

Reversible Preservatives: The Next Generation of Safer Products

BILLY HART-COOPER, KAJ JOHNSON, AND COWORKERS

BCGC

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Outline

Greener Solutions (2014) to USDA/Method cooperative R&D

Limitations of current preservatives

What would be the ideal preservative?

How can reversible bonds enable

(c) **improved performance** and (d) **minimal toxicity**?

Discussion



Greener Solutions 2014: Safer Preservatives

Industry partners: **Method**, Seventh Generation, BeautyCounter; Student team: Heather Buckley, Adam Byrne, Billy Hart-Cooper, Jiawen Liao.

Industry is eager to move away from traditional preservatives (**skin irritation, sensitization** and other toxic effects).

Nontoxic antimicrobials were identified as possible preservatives for home and personal care products.

we are
people
against
dirty[®]



Let's Create Sustainable Value





compass of clean



human health for people

EYE SAFETY

SKIN SAFETY

SKIN SENSITIZATION



environmental health for the planet

BIODEGRADATION

ALGAE SAFETY

DAPHNIA SAFETY



sustainability for the future

RENEWABILITY

CO2 FOOTPRINT

GREEN CHEMISTRY

FUTURE PROOF



packaging health for responsible resource use

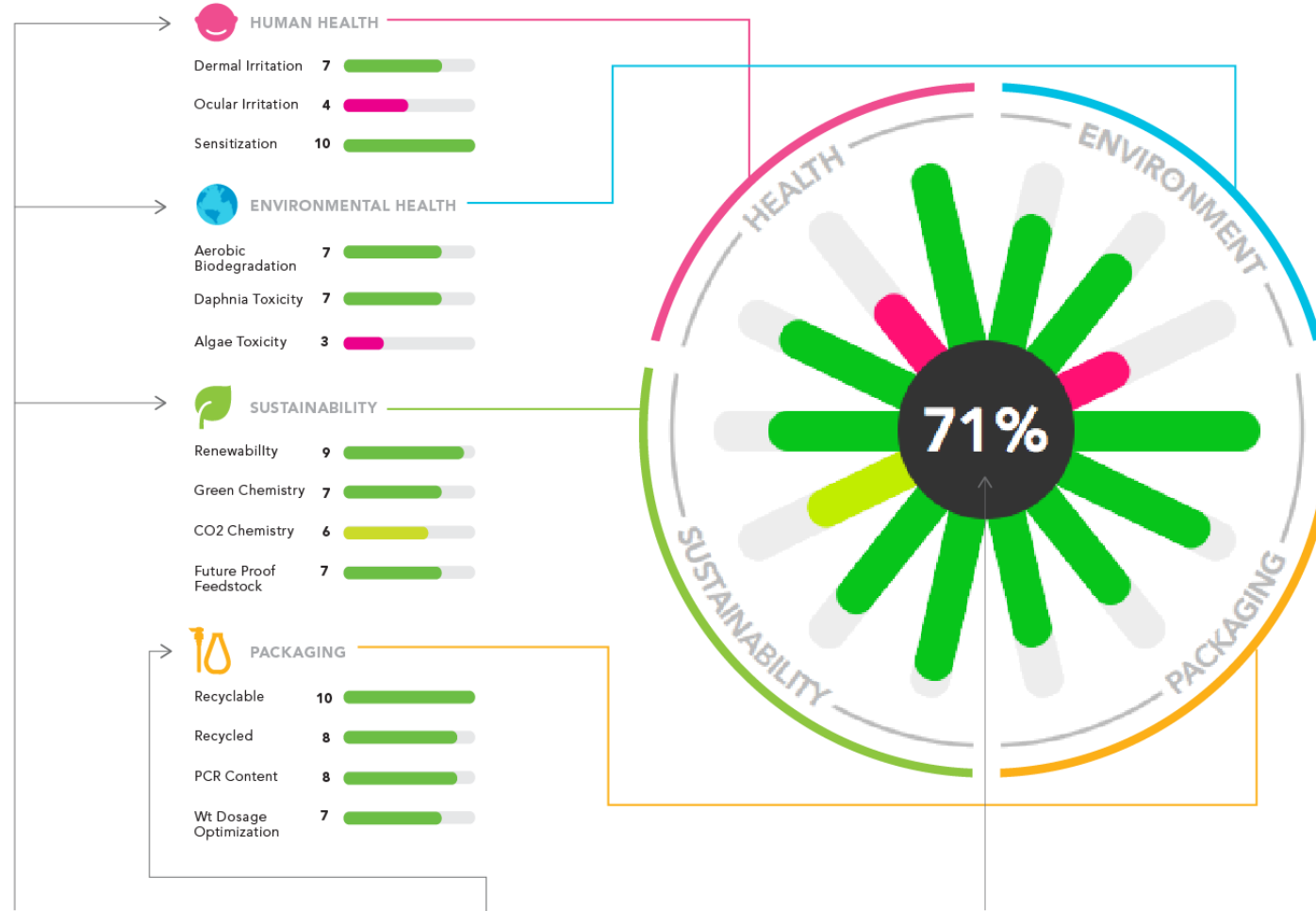
RECYCLABLE

RECYCLED

SOURCING

OPTIMIZATION

product evaluation process



ingredient ratings + packaging endpoints = product rating

