

# Importance of e-liquid preparation and stability characterization for a combinatorial safety assessment approach of flavors in e-liquids

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**2019 CORESTA SMOKE-TECHNO CONFERENCE (SSPT2019)**

**Smoke Science and Product Technology**  
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# Reduced-Risk Products and Harm Reduction



Nicotine  
Delivery

Sensory  
Experience

Ritual

TASTE

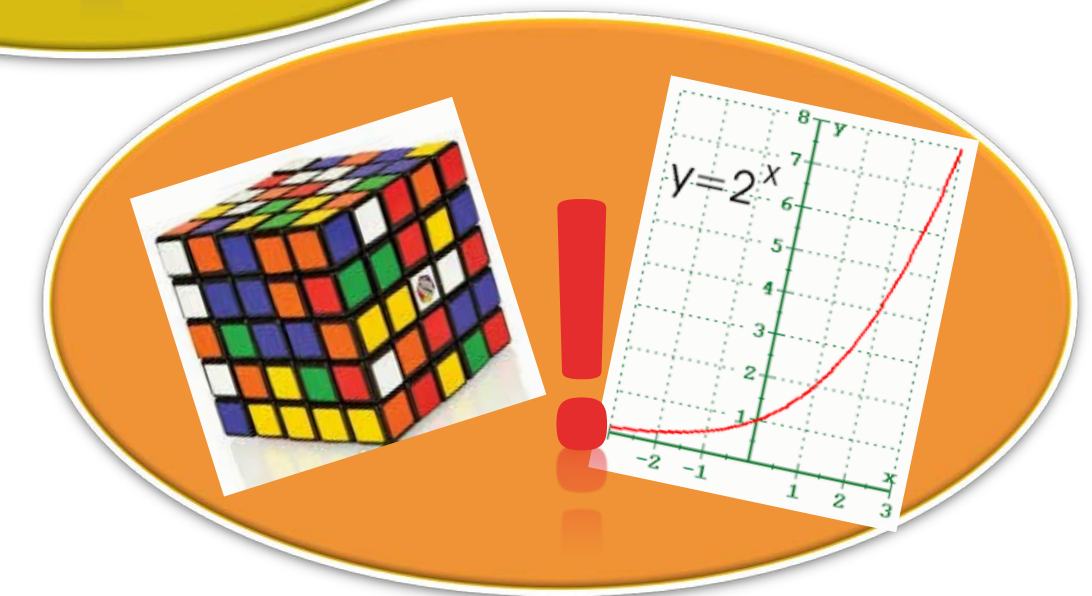
Use of flavoring substances plays an important role in achieving product acceptance by adult smokers, therefore allowing them to switch away from cigarettes.





# Safety of Flavors for Inhalation in Reduced-Risk Products

- **Many flavors** have been extensively assessed and are «Generally Recognized As Safe» (**GRAS**) for use in **food products**
- Only **limited information** available for evaluating potential toxicity by **inhalation**
- Typical flavor mixtures contain 20–30 flavors
- **Classical approaches** for evaluating safety require a **series of *in vitro* and *in vivo* studies** on individual flavors and definition of safe-use levels



Objective:

