New England SCC

Natural Preservative Options

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Cosmetic Preservation Selection Method Drivers/Pulls

- **Ethical**
- **Legal**
- **Technical**
- **Consumer**

Key Factors for Reliable Preservative Performance

- **Broad Spectrum Efficacy**
- **Stability**
  - **Structural**
  - **Aesthetic (Odor/Color)**
- **“Assayability”**
  - **Lot/Lot Variation**

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Definition of “Natural”

- **Purists:**

  Compounds extracted from plants in their fundamental state

  “No chemical change”

- **Semi-Purists:**

  Extracted intact in their fundamental state

  “Active” compounds concentrated

  Heating (“cooking”) or biological transformation may induce chemical change

- **Realists:**

  Plant-based compounds chemically modified by humans using Green Chemistry Principles to yield pure, assayable functional products that are proven safe to humans and to the environment using science

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Time Tested, Safe, Workhorse Preservatives Under Scrutiny

Parabens

- Endocrine Disruption
- Cancer

Isothiazolinones

- Sensitization

Formaldehyde Donors

- Cancer

Phenoxyethanol

- Irritation

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Parabens: Validation of Concern

Government

- EU bans isoparabens, phenylparaben, benzylparaben, pentylparaben

Industry

- Walmart releases “high priority chemicals” (HPC’s) list
- J&J eliminates parabens from baby products

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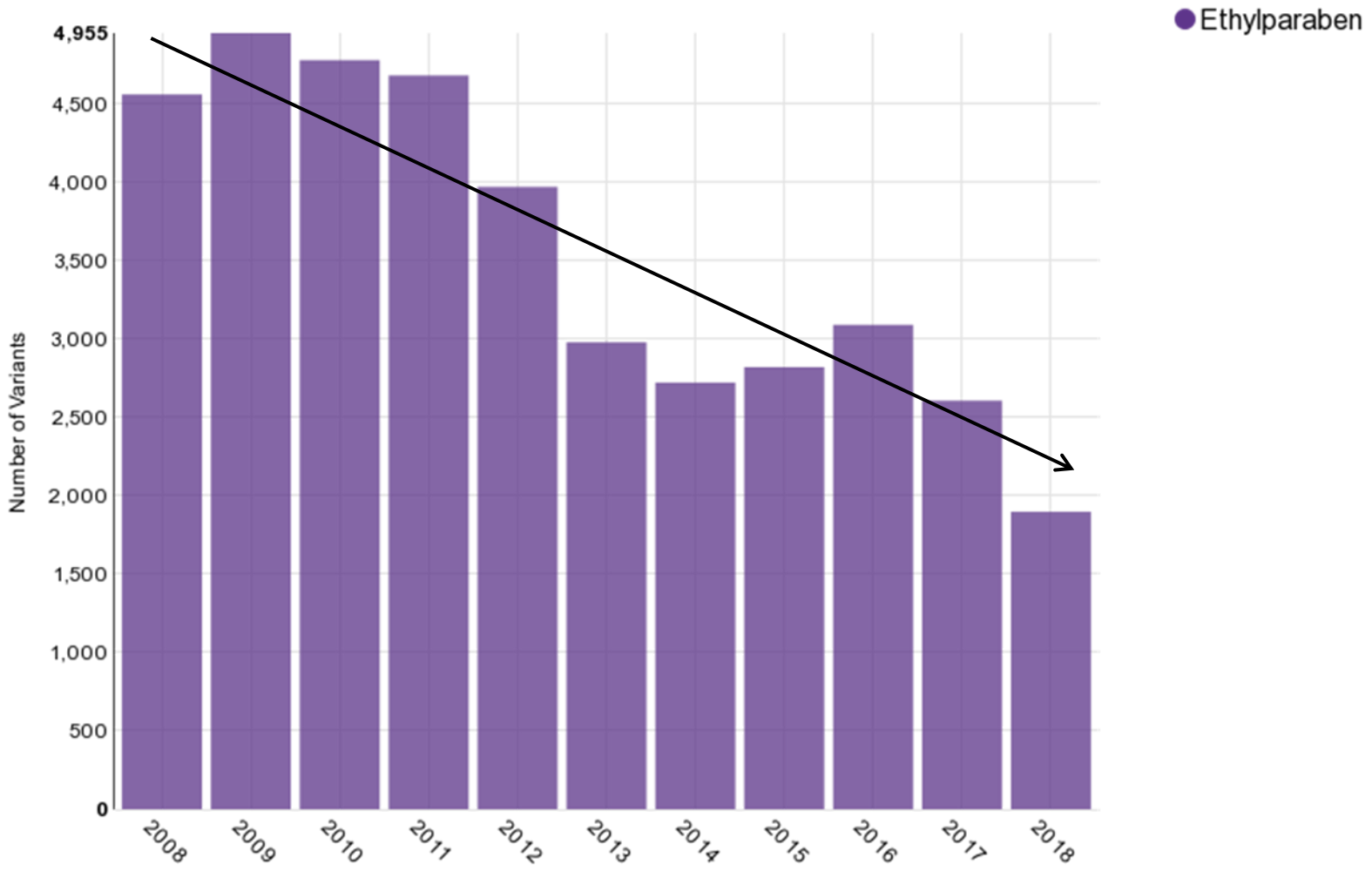
Parabens: Usage Trends



Source MINTEL

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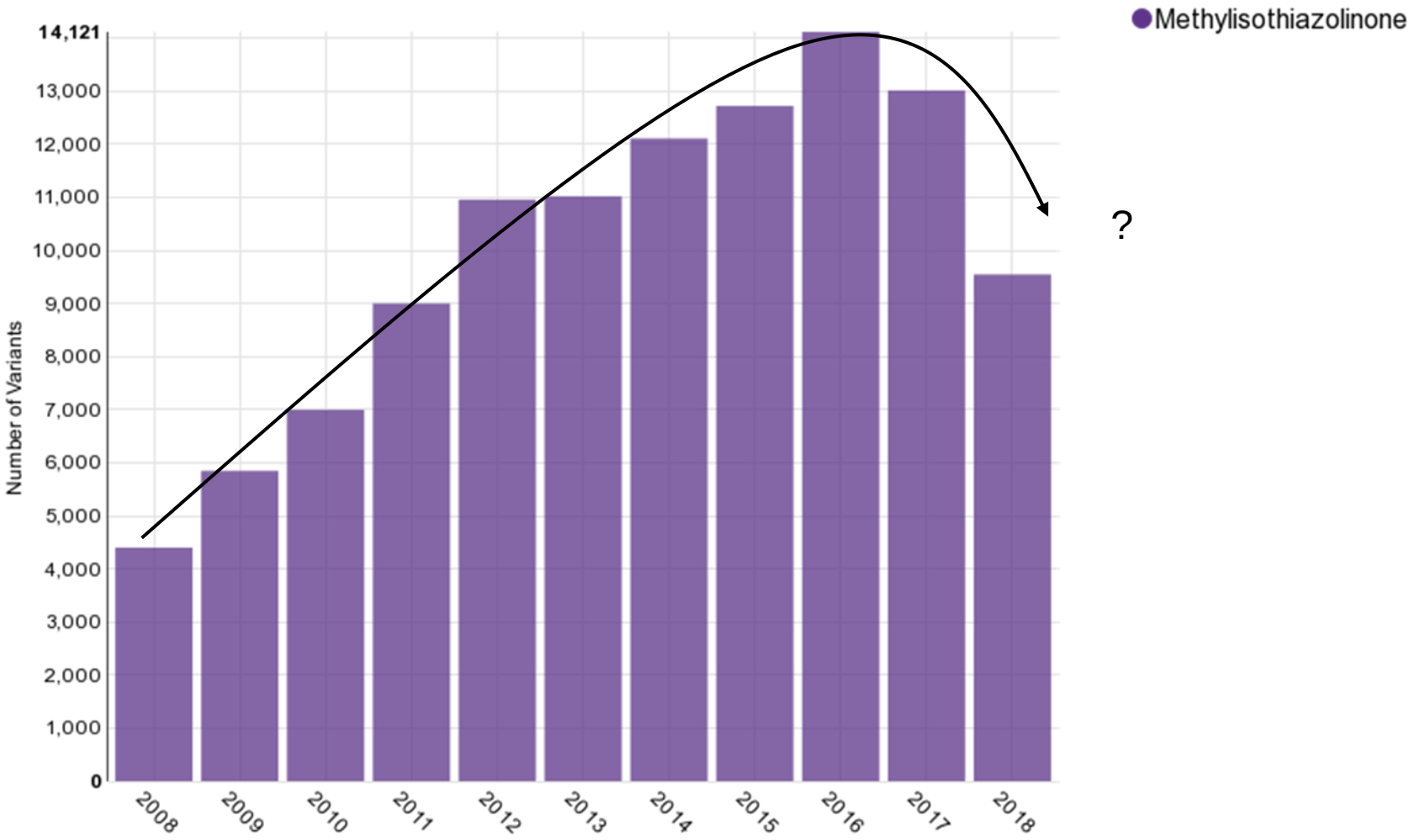
Isothiazolinones: Validation of Concern

Government

- EU limits MI to 0.01% (100 PPM) in rinse-off products
- EU bans MI in leave on products

Isothiazolinones: Usage Trends



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Formaldehyde Releasers: Validation of Concern

Johnson & Johnson FAMILY OF CONSUMER COMPANIES

SAFETY & CARE COMMITMENT

Formaldehyde Releasing Preservatives

While formaldehyde releasing preservatives are safe when used in well formulated cosmetic products, we listened to our consumers, and as a result, our baby personal care products worldwide no longer include formaldehyde-releasing preservatives. Similarly, you'll only see formaldehyde-releasing preservatives in beauty personal care products when alternatives are not feasible or safe when combined with other ingredients.

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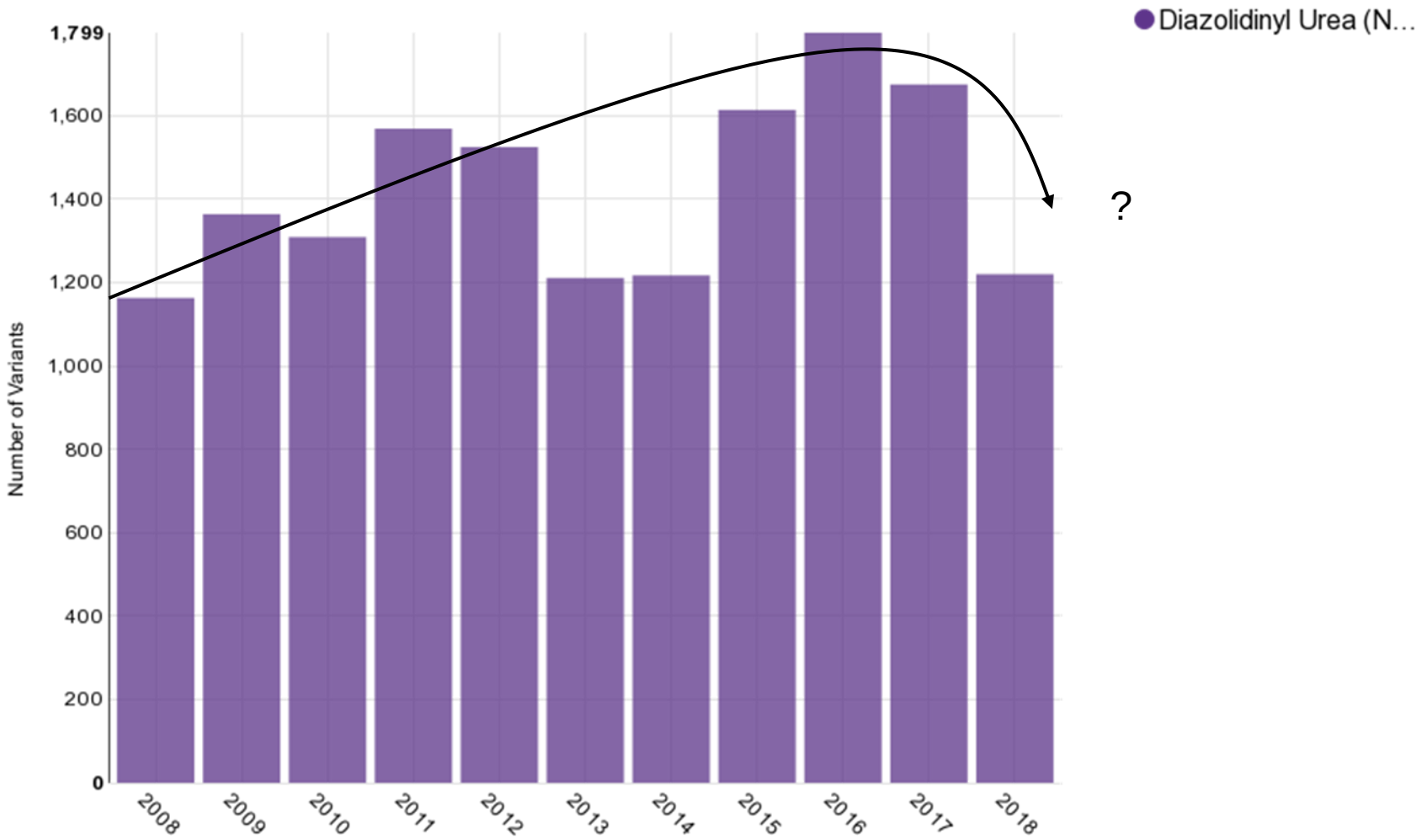
Formaldehyde Releasers: Usage Trends



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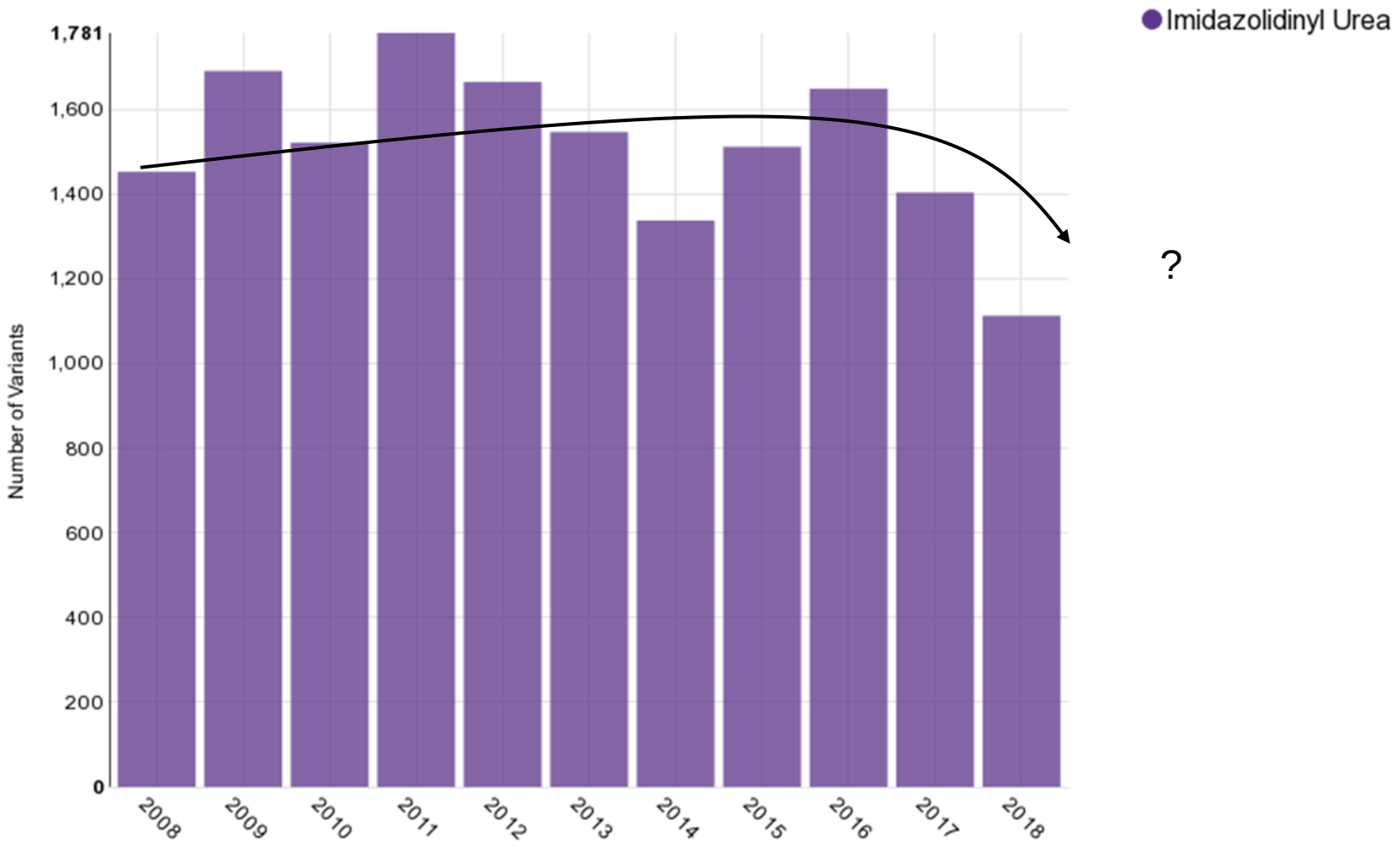
Formaldehyde Releasers: Usage Trends