evaluate all ingredients in product on 10 different compass metrics and assign cumulative score

evaluate the product's package on 10 different compass metrics and assign a score

create cumulative chart assign a percentage score

Succeed through Great Partnerships!

Competitors

Micro-Biologists

UCB

GC3

PAD

USDA

Start ups

Universities

Suppliers

Why do home and personal care products need preservatives?



Blusher
22 Months Old - Nine Months Out of Date
Tested Positive for Meningitis bacteria



Lip Gloss
One Year Old - Still in Date till Aug 2016
Tested Positive for Meningitis bacteria



Foundation
17 Months Old - Four Months Out of Date
Tested Positive for Meningitis bacteria

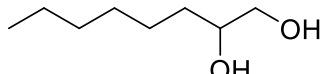
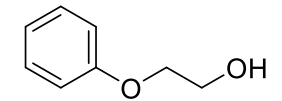
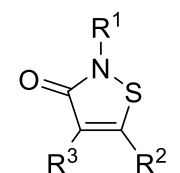
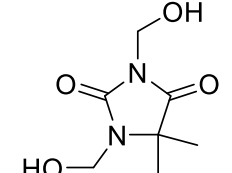


Lipstick
35 Months Old - 10 Months Out of Date
Tested Positive for Meningitis bacteria



Mascara
10 Months Old - Four Months Out of Date
Tested Positive for Enterobacter and Eubacterium

Limitations of current preservatives

		Potency	
		Low (>1 % a.i.)	High (<0.1% a.i.)
Toxicity	Low	 <p>Caprylyl glycol</p>  <p>Phenoxyethanol</p>	Desirable
	High	Undesirable e.g. methanol	 <p>Isothiazolinones</p>  <p>Formaldehyde releasers</p>

Toxicity of current preservatives

Allergic contact dermatitis affects 72 million Americans per year (2004 direct cost: \$1.6 billion).

Allergens of the year

(Amer. Contact Derm. Soc.)