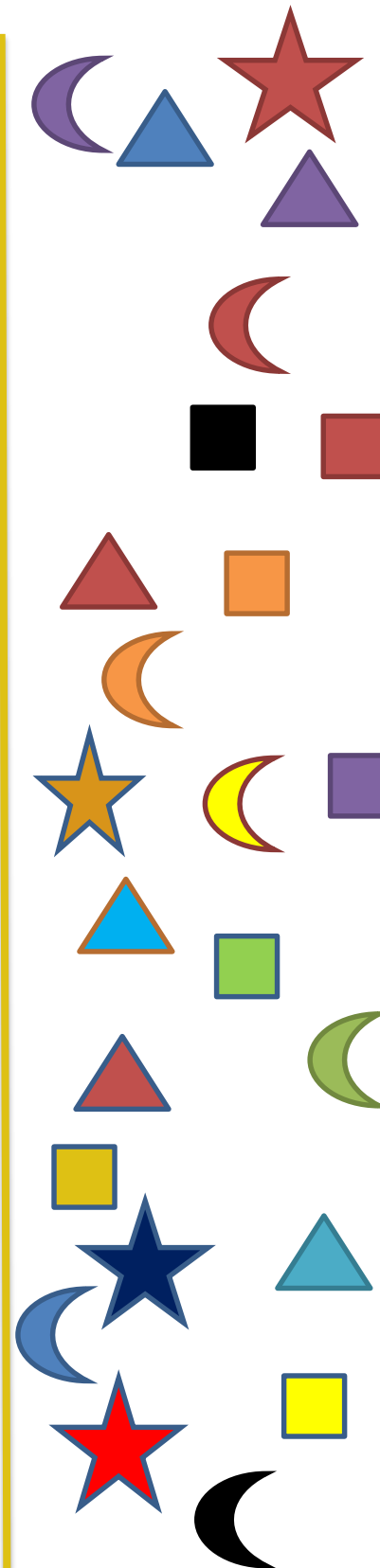
Generate a “Toolbox of Flavors” that can be used in RRP, with the indication of safety levels for each flavor