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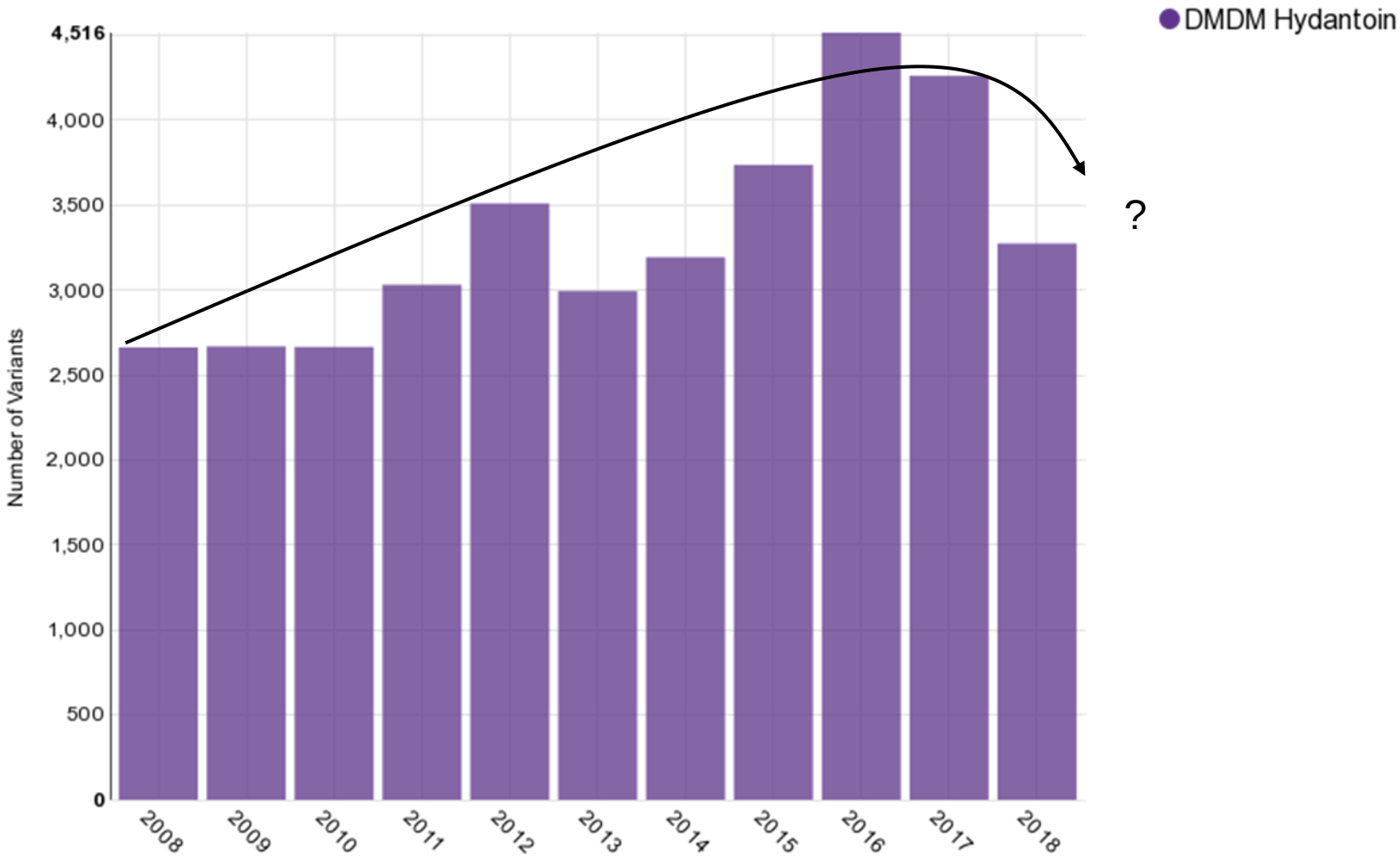
Formaldehyde Releasers: Usage Trends



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Now Phenoxyethanol?

Government

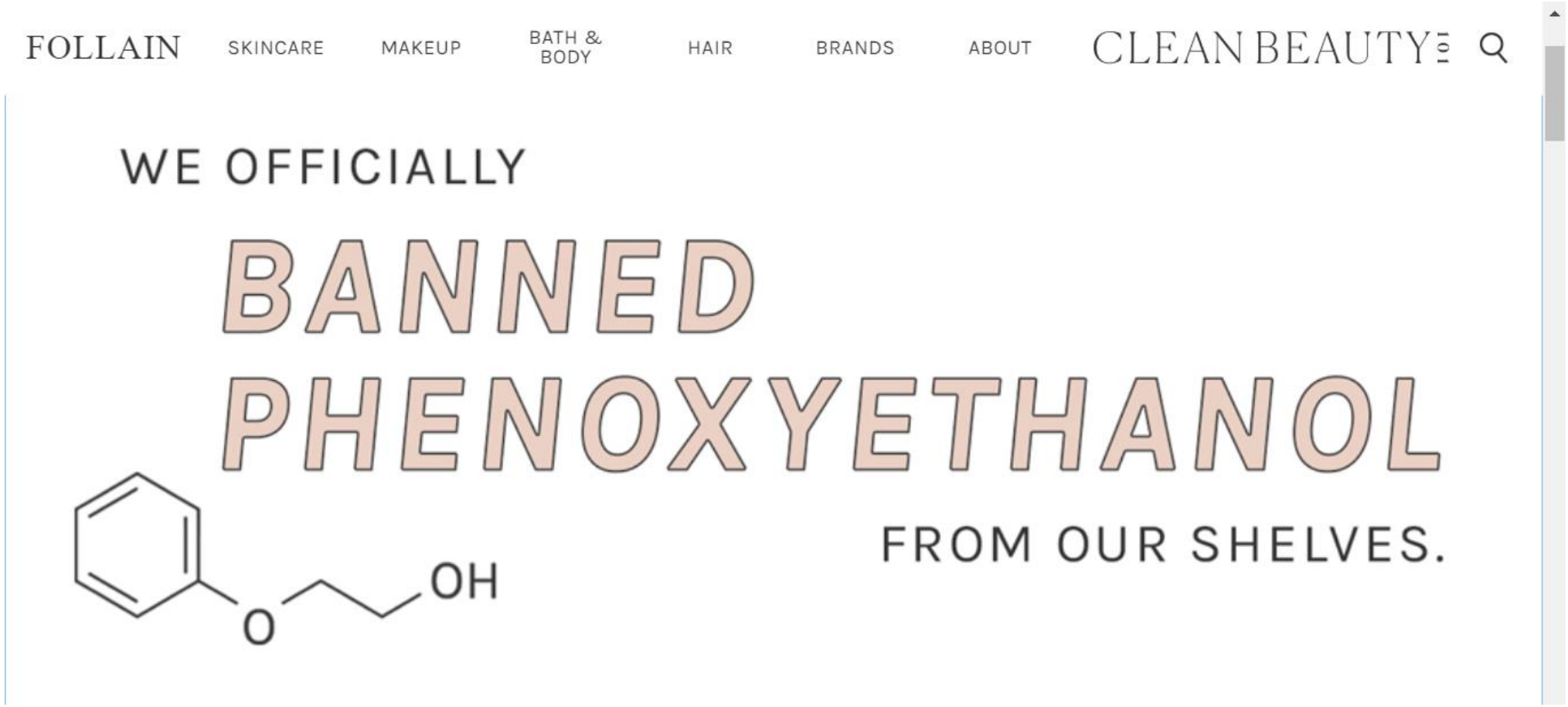
France restrictions for wipes used in the nappy area of babies

Industry

Follain incident

EWG rating

Now Phenoxyethanol?



https://follain.com/clean-beauty-101/phenoxyethanol/

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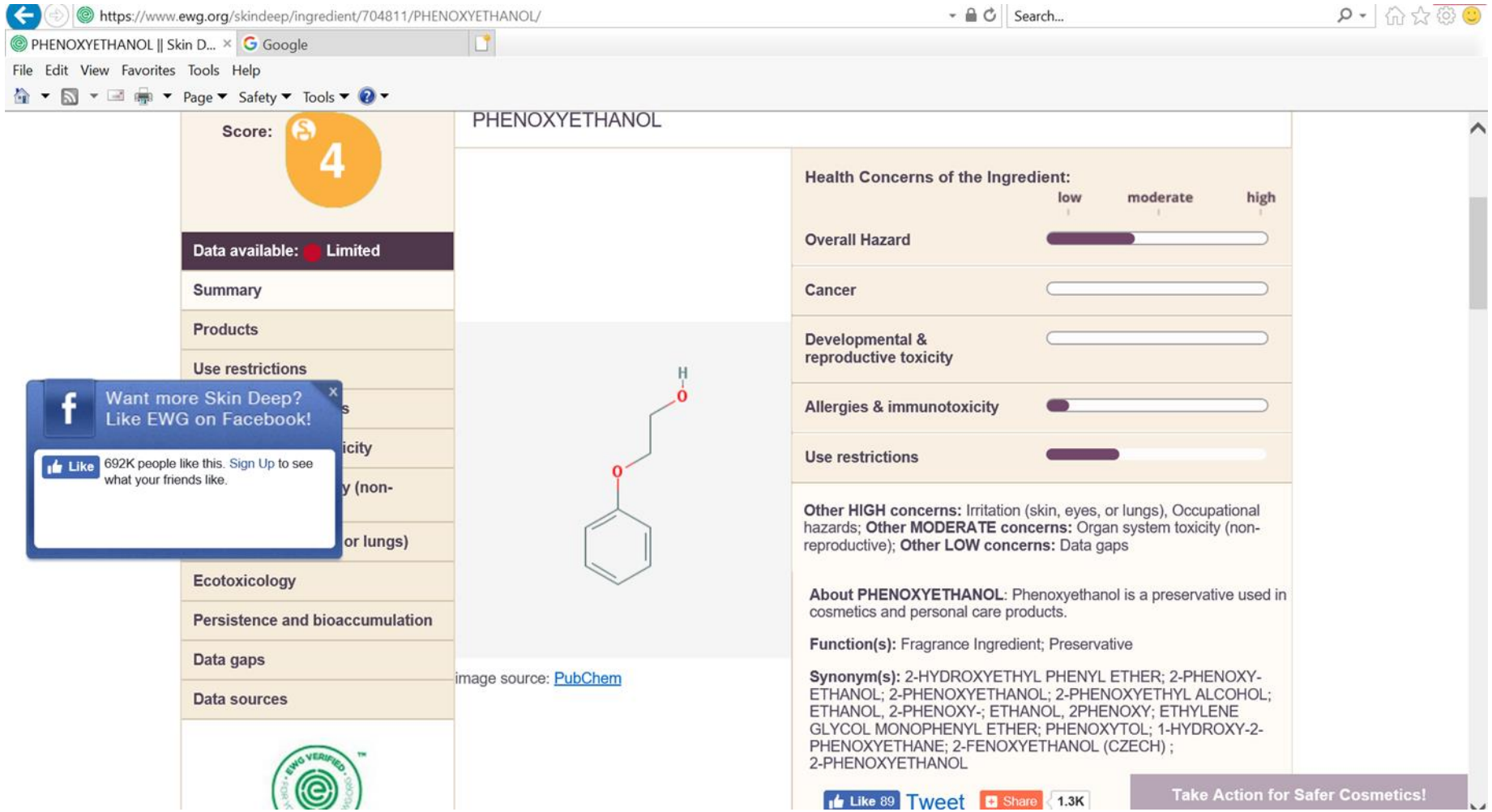
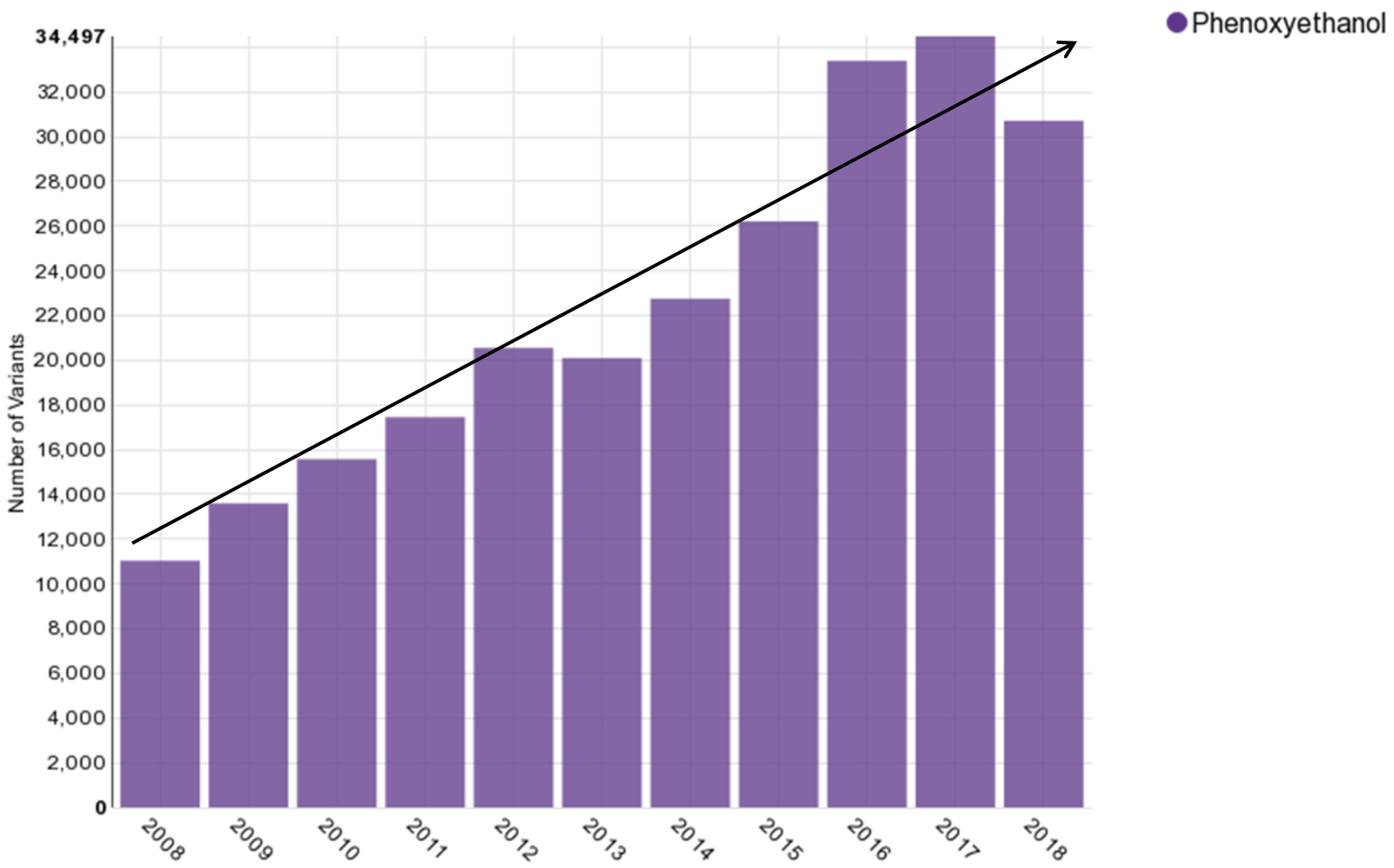
Now Phenoxyethanol?



