U.S. ARMY COMBAT CAPABILITIES DEVELOPMENT COMMAND – CHEMICAL BIOLOGICAL CENTER

Decontaminant Reactivity Screen with Select Fentanyls

Presented by: Amanda Schenning
Nov 20, 2019

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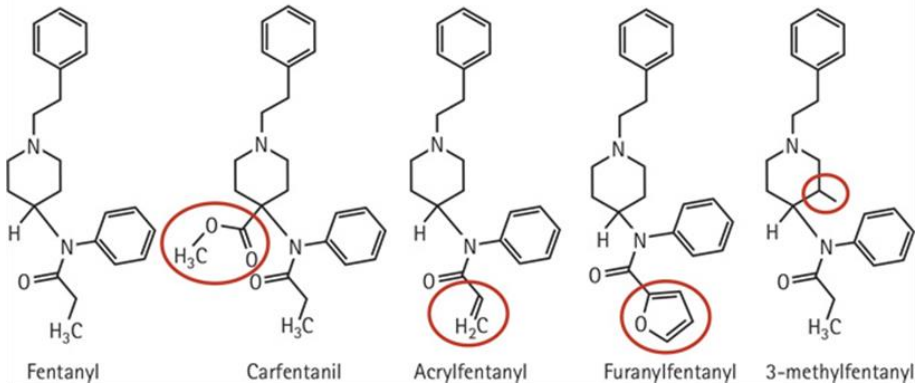
PROJECT BACKGROUND - WHAT WE WERE ASKED TO DO

Funded By: Joint Project Manager, NBC Contamination Avoidance Product Director Cross Commodity Advanced Threats & Test Infrastructure (PDCAT&TI)

Consider the problem of opioid contamination and contact transfer from the first responder point of view.

Figure 2. Molecular Structures of Fentanyl and Fentanyl Analogues of Significance to First Responders



Officer Safety Alert

Drug Enforcement Administration

Carfentanil: A Dangerous New Factor in the U.S. Opioid Crisis

Carfentanil is a synthetic opioid approximately 10,000 times more potent than morphine and 100 times more potent than fentanyl. The presence of carfentanil in illicit U.S. drug markets is cause for concern, as the relative strength of this drug could lead to an increase in overdoses and overdose-related deaths, even among opioid-tolerant users. The presence of carfentanil poses a significant threat to first responders and law enforcement personnel who may come in contact with this substance. **In any situation where any fentanyl-related substance, such as carfentanil, might be present, law enforcement should carefully follow safety protocols to avoid accidental exposure.**

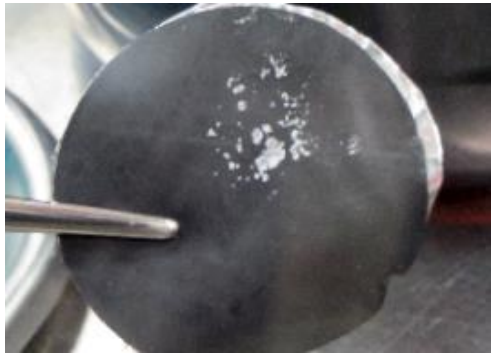
Officer & Public Safety Information

Carfentanil and other fentanyl analogues present a serious risk to public safety, first responder, medical, treatment, and laboratory personnel. These substances can come in several forms, including powder, blotter paper, tablets, patch, and spray. Some forms can be absorbed through the skin or accidentally inhaled. If encountered, responding personnel should do the following based on the specific situation:

PROJECT BACKGROUND - WHAT WE WERE ASKED TO DO

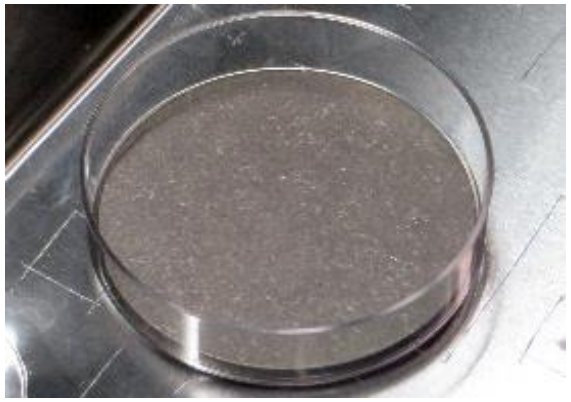
Consider the challenges associated with studying “non-liquid” contaminants.

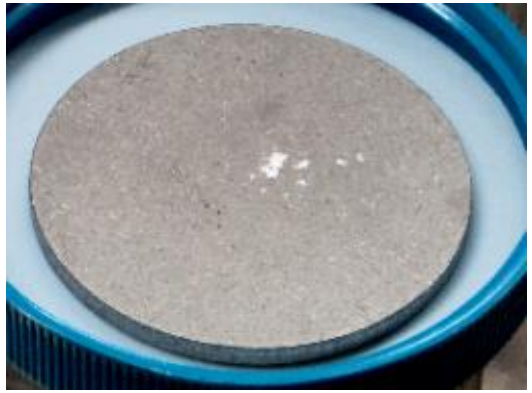
Neat material - free base vs. salt

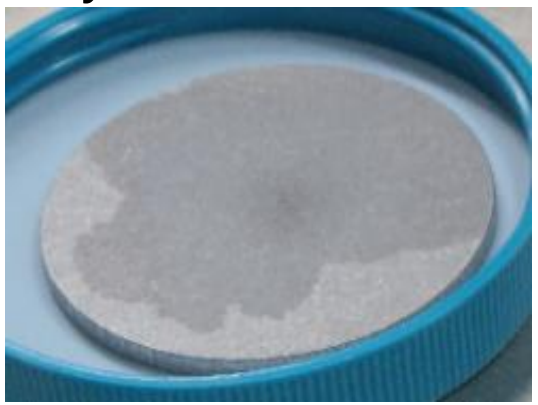


Solubility - aqueous vs. organic

Surface deposition (left to right) – aerosolized solid, dropped solid, aqueous slurry, solvent solution





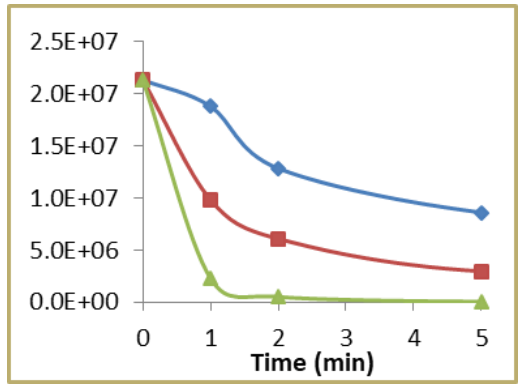


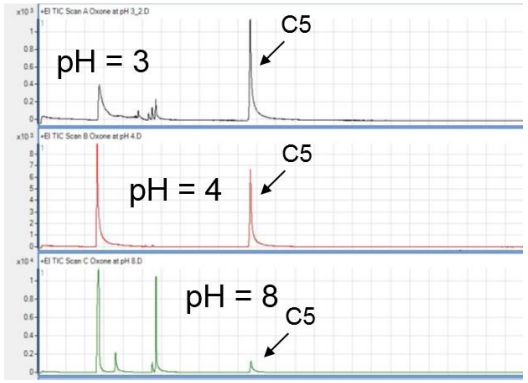
Contaminant form significantly impacts the experiment and results

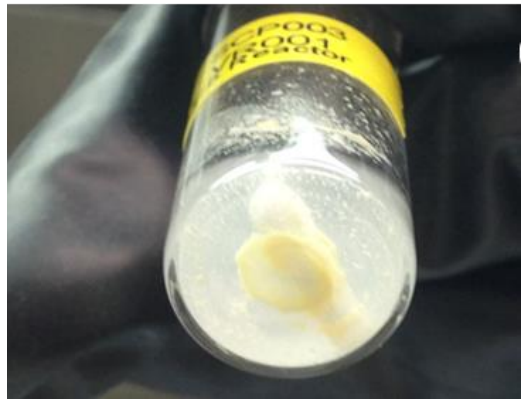
PROJECT BACKGROUND - WHAT WE WERE ASKED TO DO

Conduct a scoping study centered on opioid decontamination and contact transfer to provide the customer with some basic information needed to address the concerns of contamination avoidance.

