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Dose-response functions for the olfactory, nasal trigeminal, and ocular trigeminal detectability of airborne chemicals by humans

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Running head: Chemosensory detectability functions

Abstract

We gathered from the literature 47 odor and 37 trigeminal (nasal and ocular) chemesthetic psychometric (i.e., detectability or dose-response) functions from a group of 41 chemicals. Vapors delivered were quantified by analytical methods. All functions were very well fitted by the sigmoid (logistic) equation: $y = 1 / (1 + e^{\{-(x-C)/D\}})$, where parameter C quantifies the detection threshold concentration and parameter D the steepness of the function. Odor and chemesthetic functions showed no concentration overlap: olfactory functions grew along the parts per billion (ppb by volume) range or lower, whereas trigeminal functions grew along the part per million (ppm by volume) range. While, on average, odor detectability rose form chance detection to perfect detection within two orders of magnitude in concentration, chemesthetic detectability did it within one. For 16 compounds having at least one odor and one chemesthetic function, the average gap between the two functions was 4.6 orders of magnitude in concentration. A quantitative structure-activity relationship (QSAR) using five chemical descriptors that had previously described stand-alone odor and chemesthetic threshold values, also holds promise to describe, and eventually predict, olfactory and chemesthetic detectability functions, albeit functions from additional compounds are needed to strengthen the QSAR.

Keywords: Odor detectability functions – Chemesthetic detectability functions – Odor thresholds – Nasal and ocular irritation thresholds – Quantitative structure-activity relationships (QSAR) – Chemosensory detection – Volatile organic compounds

1. Introduction

One fundamental issue in understanding the characteristics of chemosensory perception, and of sensory systems in general, involves the topic of detection threshold sensitivity. In this article we will focus on the detectability of chemical vapors by two chemosensory modalities in humans: olfaction and trigeminal chemesthesis or chemical "feel" (Bryant and Silver 2000; Cometto-Muñiz and Simons 2015; Green 2012; Lee *et al.* 2005; Viana 2011) in the nasal and ocular mucosae (Cometto-Muñiz *et al.* 2010; Green and Lawless 1991). Trigeminal chemesthetic sensations are typically sharp or pungent, and include: irritation, freshness, coolness, stinging, prickling, burning, piquancy, tingling, and the like. A number of previous compilations have focused on human olfactory sensitivity as measured by odor detection thresholds (ODTs), e.g., (Amoore and Hautala 1983; Devos *et al.* 1990; Fazzalari 1978; Nagata 2003; van Gemert 2003). Nevertheless, the enormous variability in ODTs reported for any given chemical across studies, severely limits their practical applicability. Relatively fewer compilation and analyses studies are available on human nasal and ocular trigeminal chemesthetic thresholds, e.g., (Bruning *et al.* 2014; Ruth 1986), and, in the specific case of nasal pungency, not many of the cited studies have attempted to control for olfactory biases. Odor biases are very common since most, if not all, irritant vapors are also odorants and their odor thresholds emerge at much lower concentrations then their nasal trigeminal thresholds (Cometto-Muñiz 2001; Cometto-Muñiz and Cain 1998), making difficult to use blank stimuli (e.g., air) to account for chance detection in measuring nasal trigeminal thresholds.

In any case, a stand-alone threshold value provides much less information than concentration-detection (i.e., dose-response) functions that track the chemosensory detectability of a chemical across a critical concentration bracket that spans the complete perithreshold range: from chance detection to perfect detection. To the best of our knowledge, no studies have been published that model and analyze literature data on such comprehensive detectability functions for olfaction and chemesthesis in humans. In this review we have collected a total of 47 olfactory and 37 trigeminal chemesthetic functions for a set of 41 chemicals. From a mathematical perspective, all functions have been modeled by a sigmoid (logistic) equation, and, from a chemical perspective, they have been analyzed under a quantitative structure-activity relationship (QSAR) based on a well-established solvation equation (Abraham *et al.* 2003; Abraham *et al.* 2007; 2012).

2. Materials and Methods

2.1 Subjects. Participants in odor, nasal localization, and ocular chemesthetic detection experiments were normosmics (i.e., normal sense of smell) whereas participants in nasal pungency detection experiments were anosmics (i.e., absent sense of smell). Their sense of smell function was determined by a clinical olfactory test (Cain 1989). Table 1 describes the main characteristics of each psychometric function included in this article and its corresponding reference.