Phenoxyethanol: Usage Trends



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What Can We Do?

“Educate” the Consumer

- Phthalates
- BPA
- DDT

Or…

Give up and find safe, effective alternatives

“Traditional Preservation”

EU Definition of “cosmetic preservative”

- Any material added to a cosmetic product for the primary purpose of controlling oxidation, or preventing proliferation of growth of microorganisms
- Authorized preservatives listed in Annex V of Cosmetic Products Regulation (EC) No 1223/2009, last update 14/9/2017. Fifty nine (59) substances
- Includes phenoxyethanol, benzoic acid/salts, salicylic acid/salts, undecylenic acid/salts, benzyl alcohol, sorbic acids/salts
- Using “Annex V definition,” any preservative on Annex V is a “Traditional Preservative”

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“Alternative Preservation”

Defined many ways

- Use of “milder” materials in combination along with GMP using hurdle technology approach?
- Not using Annex V preservatives?
- Not using “frowned upon” Annex V preservatives such as parabens, formaldehyde donors, isothiazolinones, and now, phenoxyethanol?
- Self Preservation?
- Preservative-free?
- “Natural” preservation?
- What’s yours?

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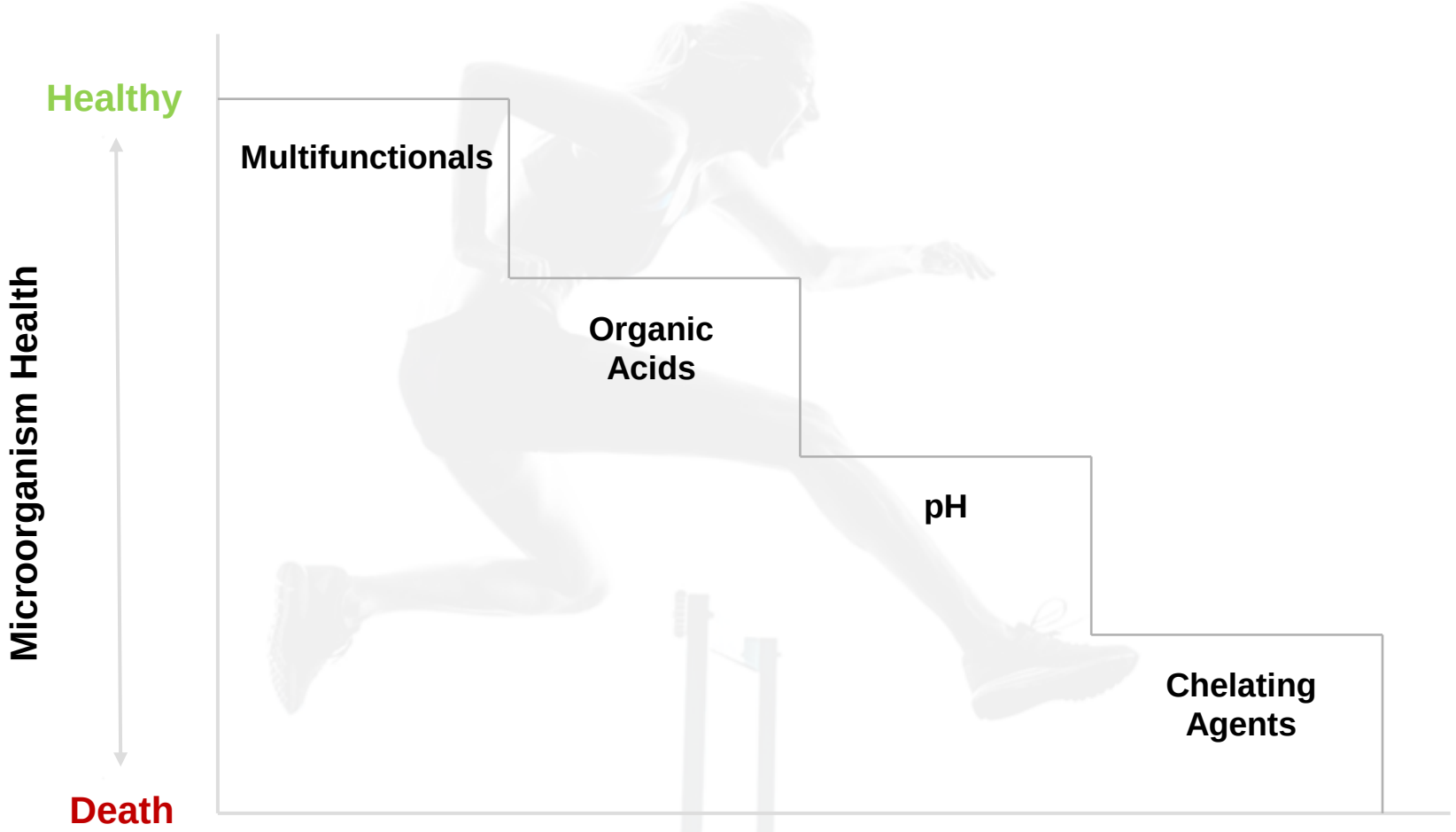
Hurdle Technology



^ The use of “milder” ingredients, other formulation factors, and good manufacturing principles in combination

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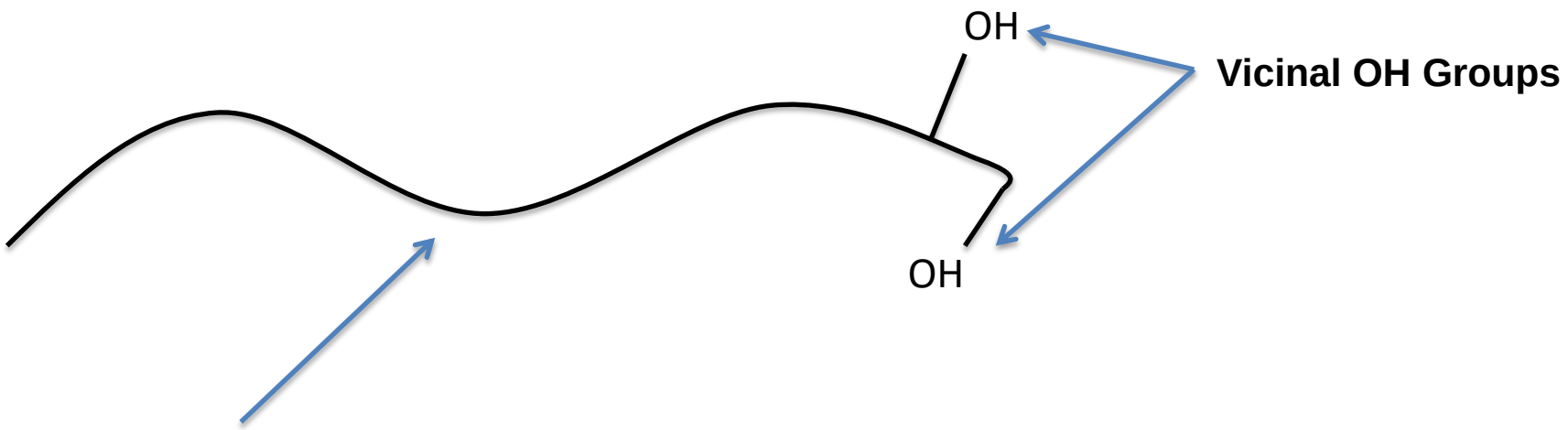
Hurdle 1: Multifunctionals (MCTD's)

Medium **C**hain **T**erminal **D**iol



MCTD's: Mode of Action

- MCTD's have affinity for both water and oil (Log P ~1.7)
- Certain MCTD's have been shown to disrupt cell membranes at relatively low concentrations
- It is thought that MCTD's have the correct hydrophobicity to interact with cell membrane lipids
- Hydroxyl groups then attract water from the cells collapsing the cells
- Many studies and industry acceptance has shown that C_8 is the optimal chain length for membrane disruption

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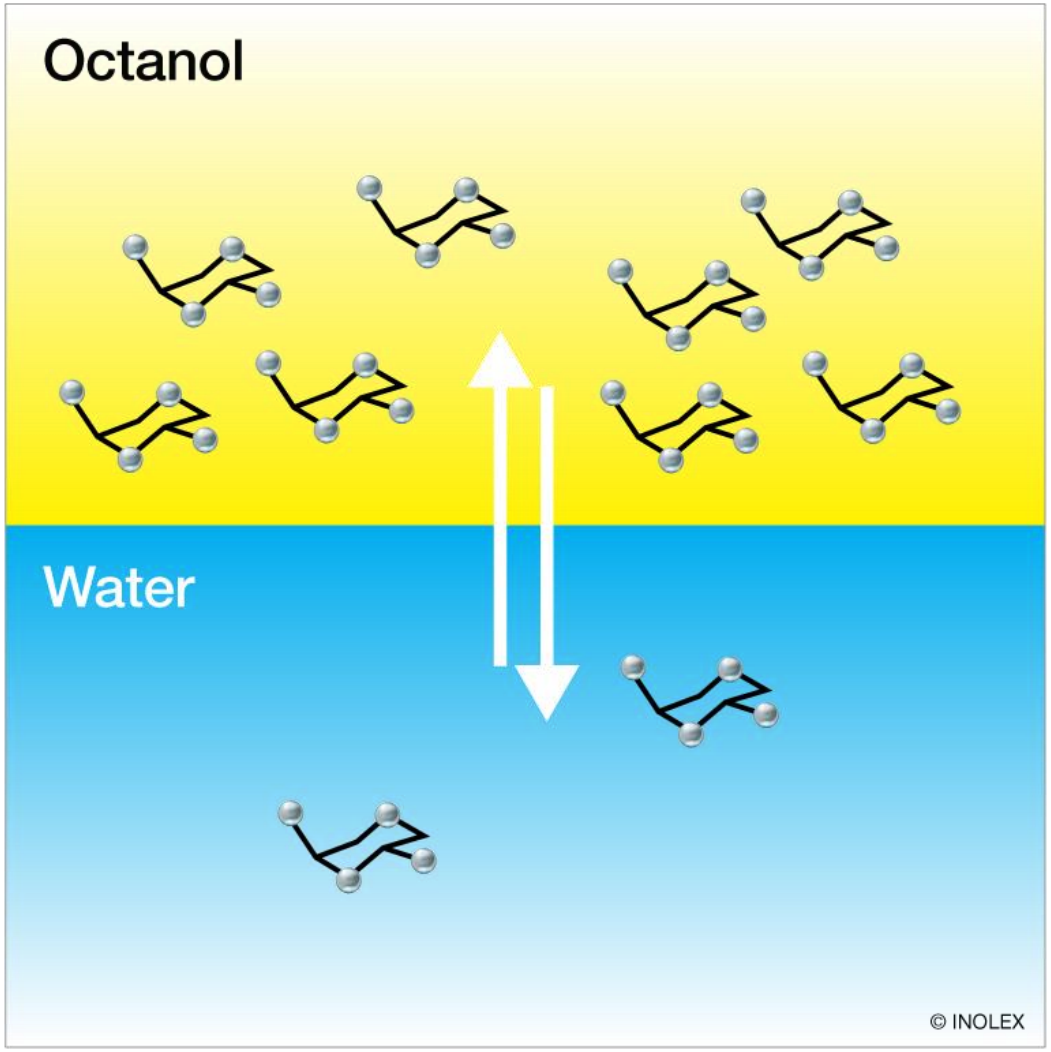
Membrane Disruption

The following compounds appear to have “membrane disruption” as their mode of action

- Parabens
- Phenoxyethanol

The Octanol-Water Partition Coefficient: Log P



- Represented by the Log P
- Quantification of a solute's hydrophobicity
- Solute mixed with two immiscible phases, concentration of solute in each phase is measured
- $\log \mathrm{P} = \log\left(\frac{[\mathrm{Solute}]_{\mathrm{octanol}}}{[\mathrm{Solute}]_{\mathrm{un-ionized\ water}}}\right)$
- Low Log P Hydrophilic
- High Log P Hydrophobic