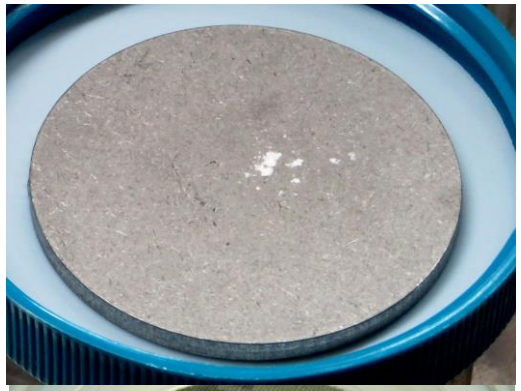
reactivity and by-product formation

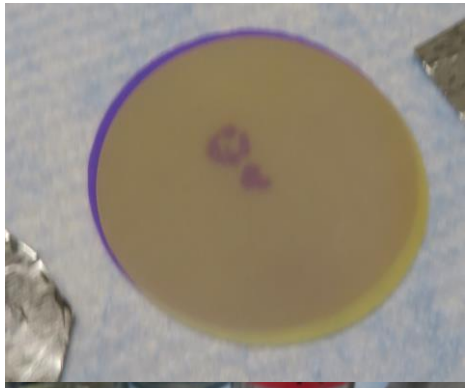


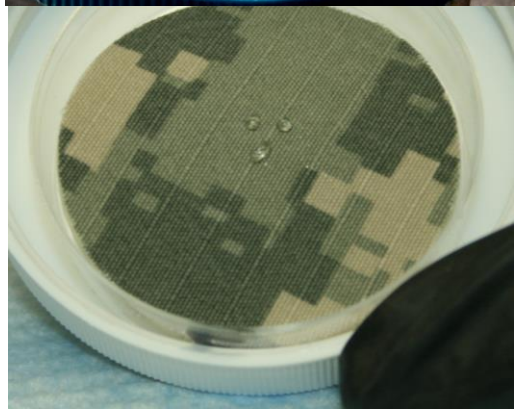




contact transfer

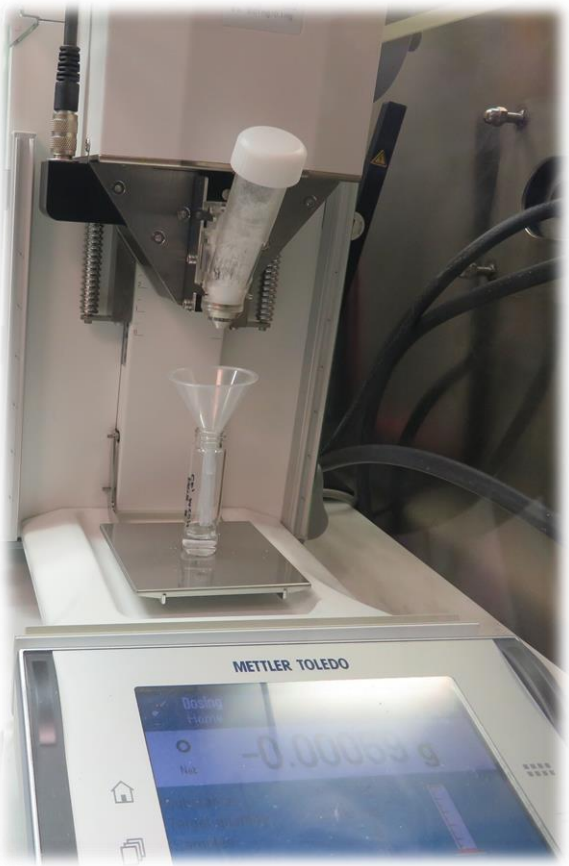




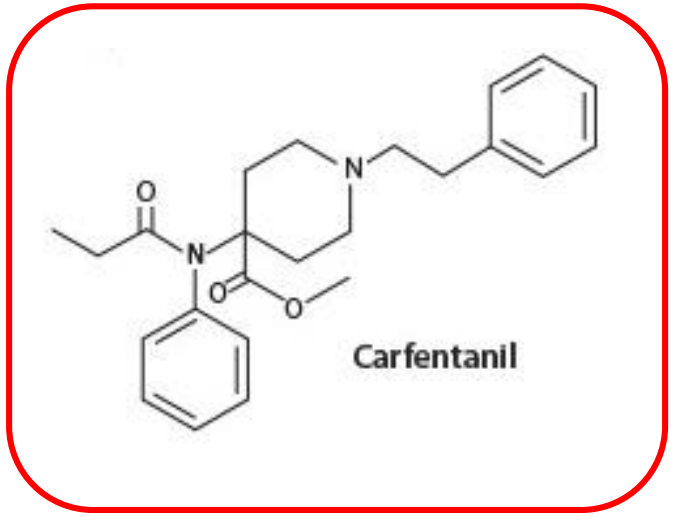


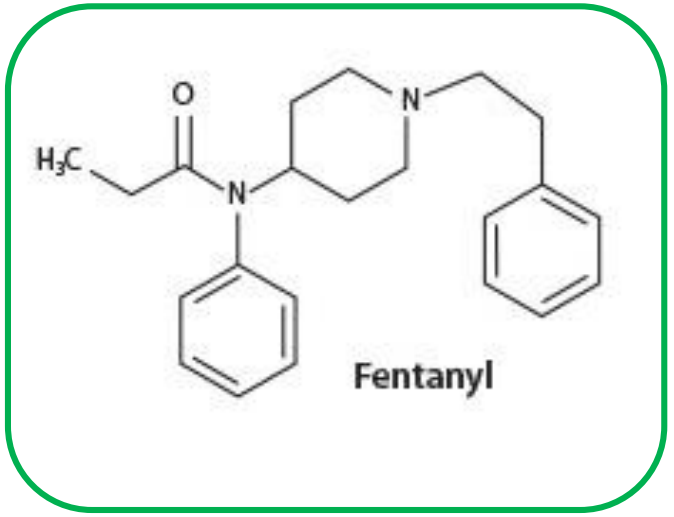
PROJECT BACKGROUND - WHAT WE WERE ASKED TO DO

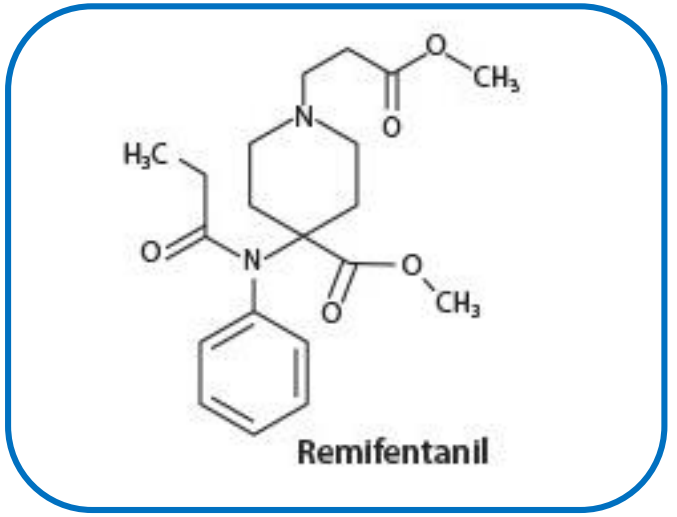
Provide feedback to the customer regarding the laboratory infrastructure needs and testing protocols needed to study decontamination of solid contaminants like opioids.

