



Drug Product Palatability

Public Workshop on “Candy-Like” Drugs



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Prepared For:



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Biography

- David Tisi is the Technical Director at Senopsys LLC
- He received a Masters in Food Chemistry from Cornell University.
- His career has been at the interface of food and pharmaceutical technology. He began his career in new product development at PepsiCo and Nestle and transitioned to pharmaceutical development, applying tools techniques and approaches from the food industry towards the development of palatable drug products.
- Mr. Tisi is the founding Technical Director of Senopsys where he directs taste assessment and taste tasking masking projects for global pharma, biotech and drug delivery companies.



Overview

1. Palatability – Current Definitions
2. Flavor – Definition and Perception
3. Aversive Flavor Attributes of Rx and OTC drug actives
4. Sensory Analysis of Pediatric Cough & Cold and Analgesics
5. Flavor Comparison – OTCs vs. Candies (Confections)

What is palatable? Common definitions of palatable are subjective as are those of regulatory agencies.

“Agreeable to the palate or taste”

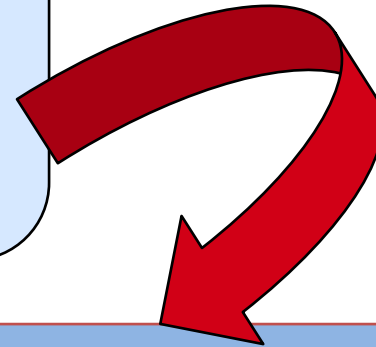
(Merriam-Webster)

“Pleasant to taste”

(Oxford)

“Acceptable to the taste; sufficiently agreeable in flavor to be eaten”

(The Free Dictionary)



“Taste masked or of acceptable taste”

(FDA)¹

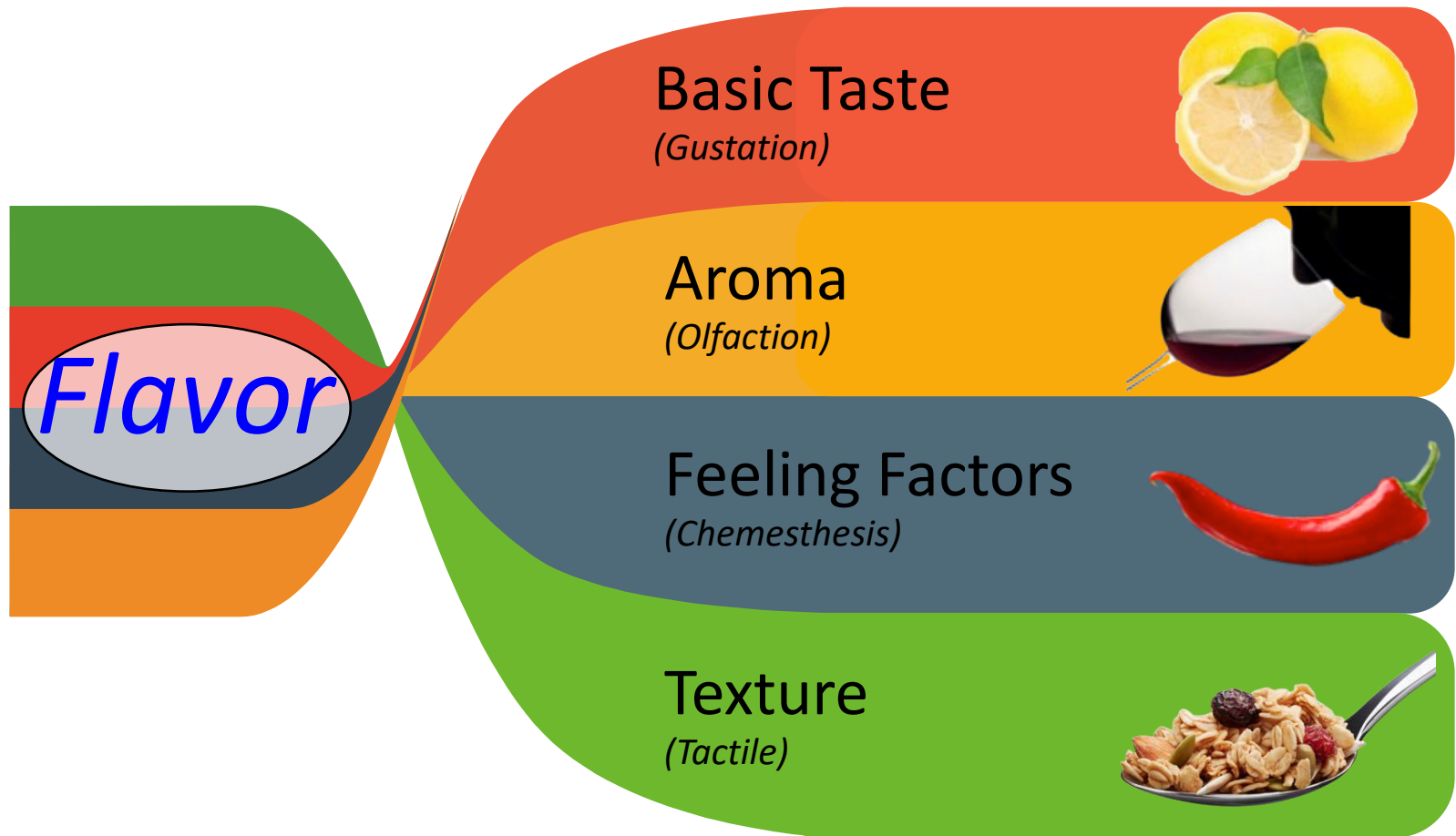
“The overall appreciation of an (often oral) medicinal product in relation to its smell, taste, aftertaste and texture (i.e., feeling in the mouth)”

(EMA)²

¹ FDA, *Guidance for Industry, Quality Attribute Considerations for Chewable Tablets*(CDER, August 2018).

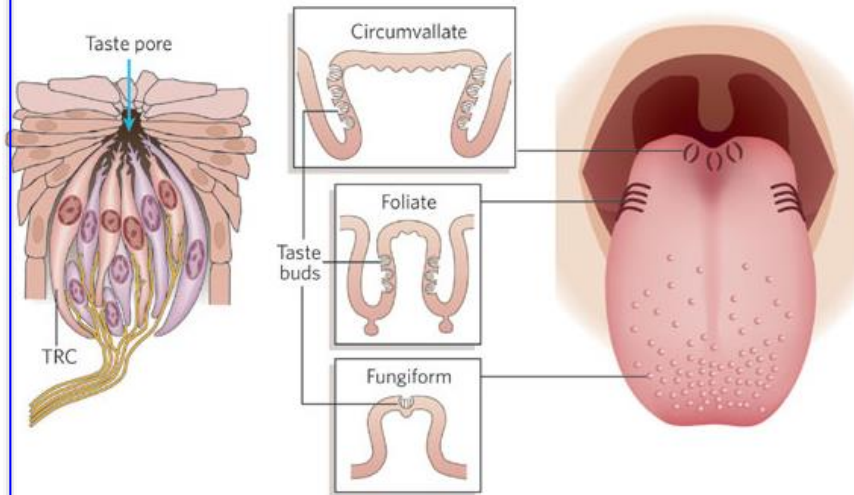
² European Medicines Agency (EMA) *Committee for Medicinal Products for Human Use (CHMP), Paediatric Committee (PDCO), Guideline on Pharmaceutical Development of Medicines for Paediatric Use*. EMA; Amsterdam, The Netherlands: 2013.

Flavor – as defined by sensory science is “*The sum of the perceptions from stimulation of the sense ends at the entrance of the alimentary and respiratory tracts.*”



Taste refers to the perception of 5 chemical sensations, known as “Basic Tastes.”