< ***Solute is hydrophobic, would have a high Log P***

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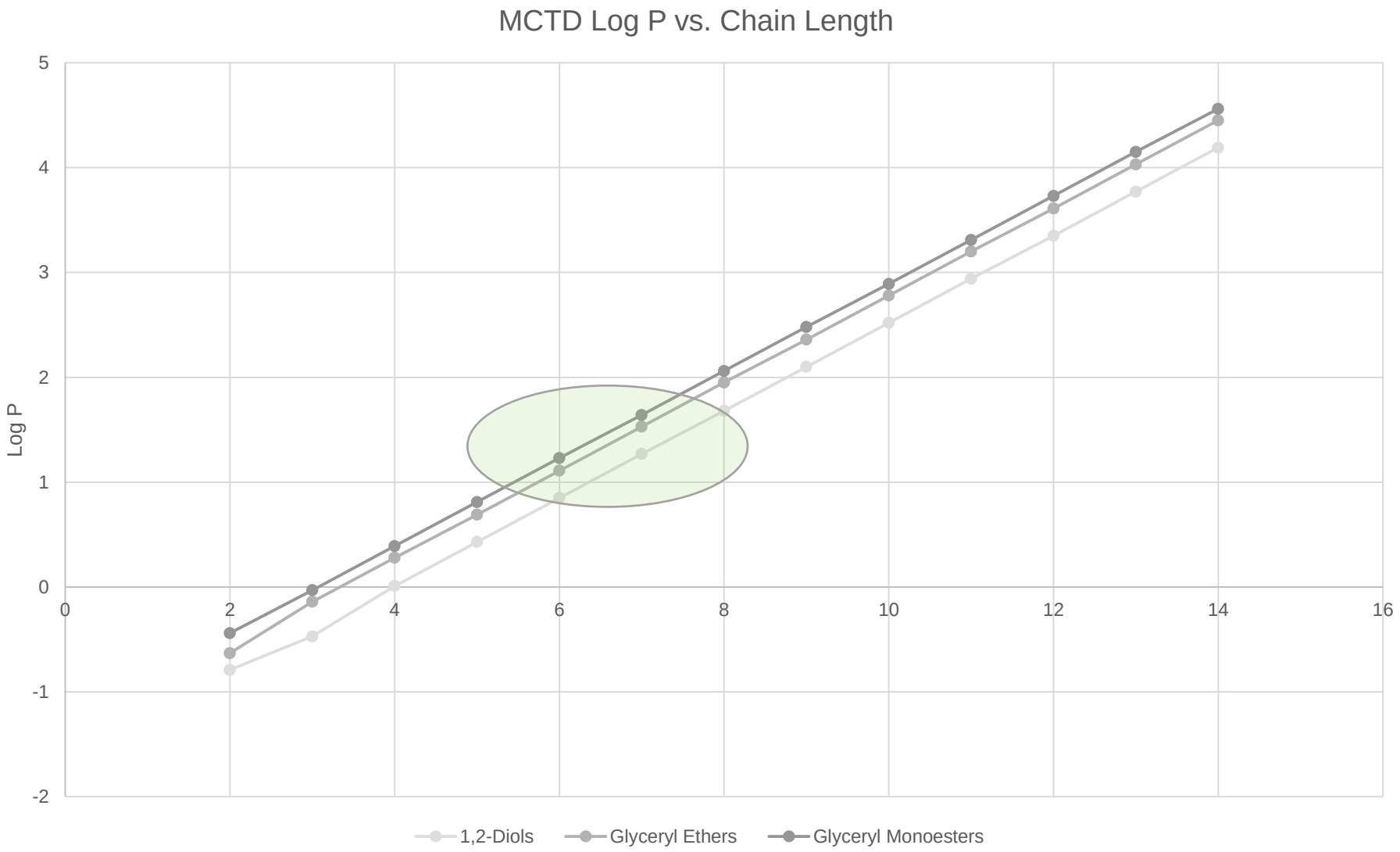
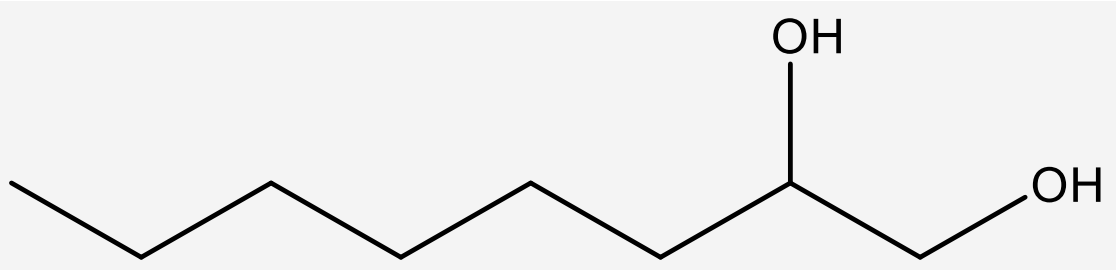
Log P vs. Chain Length



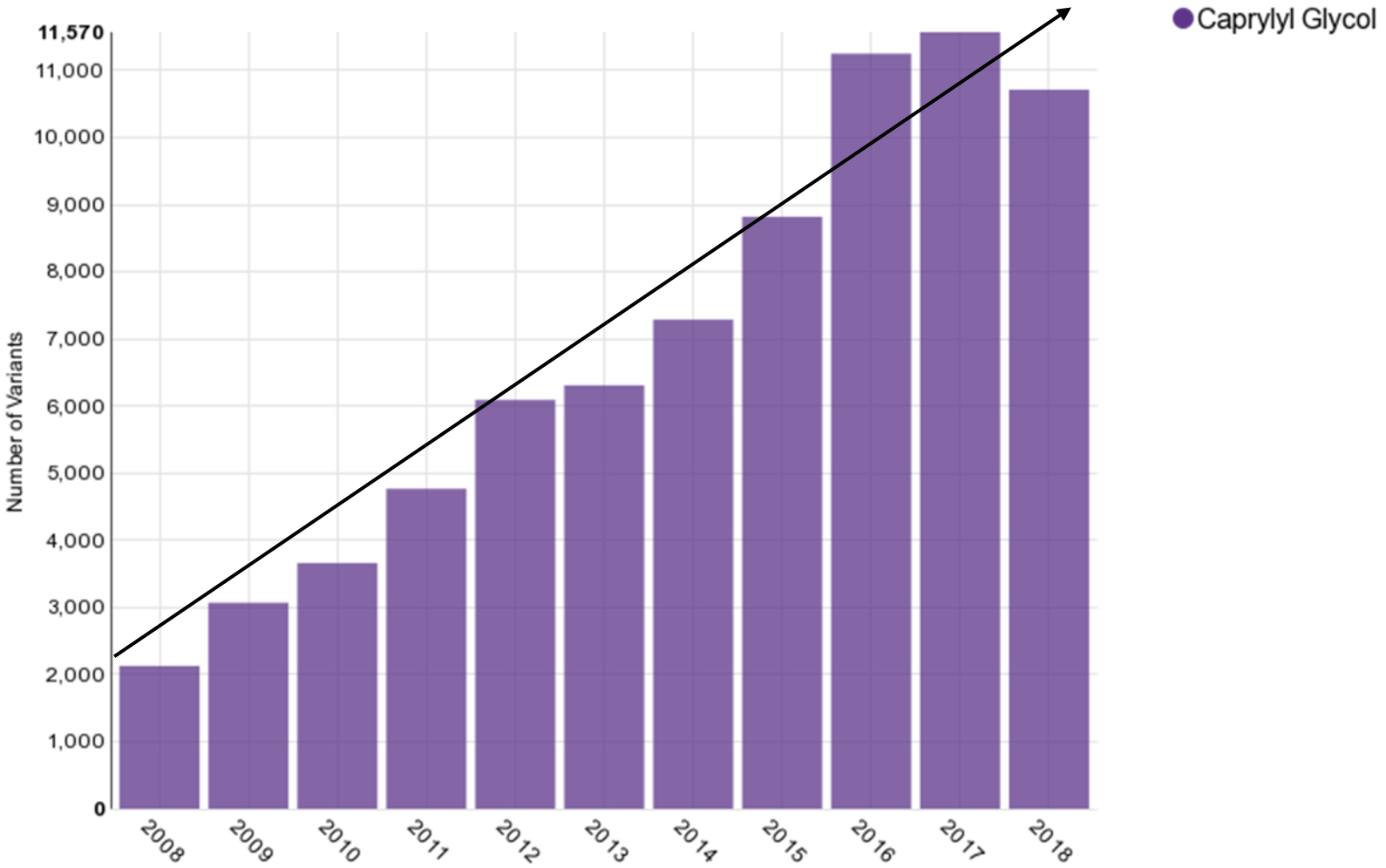
MCTD: 1,2-Diols

Caprylyl Glycol

- PCPC Function(s): Deodorant Agents; Hair Conditioning Agents; Preservatives; Skin-Conditioning Agents - Emollient
- Annex V? NO
- Petrochemically Derived
- Log P = 1.68
- Very effective against bacteria
- Weak against yeast and mold
- Use Level: 0.5 - 1.5%
- May cause irritation in sensitive areas



Caprylyl Glycol: Usage Trend



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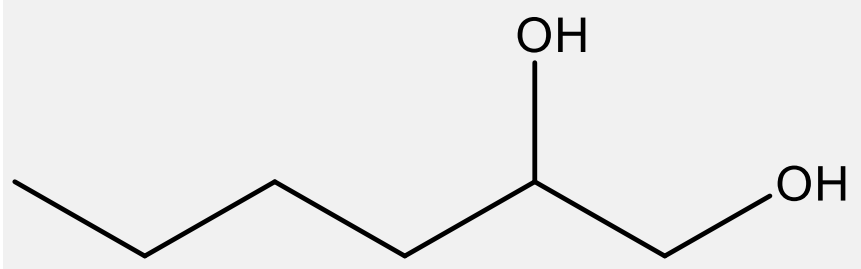
MCTD: 1,2-Diols

1,2-Hexanediol

- PCPC Function(s): Preservatives; Skin-Conditioning Agents - Miscellaneous; Solvents
- Annex V?: NO
- Petrochemically derived
- Log P = 0.85
- Weak against yeast and mold
- Use Level: 0.5 - 2.0%
- Milder than caprylyl glycol
- Very popular in Asia for sheet masks



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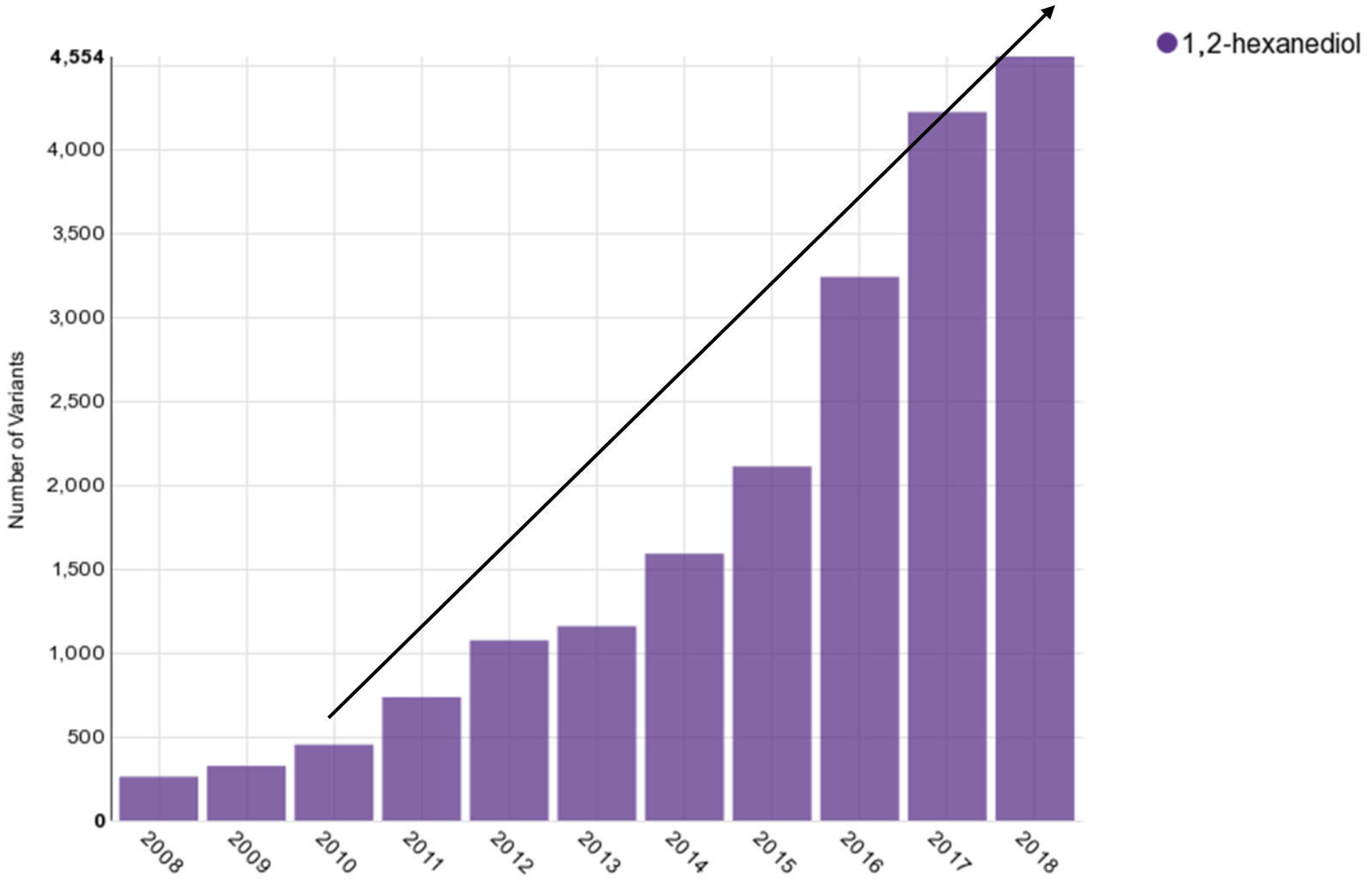
1,2-Hexanediol: Usage Trend



Source MINTEL

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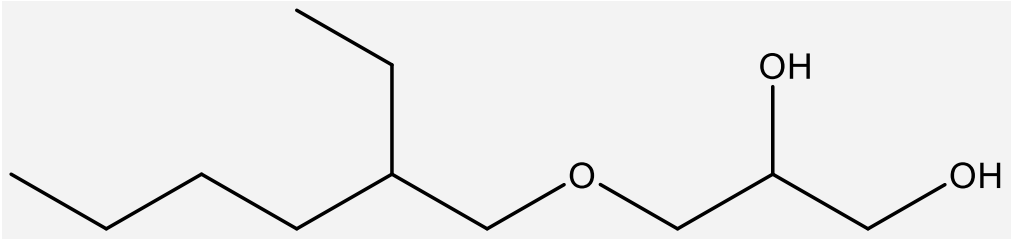
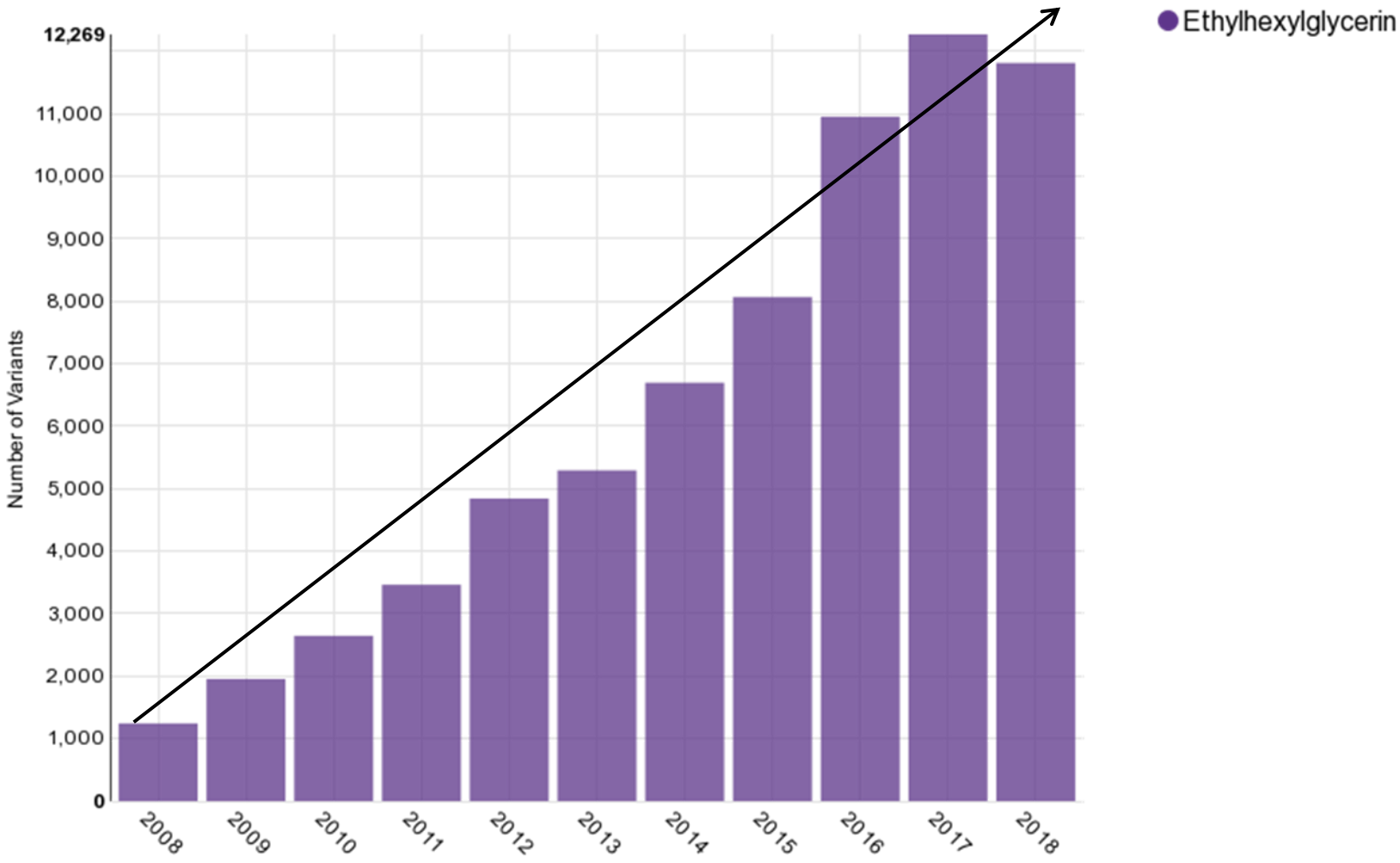
MCTD: Glyceryl Ether Diols