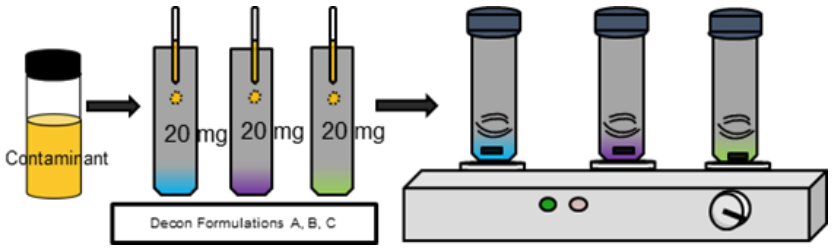


LIQUID PHASE REACTIVITY AND BY-PRODUCT FORMATION









Decontaminant Reactivity

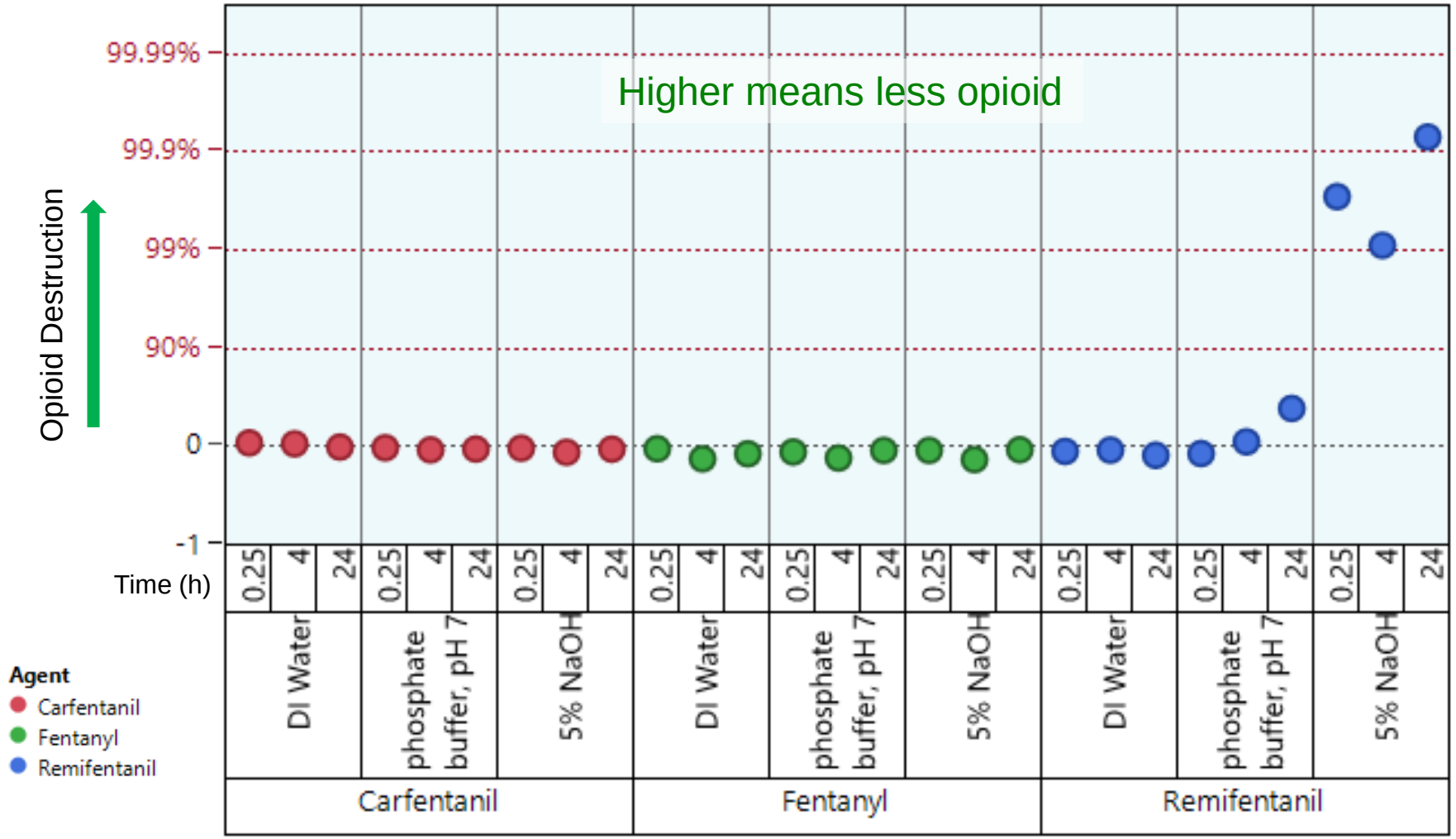
Contaminant-Decontaminant Interactions

- Contaminant loading: ~ 1 mg opioid to 1 mL of decontaminant
- Contaminant delivery: pre-diluted in methanol
- Collected multiple reaction time points up to 24 h
- Full vial characterization at each time point
- Quantification of target analytes by LC/MS/MS
- Quantitative analysis of hydrolysis products, and fentanyl N-oxide.
- Qualitative analysis of carfentanil N-oxide

DECONTAMINANTS

Decontaminants	Active Ingredient	Mode of Action	pH
Methanol	None	Positive Control	-
DI Water	Water	Hydrolysis Control	7
Phosphate buffer (pH 7)	Water, Phosphate?	Hydrolysis Control	7
5% Sodium Hydroxide	Hydroxide ion	Hydrolysis	13+
Brutabs® (1 tab : 200 mLs water, ~0.5% chlorine)	Hypochlorite	Oxidation	6
Dilute buffered chlorine bleach, (~0.5% chlorine)	Hypochlorite	Oxidation	7
Dilute chlorine bleach, (~0.5% chlorine)	Hypochlorite	Oxidation, hydrolysis	11
Clorox® Bleach (~6% chlorine)	Hypochlorite	Oxidation, hydrolysis	11
Dahlgren Decon®	Peracetic acid	Oxidation	6
FR Decon®	Peracetic acid	Oxidation, hydrolysis	10
Sprayable Decon Slurry	Hypobromite/$Zr(OH)_4$	Oxidation, hydrolysis	Neutral
RSDL	Oxime	Nucleophilic substitution	?