Taste Buds

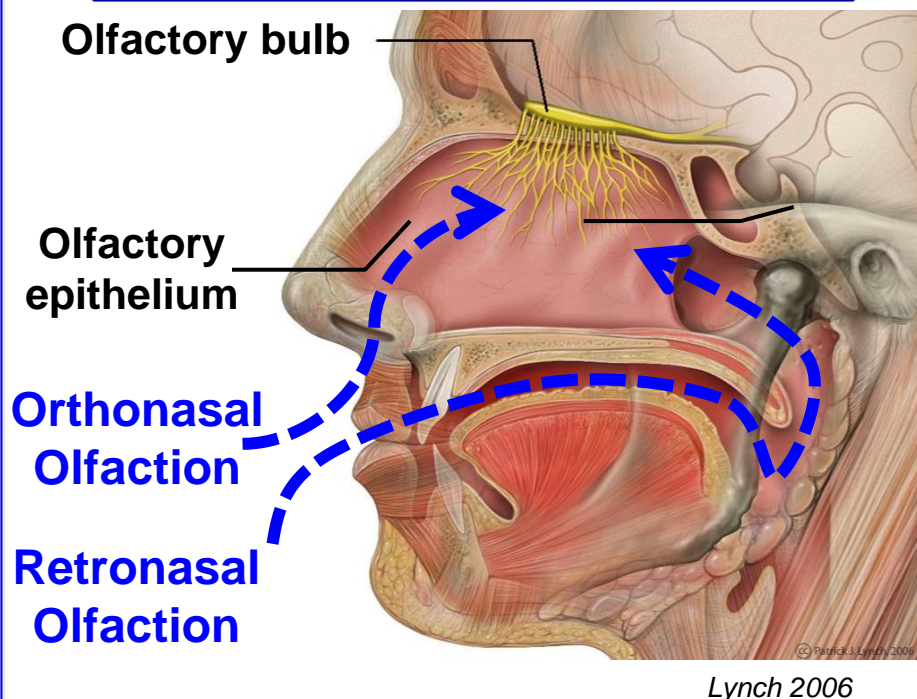


5 Basic Tastes

Basic Taste	Mechanism	Example Stimulus
Sweet	G-Protein Complex	Sucrose
Sour	Ion Channel	Hydronium ions
Salty	Ion Channel	Sodium Chloride
Bitter	G-Protein Complex	Caffeine
Umami	G-Protein Complex	MSG

Aromas are perceived through stimulation of the olfactory neurons by molecules inhaled via orthonasal or retronasal olfaction.

Olfactory Perception

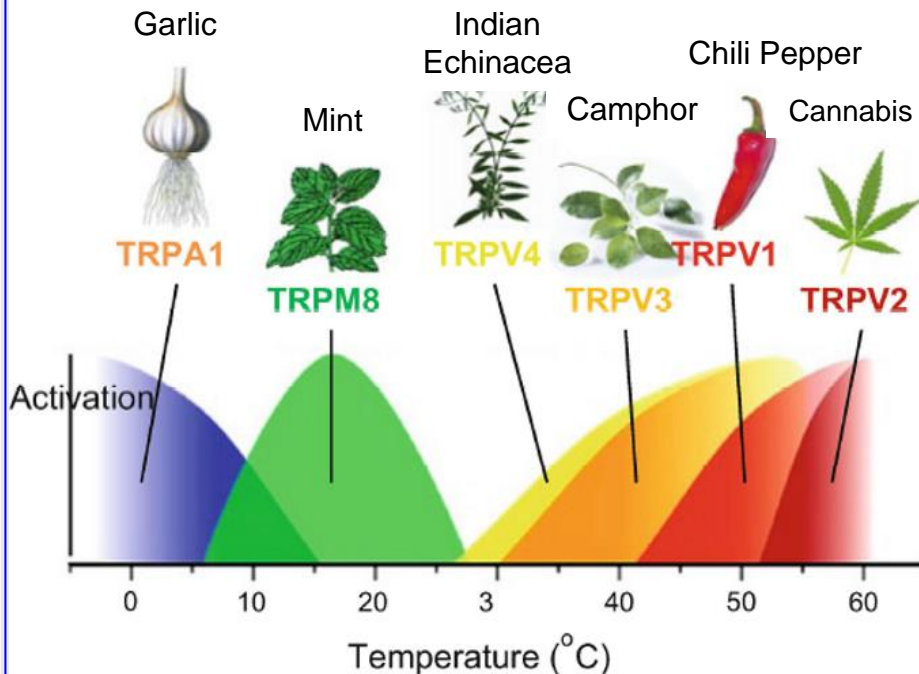


Example Aromatics

Positive Attributes (Yum)	Negative Attributes (Yuck)
Vanilla	Oxidized Oil
Orange	Fecal
Berry	Fishy
Caramelized Sugar	Smokey
Menthol	Thymol (Brown Listerine)

Feeling Factors are sensations that arise when chemical compounds stimulate the free nerve endings of the trigeminal nerve (chemesthesis).

Chemesthetic Perception



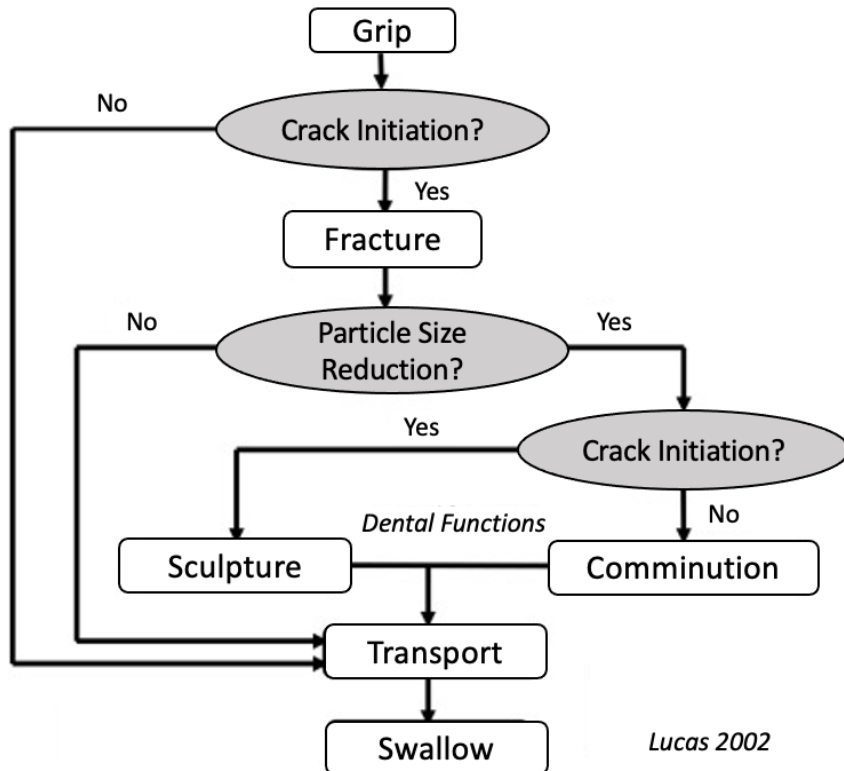
Examples

Feeling Factors (Chemesthesis)	Example Stimuli
Cooling	Menthol
Numbing	Clove / Paramens
Bite/Burn	Black Pepper / Alcohol
Tingling	CO ₂ / Schezuan Peppercorns

*Roper SD. TRPs in taste and chemesthesis. *Handb Exp Pharmacol.* 2014; 223:827-871. doi:10.1007/978-3-319-05161-1_5