Ethylhexylglycerin

- PCPC Function(s): Deodorant Agents; Skin-Conditioning Agents - Miscellaneous
- Annex V?: NO
- Petrochemically Derived
- Log P = 1.93
- Very effective against bacteria
- Weak against yeast and mold
- Use Level: 0.5 - 1.5%
- May cause irritation in sensitive areas



Ethylhexylglycerin: Usage Trend



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Other Diols

- Pentylene glycol
- Butylene glycol
- Propanediol
- Methylpropanediol

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Natural “Certifications"

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Natural “Certifications"

APPENDIX V: OTHER INGREDIENTS ALLOWED (COSMOS)
This appendix contains those ingredients that are temporarily allowed and will be reviewed on a regular basis with the aim of removing those where compliant alternatives exist.
These ingredients cannot be certified as organic.
1. Preservatives and denaturing agents from petrochemical origin (nonnatural ingredients – NNI)
Ingredient Restrictions
Benzoic Acid and its salts
Benzyl Alcohol
Salicylic Acid and its salts
Sorbic Acid and its salts
Dehydroacetic Acid and its salts
Denatonium Benzoate and Tertiary Butyl Alcohol and other denaturing agents for alcohol (excluding phthalates)
Only as denaturing agent for ethanol – where required by law

The percentage of these NNI do not count towards the limit of 2% petrochemical moiety in the total finished product.

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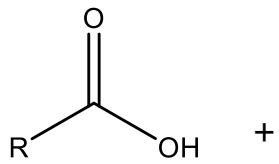
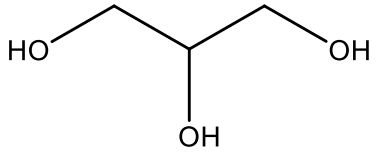
MCTD: Glyceryl Monoesters

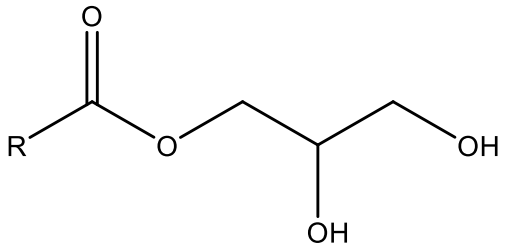


C6-C10 Fatty Acid

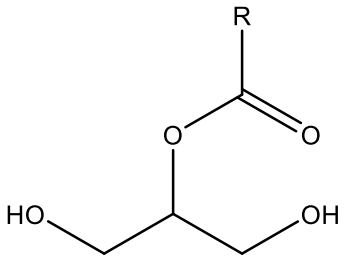
+



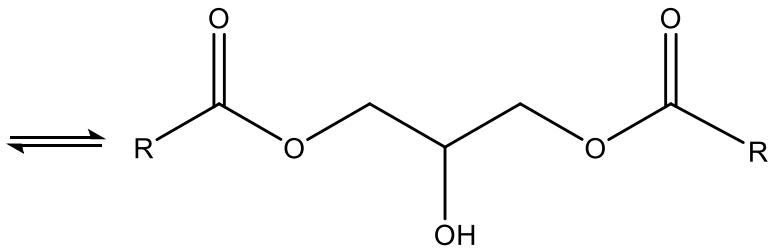
Glycerol



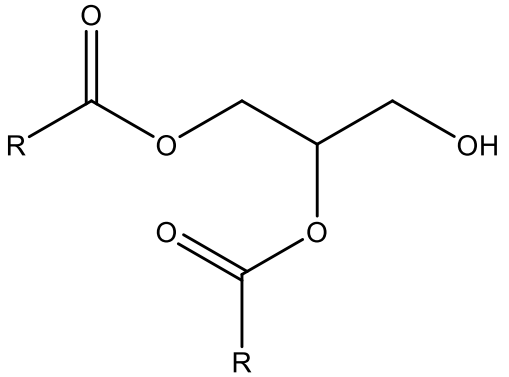
α-Monoglyceride*



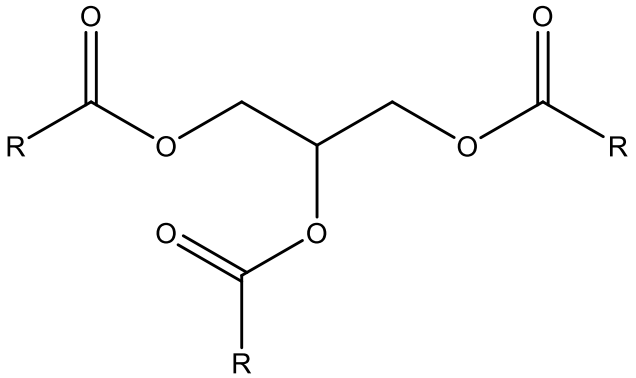
β-Monoglyceride*



α,α'-Diglyceride



α,β-Diglyceride



Triglyceride

*Antimicrobial Activity

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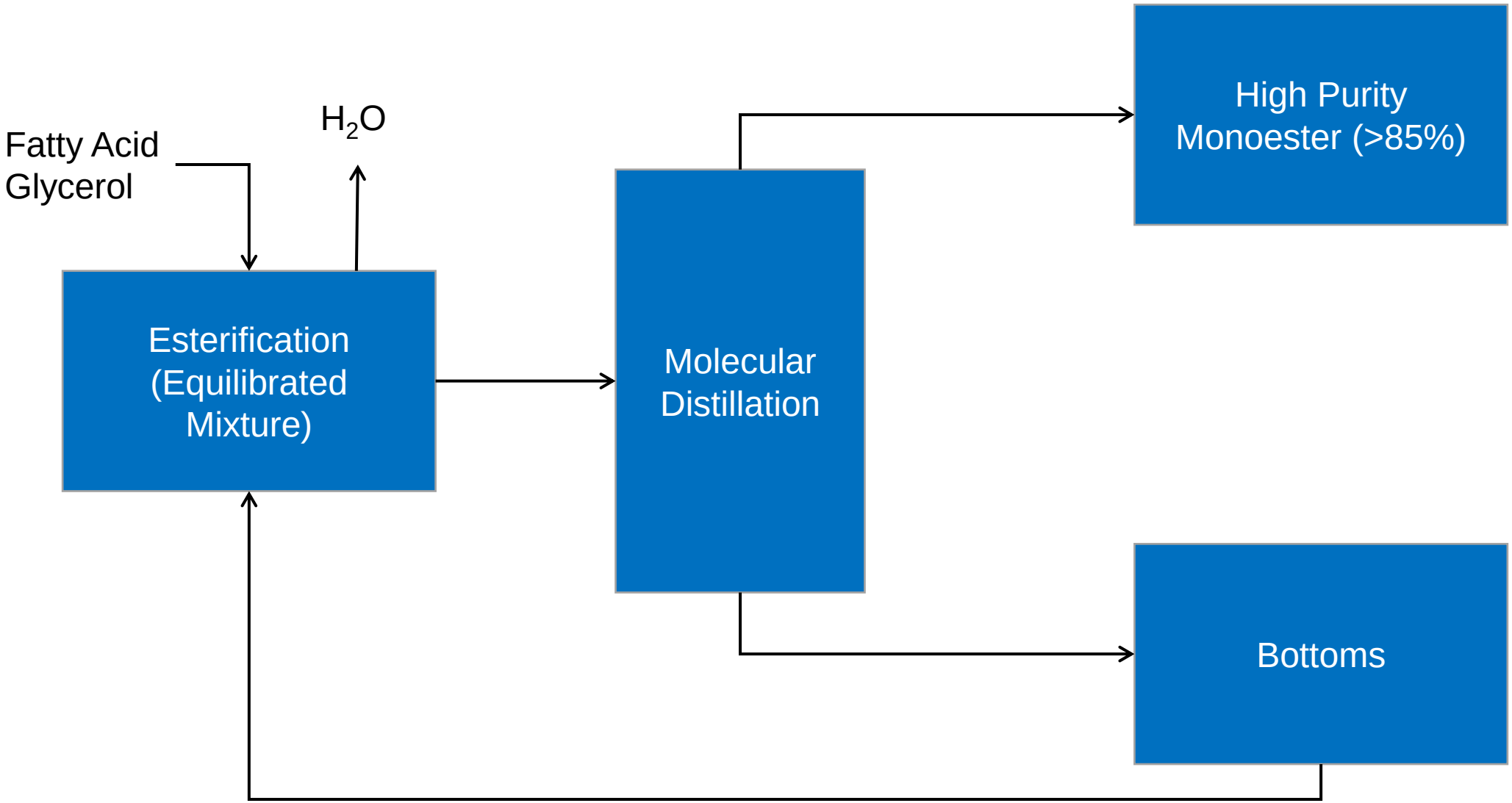
High Purity Glyceryl Monoesters



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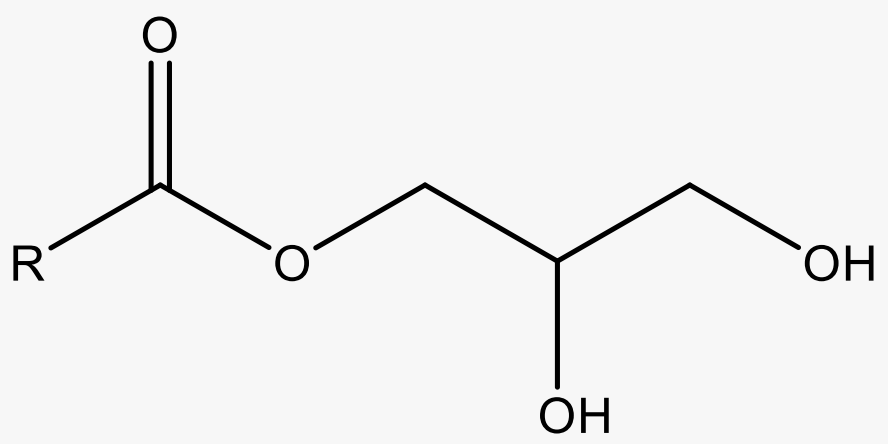
Glyceryl Monoesters

Glyceryl Caprylate

- PCPC Function(s): Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents
- Annex V?: NO
- **Non-Petrochemically Derived**
- Log P = 1.71
- Very effective against bacteria
- Weak against yeast and mold
- Use Level: 0.5 - 1.5%
- May cause irritation in sensitive areas



R = C_7, Straight Chain

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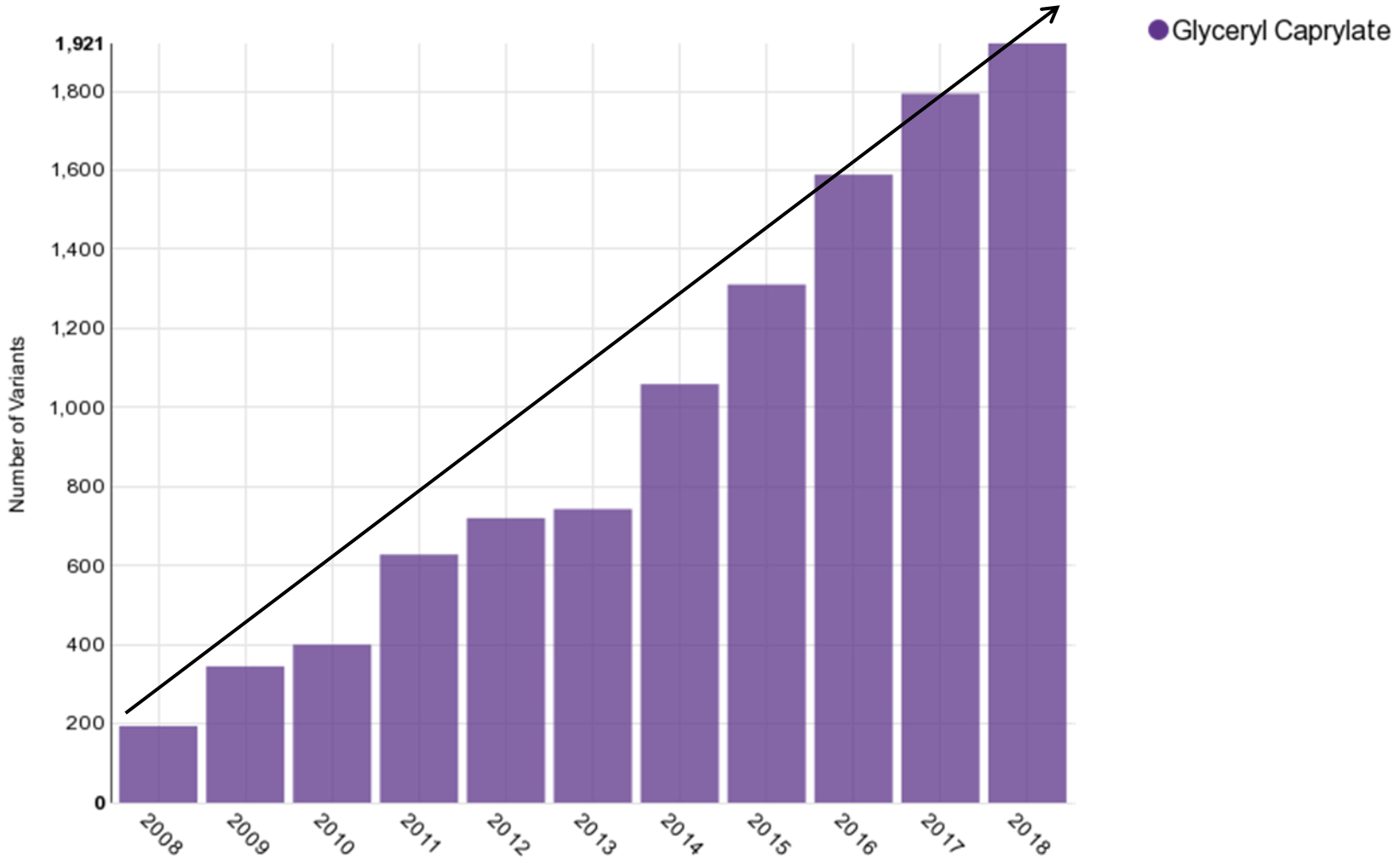
Glyceryl Caprylate: Usage Trend