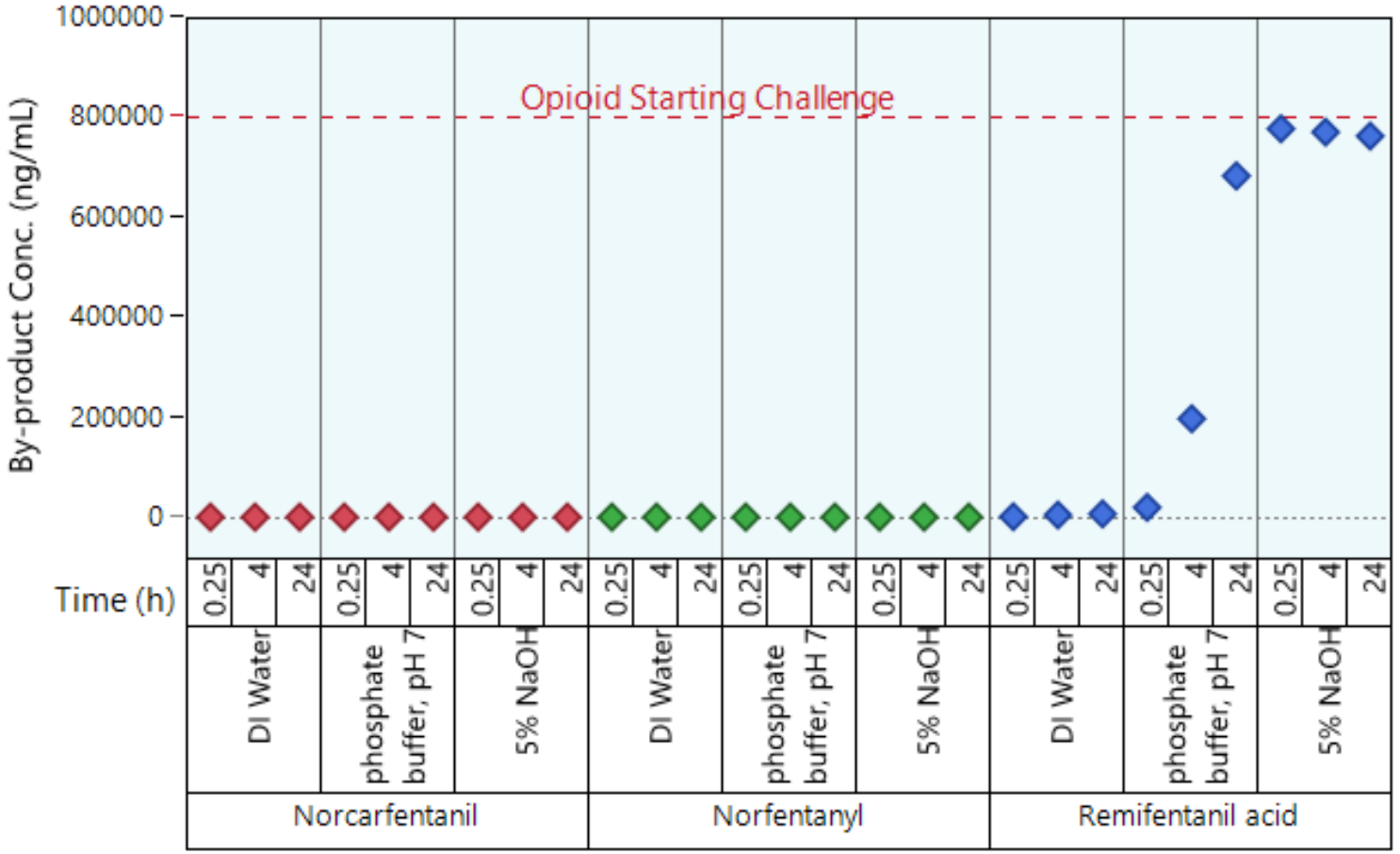
REACTIVITY IN AQUEOUS DECONTAMINANTS

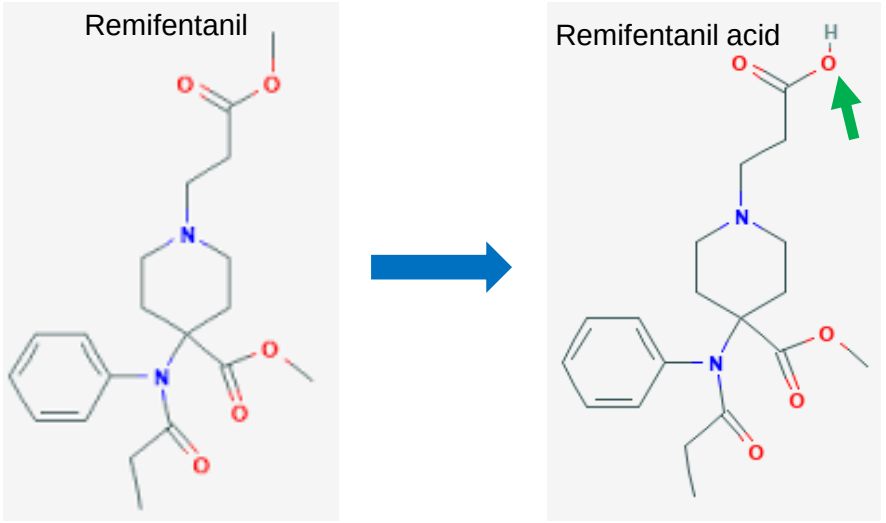


- Carfentanil and Fentanyl were stable in aqueous solutions – even caustic - for at least 24 h.
- Remifentanil is more susceptible to hydrolysis - but rate is subject to pH and time.
- Remifentanil hydrolysis is nearly complete in 15 min in caustic solution.

Destruction rate of pre-diluted opioid is not same as for neat salt or freebase

BY-PRODUCTS IN AQUEOUS DECONTAMINANTS



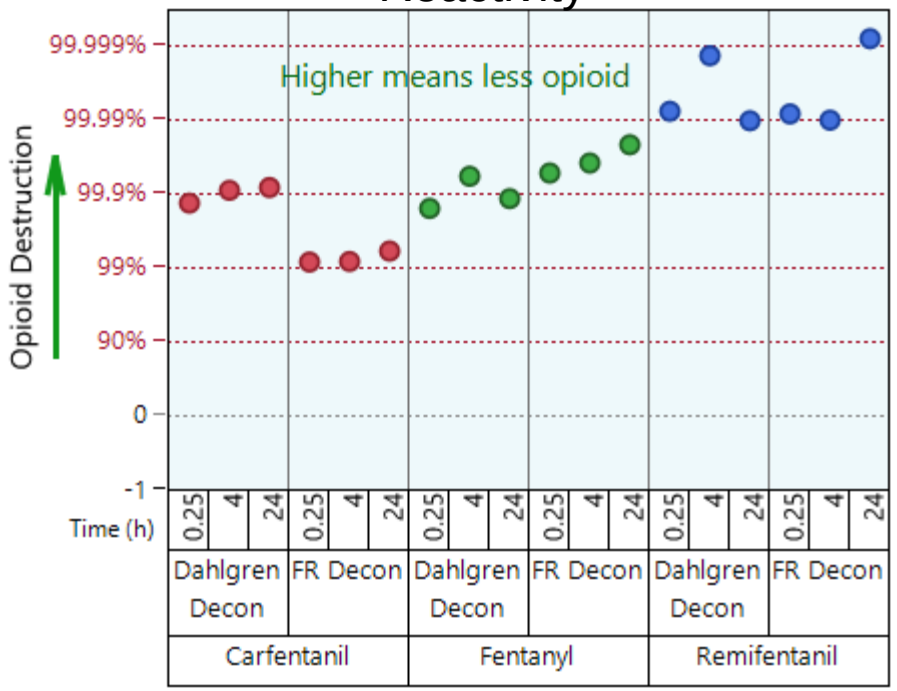


Reversible? Toxic?

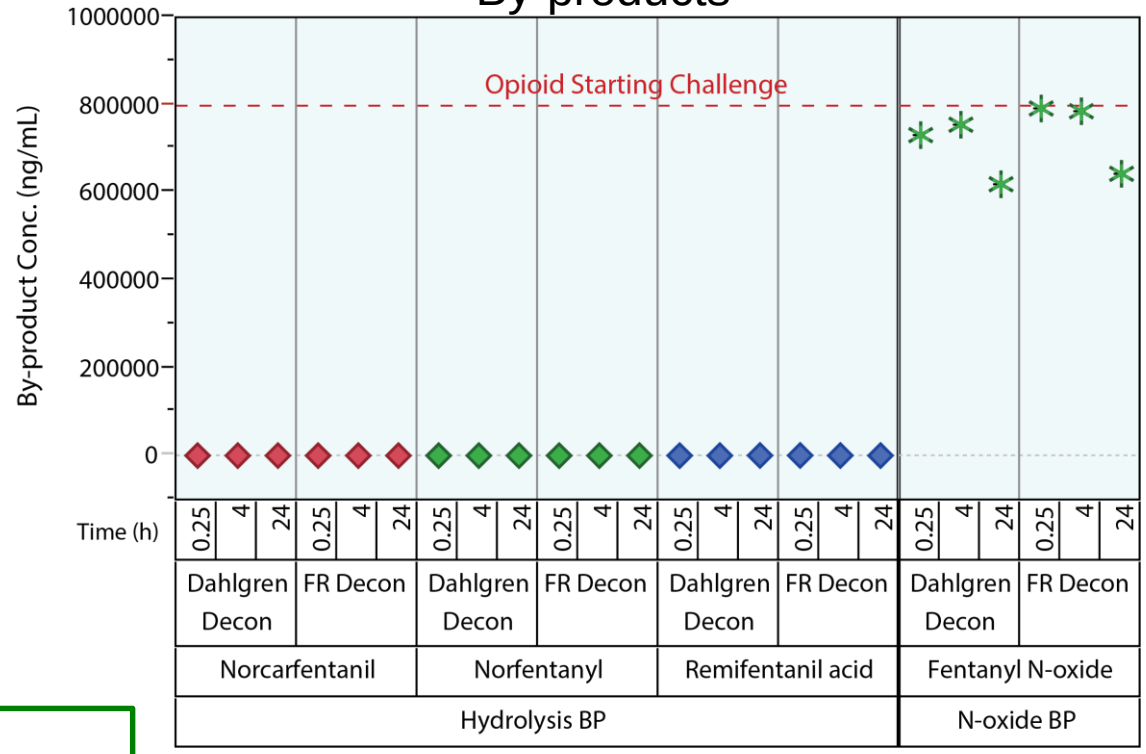
- No hydrolysis products observed for fentanyl or carfentanil in 24 h
- Near complete conversion of remifentanil to remifentanil acid in caustic
- Remifentanil oxidative products not investigated