Texture is the perception of how a product is deformed upon mastication

Mastication Process

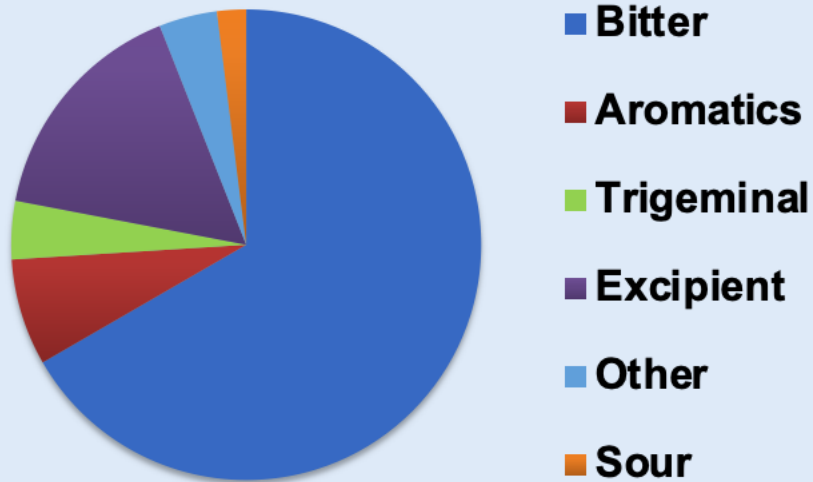


Examples

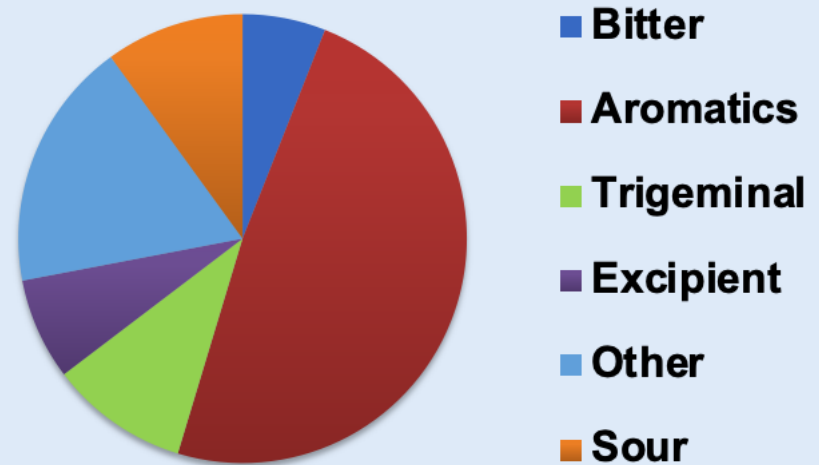
Class	Example Attributes	Example Definition
Mechanical Properties	Hardness, Brittleness	Hardness: <i>The force to attain a given deformation between the molars</i>
Geometrical Properties	Grittiness, Fibrousness, Coarseness	Grittiness: <i>The degree to which a sample contains small grainy particles.</i>
Compositional Properties	Moistness, Oiliness, Adhesiveness	Adhesiveness: <i>The force required to remove a sample from the hard palate.</i>

Aversive Attributes of Active Pharmaceutical Ingredients (APIs), mostly New Chemical Entities compiled from Senopsys studies.

Primary Masking Challenge
(n=150 APIs)



Secondary Masking Challenge
(n=150 APIs)

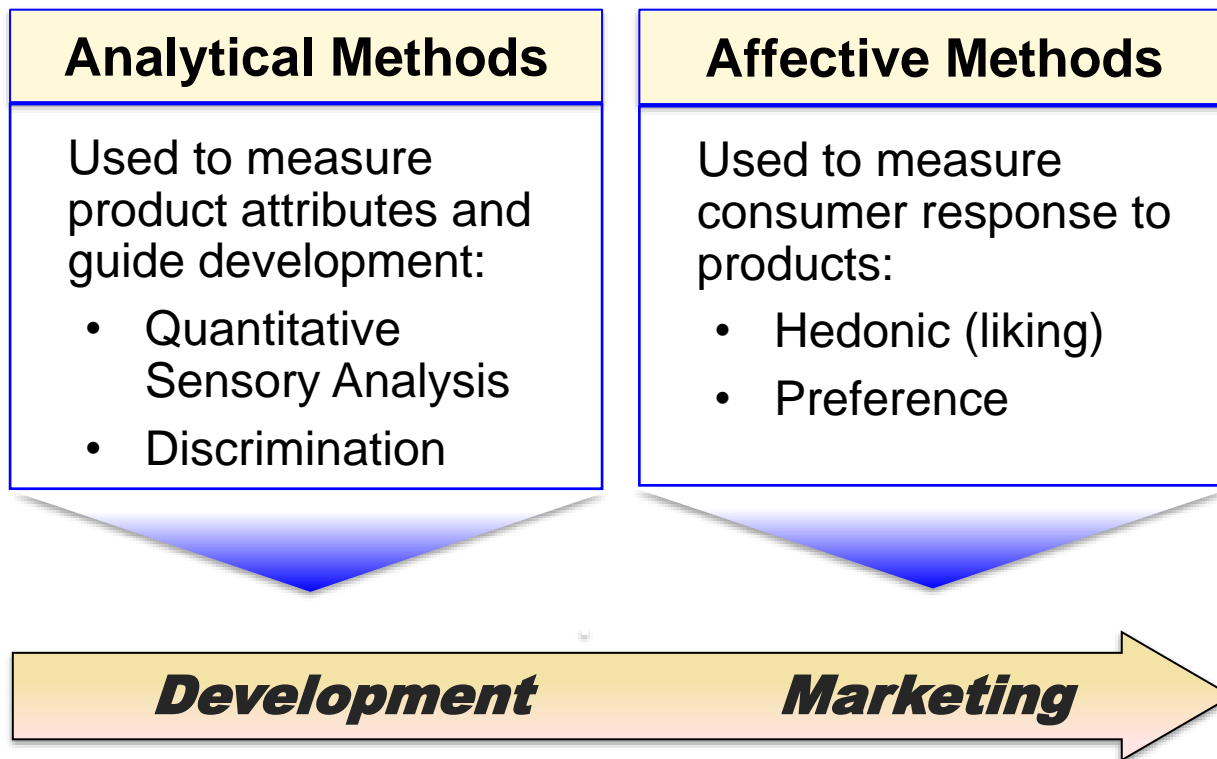


Source: Senopsys

Aversive sensory attributes of common OTC active ingredients.

Indication	Active	Taste	Mouthfeel	Other
Analgesic	Ibuprofen	Bitter	Throat Burn	Characteristic Aroma
	Acetaminophen	Bitter	Tongue Sting	-
Expectorant	Guaifenesin	Bitter	Throat Burn	Phenol Aromatic
Antihistamine	Chlorpheniramine	Bitter	-	-
Antitussive	Dextromethorphan hydrobromide	Bitter, Salt	Numbing	Burnt Plastic Aroma
Nasal Decongestant	Phenylephrine hydrochloride	Bitter	-	-
	Pseudoephedrine	Bitter	-	-

Sensory analysis is used to guide development and selection of palatable drug products.



The field of sensory science is represented across a range of peer reviewed publications, from pure science to highly applied research.



Psychology / Signal Perception Journals

- Journal of Neurophysiology
- Chemical Senses
- Attention, Perception, & Psychophysics

Sensory Science Journals

- Journal of Sensory Studies
- Food Quality and Preference
- Chemosensory Perception

Food Science/Chemistry Journals

- Journal of Food Science
- Journal of Food Quality
- Critical Reviews in Food Science and Nutrition

Commodity-Specific Journals

- Journal of Dairy Science
- Journal of Cereal Science
- Meat Science
- Journal of the Institute of Brewing

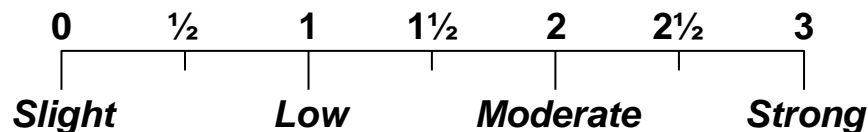
Analytical sensory analysis methods have the widest range of use in development. The Flavor Profile method* uses trained evaluators (panelists) to identify, characterize and quantify the perceived sensory attributes of products.

Elements of the Flavor Profile Method

1. Identify and Describe Attributes:

- Basic tastes – sweet, sour, salty, bitter, umami
- Aromatics – flavoring aromatics and aromatic “off-notes”
- Feeling factors – cooling, numbing, bite/burn, etc.