Source MINTEL

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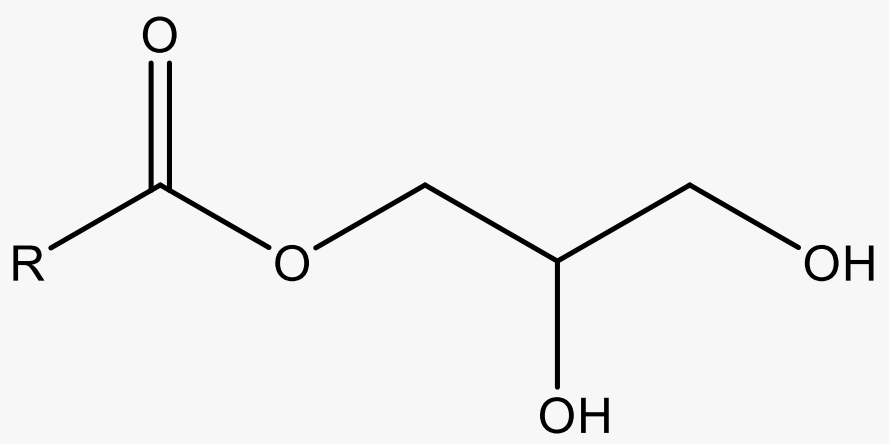
Glyceryl Monoesters

Glyceryl Undecylenate

- PCPC Function(s): Skin-Conditioning Agents - Emollient; Surfactants - Emulsifying Agents
- Annex V?: NO
- **Non-Petrochemically Derived**
- Log P = 1.92
- Very effective against bacteria
- Weak against yeast and mold
- Use Level: 0.5 - 1.5%
- May cause irritation in sensitive areas



R = C_{10}, Straight Chain Monounsaturated

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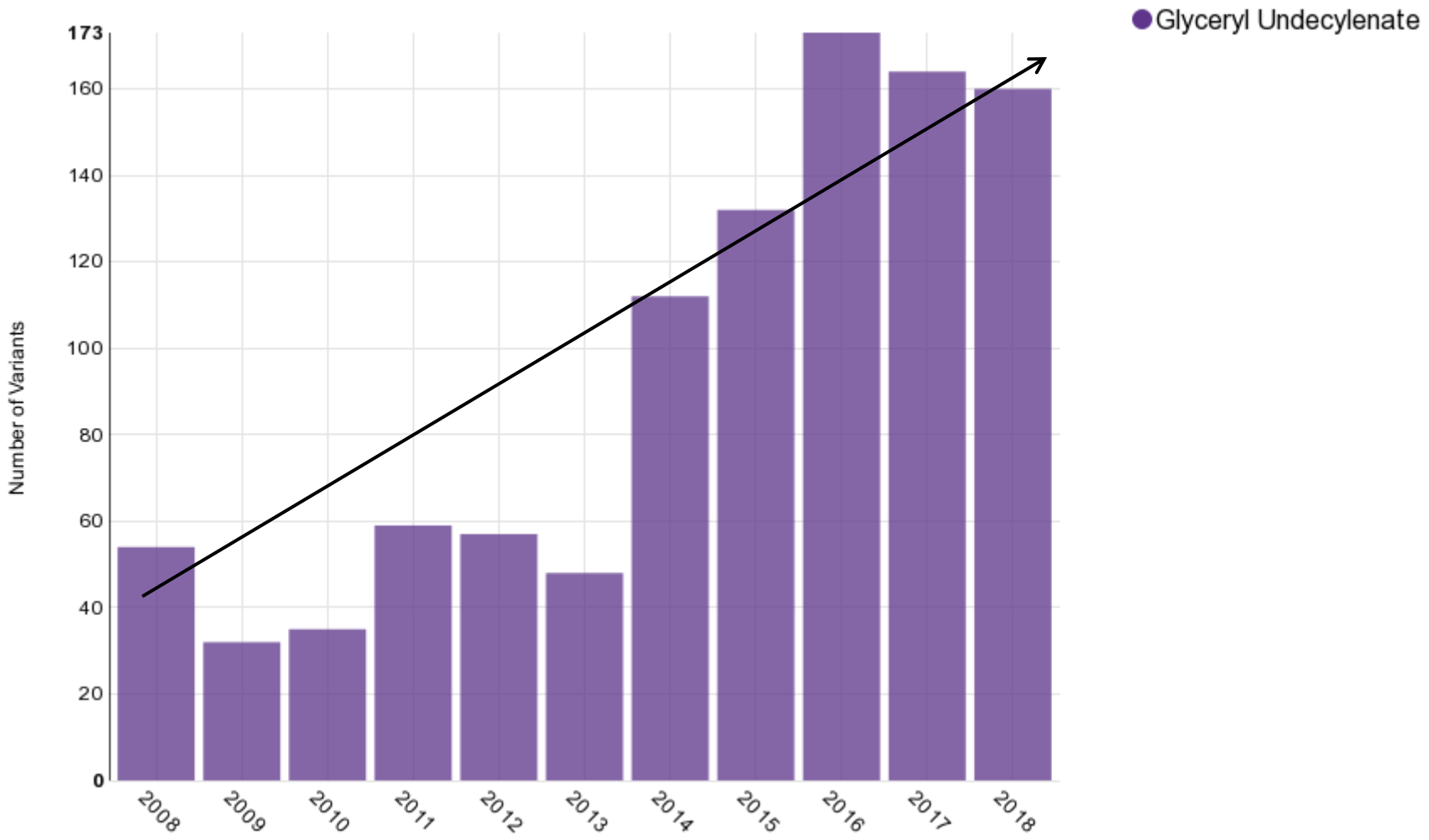
Glyceryl Undecylenate: Usage Trend



Source MINTEL

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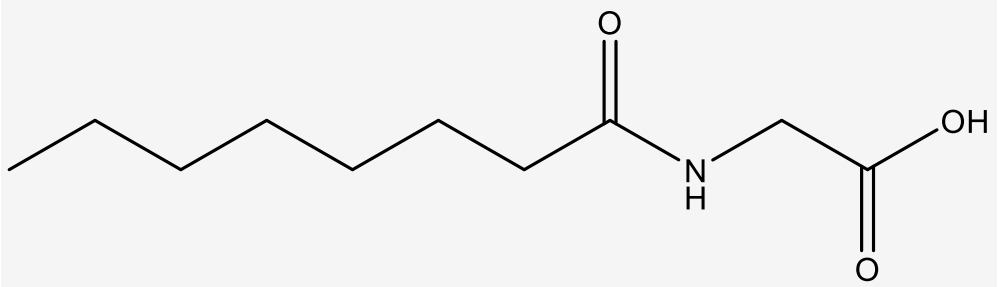
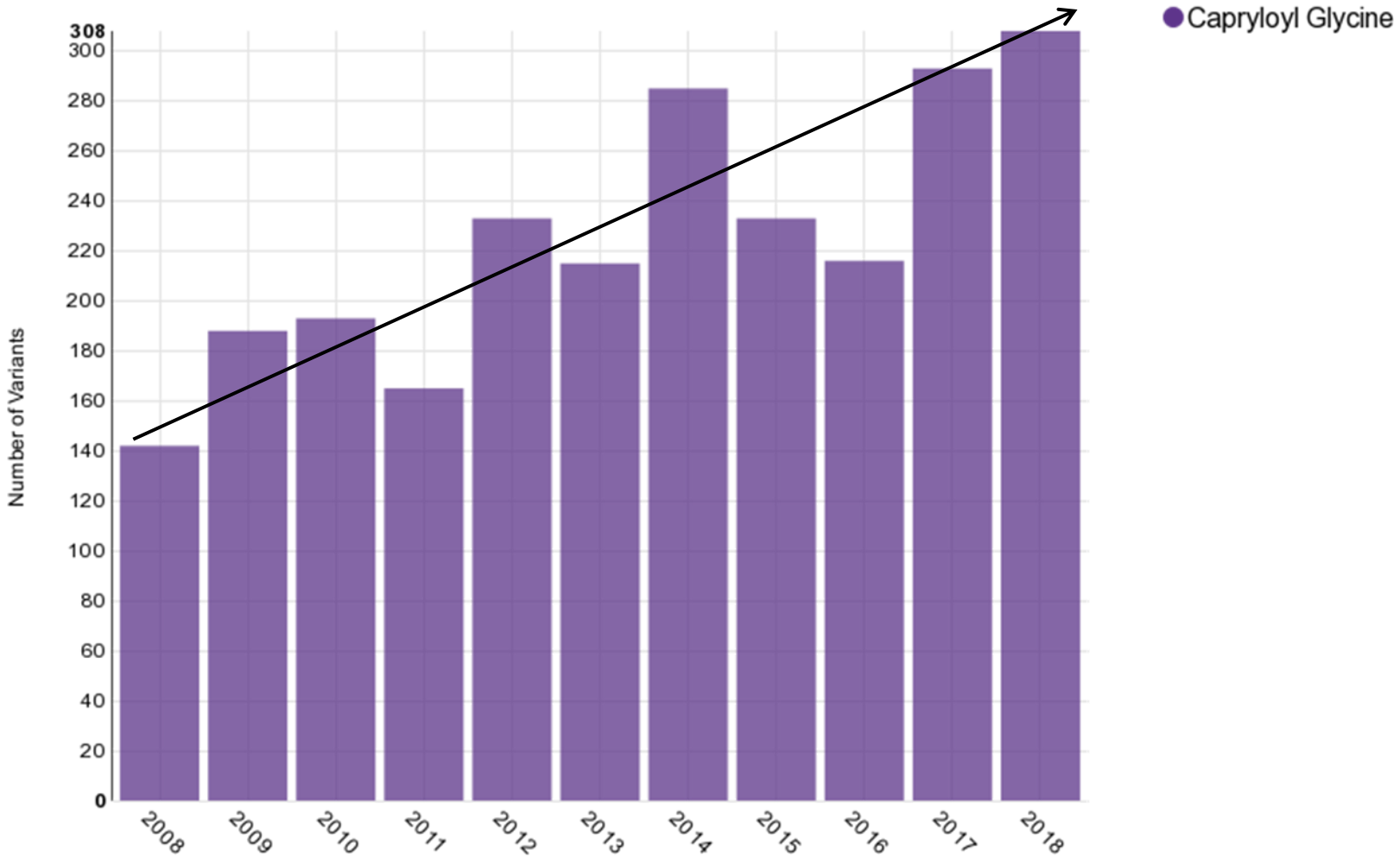
Multifunctionals: Amino Acid Derivatives

Capryloyl Glycine

- PCPC Function(s): Hair Conditioning Agents; Surfactants - Cleansing Agents
- Annex V?: NO
- **Non-Petrochemically Derived**
- Log P = 1.28
- Very effective against bacteria
- Weak against yeast and mold
- Use Level: 0.5 - 1.5%



Capryloyl Glycine: Usage Trend



Source MINTEL

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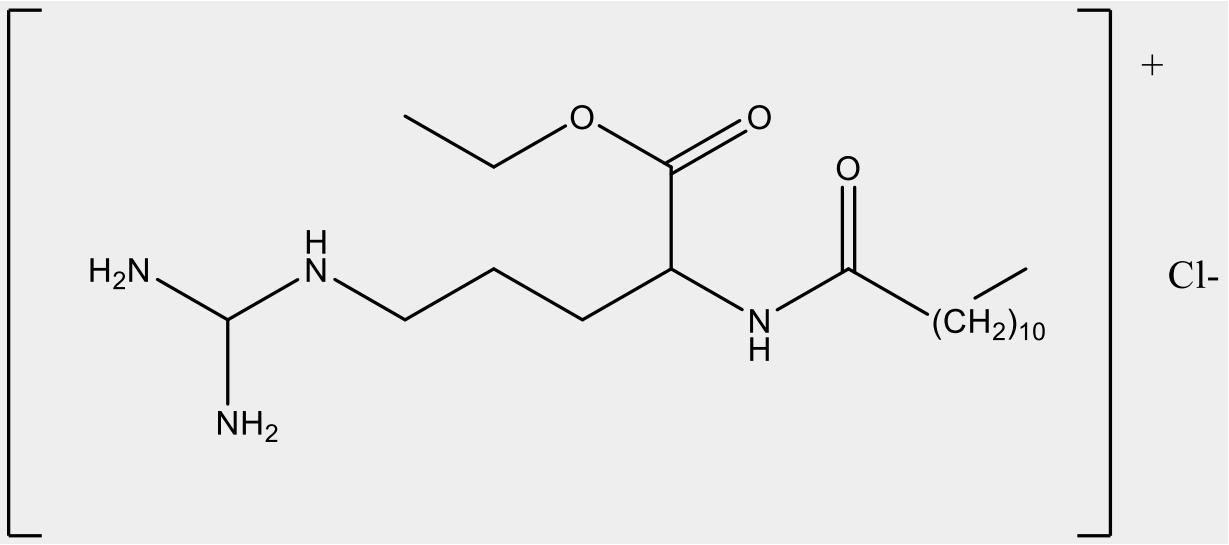
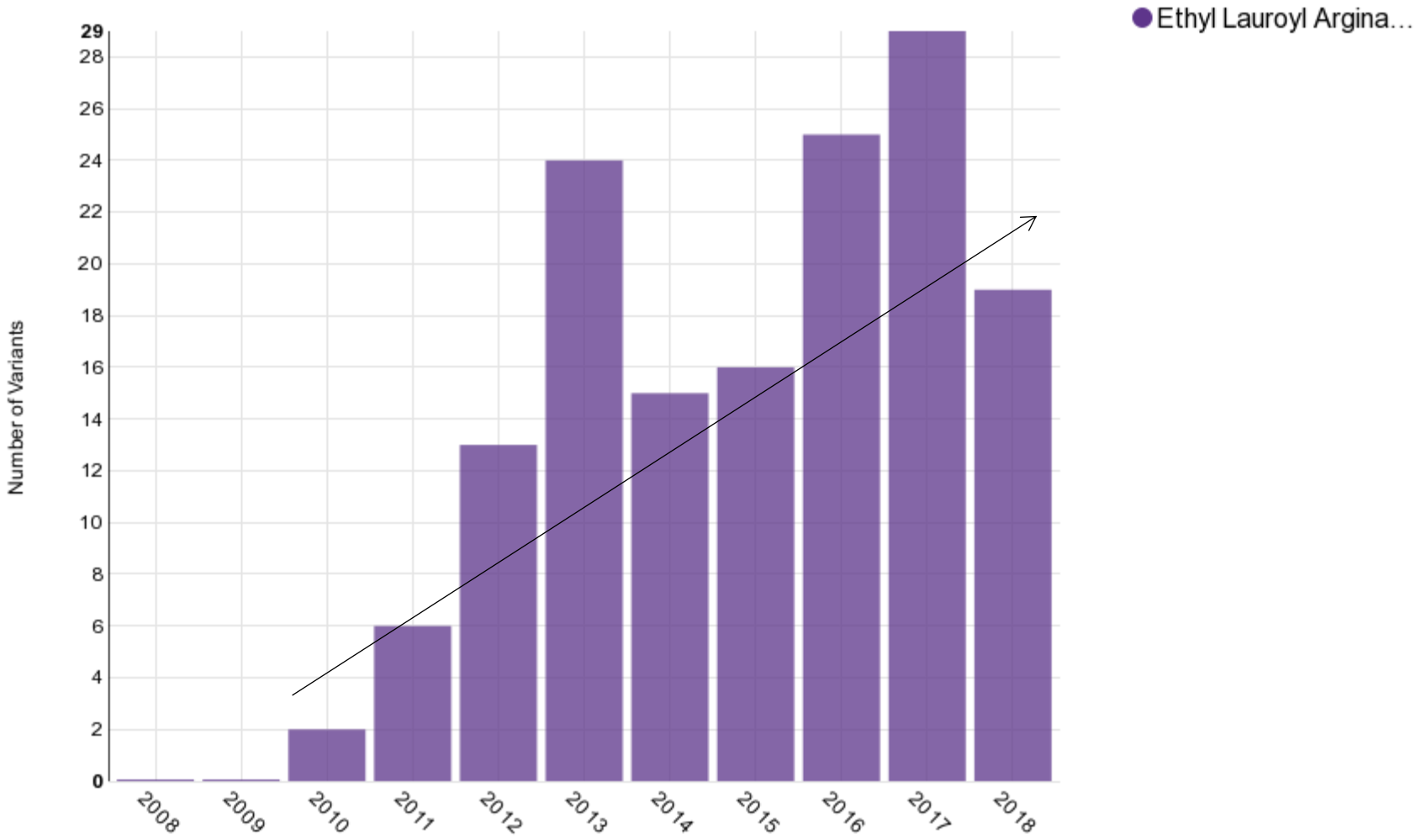
Multifunctionals: Amino Acid Derivatives