FORMULATED PERACETIC ACID DECONTAMINANTS

Reactivity

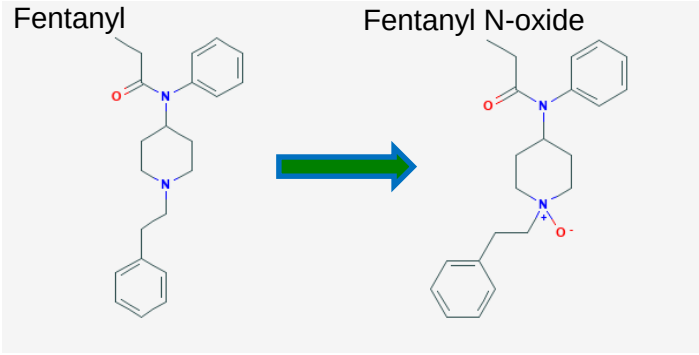


By-products

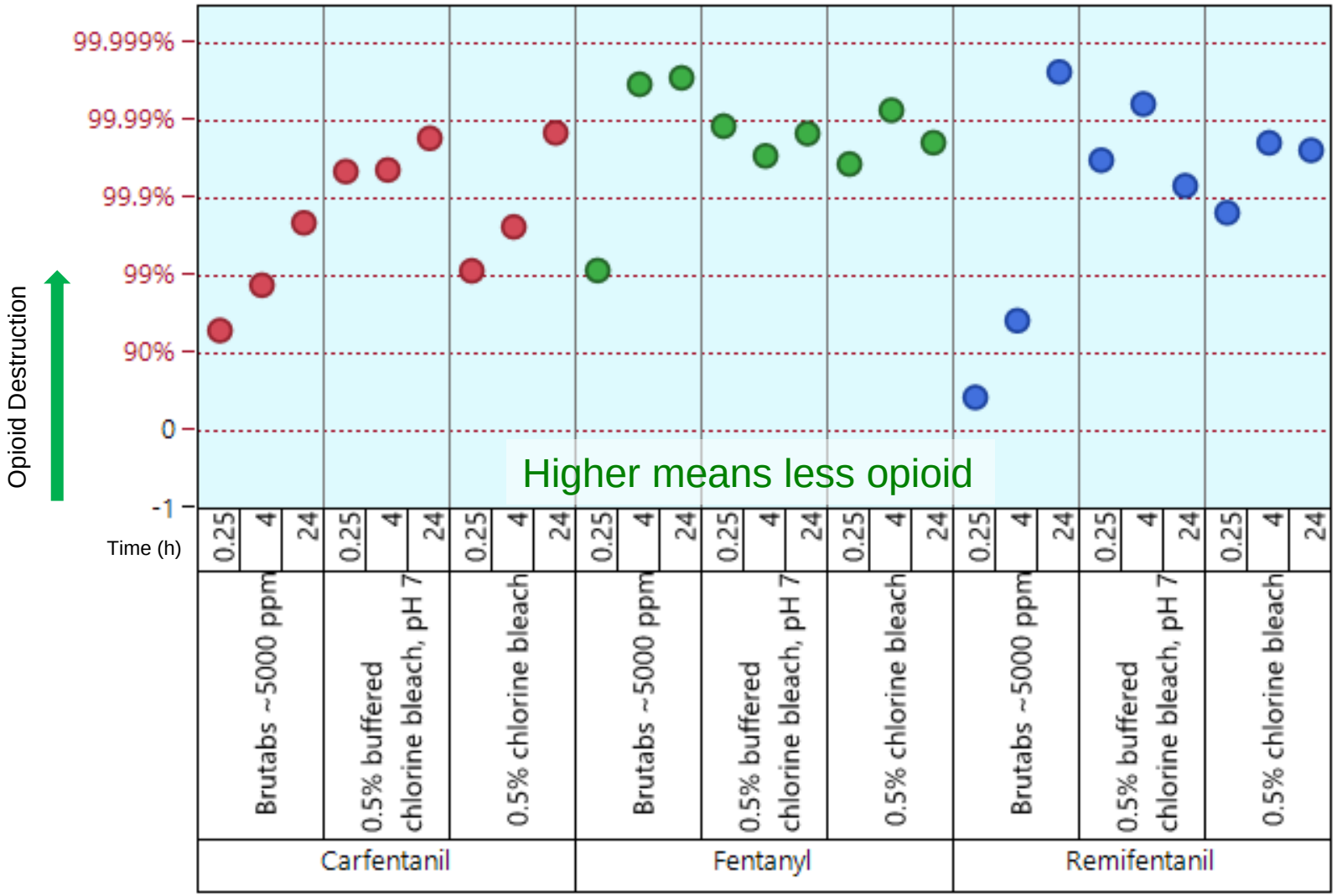


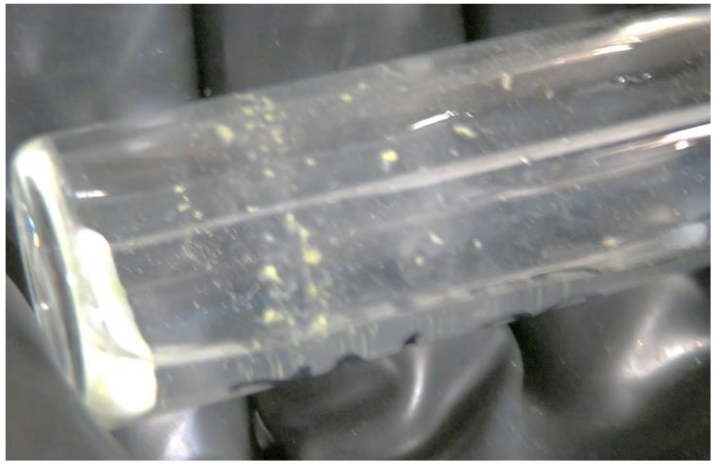
Carfentanil and Fentanyl:

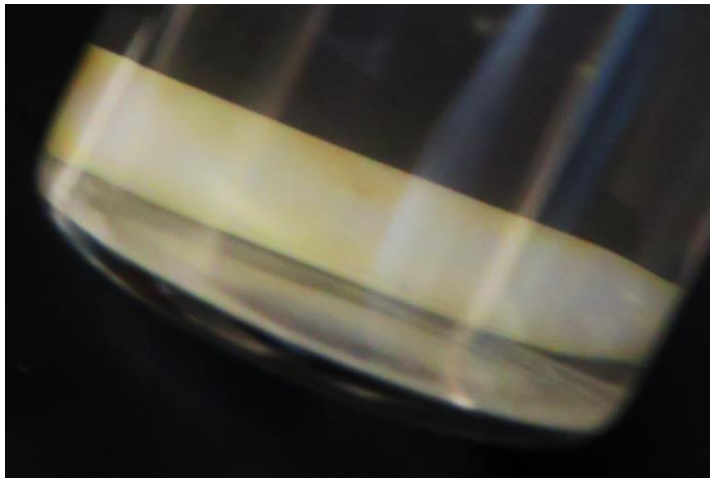
- ~ 2 log reduction in 15 minutes
- Destruction rate of pre-diluted opioid is not same as for neat salt or freebase
- N-oxide primary by-product, confirmed by LC/MS
- Near complete conversion of fentanyl to fentanyl N-oxide in <15 min
- N-oxide still predominant by-product at 24 h
- Similar trend observed for carfentanil to carfentanil N-oxide