➔ **Combinatorial Flavor-Group-Based Approach**



# Combinatorial Flavor-Group-Based Approach

## Pool of Relevant Flavor Compounds



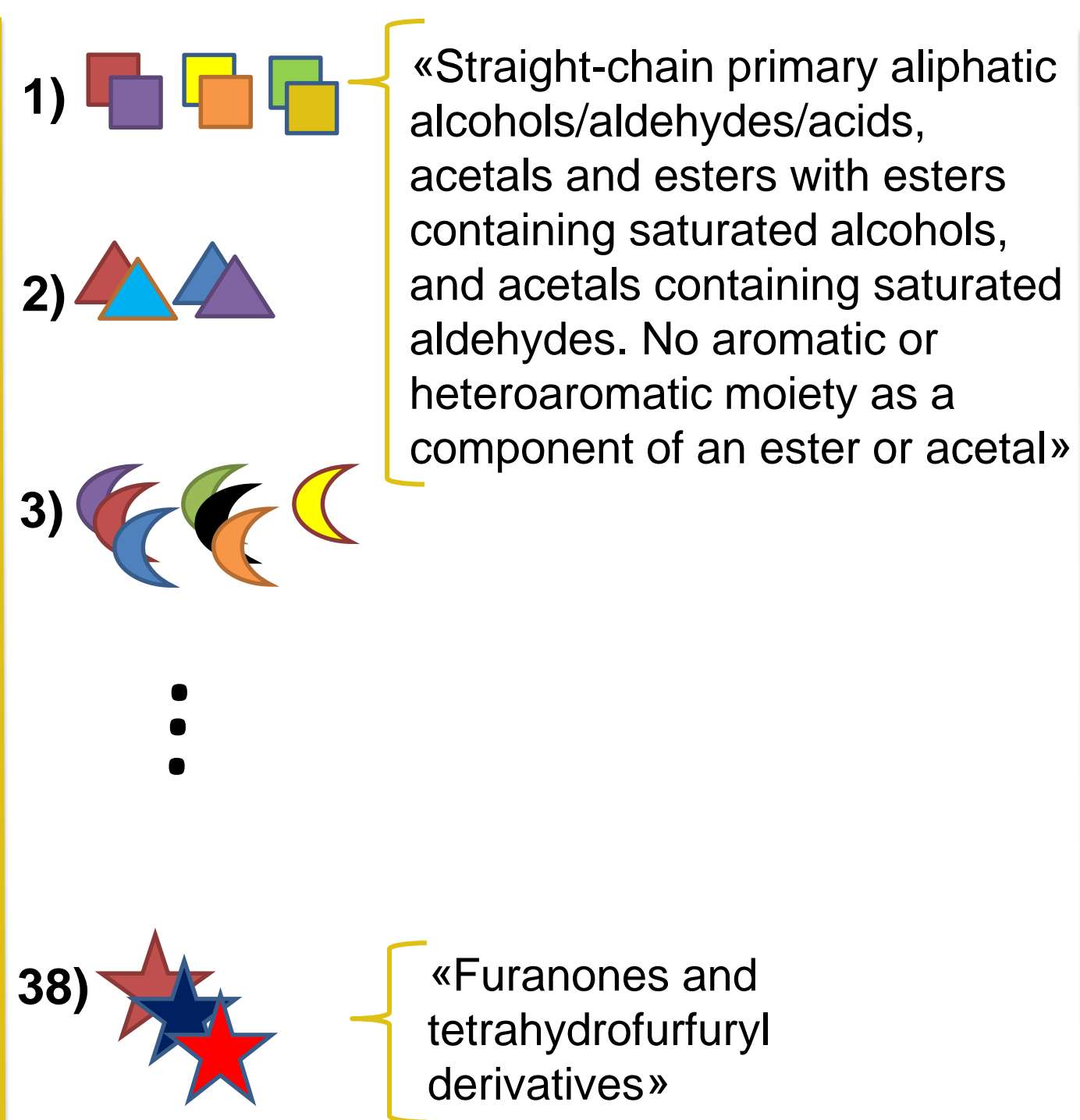
246 Substances

Clustering

According to:

- (EC) No 1565/2000
- Structural similarities

## Groups of Relevant Flavor Compounds



38 Groups

Rank based on potential for inducing toxicity

According to:

- Information from database (ECHA, Toxplanet)
- *In vitro* data
- Cramer classes
- Toxicological prediction (e.g., with TOPKAT)





## Flavor Group Representative (FGR)

- 1) Acetal
- 2) Linalool
- 3) Ethyl Lactate
- ...
- 38) Furaneol

38 Flavors

# From Selection of FGRs to Aerosolization

## Flavor Group Representative (FGR)

- 1)  Acetal
- 2)  Linalool
- 3)  Ethyl Lactate
- ...
- 38)  Furaneol

38 Flavors

Concentration definition

## Definition of FGR Concentrations

Required FGR concentrations in the final solution (µg/mL)			
Compound	Conc. Low	Conc. Medium	Conc. High
1)			
2)			
...			
38)			

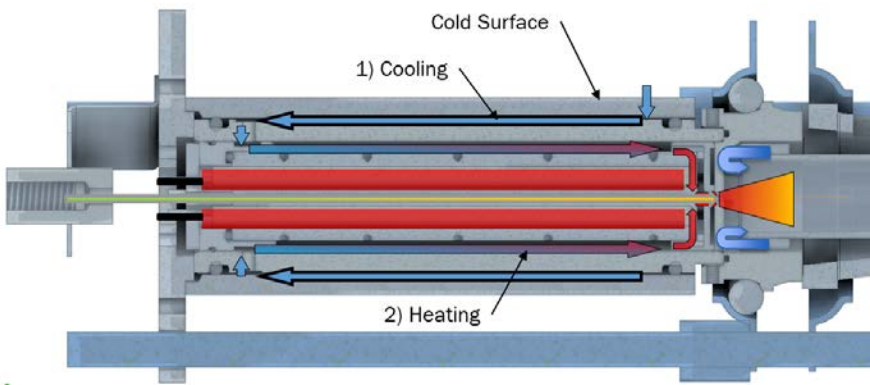
FGRs dissolved in PG/VG/water/EtOH (nicotine)  
→ Test Formulation