2015: Formaldehyde

2013: Methylisothiazolinone

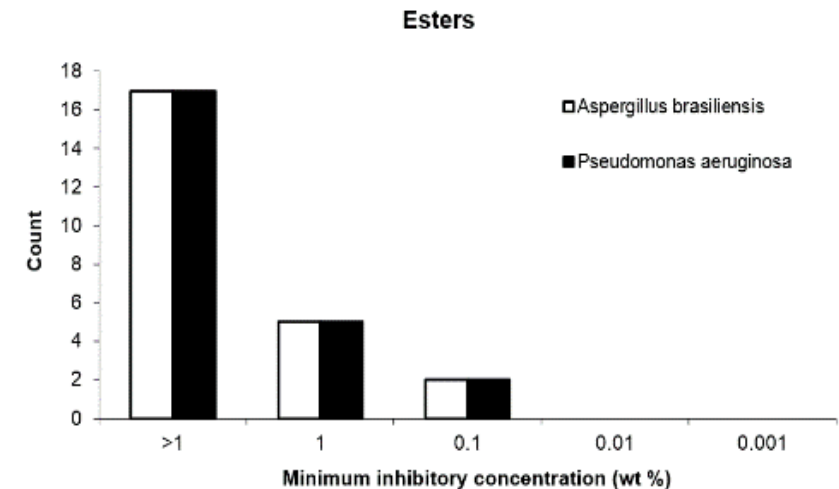
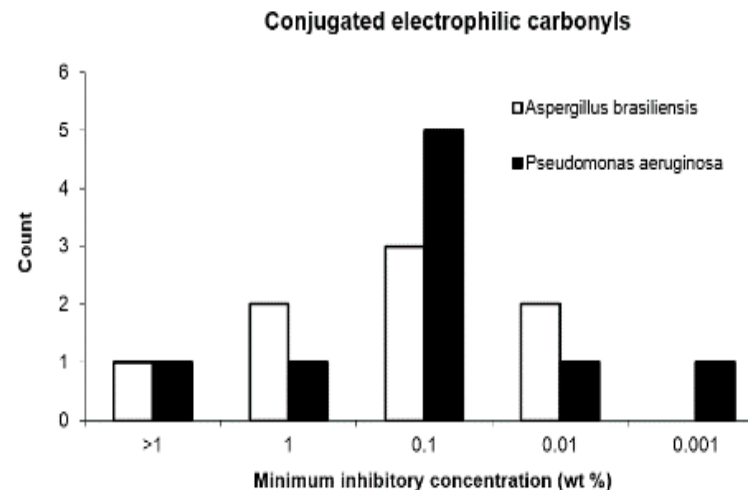
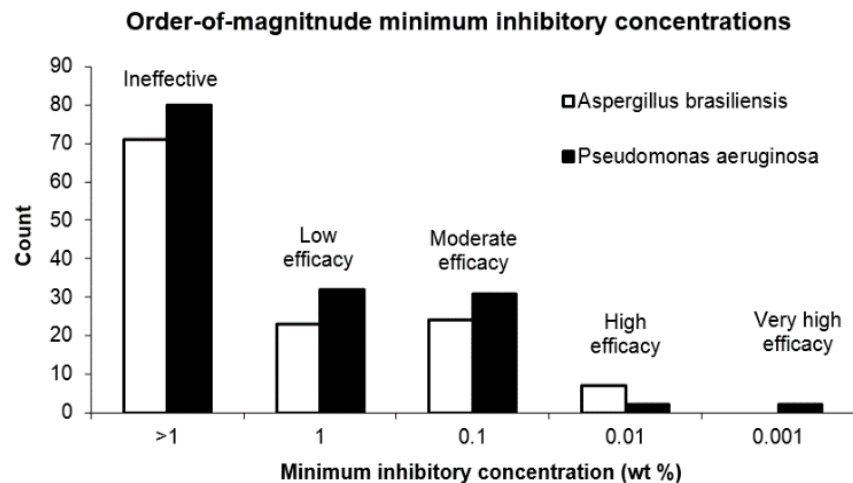


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Setting up an antimicrobial testing lab

USDA, Agricultural Research Service, Western Regional Research Center has facilities, expertise and interest in developing safer antimicrobials.

Evaluated 500+ test substances against *P. aeruginosa* ATCC 9027 (shower bacteria) and *A. brasiliensis* ATCC 16404 (grout mold).



Common challenges with current antimicrobials

1. Toxicity correlated
with potency
(irritation,
allergenicity)

2. Collateral
environmental
toxicity

3. Potential to cause
antimicrobial
resistance

An ideal
preservative...

Decouples toxicity from performance

Is active in the formulation, inactive
outside

Works well in formula
(1% or lower)

Does not cause antimicrobial
resistance

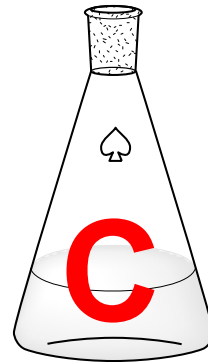
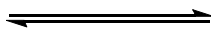
Our novel approach