2. Measure the strength (intensity) of the perceived attributes:

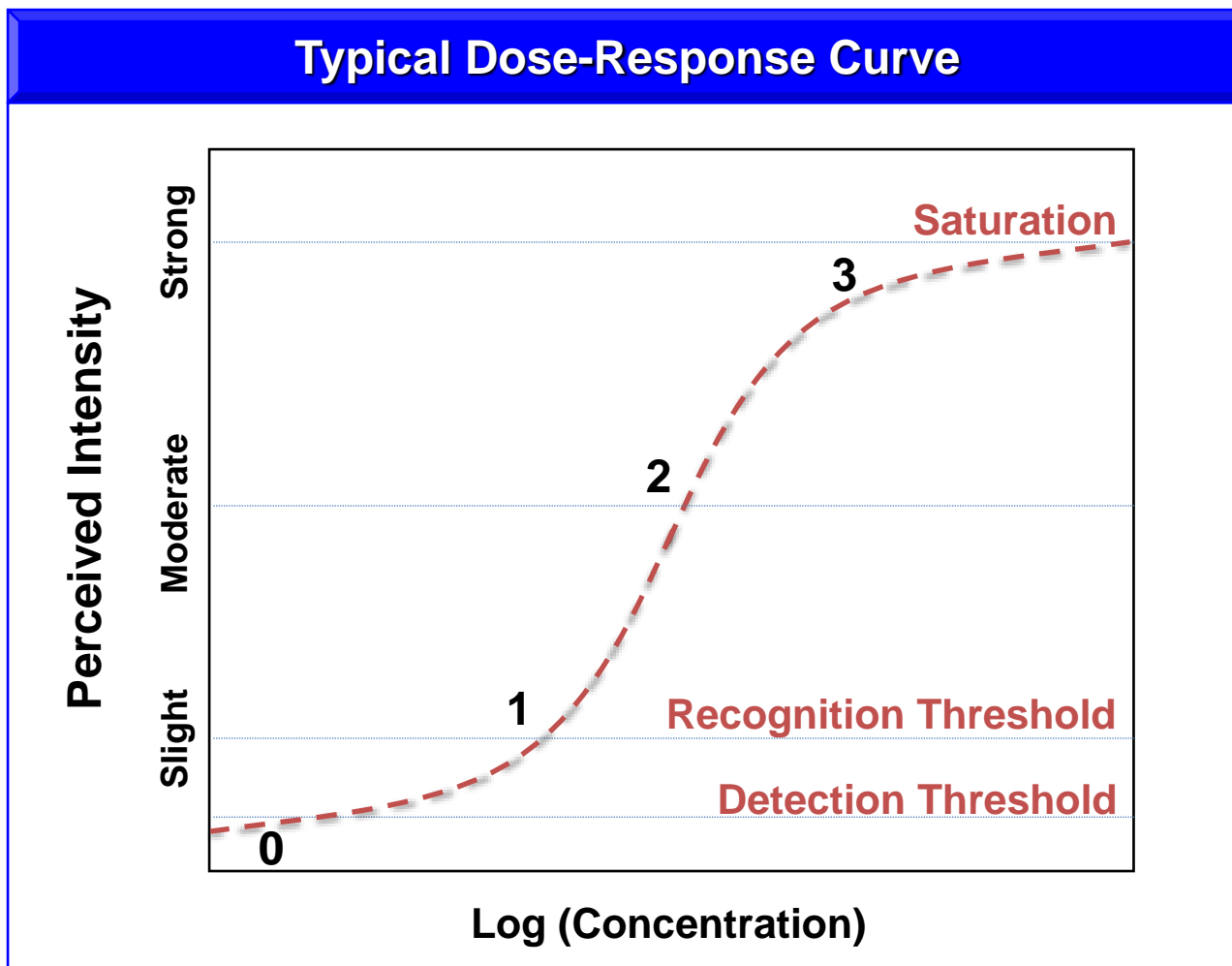


Chemical reference standards are used to establish the intensity scale for on-going panelist calibration.

3. Measure all sensations remaining in the aftertaste at selected intervals.

*Keane, P. *The Flavor Profile Method*. In C. Hootman (Ed.), *Manual on Descriptive Analysis Testing for Sensory Evaluation ASTM Manual Series: MNL 13*. Baltimore, MD. (1992).

Most compounds have a sigmoid dose-response curve. The Flavor Profile scale spans the linear portion of the dose-response function.