Solution containing 38 flavors in defined amounts

Aerosolization

## Aerosolization

Capillary Aerosol Generator (CAG) generates aerosol for *pre-clinical* tests

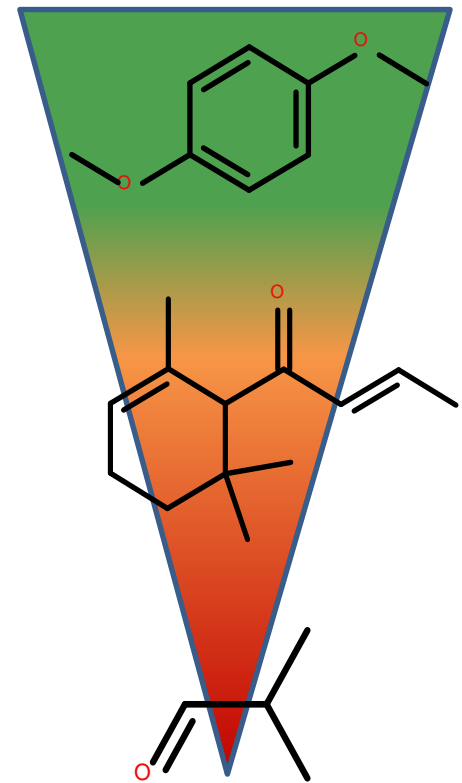


1/3 compounds transferred between 85–100%

1/2 compounds transferred between 55–85%

1/6 compounds not trapped on cartridge, but transferred to aerosol

High transfer rate / trapping efficiency



Lower transfer rate / trapping efficiency



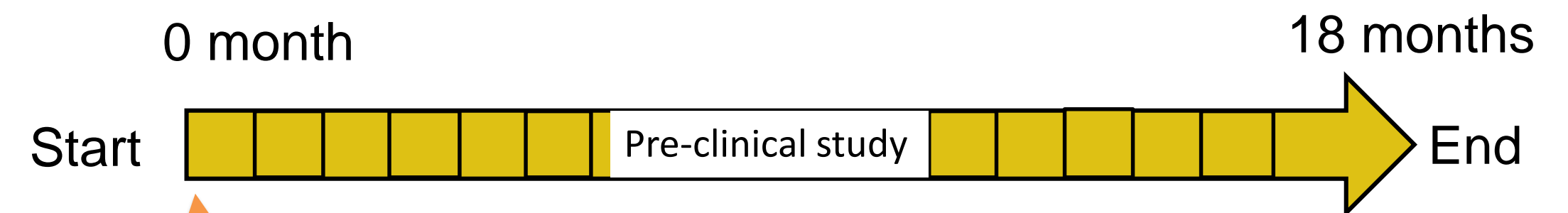
## Practical Feasibility Aspects

### Parameters to focus on

- Commercial availability of standards
- Huge range of concentrations
- Solubility at high concentrations
- Overall workload regarding long duration of preclinical tests
- Test item verification
- Chemical stability of solutions

Intra-molecular reactions  
Degradation  
pH effects  
Temperature effects

Preliminary assessment of test formulation containing 38 flavor compounds revealed poor stability

