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Pilot Experiment: The Effect of Added Flavorants on the Taste and Pleasantness of Mixtures of Glycerol and Propylene Glycol

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Abstract

Introduction—The US Food and Drug Administration banned most "sweet" flavorants for use in cigarettes due to the concern that sweet flavors appeal to young, beginning smokers. However, many of the same flavors, including fruity and confection-associated aromas (e.g. vanilla) are still used in e-cigarettes. Sweet flavors may have a number of effects, including enhancement of the taste of other ingredients. The current work focused on the impact of model flavorants on the taste of a mixture of propylene glycol and vegetable glycerine, solvents used in most e-cigarettes and related products.

Methods—A device delivered mixtures of propylene glycol and vegetable glycerine into the mouth in parallel with puffs of clean air (control) or odorized air. Aromas included two "fruity" esters ("pineapple" and "banana"), two confection-associated aromas ("vanilla" and "caramel/malty"), menthol (not a "sweet" aroma, but commonly used in e-cigarettes), and a "burnt" aroma not expected enhance flavor. Twenty young adults, aged 18–25, rated the sweetness, bitterness, and pleasantness of all stimuli (within-subjects design).

Compliance with Ethical Standards

Conflict of interest: [Outlined in separate page to comply with double-blind review]

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments. All procedures were approved by an Institutional Review Board (IRB) at the University of [not included here to comply with double-blind peer review].

Informed consent: Written, informed consent was obtained from all individual participants in the study, using IRB approved forms, before any study procedures were performed.

Conflict of Interest [included here in full to comply with double-blind peer review]: PMW currently receives research funding from major food, beverage, and food ingredients companies. None of these companies provided funding for or were in any way involved in the current research. AAS has active research grants from the US National Institutes of Health (NIH) and US Food and Drug Administration (FDA), and has previously been funded by NIH and FDA, as well as a peer-reviewed GRAND grant sponsored by Pfizer (2008–2011). HN has recently been hired as a full-time employee by Kerry, a flavor and nutrition company. PDR declares that she has no potential conflicts of interest.

Results—Both fruity aromas significantly enhanced sweetness, both confection-associated aromas significantly enhanced pleasantness, and the caramel/malty aroma significantly reduced bitterness. Menthol and the "burnt" aroma had no measurable effects on the taste of solvent mixtures.

Conclusion—Some flavorants modulated the taste of solvents commonly used in e-cigarettes in ways consistent with an enhanced sensory profile.

Implications—If similar effects occur in actual products, improved flavor profiles could facilitate continued use, particularly in non-smokers experimenting with e-cigarettes and related products.

Keywords

Flavor; E-cigarettes; vaping; abuse-potential

Introduction

Electronic cigarettes (e-cigs) and related devices deliver aerosolized nicotine solution for inhalation. Use of e-cigs, often called "vaping," is growing rapidly (Giovenco et al. 2015). Cigarette smokers might perceive e-cigs as lower harm alternatives or cessation aids (Mcneill et al. 2015; Kong et al. 2015). However, e-cigs might also appeal to non-smokers, potentially increasing the risk of nicotine dependence or eventual use of other tobacco products (Krishnan-Sarin et al. 2014). In this regard, the fact that an increasing number of youth are using e-cigs is of concern (Ambrose et al. 2015). Accordingly, it is important to understand the factors that contribute to the appeal of e-cigs, especially for young non-smokers.

Added flavors may be one important factor (Ambrose et al. 2015; Pepper et al., 2016). Sweet-flavored tobacco products have been disproportionately used by young and beginning smokers (Connolly 2004; O'Connor et al. 2007; Klein et al. 2008; Minaker et al. 2014). This trend motivated the US Food and Drug Administration to restrict the flavorants added to cigarettes (Oliver et al. 2013), but "sweet" smelling flavorants are still added to e-cigs (Pepper et al., 2013; Wang et al., 2015; Youth 2015; Berg 2016). In 2013, fruit (e.g., berry, cherry) and other (e.g. vanilla and coffee) flavored products accounted 2.6 and 3.4 percent of the market, respectively. However, these market shares had increased by 44 and 325%, respectively, relative to 2012 (Giovenco et al. 2015).