A + B

Nontoxic subcomponents

History of safe use
Human and animal testing
Naturally sourced

Formulation



Active reversible complex

Non-irritating
Non-volatile
Water soluble
Low skin penetration

Disposal



A + B

Dissociated subcomponents

Nontoxic to microbes
Biodegradable
Low risk for antimicrobial resistance

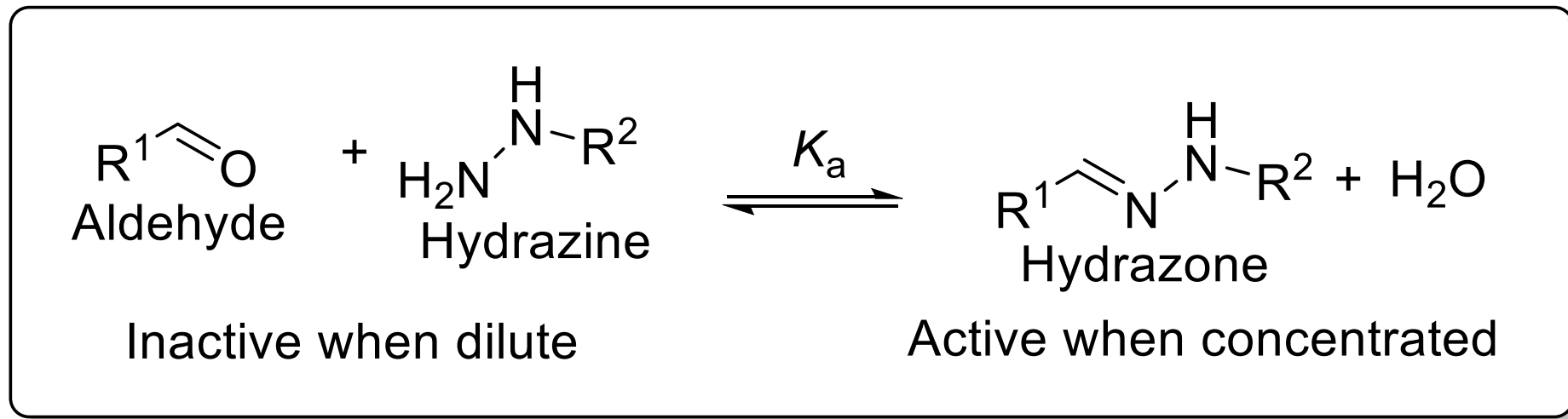
CO₂, H₂O, NH₃

Biodegradation

Wastewater
Ambient temperature

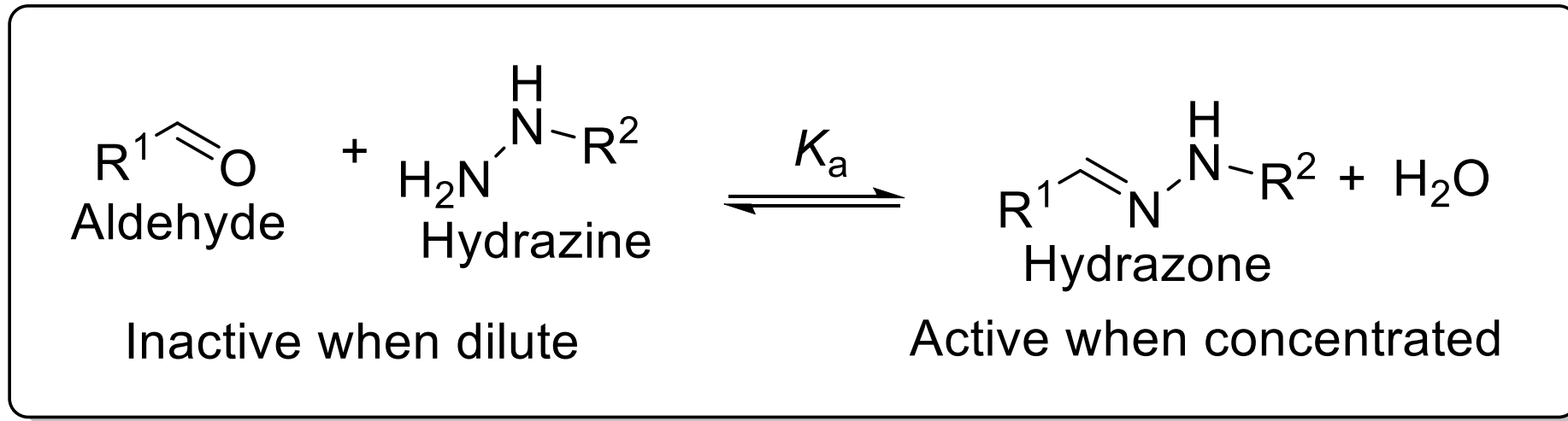


What interactions could form reversible antimicrobials?



$$K_a = \frac{[\text{Hydrazone}]}{[\text{Aldehyde}][\text{Hydrazine}]} \approx 10^6 \text{ M}^{-1}$$

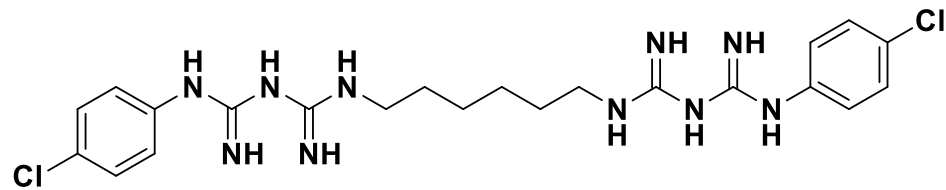
At which concentrations will hydrazones dissociate?