REACTIVITY IN AQUEOUS HYPOCHLORITE DECONTAMINANTS

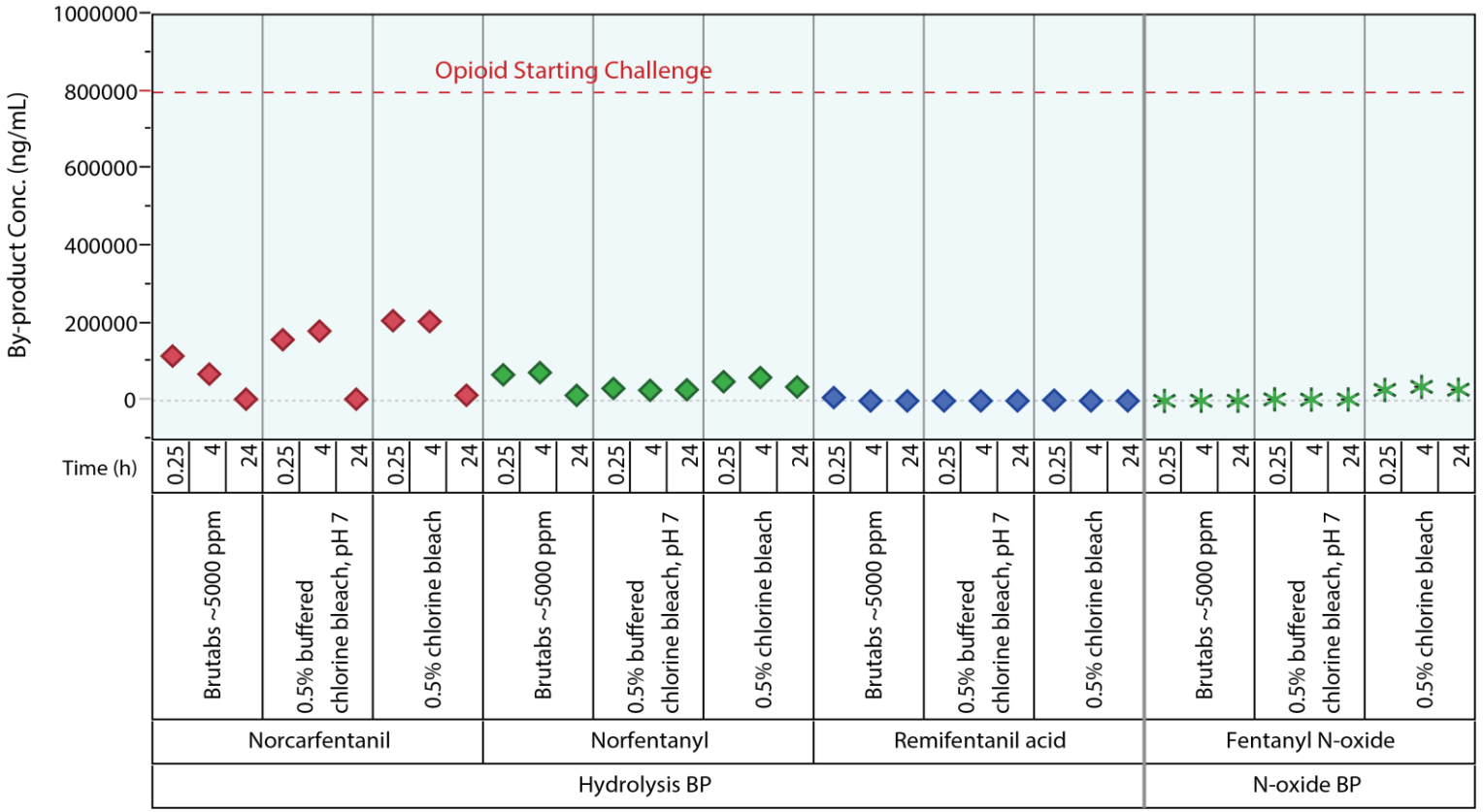




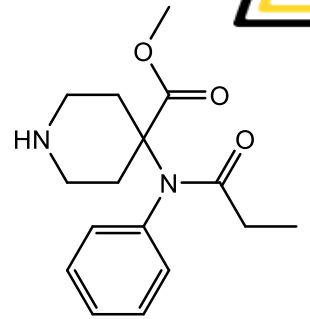


Sticky, semi-solid formed in all 3 decontaminants, inhibited mixing

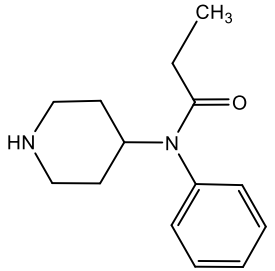
BY-PRODUCTS IN AQUEOUS HYPOCHLORITE DECONS (QUANTITATIVE LC/MS/MS)



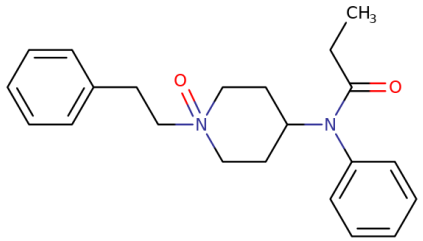
- Partial conversion of opioid to hydrolysis product and N-oxide components
- Qualitative analyses by GC/MS and LC/MS were used to identify additional products.
- Other techniques, such as NMR, are needed to elicit pathways and mass balance