Youth-friendly brands such as "Cherry Crush," together with vivid, colorful packaging, might increase marketing appeal (Youth 2015; Carpenter et al. 2005; Lewis and Wackowski 2006). Regarding sensory impact, flavorants presumably impart a pleasant sensation, ameliorate unpleasant sensations from other ingredients, or enhance pleasant sensations from other ingredients. In one of the few published sensory experiments using e-cigs, smokers rated "sweet" flavors like "Pina Colada" and "Vivid Vanilla" as sweeter or less bitter than a tobacco flavored product (Kim et al., 2016). In another recent experiment, smokers temporally abstaining from cigarettes worked harder for puffs of flavored e-cigs than for puffs of unflavored e-cigs with the same nicotine content, suggesting that flavored

The current experiment took a different approach, starting with simpler, more controlled stimuli to study a particular flavor interaction, viz. modulation of the taste of propylene glycol (PG) and vegetable glycerine (VG). PG and VG are often used as humectants in foods, but their primary function in e-cigs is to create vapor that appears smoke-like. Both compounds taste slightly sweet, and PG also has a bitter taste. In the flavor literature, "sweet-smelling" aromas, including fruit and confection-associated flavorants, have been shown to enhance the rated sweetness of solutions of sugar and non-nutritive sweeteners (e.g., Frank and Byram 1988; Labbe et al. 2007; Isogai and Wise, 2016). Sweet-smelling aromas might also suppress rated bitterness (Isogai and Wise, 2016). If fruit and confection aromas have similar effects on the taste of PG and VG, the effect might contribute to enhanced palatability, thereby reducing barriers to continued use after initial experimentation.

studies were conducted with smokers, so results may not generalize to non-smokers.

The current study was conducted to collect pilot data on the effects of volatile flavor compounds on the taste of mixtures of PG and VG to inform future flavor research. To focus on the effects of aromas on the taste of PG-VG mixtures, we used simple aqueous solutions without nicotine (lack of nicotine also made it less problematic to study non-smokers). To avoid potential taste-effects of flavorants, aromas were delivered into the mouth as odorized air, in parallel with PG-VG mixtures, using an automated olfactometer-gustometer (Isogai and Wise, 2016). Subjects tasted PG-VG solutions either accompanied by representative fruity aromas, representative confection-related aromas, or clean air blanks (control condition). In addition, we examined the impact of menthol, since this compound is also a common e-cig flavorant (Giovenco et al., 2015), and a "burnt" aroma which should not enhance sweetness. Subjects rated sweetness, bitterness, and pleasantness, endpoints which could reasonably be expected to relate to palatability.

Materials and Methods

Participants

Twenty adults, ages 18–25 yr and healthy by self-report, participated (Table 1). All had 1) smoked at least one cigarette and/or vaped at least one time, 2) had smoked and/or vaped fewer than 100 times in their lives, and 3) did not regularly use tobacco products (including e-cigs and related devices) at the time of testing. As young adults who had proven willing to experiment, participants represented a subset of people potentially at risk for regular use. Participants were a convenience sample from the Monell Chemical Senses Center staff and local universities who responded to fliers, and were paid. The work was approved by an Institutional Review Board (IRB) at the University of Pennsylvania. Informed consent was obtained from all individual participants included in the study.

Stimulus Materials

Since exact flavor ingredients seldom if ever appear on e-cig packaging, the common fruity flavorants iso-amyl acetate ("banana") and ethyl butyrate ("pineapple") were chosen to represent fruity aromas. Similarly, vanillin ("vanilla") and ethyl maltol ("caramel/malty") represented confection/dessert-related aromas. We selected (-)-menthol as another commonly-used flavorant in e-cigs (Giovenco et al., 2015). Finally, we selected isovaleraldehyde (with a significant "burnt" note), as an odorant not expected to enhance sweetness (Isogai and Wise, 2016).

Flavorants were diluted in either PG or filtered, light mineral oil, according to solubility. Two concentrations of each flavorant (Table 2) were selected to produce both a moderately intense and weaker aroma (according to pilot work) as presented from the apparatus (see Apparatus, below). PG and VG were mixed in a ratio of 1:1 by volume, then diluted in Millipore® filtered, distilled, de-ionized water to form taste solutions. The ratio was selected as representative of those used in many e-cigs and related devices. The PG-VG mixture was diluted to 5 % v/v and 2.5 % v/v to produce relatively subtle sweetness.