Ethyl Lauroyl Arginate HCl

- PCPC Function(s): Antidandruff Agents; Hair Conditioning Agents; Preservatives; Skin-Conditioning Agents - Miscellaneous
- Annex V?: YES
- **Non-Petrochemically Derived**
- Log P = -0.96
- Very effective against bacteria
- Weak against yeast and mold
- Use Level: 0.5 - 1.5%



Ethyl Lauroyl Arginate HCl: Usage Trend



Hurdle 2: Organic Acids

- Studied since early 1900’s
- Disrupt cell membranes
- Affect biostatsis by pH effects
- Used extensively in combination with MCTD’s to assist in mold control

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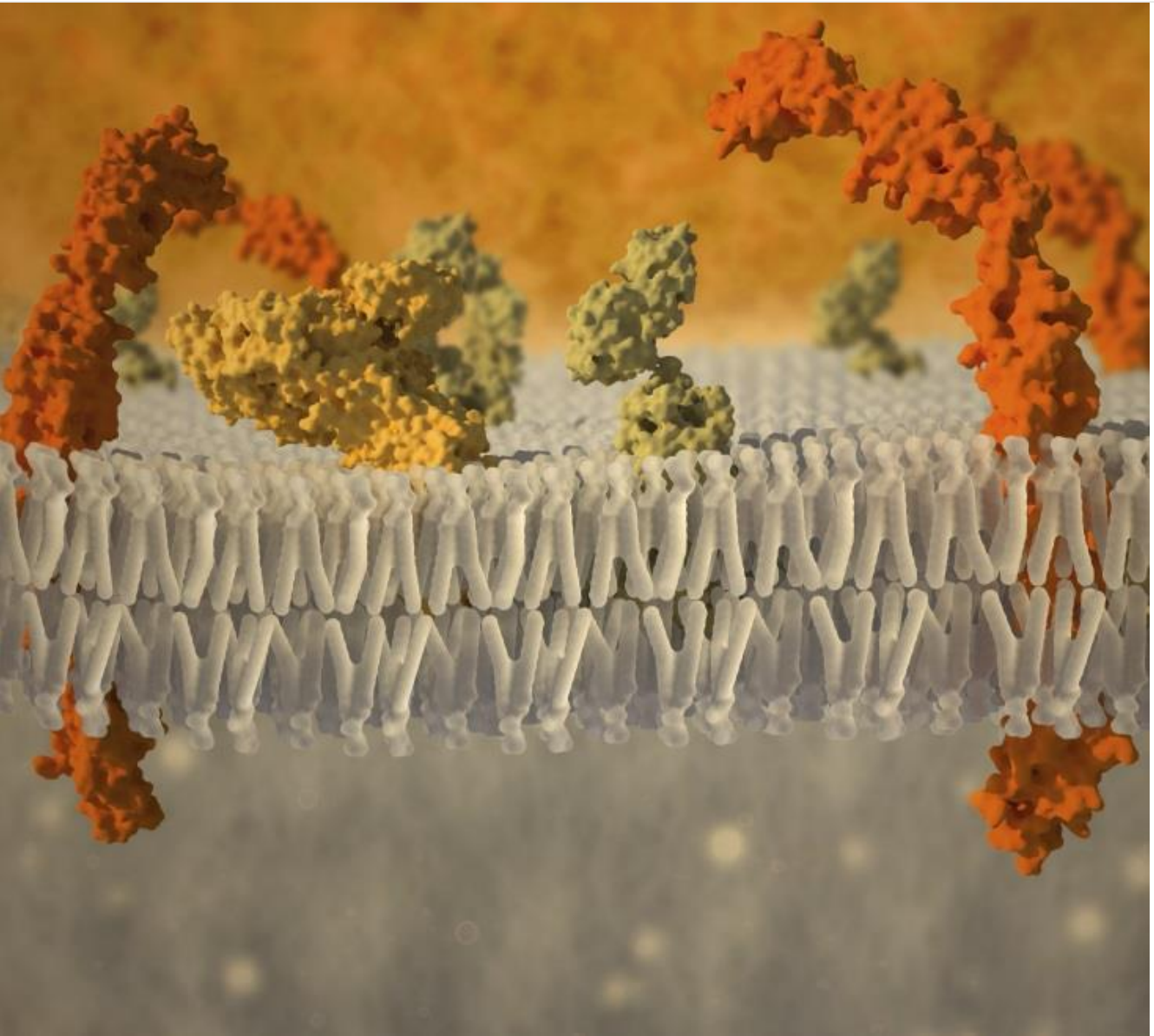
Organic Acids: Hydrophobicity



- Microbial cell walls/membranes contain lipid material.
- Like MCTD's, optimal organic acids have the right amount of hydrophobicity to facilitate interaction with cell membrane lipids.
- Most effective organic acids have Log P between about 0.0 and 2.0.
- Adjusting pH with organic acids has a dual effect in microbial control. The effect of adjusting pH with organic acids is different from adjusting pH with mineral acids.

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Organic Acids: The Standards

Organic Acid	pKa	Log P	Annex 5?	COSMOS?	Petro Derived?
Dehydroacetic Acid	**N/A**	**0.22**	**Y**	**Y**	Y
Benzoic Acid	**4.20**	**1.59**	**Y**	**Y**	**Y**
Sorbic Acid	**4.76**	**1.26**	**Y**	**Y**	Y
Salicylic Acid	**2.98**	**1.20**	**Y**	**Y**	Y
Levulinic Acid	**4.36**	**-0.13**	**N**	**Y**	N
Anisic Acid	**4.25**	**1.46**	**N**	**Y**	N

Organic Acids: pKa

- Organic acids are weak acids, and dissociate in aqueous solution.

$$RCOOH \underset{\text{acid}}{\overset{\text{base}}{\rightleftharpoons}} RCOO^-$$

- To be effective as antimicrobials, organic acids must be in the undissociated form to transport across cell membranes and affect cell biochemistry.
- From pKa, the amount of undissociated acid may be determined at any given pH. Higher pKa = higher level of undissociated acid.

$$K_a = [RCOO^-][H^+]/[RCOOH] \qquad pK_a = -\log_{10} K_a$$

$$pH = pK_a + \log_{10}([RCOO^-]/[RCOOH])$$

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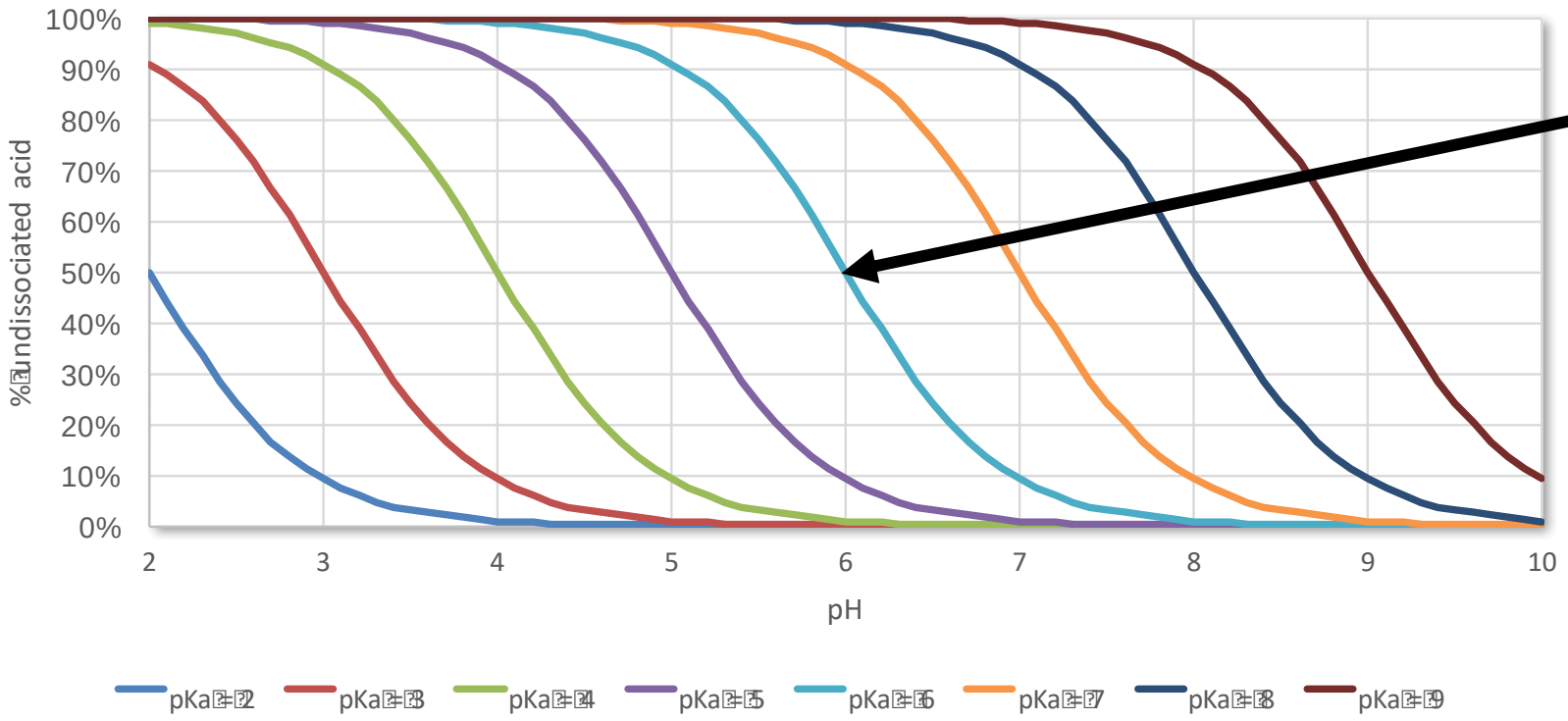
Organic Acids: pKa



At pH 6, pKa must be at least 6 for acid to be 50% active.

For acids with various pKa, % undissociated acid drops off non-linearly as pH increases. pH “drift” must be carefully monitored during development phase and production.

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Organic Acids: Data for Common Acids

Percent Undissociated Acid as a function of pH

% Undissociated Acid					
pH →	**3**	**4**	**5**	**6**	**7**
Dehydroacetic Acid	99.5	94.9	65.1	15.7	1.8
Benzoic Acid	94.1	61.3	13.7	1.6	0.2
Sorbic Acid	98.3	84.9	36.0	5.3	0.6
Salicylic Acid	48.3	8.5	0.9	0.1	0.0
Levulinic Acid	97.5	79.9	28.5	3.8	0.4
Anisic Acid	96.9	76.0	24.0	3.1	0.3

Most typically used organic acids have little to no activity above pH 6.

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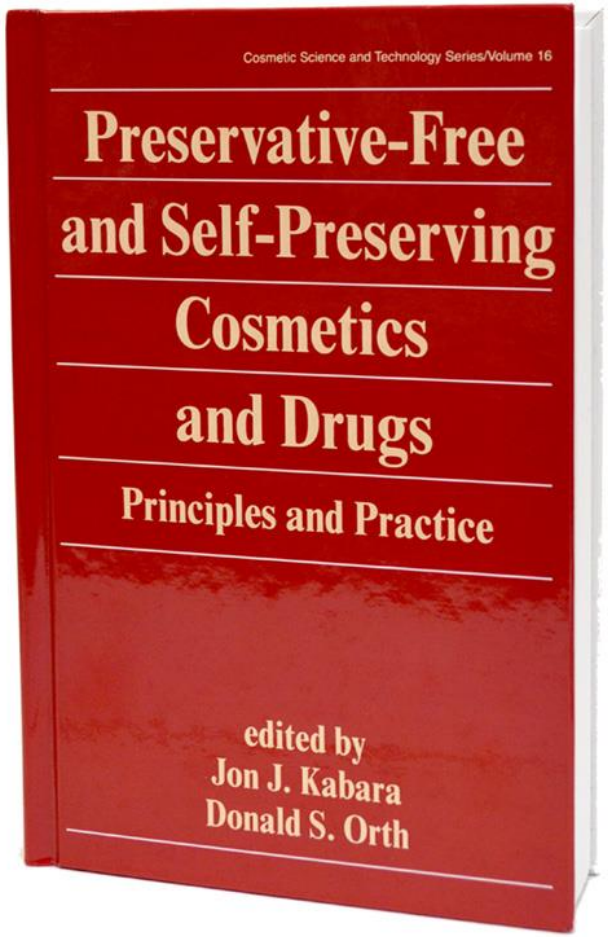
Hurdle 3: pH

- Microorganisms do not like extremes of pH
- pH must be taken into consideration when using organic acids/salts

Hurdle 4: Chelating Agents



- Potentiators (“boosters”) of other preservatives
- Disrupt cell walls by binding metals
- Synergy with traditional preservatives
- Sequester metals required for cell growth
- Effect of binding of Iron discussed extensively by Kabara and Orth

Kabara, J.J. and Orth, D.S., eds., Preservative-Free and Self-Preserving Cosmetics and Drugs., Marcel Dekker,Inc, 1997.