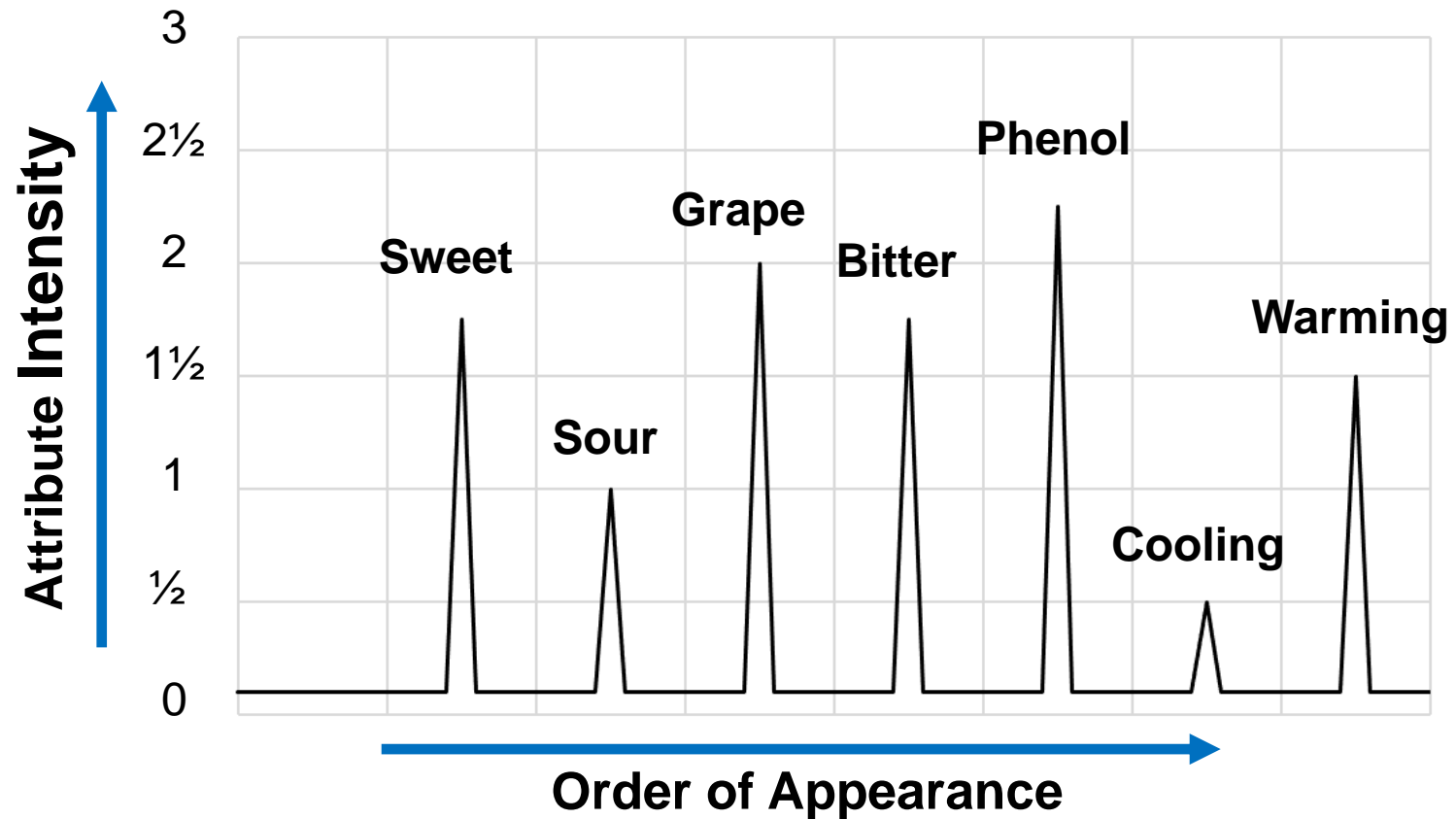
Flavor Profile Evaluation

Children's Dimetapp – Multi Symptom Cold and Flu

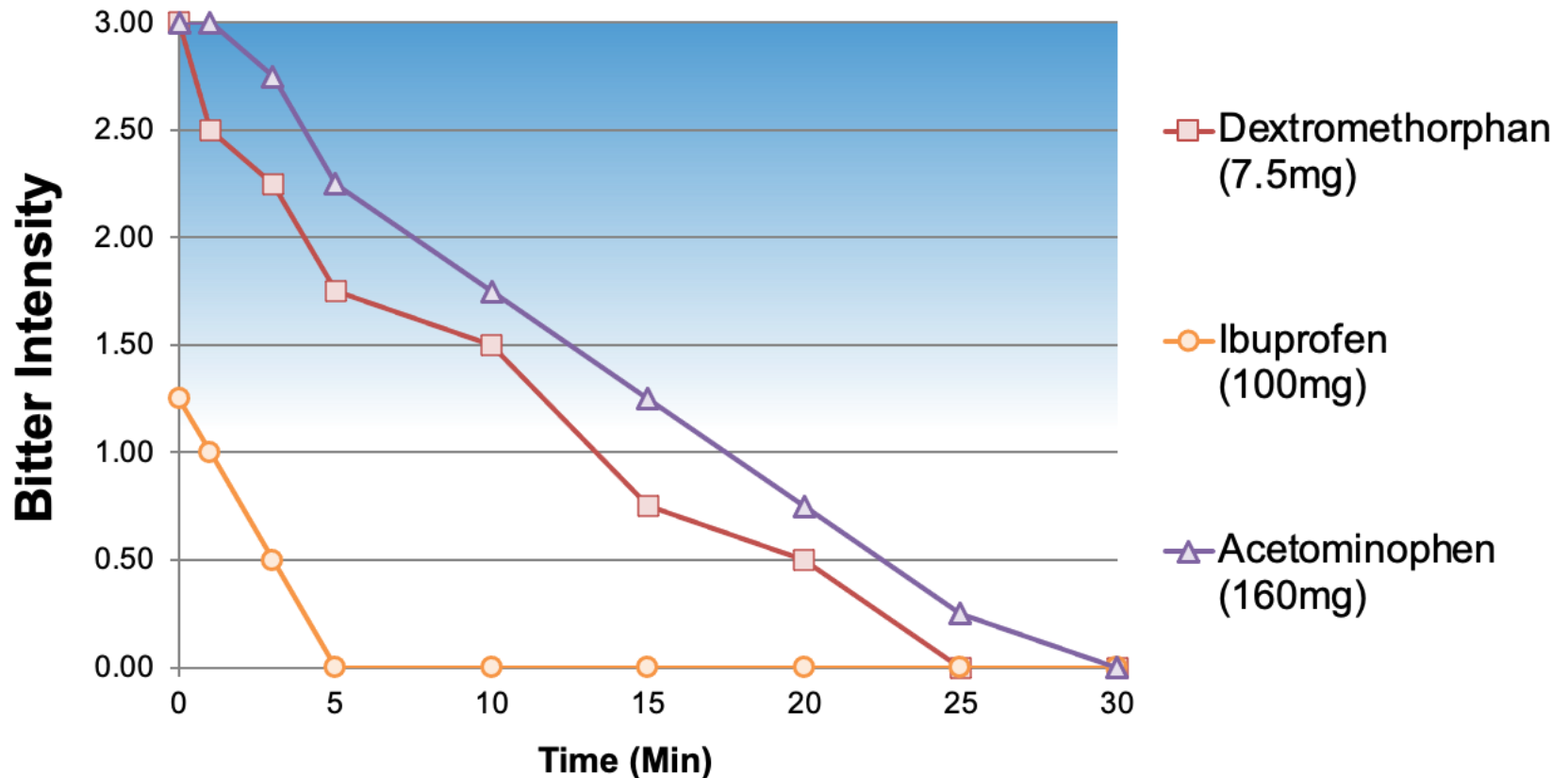
Flavor Profile			
Children's Dimetapp – Multi Symptom Cold and Flu			
Flavor	Intensity		
Sweet	1½ - 2		
Sour	1		
Grape and Black Cherry Aromatic	2		
Bitter	1½ - 2		
Phenol Aromatic	2 - 2½		
Syrupy Mouthfeel	1½		
Cooling	½		
Bite and Burn	1		
Warming	1½		
Aftertaste	1 min	3 min	5 min
Sweet	1-1½	½ - 1	0-½
Grape Aromatic	1-1½	½	0-½
Phenol Aromatic	1½	½-1	½
Bitter	1-1½	½-1	½-1
Bite and Burn	½-1	½	½
Warming	1	½	½



The output of a Flavor Profile is analogous to a chromatogram.



Many OTC actives have a strong and lingering bitterness, amongst other aversive attributes.



With an understanding of the science of perception, the definition of palatable that Senopsys uses is:

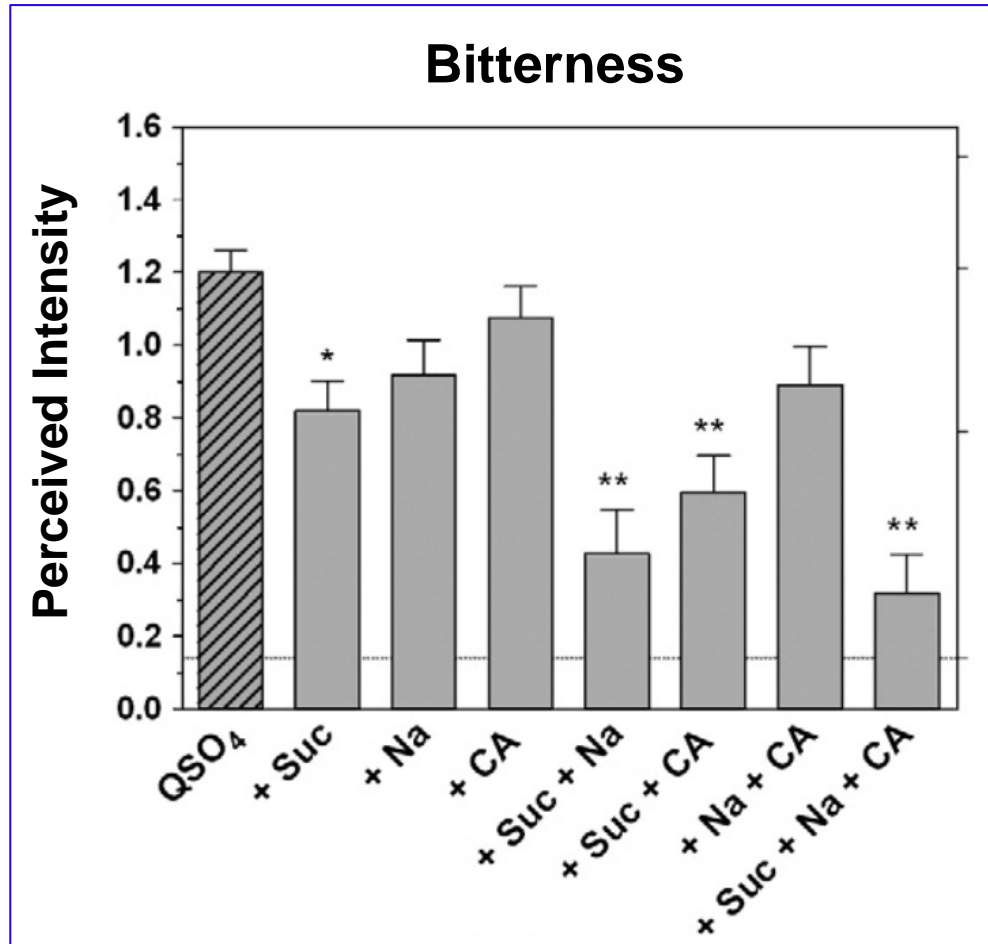
“Palatable drug products have aversive sensory attributes near or below the recognition threshold”

Five "taste masking" approaches are available to formulators

1. Flavor System Addition
2. Physical Encapsulation
3. Alternative API Forms
4. Chemical Complexation
5. Signal Interruption (early research)

* Most commonly employed approaches in OTCs

“Mixture Suppression” (also known as “Taste/Taste Interaction”) is the decreased intensity of a taste stimuli when presented in mixtures.



QSO₄ = Quinine Sulfate

Suc = Sucrose

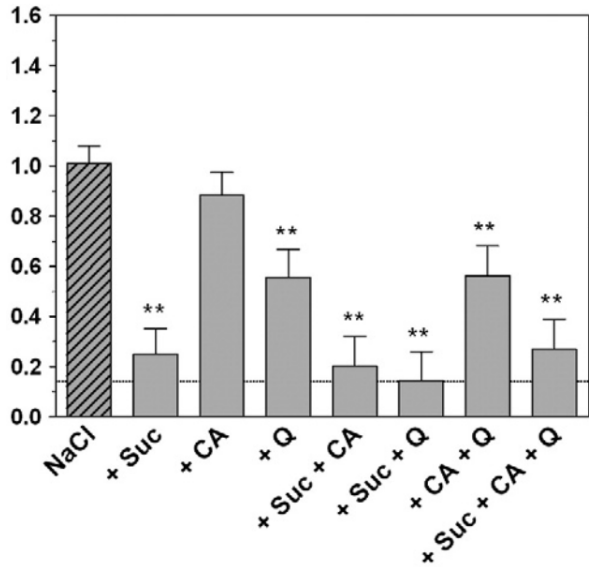
Na = Sodium Chloride

CA = Citric Acid

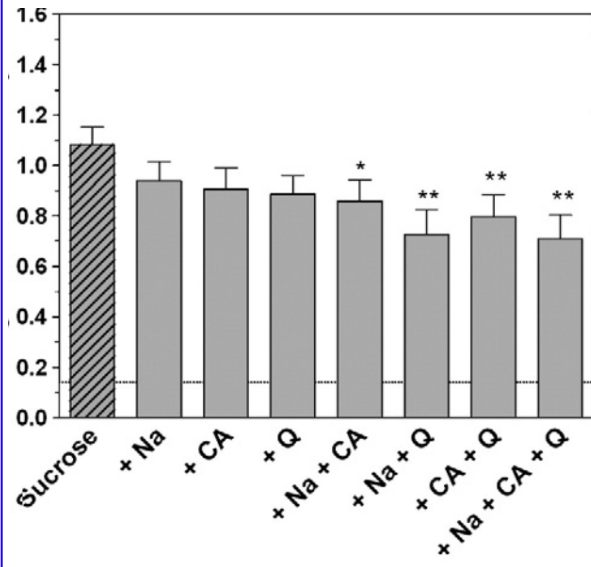
*Green BG, Lim J. Taste Mixture Interactions. *Physiology & Behavior*. 2010

Mixture suppression is consistent across modalities.