Insert Table 1 about here

2.2 Stimuli and Equipment. We include 41 stimuli (Table 1). All chemicals were high purity, typically >99%, as provided by the chemical suppliers. Whenever available,

chemicals met Food Chemical Codex (FCC) quality. Their delivered vapor concentrations were confirmed analytically by gas chromatography (GC), high performance liquid chromatography (HPLC) or a chemical-specific instrument (e.g., ozone analyzer). In a few cases, concentrations were calculated from total mass of chemical evaporated and volume of dilution air or nitrogen. All concentrations are expressed as log ppm by volume. Presentation of stimuli (Cain *et al.* 1992) involved a dynamic system via a vapor delivery device (VDD2 and VDD) (Cometto-Muñiz *et al.* 2007; Schmidt and Cain 2010), and/or a static system via squeeze bottles (SB) (Cometto-Muñiz and Cain 1993) and/or glass vessels (GV) (Cometto-Muñiz *et al.* 2000) (see Table 1). For nasal stimulation with a static system, SB and GV ended, respectively, in a single spout or two nosepieces (Cometto-Muñiz *et al.* 2000). For ocular stimulation with a static system, SB and GV ended in a single eyepiece (Cometto-Muñiz *et al.* 2001). When using GV, flowrate to the eye was set to 4 L/min. (When using SB, subjects were instructed to squeeze with approximately equal strength on all trials.) When using the VDD, the linear velocity of stimulus and blanks (carbon-filtered air) was ≈13 cm/sec, similar to that found in a typical indoor environment (Knudsen *et al.* 1997; Knudsen *et al.* 1998), even when the corresponding total volume flow (40 L/min) was high enough to fully accommodate the most forcible instantaneous sniffs (Laing 1982; 1983). This was achieved by delivering the sample from specially designed glass cones where the participant exposed nose or eyes (Schmidt and Cain 2010).

2.3 Procedure. All chemosensory testing involved using a two- or three-alternative forced-choice procedure between stimulus and blanks (Macmillan and Creelman 1991). For static delivery, blanks comprise the headspace above mineral oil (light, FCC) carried by either nitrogen or air. For dynamic delivery, blanks comprised carbon-filtered air.

2.4 Data analysis. The outcome is summarized in terms of detection probability, i.e., detectability, as a function of stimulus vapor concentration. Detectability was corrected for chance according to (Macmillan and Creelman 1991):

$$P = \{m \cdot p(c) - 1\}/(m - 1) \quad (1)$$

Where P = detection probability corrected for chance, m = number of choices in the forced-choice procedure (i.e., 2 or 3), and p(c) = proportion correct (i.e., number of correct trials / total number of trials).

Concentration-detection (also called psychometric or detectability) functions were modeled by a sigmoid (logistic) equation of the form:

$$y = 1 / (1 + e^{\{-(x-C)/D\}}) \quad (2)$$

where y = detectability (P) as defined in equation (1), x = vapor concentration of the chemical stimulus (in log ppm by volume), C and D are parameters. Note that C represents the concentration of the stimulus (i.e., x) when y = 0.5, that is, when detectability is half way (i.e., P =0.5) between chance detection (i.e., P = 0.0) and perfect detection (i.e., P = 1.0). This concentration is often taken as the chemosensory threshold. In turn, the value of parameter D governs the steepness of the detectability function, such that the lower the value of D, the steeper the function.

3. Results and Discussion

Figure 1 depicts the 84 olfactory and trigeminal chemesthetic (nasal and ocular) detectability functions gathered from 41 substances grouped by chemical family: n-alcohols, acetate esters, ethyl and butyl esters, 2-ketones, carboxylic acids, alkylbenzenes, naphthalenes, aldehydes, and miscellaneous chemicals. The figure

illustrates the excellent fit to the data provided by the sigmoid equation (2) (see also Tables 2 and 3). It also reveals that olfactory functions and trigeminal nasal/ocular chemesthetic functions show no overlap, with odor detection typically in the parts per billion (ppb) range (or lower) and trigeminal detection typically in the parts per million (ppm) range (with the exceptions of glutaraldehyde and chloropicrin whose trigeminal functions end at around 1 ppm).

Insert Figure 1 about here

3.1 Olfactory detectability functions

Table 2 lists the values of C (± standard error, SE), D (±SE), and two estimates of goodness of fit (chi square and R^2) from 41 odor functions. It also includes the average, standard deviation (SD), maximum, and minimum for the parameters C and D across all odor functions, and across all odor functions except those for stimuli "7b. Butyl acetate" (D=1.59) and "18b. Toluene" (D=1.37), whose values for D are notably higher than all others. When these two odor functions are taken out, the average value of D decreases from 0.39 to 0.34 with a concomitant reduction in its variability (SD) from 0.27 to 0.14. In contrast, the average value of C and its variability (SD) remain essentially the same with or without these two odor functions: -2.16 ±1.16 and -2.16 ±1.18, respectively. As a probable explanation for the two very shallow functions noted, consider that all 9 or 11 concentrations steps tested in those two cases are confined to only the upper half of the detectability range (P≥0.40). Such perceptual constriction for the subjects likely resulted in the observed very shallow functions. The minimum (D=0.15) and maximum (D=0.75) (leaving out the two exceptions noted) values for the parameter D indicate that the odor functions cover the range between close to chance (P=0.05) and almost perfect

(P=0.95) detection within a span of 0.88 (for “36b. Hexanoic acid”) to 4.42 (for “25a. 2-Methyl naphthalene”) orders of magnitude in concentration. Considering the average value of D=0.34 (leaving out the two exceptions), the average (±SD) span for odor functions is about 2.01 (±0.83) orders of magnitude in concentration, whereas when considering an average D=0.39 (which includes the two exceptions) the average span is 2.29 (±1.60) orders of magnitude.