Apparatus

Another report describes the apparatus in detail (Miyazawa and Wise, 2016). In brief, the device delivered metered aliquots (5 ml) of taste solution in parallel with barely perceptible (1.7 ml/s) air-flow (odorized or not) into the mouth via separate tubes. The tubes met at a Teflon® mouthpiece which participants held between the lips during experimental trials, maintaining a seal. Air-flow began when the liquid stimulus was released into the mouth and continued for 5 s.

To obtain clearly perceptible aroma intensities as presented in the olfactometer, relatively high liquid-phase concentrations were required for some compounds. To enhance solubility, some stimuli were heated (Table 2). The desired solution temperatures were maintained using heating tape connected to a digital temperature controller (SDC Benchtop Digital Temperature Controller; Briskheat, Columbus, OH). However, there were no measureable differences in stimulus temperature at the output of the olfactometer, regardless of solution temperature.

A computer controlled stimulus timing and guided subjects through sessions. Participants rated the intensity of sweetness and bitterness using a mouse to mark a labelled magnitude scales (LMS) displayed on the computer screen (Green et al., 1996; Bartoshuk et al., 2004). Participants also rated pleasantness on a visual analog scale anchored with "extremely unpleasant" (-11) at one end, "extremely pleasant" (11) at the other end, and "neutral" (0) in the middle.

Design and Procedures

In an initial session, participants provided information on demographics, health, and history of tobacco, alcohol, and substance use (Table 1). Next, participants received instructions on the use of the rating scales (Green et al., 1993), including making ratings of the strength of remembered or imagined sensations to verify basic understanding of instructions. Next,

subjects acclimated to the apparatus, and completed practice trials. Analysis of practice trials showed that subjects tended to rate water blanks as having very low sweetness, and tended to rate stronger VG-PG solutions as sweeter than weaker VG-PG solutions. Over the next three sessions, data were collected in six blocks (two per session). Each block was devoted to one of the six flavor additives, in irregular order. Within a block, subjects completed 18 trials: 3 levels of aroma strength (weak, moderate, and clean air blank) X 3 levels of tastant (0, 2.5, and 5 v/v PG-VG) X 2 replicates (blocked random order). The design was completely within-subjects. Breaks of 20–30 min separated successive blocks within a session. One to four days separated successive sessions.

Within a block, a trail began with a prompt for the participant to place her lips on the mouthpiece, then indicate readiness with a mouse-click. After a 3 s countdown, the stimulus was delivered. Participants rolled the stimulus around in the mouth for several seconds before the rating scales appeared on a screen. After entering ratings with a mouse-click, participants expectorated and rinsed with bottled drinking water to begin an inter-trial interval of 35 s.

Note that the design did not include a manipulation of response context (Frank, 2002; Wise and Breslin, 2011). In many past studies, enhancement of taste by retronasal aroma tended to be more robust when subjects rated taste alone than when they also rated aroma intensity (Lawless and Clark 1992; Clark and Lawless 1994; Frank 2002). Prescott (2012) and others have suggested that response context affects attentional strategy. For example, asking subjects to rate only sweetness might encourage them to judge stimuli as a whole, a synthetic approach in which taste and aroma are combined in judgments of sweetness. We sought to encourage synthesis between tastes and aromas, as this might be more representative of how consumers typically approach products in natural situations (Prescott, 2004). However, we wished to collect ratings of both sweetness and bitterness, since both might be important in perception of VG-PG mixtures. Requiring subjects to rate both taste qualities each trial might encourage some analysis, but is more efficient. Ultimately, we decided to accept the risk of encouraging a degree of analysis for the sake of efficiency, though we hoped analysis of different taste qualities would be less likely to discourage synthesis between tastes and aromas than asking subjects to rate aroma.

Data Analysis

Intensity ratings were averaged across replicate judgements within subjects, then log transformed before inferential analysis (LMS ratings tend to be positively skewed across subjects; Green et al. 1993). Next, since past work has found little or no effect of added aromas on pure water (Isogai and Wise, 2016), data for water blanks were examined separately. Finally, for each flavor additive, log sweetness, log bitterness, and pleasantness were submitted to an Aroma level (air blank, weak, moderate) X PG-VG level (2.5 and 5.0 % v/v), repeated measures analysis of variance (ANOVA), with a significance criterion of p < 0.05. Significant effects of Aroma were investigated using a Dunnet test (Dunnet, 1955) vs. the air blank.