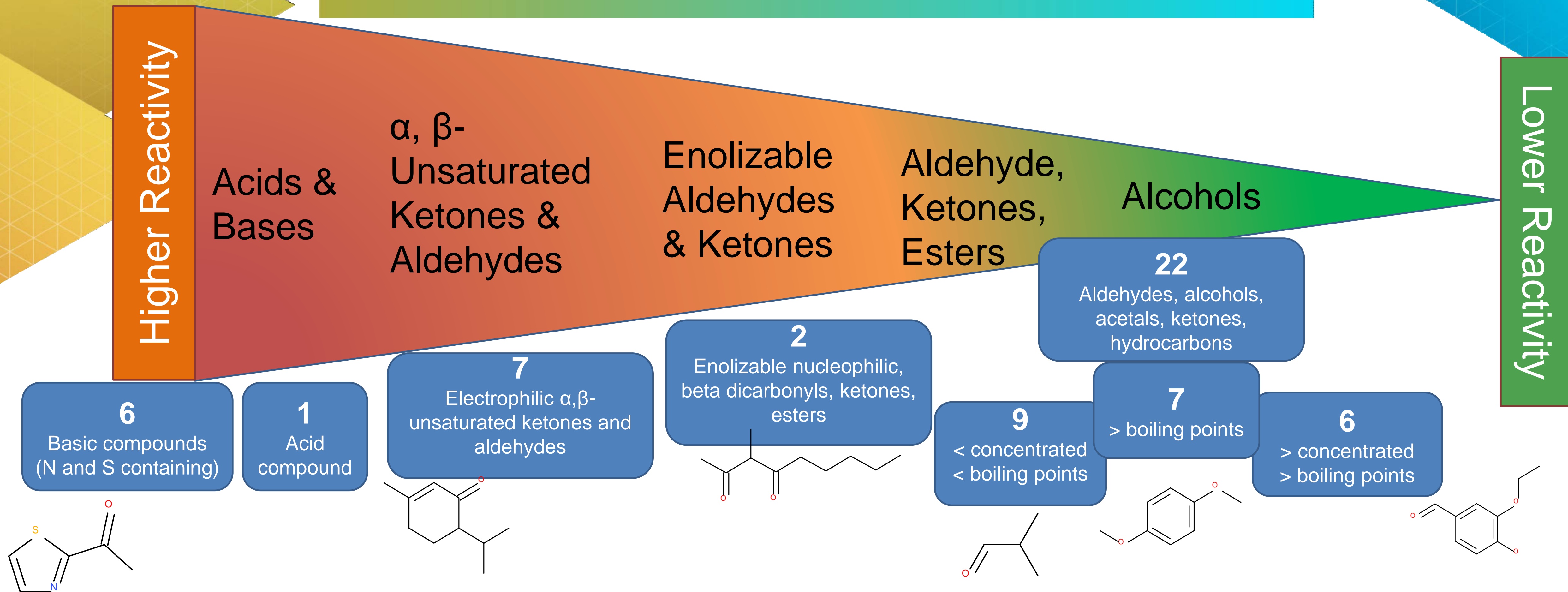


Stability of full mix containing 38 flavor compounds



«Endless» repetition of FGR mix preparation

## Grouping into Stable Pre-Blends



- ➔ Grouping of compounds in a minimum number of categories shortens and simplifies the preparation time of pre-blends
- ➔ Workload for preparing test formulation (38 FGR) from pre-blends is significantly lower than that for full preparation
- ➔ Stability period of pre-blends is expected to be longer than that of the full 38 FGR mix
- ➔ Test item verification simplified

Stability Investigation – Study Design

Relevant Parameters

Acceptance

Concentration

pH

Temperature

Time

Criteria

Concentration  
of flavors in  
test  
formulation  
(all 38 flavors)  
and in pre-  
blends