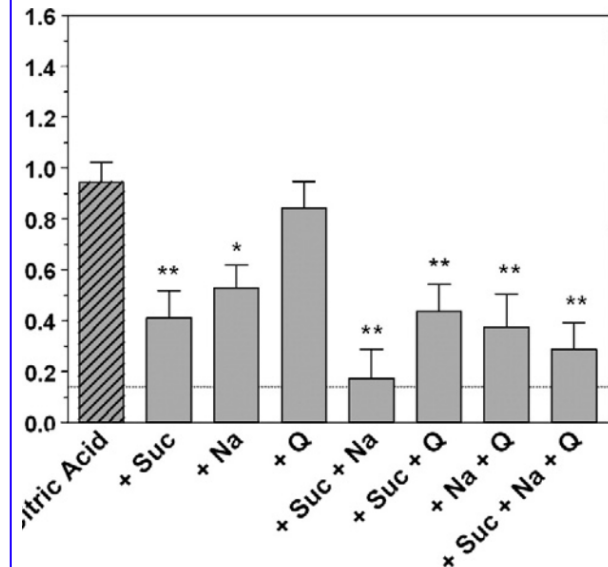
Salty



Sweet



Sour



QSO4 = Quinine Sulfate

Na = Sodium Chloride

Suc = Sucrose

CA = Citric Acid

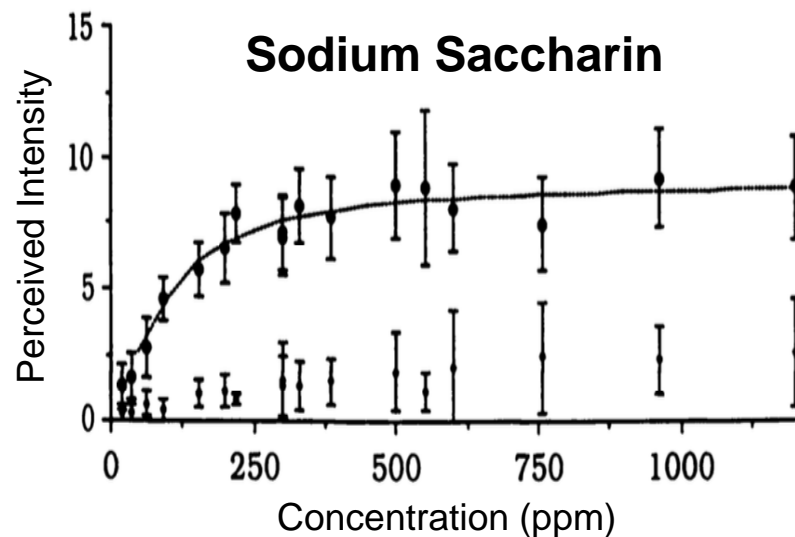
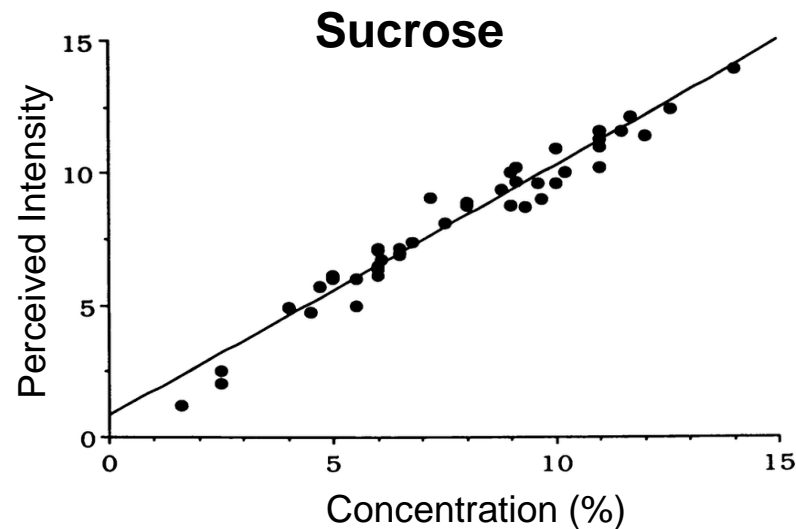
*Green BG, Lim J. Taste Mixture Interactions. *Physiology & Behavior*. 2010

The addition of sucrose to lemon juice to prepare lemonade is an illustration of the concept of taste-taste interaction.



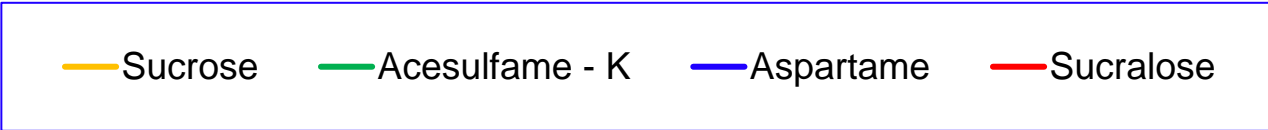
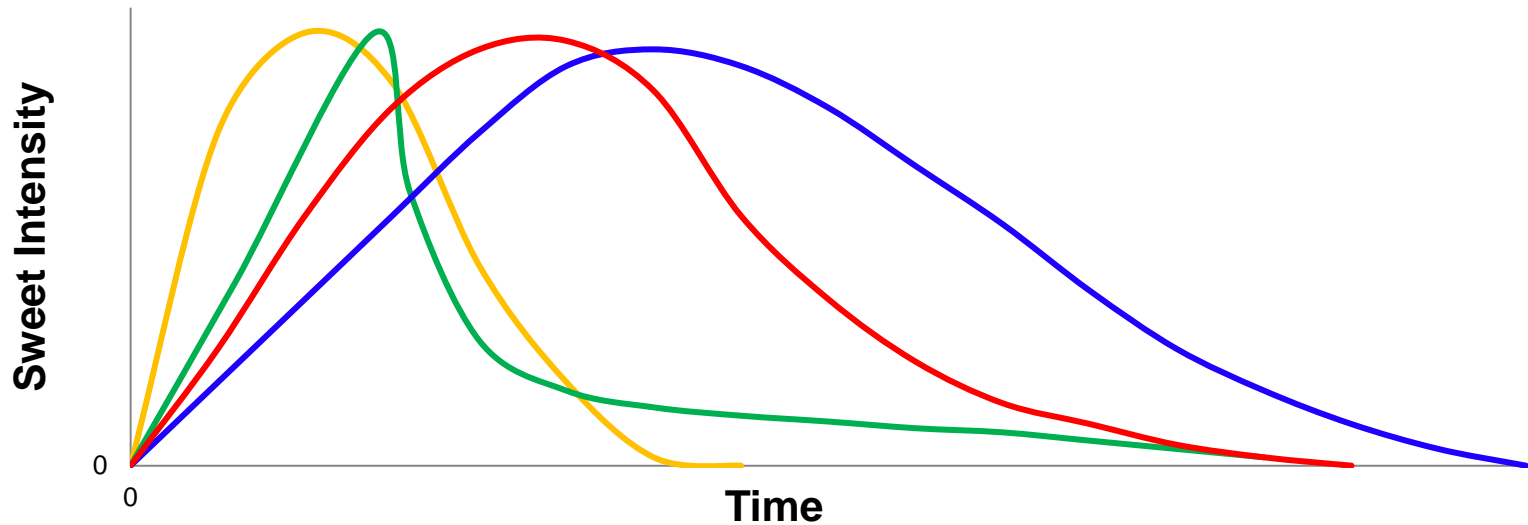
There are numerous sweetener choices; each has a different relative sweetness.