Results

Ratings for water blanks

For water blanks, ratings of sweetness and bitterness were low (around "barely detectable"), and pleasantness ratings were close to neutral (Fig. 1–3). One-way ANOVAs on Aroma level yielded no significant results (0.09). Ratings for water blanks were not considered further.

Fruity Aromas Increased Rated Sweetness

For both ethyl butyrate and isoamyl acetate, aroma level influenced rated sweetness, F(2,39) = 3.65, p = 0.035 and F(2,39) = 3.77, p = 0.032, respectively (Fig. 1). Dunnet tests vs. clean air blanks revealed significant enhancement for the higher concentration of ethyl butyrate (36% increase in sweetness, averaged across PG-VG concentration) and for the lower concentration of isoamyl acetate (37% increase).

Sweetness increased with PG-VG level for both ethyl butyrate and isoamyl acetate, F(1,19) = 49.13, p < 0.001 and F(1,19) < 14.86, p = 0.001, respectively. Bitterness also increased with PG-VG level, F (1, 19) = 4.97, p = 0.038 and F (1, 19) = 5.39, p = 0.031. Both are expected dose-response effects of the taste stimulus. No other main effects or interactions reached statistical significance (p > 0.18).

Dessert/Confection-Associated Aromas Enhanced Pleasantness, with Significant Suppression of Bitterness by Ethyl Maltol

For both vanillin and ethyl maltol, aroma level influenced rated pleasantness, F(2,38) = 3.33, p = 0.047 and F(2,38) = 5.10, p = 0.011, respectively (Fig. 2). Dunnet tests revealed significant enhancement of pleasantness for the higher concentration of vanillin (3.6 scale point change, averaged across PG-VG level, from approximately neutral to somewhat pleasant), and for both concentrations of ethyl maltol (increases of 4.4. and 3.3 scale points, respectively, from approximately neutral to pleasant). The only other effect of Aroma level was a significant decrease in rated bitterness for ethyl maltol, F(2, 38) = 4.31, p = 0.021. A Dunnet test revealed a significant decrease for the lower concentration (decrease of 35%).

Sweetness increased with PG-VG concentration for both vanillin and ethyl maltol, F(1,19) = 20.58, p = 0.001 and F(1,19) = 6.434, p = 0.02, respectively. Bitterness also increased with PG-VG concentration for both aromas, F(1, 19) = 6.74, p = 0.018 and F(1, 19) = 10.37, p = 0.005, respectively. No other main effects or interactions reached significance (p > 0.19).

Menthol and Isovaleraldehyde Had Little or No Effect On Sensory Ratings

For both menthol and isovaleraldehyde, the effect of PG-VG level on sweetness reached statistical significance, F(1,19) = 6.74, p = 0.001 and F(1,19) = 30.54, p < 0.001, respectively (Fig. 3). No other main effects or interactions reached significance (p > 0.12).

Discussion

The impact of flavorants on the taste of PG-VG mixtures

Both fruity flavorants increased rated sweetness, but the dessert/confection-related flavorants did not. Some previous flavor studies have found enhancement of sweetness by vanillin and ethyl maltol (e.g., Sakai et al. 2001; Bingham et al. 1990). Aromas may acquire "sweet" notes, and the ability to enhance sweetness, after being paired with sweet tastes (Stevenson et al., 1995; Prescott, 1999). While PG and VG are sweet, they do not taste exactly like sugar. Perhaps these "sweet" aromas are not compatible with PG-VG because people lack sufficient experience with that combination to develop learned associations. However, if this explanation is correct, we might expect lack of enhancement of sweetness for the fruity aromas, as well.