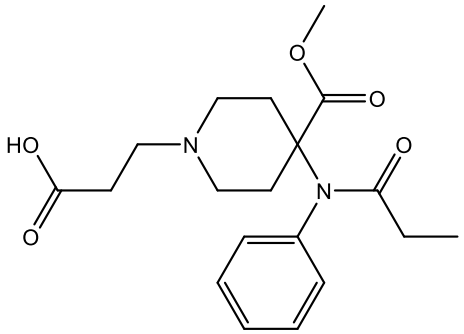
Norcarfentanil



Norfentanyl

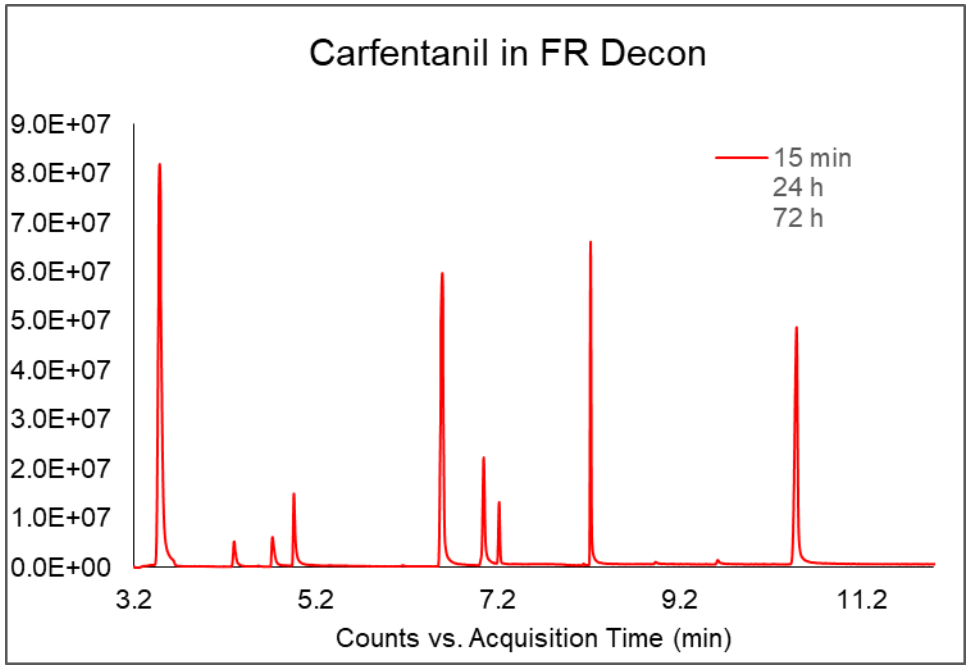


Fentanyl N-oxide

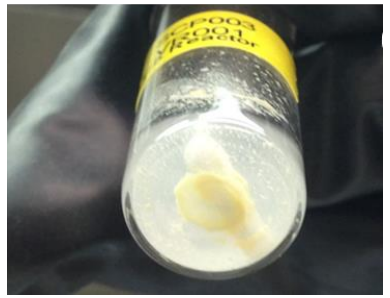


Remifentanil Acid

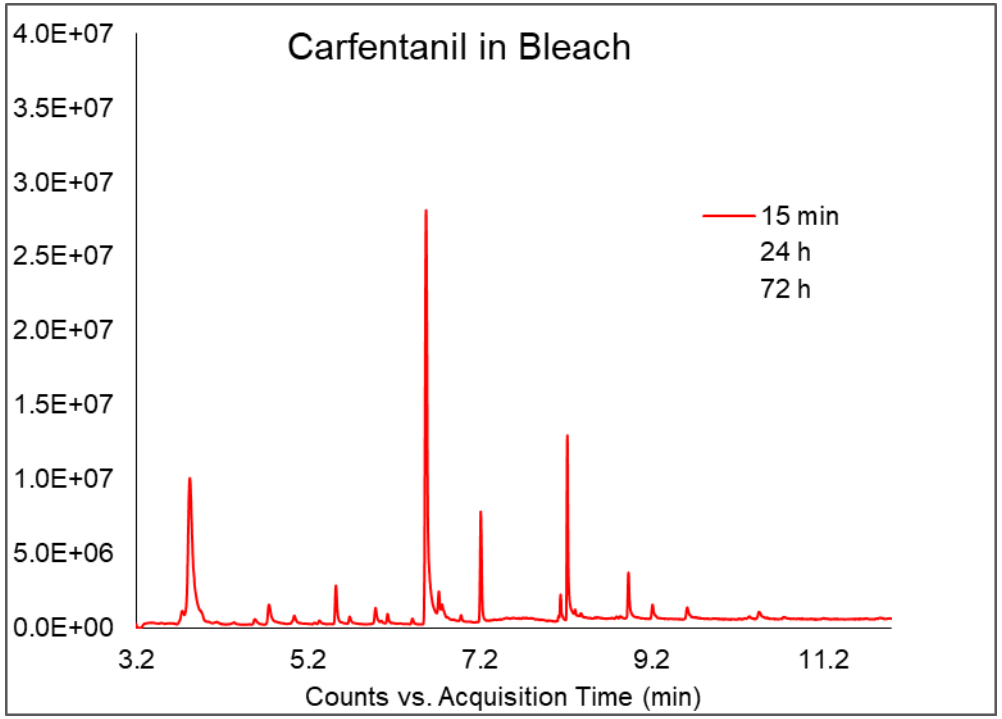
BY-PRODUCTS
PERACETIC ACID VS. HYPOCHLORITE



15 min

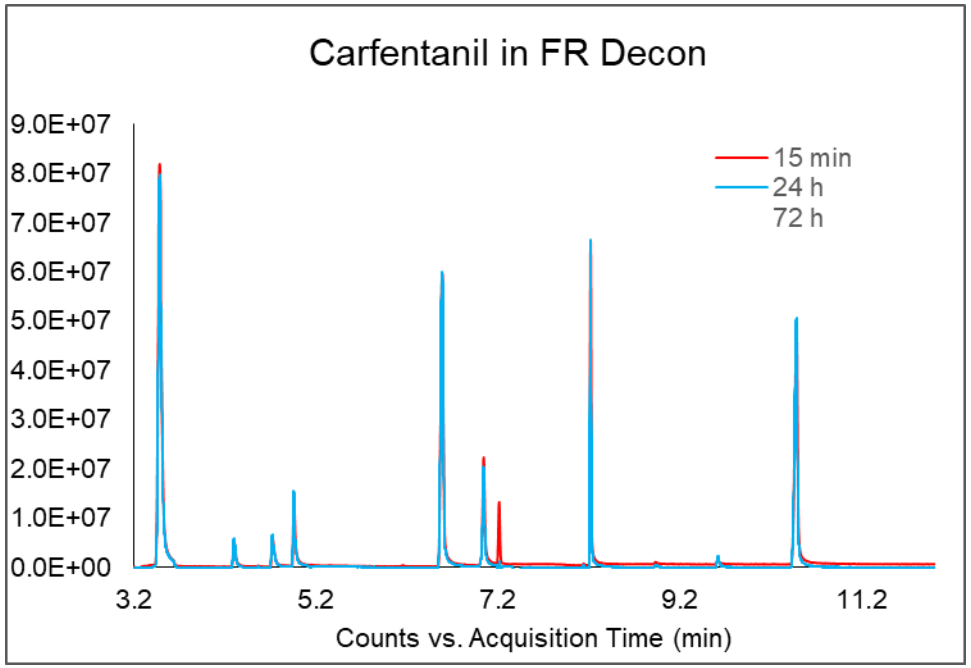


72 h

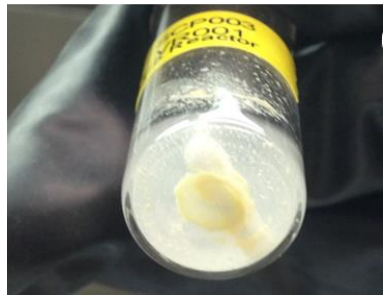


- Qualitative analysis by GC/MS to look for other by-products
- FR Decon - no change observed in by-product formation over 72 hours (GC/MS extractable)
- Bleach - Formation of multiple by-products with continual reactivity observed with time

BY-PRODUCTS
PERACETIC ACID VS. HYPOCHLORITE



15 min



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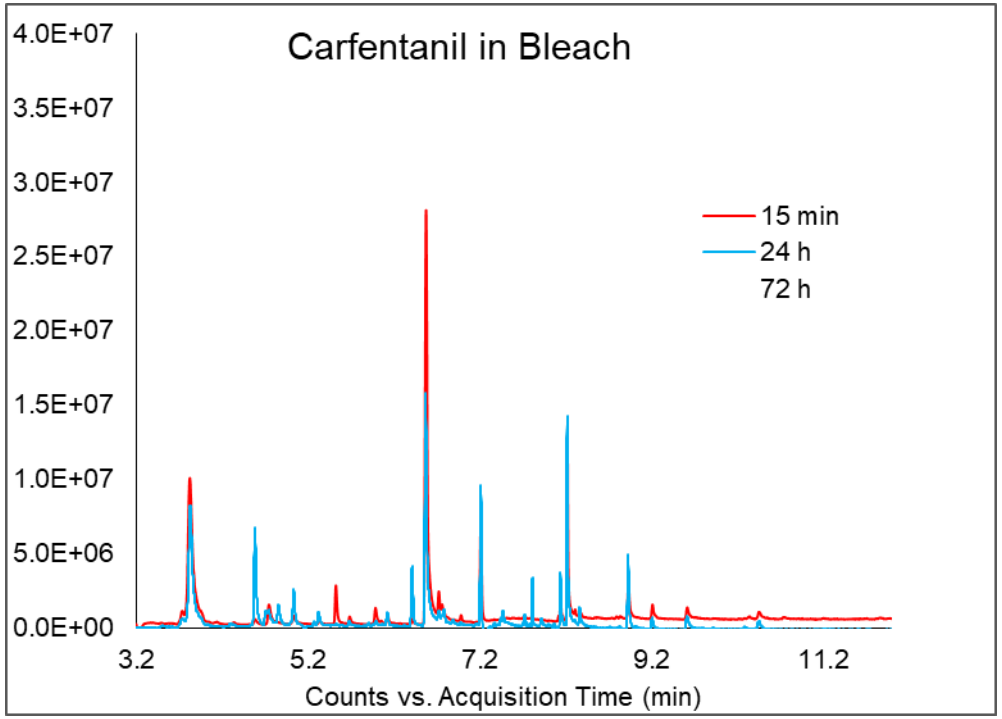

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BY-PRODUCTS
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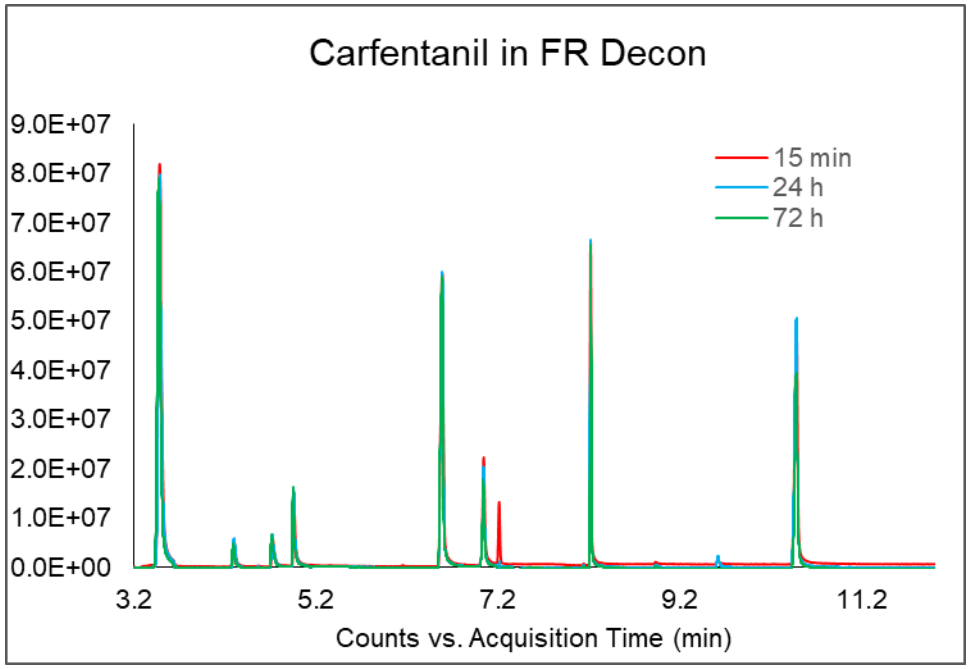