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Chelating Agents

Caprylhydroxamic Acid

- PCPC Function(s):Chelating Agent
- Annex V?: NO
- **Non-Petrocemically Derived**
- Log P = 1.71
- Used in combination with MCTD’s for control against fungi at higher pH
- Use Level: 1000-1500 ppm

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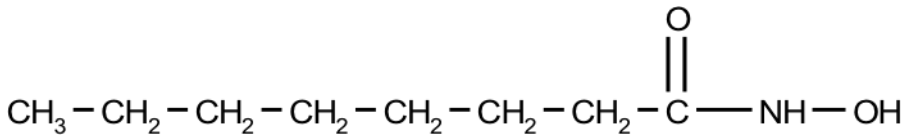
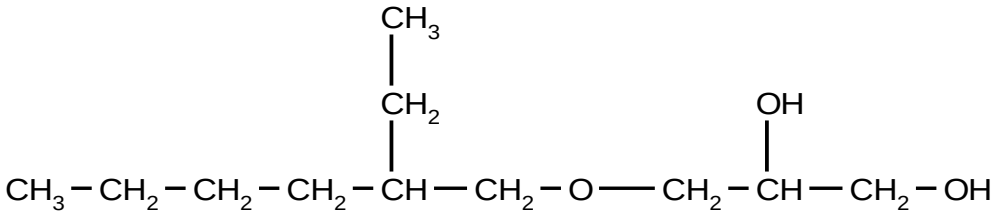
CHA Structure Comparison to MCTD's

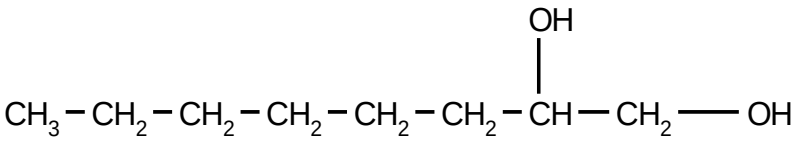
Caprylhydroxamic Acid



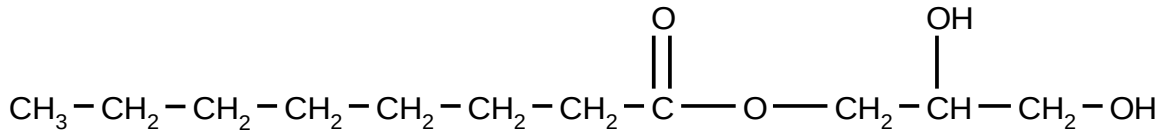
Ethylhexylglycerin



Caprylyl Glycol



Glyceryl Caprylate



C_8 Alkyl Chain **Polar Groups**

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Partition Coefficient Comparison

Compound	**Log P**(Estimated)*
CHA	1.71
Caprylyl Glycol	1.68
Glyceryl Caprylate	1.71
Ethylhexylglycerin	1.93
Methylparaben	2.00
Propylparaben	2.98

LOWER HYDROPHILICITY

*** ECOWIN V99h**

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CHA: A Unique Acid

% Undissociated Acid					
pH →	**3**	**4**	**5**	**6**	**7**
Dehydroacetic Acid	99.5	94.9	65.1	15.7	1.8
Benzoic Acid	94.1	61.3	13.7	1.6	0.2
Sorbic Acid	98.3	84.9	36.0	5.3	0.6
Salicylic Acid	48.3	8.5	0.9	0.1	0.0
Levulinic Acid	97.5	79.9	28.5	3.8	0.4
Anisic Acid	96.9	76.0	24.0	3.1	0.3
CHA	**100**	**100**	**100**	**99.9**	**99.0**

^ **CHA is the only organic acid that is fully active at neutral pH.**

- CHA is not a carboxylic acid.
- Hydroxamic acids have much higher pKa's than carboxylic acids, so they remain active at higher pH.

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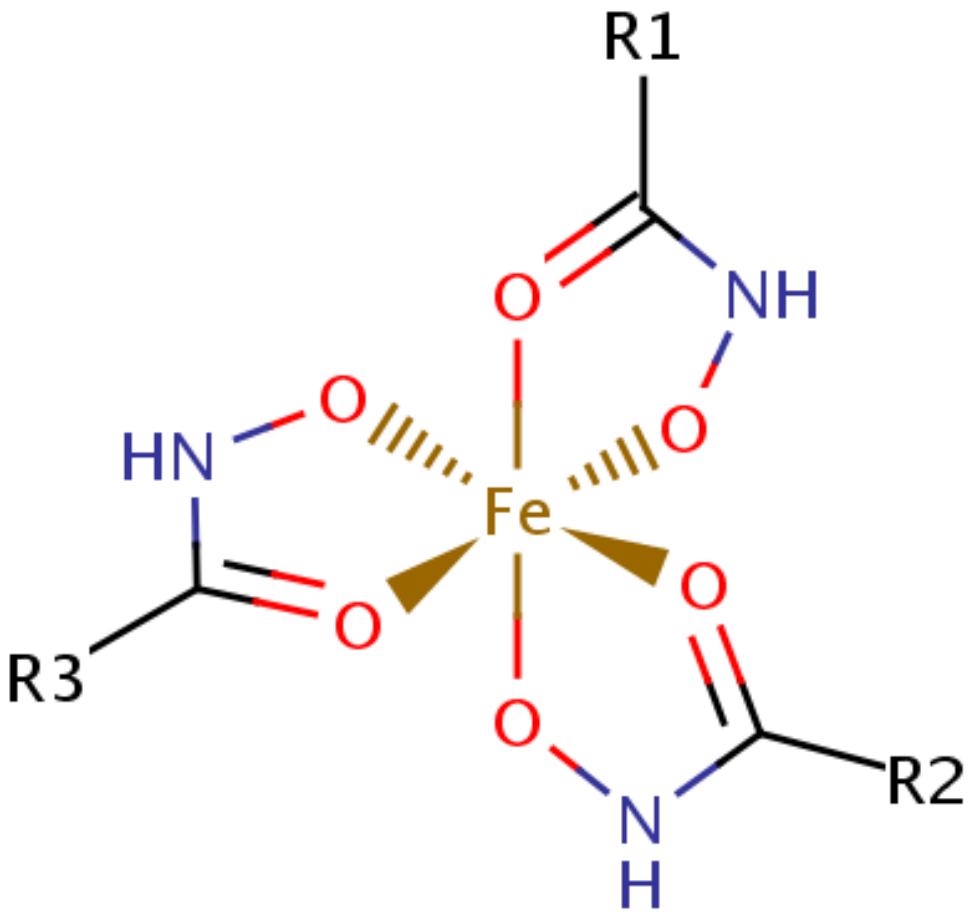
CHA: A Powerful Chelating Agent



- CHA is a powerful chelating agent for Fe(III).
- Microorganisms have reduced survival rate in Iron limited environments.

< **Fe III Hydroxamate Complex**

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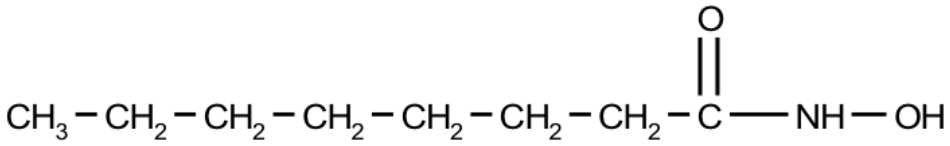
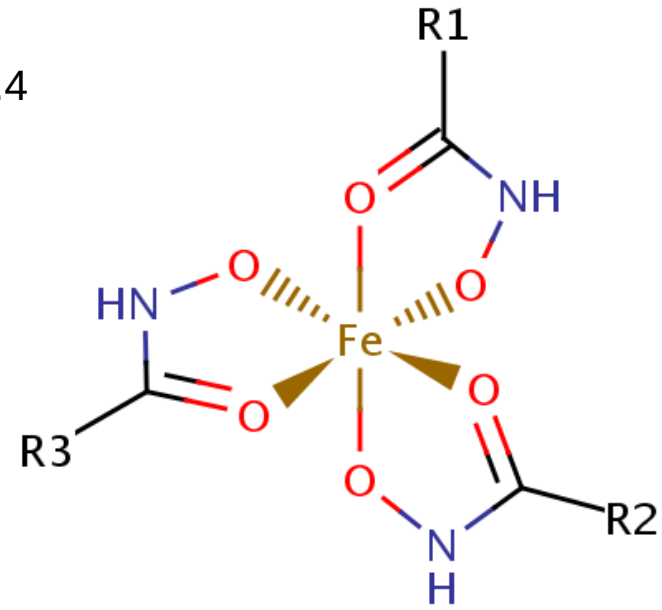
CHA: Summary

Medium Chain Surfactant



Organic Acid pKa ~ 9.4

Chelating Agent



^ **CHA provides three** (3) **hurdles in one substance.**

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Popular Cocktails

- Phenoxyethanol + Ethylhexylglycerin
- Caprylyl Glycol + Ethylhexylglycerin
- Different Chain Length Diols
- Glyceryl Caprylate + Glyceryl Undecylenate (A “natural” option)
- Glyceryl Caprylate + Glyceryl Undecylenate + Organic Acid (A “natural” option)
- Glyceryl Caprylate + CHA (A “natural” option that is effective at higher pH)

Becoming too numerous to count!

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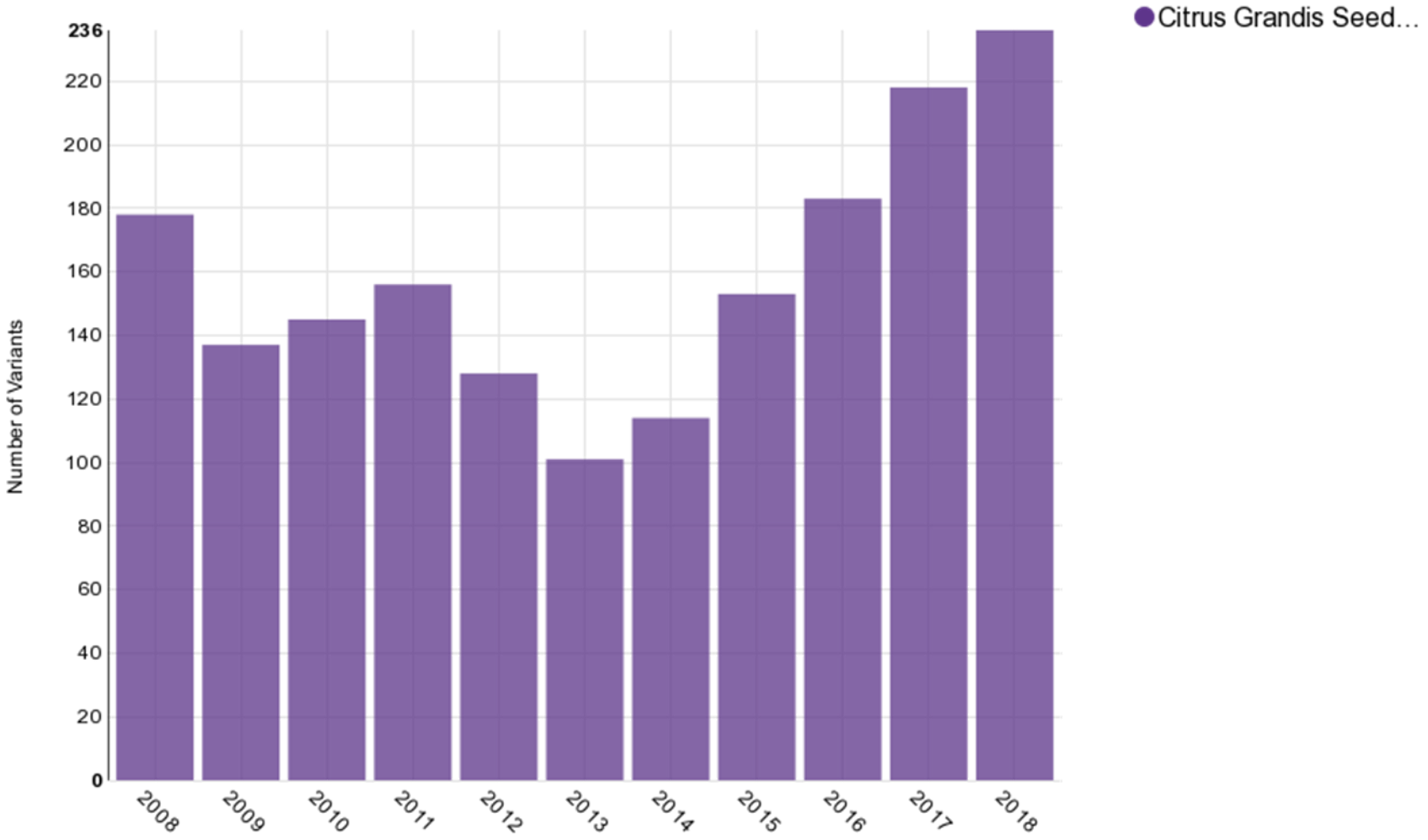
Antimicrobial “Active” Components

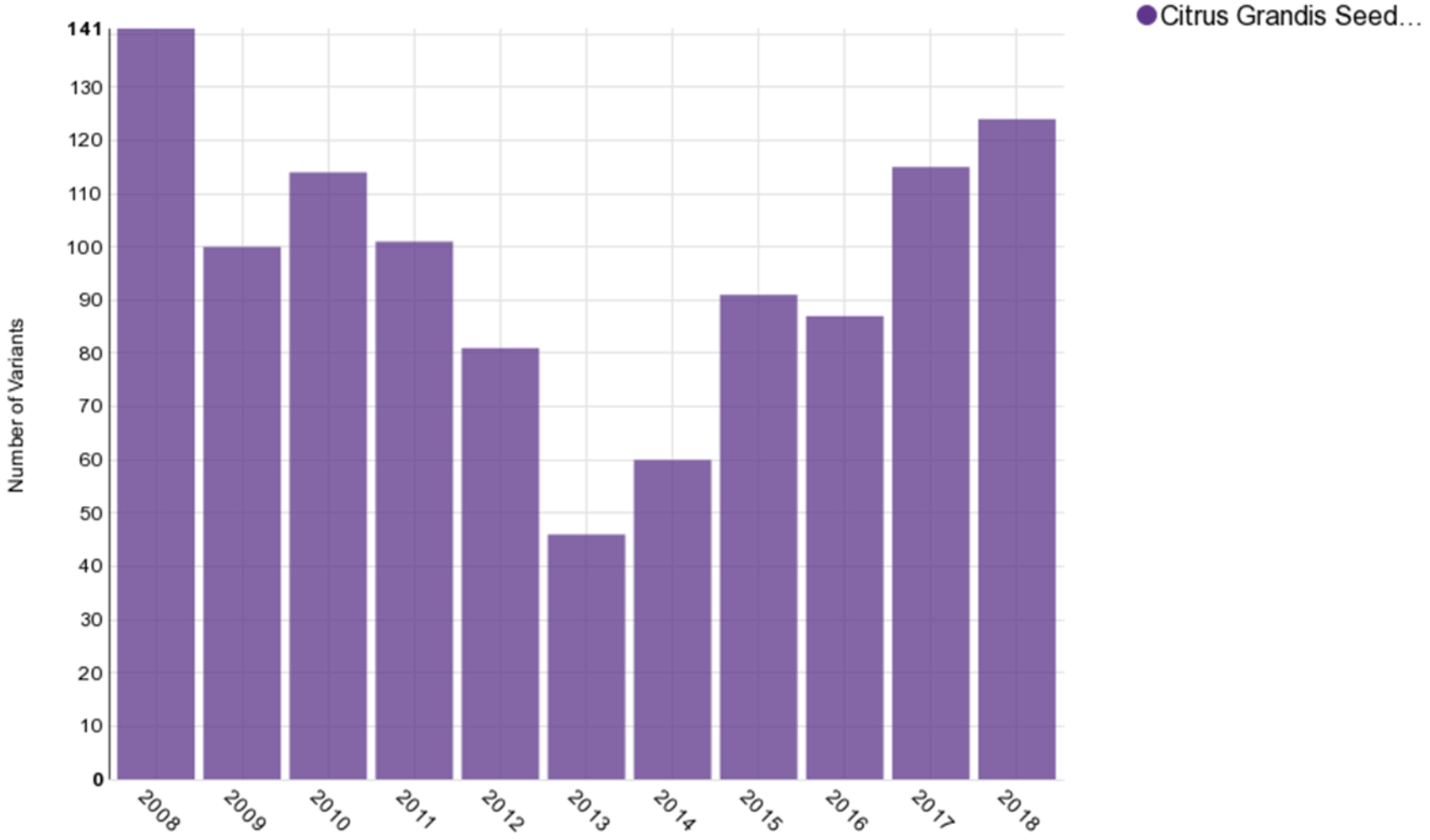
- Essential Oils
- Extracts
- Biotechnological Materials

Natural” Preservatives: Example



Natural” Preservatives: Example

•where **Ingredient Search** matches *Citrus Grandis Seed Extract* but does not match one or more of *[Phenoxyethanol, Caprylyl Glycol, Glyceryl Caprylate, 1,2-hexanediol, Ethylhexylglycerin] as the Ingredients*



Closing Thought

Every formulation is a **world of its own**...

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THANK YOU

References available on request

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