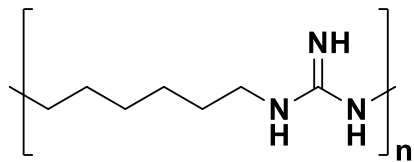
Scenario	Total concentration (wt. %)	Dissociation (molar)
Product bottle (1 L)	1%	0.9%
25 meter swimming pool (375,000 L)	0.000003%	94%

Can reversible polyguanides mimic conventionals?

1. Conventional polyguanide antimicrobials



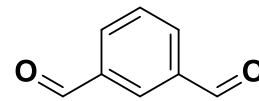
a. Chlorhexidine



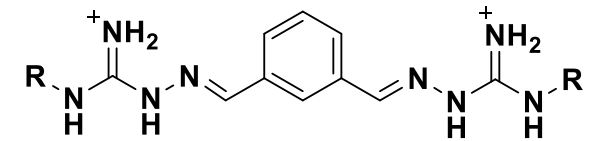
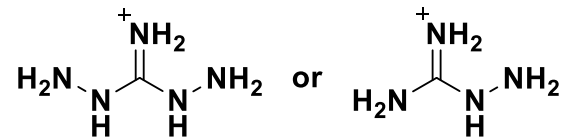
b. Polyhexamethylene guanidine

- i. Often toxic
- ii. Persistent in the environment

2. Self-assembled polyguanide antimicrobials

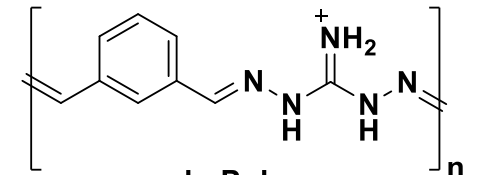


+



R = H or NH₂

a. Small molecule



b. Polymer

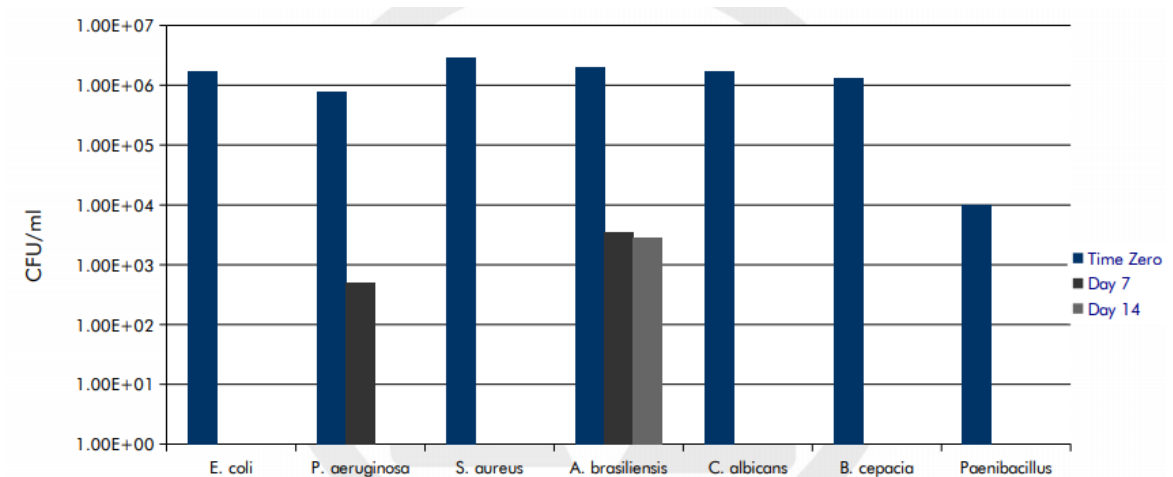
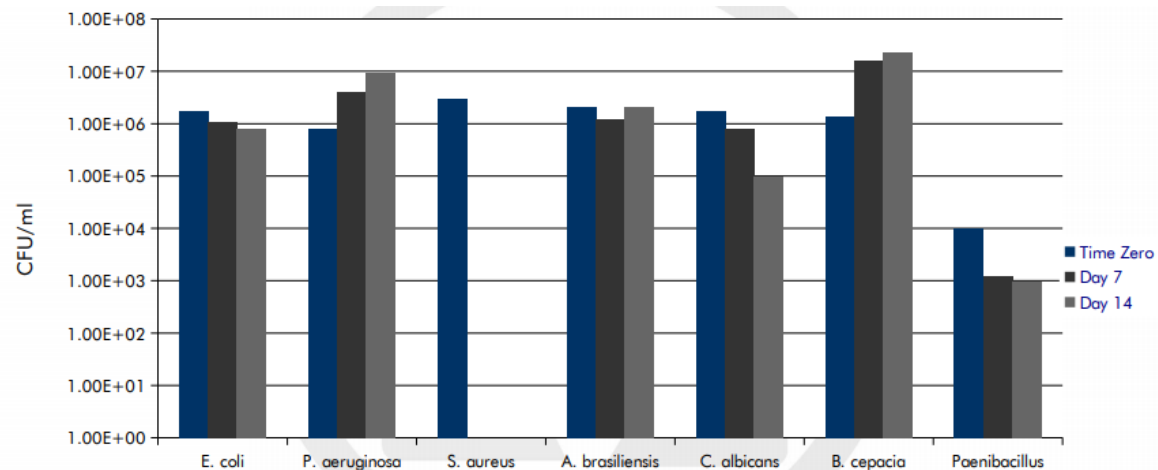
- i. Assembled from less-toxic subcomponents
- ii. Disassembles with changes in pH, concentration