Sweetener	Sweetness Relative to Sucrose
Neotame	8000
Sucralose	600
Sodium Saccharin	300
Stevioside	250
Aspartame	200
Acesulfame Potassium	200
Monoammonium Glycyrrhizinate	100
Fructose	1.3
Sucrose	1
Glucose	0.6
Mannitol	0.4



*DuBois G *Concentration–Response Relationships of Sweeteners*. ACS Symposium Series. 1990

Importantly, the time/intensity profile of the flavor system should match the profile of the target drug.



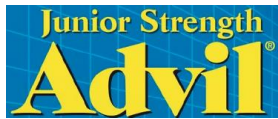
** B. DeFer, Food ingredients — Sweetener Technical Overview and Allowable Daily Intake (Adapted), The NutraSweet Company, Chicago, 2010. 22.*

To illustrate the flavor of “typical” OTC medications, sensory data of marketed products were compiled.

- Data were compiled from pediatric cough, cold, flu and analgesic products, which represent:
 - Categories of OTCs with highest sales
 - Highest poison control medication exposures
- 97 branded pediatric products were included (32 analgesic, 65 cough and cold):
- Drug forms include:
 - Suspensions and Solutions
 - Drops
 - Chewable Tablets



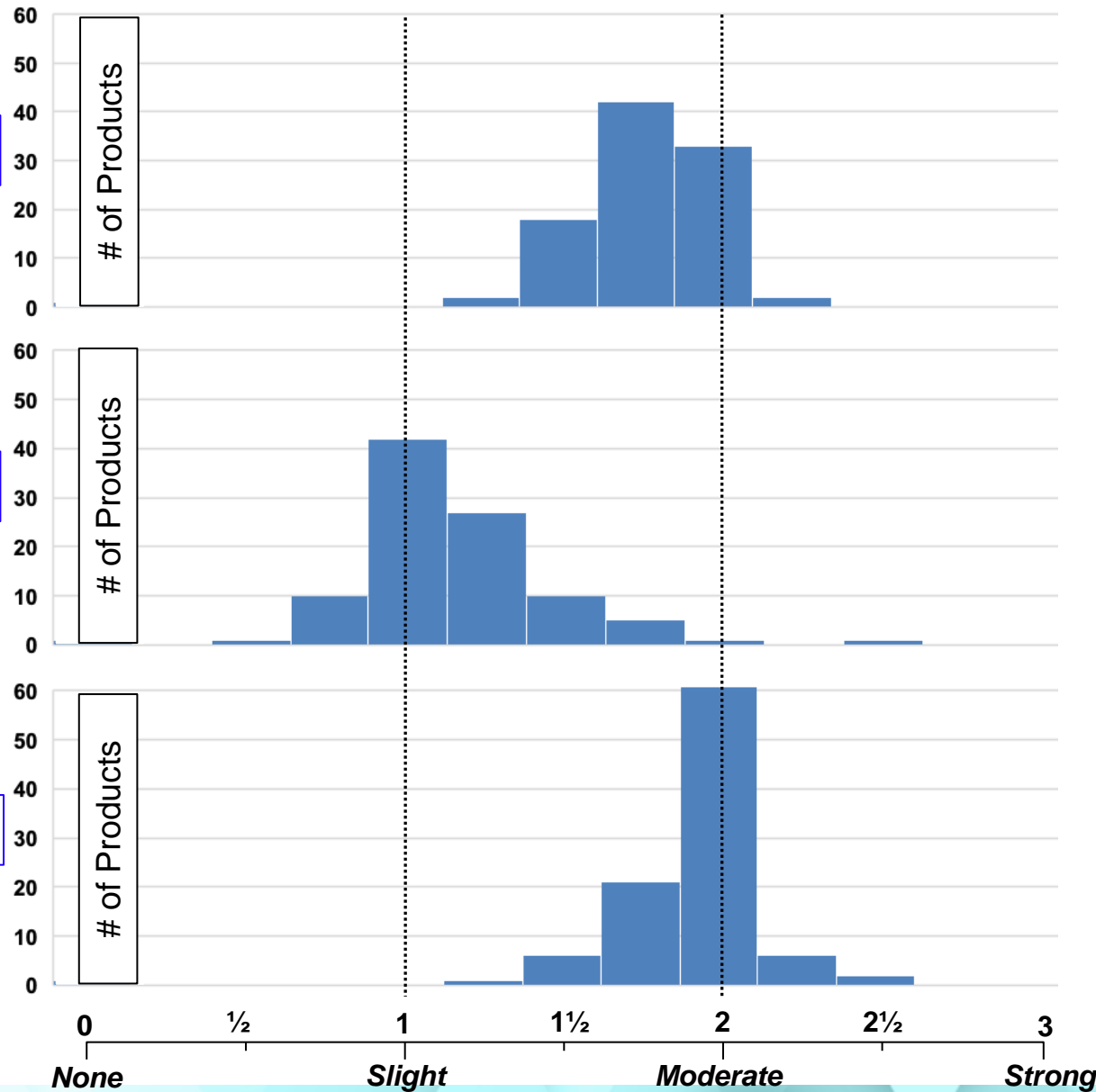
Histograms of selected flavor attributes of pediatric OTCs



Sweet

Bitter

Aromatics



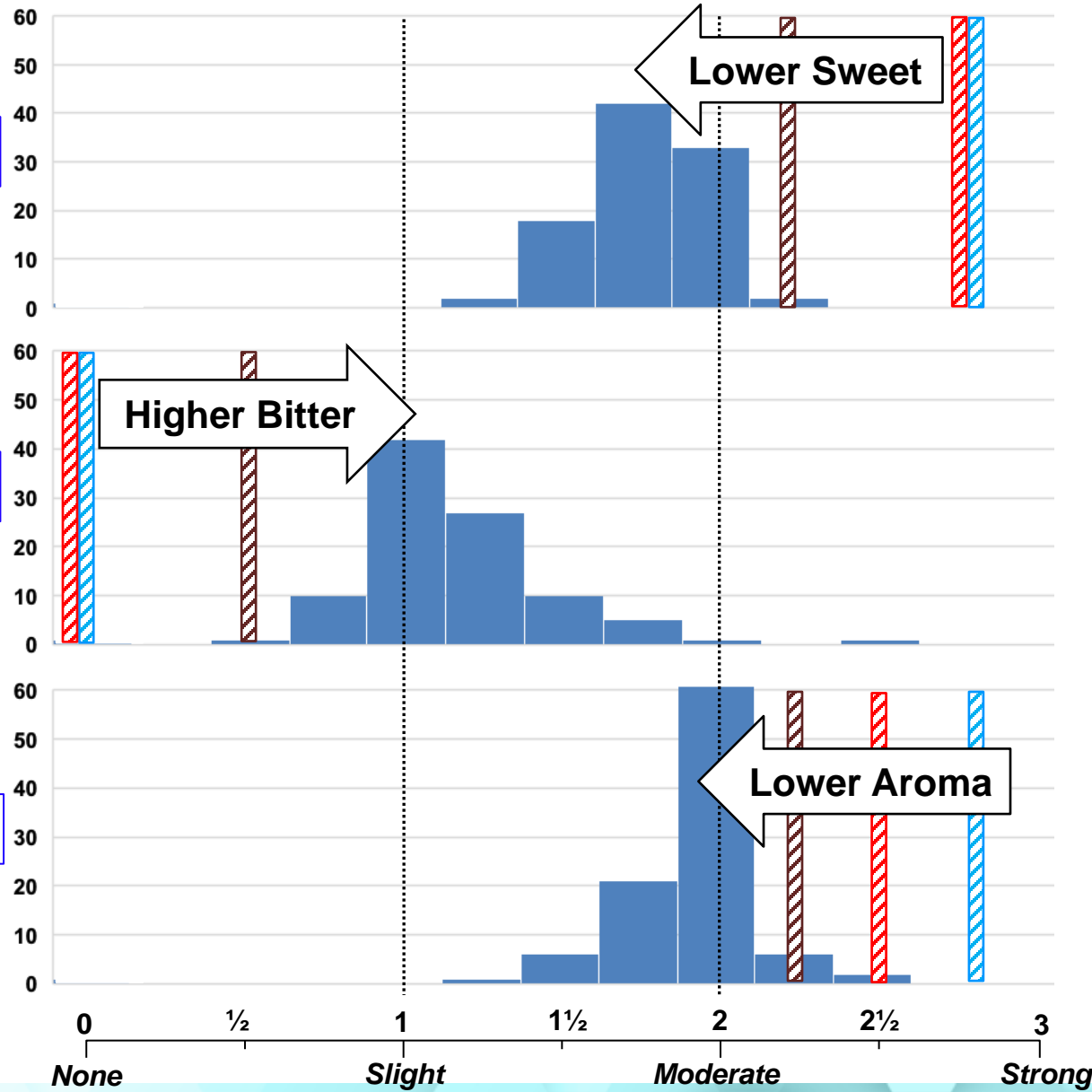
Flavor of pediatric OTCs vs. marketed candy products