Enhancement of sweetness by the fruity aromas was not associated with increased pleasantness. Further, rated pleasantness increased with added vanillin and ethyl maltol, despite lack of measurable changes in sweetness. Ethyl maltol decreased bitterness slightly, an effect that has been observed with other sweet-smelling aromas (Ukai et al. 2007; Isogai and Wise, 2016). Though the effect of aroma on bitterness failed to reach significance for vanillin, there was an apparent trend in that direction similar to the results for ethyl maltol (Fig. 2). Whether this apparent reduction in bitterness drove associated increases in pleasantness is unclear, especially considering ratings of bitterness were low overall.

The reader should also note that enhancement of taste by aroma can differ among laboratory studies, even for particular flavorants (reviewed in Green et al., 2012; Isogai and Wise, 2016). The matrix (or stimulus-context) clearly matters. For example, in one report ethyl butyrate, which enhanced sweetness in the current experiment, enhanced the rated sweetness of an aqueous sucrose solution, but did not enhance the rated sweetness of sugar-containing aronia berry juice (Duffy et al., 2016). Various methodological differences might also play a role in conflicting results, including response-context (as discussed in Design and Procedures, above). Enhancement of taste by retro-nasal aroma is generally more robust when subjects adopt a synthetic approach, which is in turn more likely if subjects rate only taste intensity instead of rating both taste and aroma. In the current study, subjects did not rate aroma, but they did rate both sweetness and bitterness. This response-context might have encouraged some degree of analysis, which in turn could have made enhancement of sweetness less robust than in some previous work (Lawless and Clark 1992; Clark and Lawless 1994; Frank 2002).

Menthol, the most commonly-used flavorant in e-cigarettes, produced no measurable effects on the taste of PG-VG mixtures. Recent sensory work found that menthol in e-cigarettes reduced sensations of airway irritation caused by high concentrations of nicotine, and contributed to perceived irritation at low nicotine levels (Rosbook and Green, 2016). The results of Rosbook and Green are broadly consistent with previous suggestions that menthol can modulate sensitivity to airway irritation in both humans and animal models (e.g., Wise et al., 2011; Willis et al., 2011; Plevkova et al. 2013), and with analysis of internal sensory work on mentholated cigarettes by the tobacco industry (Kreslake et al., 2008). Accordingly,

the key sensory interaction with menthol may be with irritation from nicotine, which was not used in the current study. More work will be required to answer these questions.

Practical implications

On September 22, 2009, the FDA banned flavors in cigarettes under the authority of the Family Smoking Prevention and Tobacco Control Act (FSPTCA, 2009). The ban aimed to eliminate candy and fruit-flavored cigarettes, which appealed to youth and young adults (Klein et al., 2008), with the goal of reducing initiation of cigarette smoking. Since then, cigarette companies have increasingly marketed e-cigs, particularly to youth (Duke et al., 2014), and an increase in e-cig use has been observed (King et al., 2015). Given that youth are particularly vulnerable to transitioning from experimentation to regular use (Mermelstein et al., 2016), the National Cancer Institute and FDA have prioritized prevention of continued use among this age group. On August 8, 2016, the FDA extended their authority to include all tobacco products, including e-cigarettes (FDA, 2016a). The FDA specifically identified flavorants as components of e-cigarettes it claims authority to regulate (FDA, 2016b). Therefore, if sufficient evidence existed to suggest flavorants in e-cigarettes pose a risk to public health, this new authority would permit limits on the kinds or amounts of flavorants in these products.

As a whole, the current results suggest that for our sample of young, non-smokers: 1) Some added flavorants affect the perceived taste of solvents commonly used in e-cigarettes; 2) when flavorant effects were observed, they were in the direction of more positive flavor profiles, i.e., increased sweetness, increased pleasantness, or decreased bitterness; and 3) different "sweet-smelling" aromas may have different specific sensory effects (though, at this point, it would be premature to conclude that inconsistencies in the particular sensory attributes affected by dessert vs. fruity aromas will generalize to other members of these categories). If similar effects are seen in actual products, they could contribute indirectly to a more desirable flavor profile by improving the taste of other components in addition to direct sensory contributions of "fruity" or "sweet" flavor. Improved flavor profile could, in turn, lower barriers to continued use of e-cigarettes, particularly for people without a nicotine habit who have just begun to experiment.