Absence/  
presence of  
nicotine

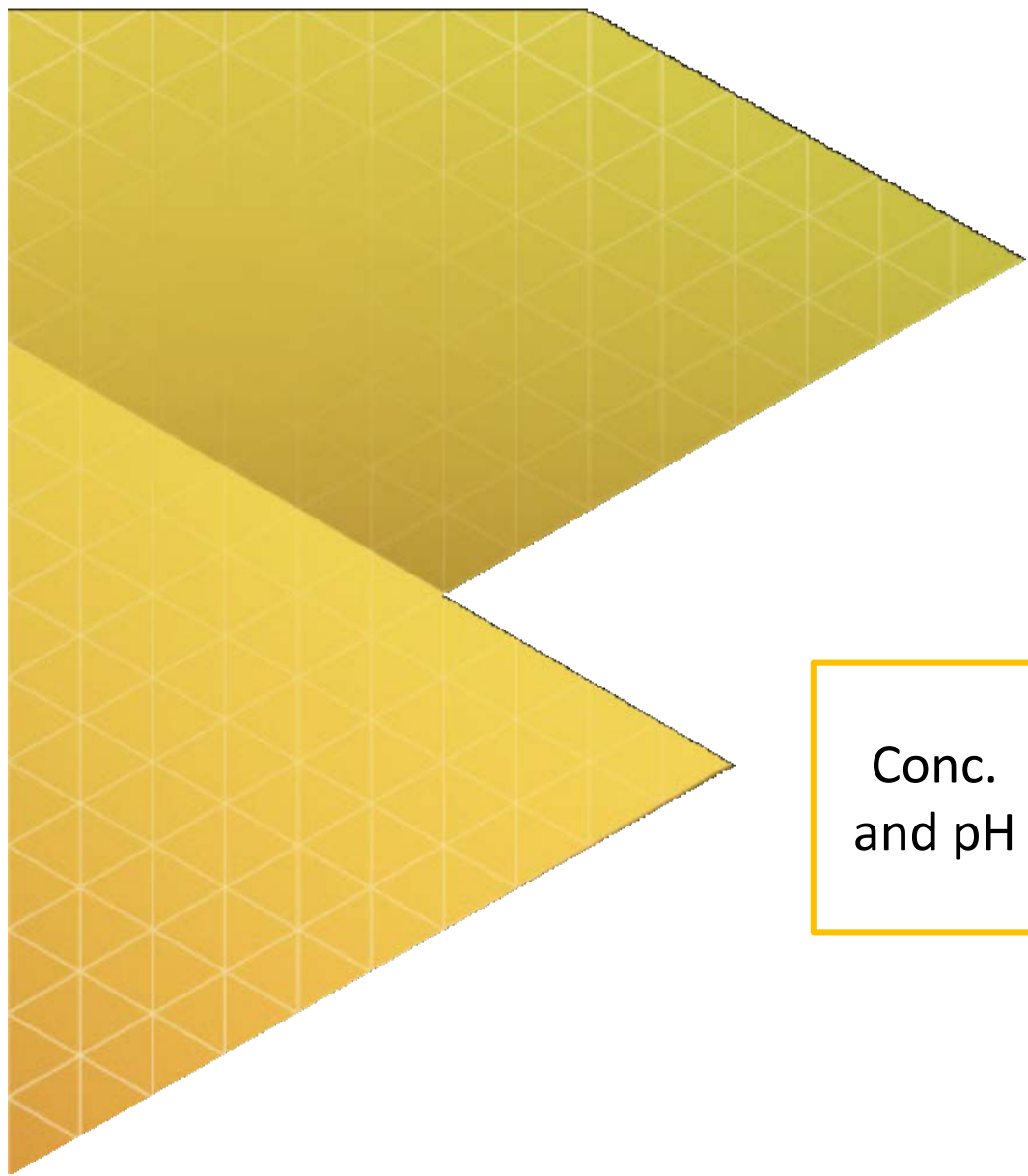
- Freezer
- Fridge
- RT

Hours  
Days  
Months

1 month for pre-blends  
(fridge and RT)  
 $\pm 15\%$  of initial value

10 days for test formulation  
(fridge and RT)  
 $\pm 20\%$  of the initial value





# Stability Investigation – Results

Sample	Storage condition	Aim	Acceptance criteria fulfilled
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Conc.  
and pH



## Wrap-Up

### Combinatorial Flavor-Group- Based Approach

- Allowed selection of a representative mixture that covers >200 flavors for pre-clinical testing
- Time saving: No need to generate data for each individual flavor
- Reduces the need for animal testing

- Overall mixture toxicity could be driven by most toxic compound  
→ overestimation of toxicity
- Solubility

### Use of Pre-Blends

- Can simplify timely preparation and characterization necessary for preclinical testing
- Pre-blends can be stable for months under refrigerated conditions

- pH can significantly influence stability characteristics

### Aerosolization

- Capillary aerosol generator (CAG) is suitable for long-term studies requiring constant aerosol delivery
- Flavor transfer from liquid formulation into the aerosol was confirmed

- Impact of flavor's boiling point on transfer rate



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# Flavor Transfer Rate and Test Item Verification

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How much