Lead substance performs in a commercial formula

Naturally-derived example preserves a spray cleaner (pH 5.5-6.0) at 0.1-0.2 wt %.

Left: unpreserved formula; Right: same formula with **0.2% active ingredient**

Repeated insult patch testing caused **no skin irritation or allergy** (0.2 and 1% a.i.).



Safety of reversible preservatives: available data

	Acute LD50	Skin/Eye Irritation	Group I (C, M, R/D/E)	Group II (AT, ST, N)	Environmental Fate/Tox	Potency
Aminoguanidine	1	1-2	2	2	1	>1%
Cuminaldehyde	1	1-2	1	1	1	>1%
Analogues of AG-cuminaldehyde	2	1	2	2	2	0.1%
MIT	3	3	1-2	3	2-3	0.1%

1: low hazard

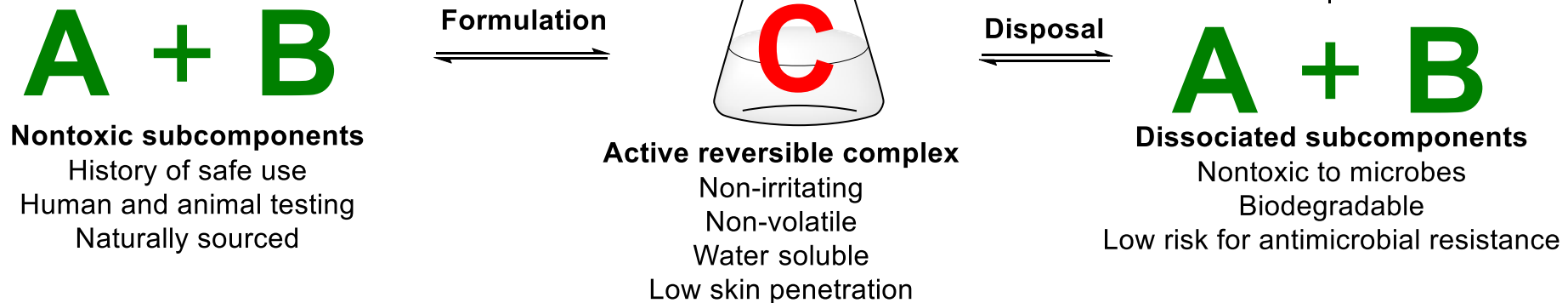
2: medium hazard

3: high hazard

Conclusion: our novel preservative system...

Decouples toxicity from performance

Designed to minimize antimicrobial resistance – **diverse platform of 100+ derivatives**



Acknowledgements

Our Team:

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