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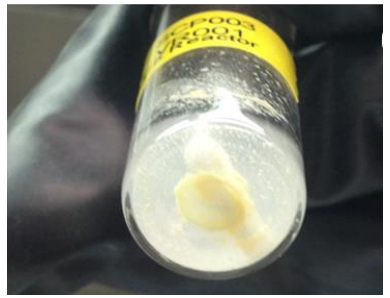

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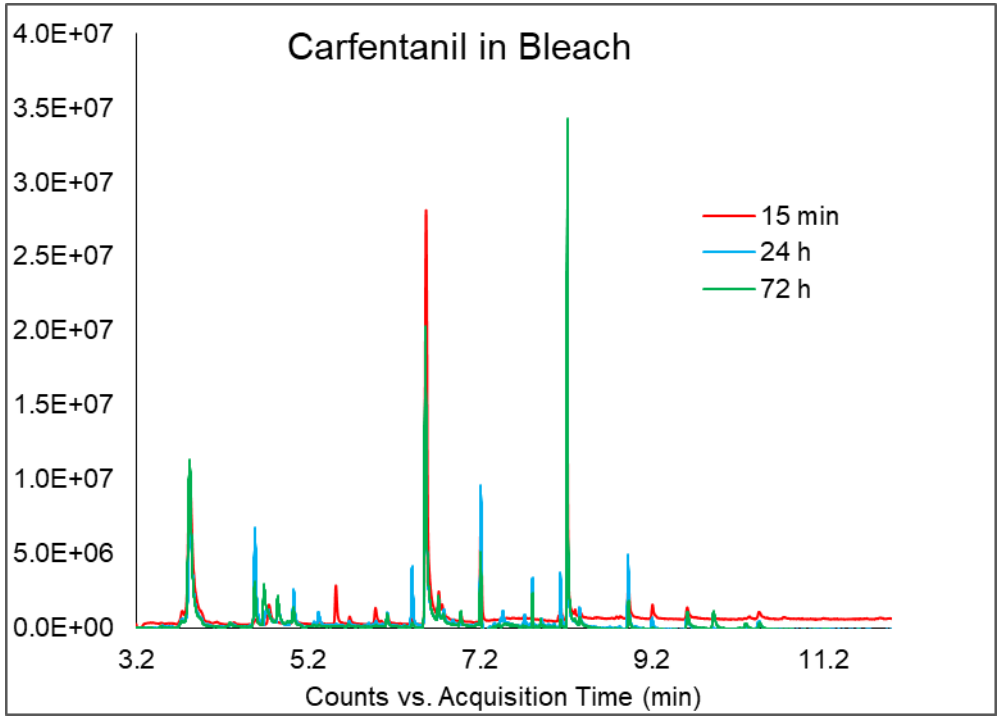


WHY DO BY-PRODUCTS MATTER?

- By-products may potentially be as toxic as the original compound
- While the toxicity of an ultra-potent opioid such as carfentanil can be significantly reduced the by-product may still present a lethal or harmful response
- Even if we can identify all the by-products we don’t know their toxicity
- Collaborative metabolite toxicity studies are ongoing between CCBC-CDC and Defence Science and Technology Laboratory (DSTL)
- A publication in the ACS Medicinal Chemistry Letters is forthcoming
- Further by-product studies including toxicity are needed

OTHER DECONTAMINANTS - RSDL

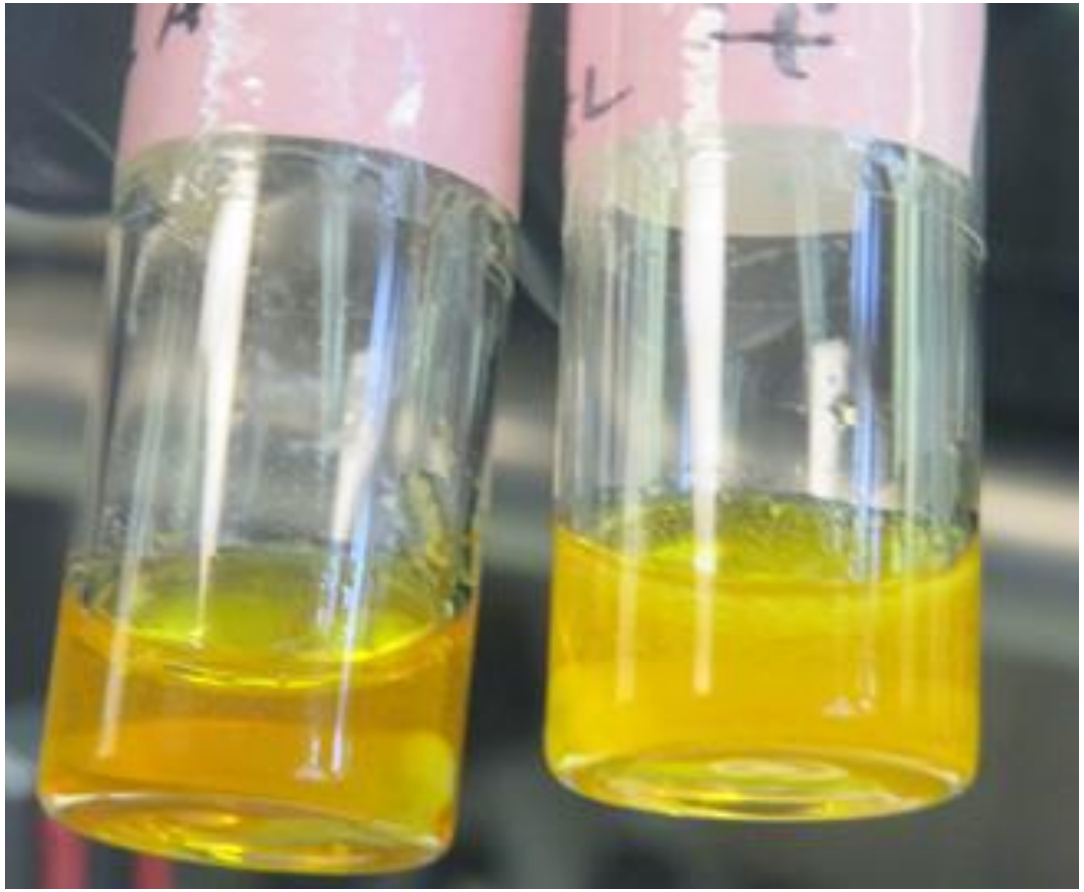
Screened for reactivity with oxalate salts of carfentanil, remifentanil and fentanyl.

Delivered in methanol solution and as neat solid.

Salt form did not appear soluble.

No reactivity observed with carfentanil and fentanyl.

Some reactivity with remifentanil – attributed to hydrolysis from high pH



Question: Physical removal or further spread of contamination?

CONCLUSIONS

- Opioids - hazard for lab researchers as well as first responders
- CCDC-CBC ongoing scoping study
- Fentanyl analogs readily react with oxidative decons
- Decon performance is heavily influenced by pH, formulation
- Different chemistries result in different by-products
  - Peracetic acid yields predominantly N-oxide
  - Hypochlorite yields multiple reaction products
- Toxicity of reaction products is unknown
- Contaminant form (solvent delivered vs. neat solid) has a significant impact on experimental outcomes
- Further study of solid contaminant requires laboratory upgrades and dedicated test infrastructure

ACKNOWLEDGEMENTS

- Funding provided by the Product Director for Cross-Commodity Advanced Threats & Test Infrastructure (PDCATTI) under the Joint Project Manager for NBC Contamination Avoidance (JPM NBC CA)

- Technical and Analytical Support from the CCDC-CBC Decontamination Sciences Team
  - Amanda Schenning
  - Michelle Sheahy
  - Jill Ruth (Leidos)
  - Melissa Sweat (DTRA)
  - Michael Chesebrough (DCS)
  - Craig Schenning (Leidos)

- Synthesis of neat opioids provided by the CCDC-CBC Agent Chemistry Branch