido Romano <sup>2</sup>, Nunziata Barbera <sup>2</sup>

Affiliations + expand

PMID: 26866560 DOI: [10.1016/j.forsciint.2016.01.005](https://doi.org/10.1016/j.forsciint.2016.01.005)

### Abstract

Levamisole has been identified as a cocaine adulterant in the United States since 2002. Although there is a variation in the percentage of levamisole in cocaine samples between European countries, measurement of levamisole in human samples of cocaine users has become increasingly important. To our best knowledge, only five deaths are reported (one twice) as a result of complications secondary to levamisole-tainted cocaine and none of these cases reports the post-mortem levamisole concentration. In this article, we present the post-mortem levamisole concentrations in fluids and tissues in two young cocaine users, dead after levamisole-adulterated cocaine intake. With the dearth of levamisole reported concentrations in literature, this particular report is of interest to the forensic toxicological and pathological communities. This article aims to be a supplementary alert to aware the risk that may occur using levamisole-adulterated cocaine and an incentive to publication of toxicity reports and new researches involving the combination of levamisole and cocaine.



# Levamisole-induced Vasculitis/Purpura



**Give your friendly  
local poison  
center a call.**

WE'RE ALWAYS AVAILABLE TO HELP

Questions?



## Notes:

# References:

1. Goldfrank's Toxicologic Emergencies, Eleventh Edition 11th Edition
2. <https://www.sciencedirect.com/science/article/abs/pii/S0196064405820025>
3. Levamisole-Adulterated Cocaine: A Case Series. Gerald W. Morris. The Journal of the American Board of Family Medicine Jul 2012, 25 (4) 531-535; DOI: 10.3122/jabfm.2012.04.110287
4. <https://www.justice.gov/archive/ndic/pubs11/12208/index.htm#What>
5. Strang J, Griffiths P, Gossop M. Heroin smoking by 'chasing the dragon': origins and history. *Addiction*. 1997 Jun;92(6):673-83; discussion 685-95. doi: 10.1046/j.1360-0443.1997.9266734.x. PMID: 9246796.
6. Buxton, J.A., Sebastian, R., Clearsky, L. et al. Chasing the dragon - characterizing cases of leukoencephalopathy associated with heroin inhalation in British Columbia. *Harm Reduct J* 8, 3 (2011). <https://doi.org/10.1186/1477-7517-8-3>
7. Cremer JE, Seville MP. Comparative effects of two pyrethroids, deltamethrin and cismethrin, on plasma catecholamines and on blood glucose and lactate. *Toxicol Appl Pharmacol*. 1982;66(1):124-133.
8. LoVecchio F, Knight J. Injection of pyrethroids without significant sequelae. *Am J Emerg Med*. 2005;23(3):406.
9. Goldberg LH, Shupp D, Weitz HH, Zeccardi JA. Injection of household spray insecticide. *Ann Emerg Med*. 1982;11(11):626-629.
10. Gheshlaghi, Farzad & eizadi-mood, Nastaran & Piri Ardakani, Mohamadreza & Sabzghabae, Ali M. & A, Firoozfar. (2011). Status epilepticus following intravenous injection of pyrethroid insecticide for attempted suicide: a not yet reported case. *Journal of Clinical Toxicology*. 001-003.
11. Ramachandran, P., U. Devaraj and G. D'Souza. "A Rare Poisoning with Pyrethroid by an Uncommon Route of Self Injection." *Emergency Medicine Australasia* 2014 (2014): 1-3.
12. Darnell JL, Fleisch SB. Methamphetamine and Wasp Spray: A Unique Way to Get a Stinging High. *Psychosomatics*. 2019;60(5):535-536.
13. Poulos L, Athanasis S, Coutselinis A. Acute intoxication with cypermethrin (NRDC 149). *J Toxicol Clin Toxicol*. 1982;19(5):519-520.
14. Sewell C, Ramaniuk A, Jordan, K. Emerging Lethal E-cigarette Drug Trends: ARDS and Death from "Wasping". A49. Case Reports in Lung Disease Associated With Inhalational Exposures: A1816-A1816
15. Note that other articles are not listed herein if specifically documented elsewhere within this presentation.