Sweet

Bitter

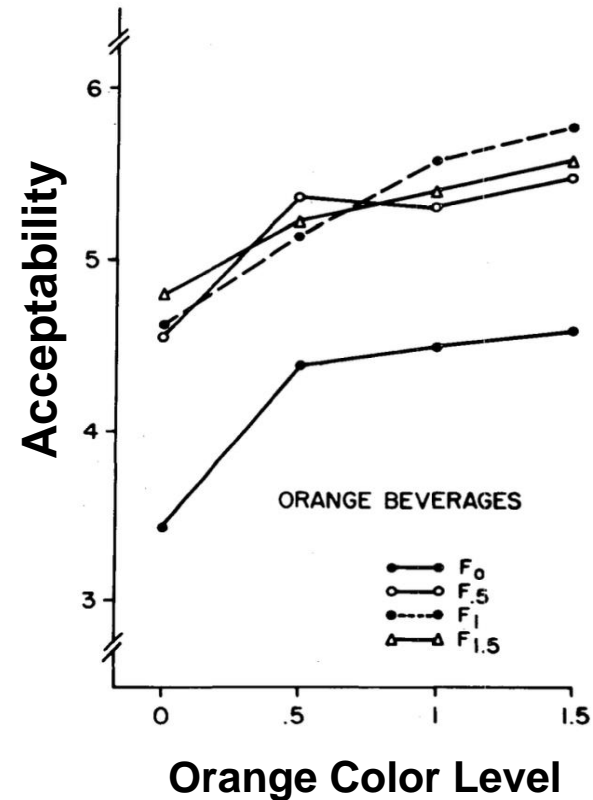
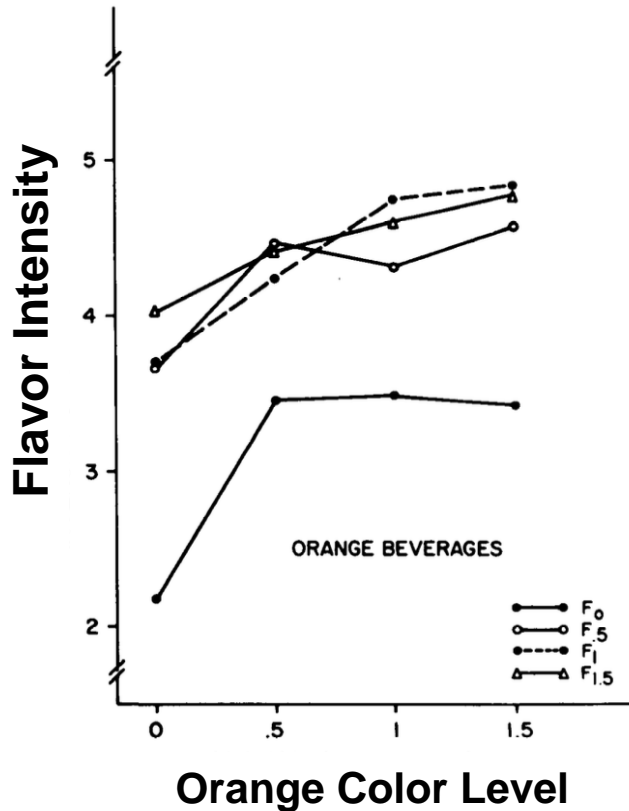
Aromatics



In addition to the taste and aromatic differences, OTC drugs and candy differ in other ways.

- Sour intensity
- Novelty of texture
- Branding
- Packaging
- Color intensity

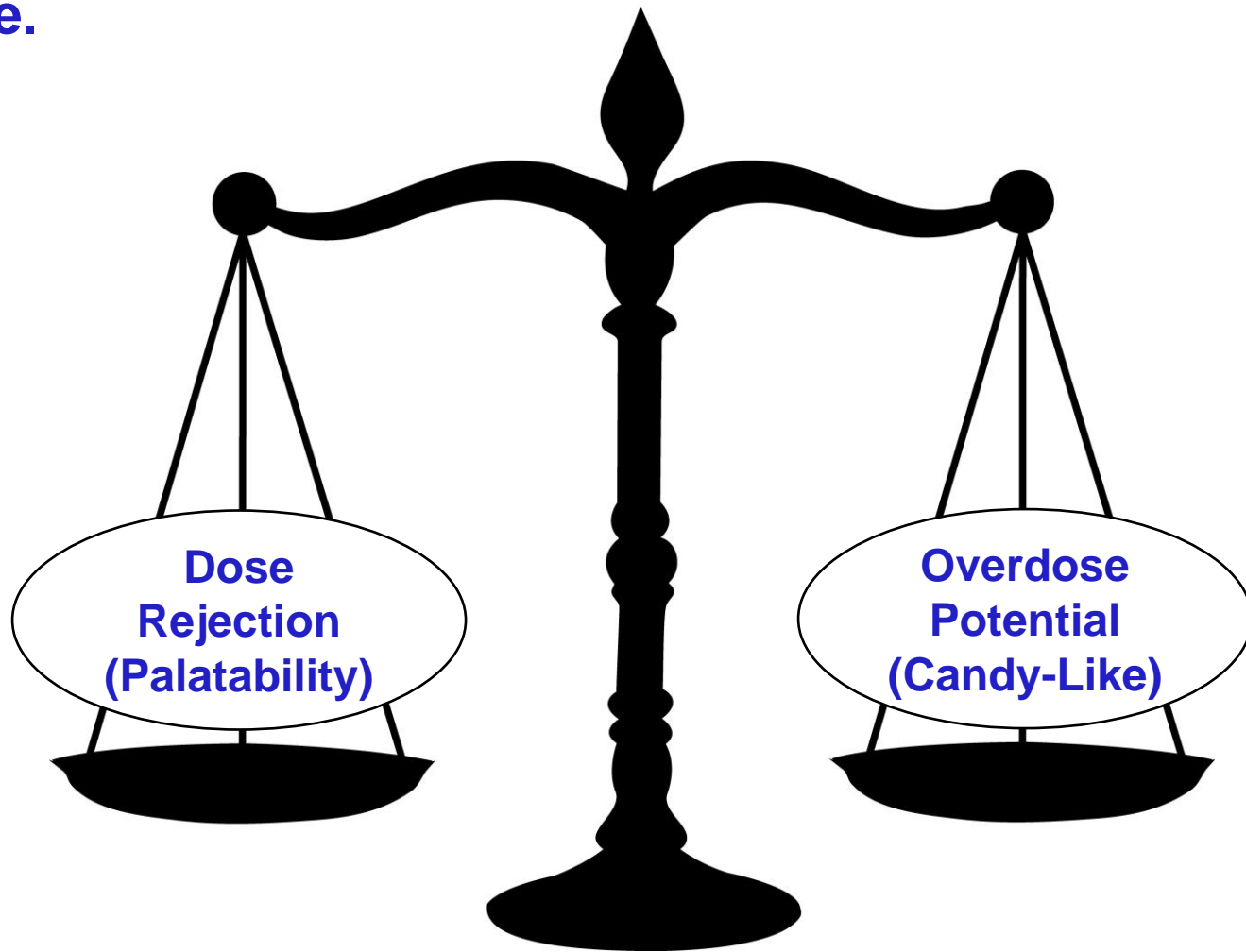
Although colors impart no taste, consumers rate colored products as higher in flavor intensity and overall acceptability.



* DuBose C, Cardello A, 1980

The flavor question is not limited to traditional oral liquids – If presented in another form (gummy, film, chocolate), drug flavor would be controlled by the same underlying API flavor will all require taste masking and have similar profiles.

Have nonprescription drugs been developed for palatability (taste masking) or to promote liking (marketing)? It's a balance.



The dual meaning of Trick or “Treat”





Thank You!

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Senopsys

Taste Masking Specialists