Limitations

Our apparatus and stimuli provided tight stimulus control and allowed a focus on the effects of flavorants on particular e-cigarette ingredients. Lack of nicotine also made it less problematic to study non-smokers, overcoming an important limitation of the few previous sensory studies on e-cigs (Audrain-McGovern et al., 2016; Kim et al., 2016). However, these advantages come with important drawbacks. Tasting liquid may be different than inhaling vapor, the unmixed (single molecule) flavorants may give different results than commercial flavor blends, the presence of nicotine could modulate the observed odor-taste interactions, and heating elements in e-cigarettes could transform flavorants via chemical reactions. Further, participants did not include adolescents, though it is not unusual for college-age adults to acquire a regular nicotine habit (USDHHS, 2012, 2014). For all of these reasons, current results may not generalize to use of actual e-cigarettes in all sub-populations. Finally, the sample size and number of replicate trials per condition in this pilot experiment might

limit the power to resolve some flavor effects. Thus, more work, including work with more realistic models, is needed before any policy suggestions can be made. However, current results suggest that larger-scale studies are likely to yield significant flavor effects.

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Fig. 1.

Sensory ratings for fruity aromas. Ratings for a given flavorant are in rows, and ratings for a given sensory attribute (sweetness, bitterness, pleasantness) are in columns. For sweetness and bitterness, the secondary y-axis shows the position of labeled magnitude scale descriptors: BD = "barely detectable," W = "weak," and M = "moderate." Values for sweetness and pleasantness are geometric means, since analyses were performed on long-transformed values. Thus, positive and negative error bars (± sem) can be asymmetric for sweetness and bitterness.



Fig. 2.

Sensory ratings for confection/dessert-associated aromas. Ratings for a given flavorant are in rows, and ratings for a given sensory attribute (sweetness, bitterness, pleasantness) are in columns. For sweetness and bitterness, the secondary y-axis shows the position of labeled magnitude scale descriptors: BD = "barely detectable," W = "weak," and M = "moderate." Values for sweetness and pleasantness are geometric means, since analyses were performed on log-transformed values. Thus, positive and negative error bars (± sem) can be asymmetric for sweetness and bitterness.



Fig. 3.

Sensory ratings other aromas (menthol and isovaleraldehyde). Ratings for a given flavorant are in rows, and ratings for a given sensory attribute (sweetness, bitterness, pleasantness) are in columns. For sweetness and bitterness, the secondary y-axis shows the position of labeled magnitude scale descriptors: BD = "barely detectable," W = "weak," and M = "moderate." Values for sweetness and pleasantness are geometric means, since analyses were performed on log-transformed values. Thus, positive and negative error bars (± sem) can be asymmetric for sweetness and bitterness.

Table 1

Subject characteristics and history of substance use.

Sex	n
Male	12
Female	8
Basic biometrics	Mean (±SD)
Age (yr)	23.84 (0.98)
Weight (kg)	67.26 (11.28)
Height (cm)	166.16 (9.7)
BMI	24.30 (3.23)
History of substance use	Mean (±SD)
Alcohol intake (AUDIT) ^{a}	3.64 (2.96)
Drug use (DAST-10) ^b	0.00
Tobacco products ^C (# times used)	38.8 (15.18)
Cigarettes (# smoked)	11.40 (21.14)
Menthol-flavored cigarettes (# smoked)	1.6 (3.60)
E-cigarettes (# of times vaped)	6.67 (14.12)
Fruit-flavored e-cigarettes (# times vaped)	3.60 (6.78)
Confection-associated flavored e- cigarettes (# times vaped)	1.70 (4.55)
E-cigarettes, other flavors (# times vaped)	1.12 (3.14)

^aAUDIT: A score of less than 8 is considered normal(Bohen et al., 1995).

^bDAST-10: A score of 0 indicates no drug use (Skinner, 1982).

^CIncluding cigarettes, e-cigarettes, hookahs, or cigars.

Table 2

Stimulus preparation details.

Flavor compound	Lower intensity (%w/w)	Higher intensity (%w/w)	Solvent	Solution Temp. (°C, ± 3)
Ethyl butyrate	4.75	9.75	MO ^a	22
Iso-amyl acetate	15	30	MO	22
Isovaleradehyde	1	2	MO	22
Ethyl Maltol	15	30	PG^b	77
Vanillin	25	50	PG	77
(-)-Menthol	25	50	MO	35

^aFiltered, light mineral oil

b Propylene glycol