Insert Table 2 about here

There are five compounds for which there are more than one odor function (irrespective of delivery technique): ethanol (with 3 functions), 1-butanol (with 2 functions), butyl acetate (with 3 functions), toluene (with 3 functions), and hexanoic acid (with 2 functions). For all of them, except butyl acetate, the maximum difference across C values (i.e., the odor detection threshold, ODT, in log ppm) for any particular chemical ranges from 0.16 to 0.63 orders of magnitude. Specifically, the ratio between the highest ODT and the lowest ODT is: 3 times for ethanol, 4.3 times for 1-butanol, 3.3 times for toluene, and 1.5 times for hexanoic acid. For butyl acetate, variability is higher: 1.62 orders of magnitude across the highest and lowest C value, which represents a ratio of 43 times in ODTs.

3.2 Trigeminal chemesthetic detectability functions

In turn, Table 3 provides analogous data for the 37 trigeminal chemesthetic functions considered separately, i.e., nasal pungency (NP), nasal localization (NL), and ocular chemesthesis (also labeled here eye irritation, see (Acosta *et al.* 2001)) (EI), or taken all together as chemesthetic functions. We note For 16 compounds there are at

least one odor function and one trigeminal function; they are: ethanol, 1-butanol, ethyl acetate, butyl acetate, hexyl acetate, ethyl propanoate, ethyl butanoate, ethyl heptanoate, 2-heptanone, toluene, naphthalene, 1-methyl naphthalene, 2-methyl naphthalene, glutaraldehyde, chloropicrin, and TXIB. These compounds provide for a total of 60 olfactory-trigeminal comparisons in terms of detection sensitivity. Across them, and in terms of the respective parameter C, trigeminal detection functions emerge on average (±SD) at concentrations 4.6 (±1.2) orders of magnitude higher than odor detection functions. Within this average, two extreme values stand out: for ethyl butanoate there is an 8.4 orders of magnitude difference in C between odor and nasal localization, whereas for chloropicrin there is just a 0.2 orders of magnitude difference in C between odor and eye irritation.

Insert Table 3 here

In terms of the steepness parameter D, trigeminal chemesthetic functions show an overall average (±SD) of D=0.18 (±0.075), considerably steeper than the average olfactory one (D=0.34 or D=0.39). The minimum (D=0.026) and maximum (D=0.38) values of D indicate that the chemesthetic functions cover the range between close to chance (P=0.05) and almost perfect (P=0.95) detection within a span of 0.15 (for “18e. Toluene”) to 2.24 (for 7g. Butyl acetate) orders of magnitude in concentration. Considering the average value of D=0.18, the average (±SD) span for chemesthetic functions overall is about 1.07 (±0.44) orders of magnitude in concentration, about half the average span for odor functions.

There are three compounds for which there are more than one chemesthetic function (irrespective of specific trigeminal endpoint or delivery technique): ethanol (with

2 functions), butyl acetate (with 4 functions), and toluene (with 4 functions). For all of them, the maximum difference across C values (i.e., the trigeminal chemesthetic threshold, Trigem, in log ppm) for any particular chemical ranges from 0.21 to 0.55 orders of magnitude. Specifically, the ratio between the highest and the lowest trigeminal chemesthetic threshold is: 1.6 times for ethanol, 2.3 times for butyl acetate, and 3.5 times for toluene.

3.3. Chemical modeling of the psychometric parameters C and D from the sigmoid equation

We have stressed that the concentration-detection or psychometric functions of the form of the sigmoid equation (2) contain a great deal more information than a stand-alone threshold value. It takes considerably more effort to determine a full psychometric function than a threshold value, and so it is of importance if the psychometric functions for further compounds could be estimated. Since the psychometric functions are well represented by the sigmoid equation (2), this is tantamount to an estimation of the C and D parameters. We have already shown (Abraham *et al.* 2007; 2012; Abraham *et al.* 2010) that two general equations can be applied to the correlation and estimation of chemosensory thresholds and biological and toxicological activities, equation (3) and equation (4).

$$SP = c + e\,\mathbf{E} + s\,\mathbf{S} + a\,\mathbf{A} + b\,\mathbf{B} + v\,\mathbf{V} \quad (3)$$

$$SP = c + e\,\mathbf{E} + s\,\mathbf{S} + a\,\mathbf{A} + b\,\mathbf{B} + l\,\mathbf{L} \quad (4)$$

In these equations, *SP* is the dependent variable, in the present case C or D. The independent variables, or descriptors, are properties of the compounds as follows (Abraham *et al.* 2007; 2012): **E** is the compound excess molar refraction in $cm^3\,mol^{-1}/10$, **S** is the solute dipolarity/polarizability, **A** is the overall compound hydrogen bond acidity,

B is the overall compound hydrogen bond basicity, **V** is McGowan's characteristic molecular volume in cm^3 $mol^{-1}/100$ and **L** is the logarithm of the gas to hexadecane partition coefficient of the compound at 298 K. The coefficients *c*, *e*, *s*, *a*, *b*, *v* and *l* are fitting constants obtained by the method of multiple linear regression analysis, MLRA.

In Table 2 are given values of C and D for odor psychometric functions obtained with three delivery techniques, VDD, GV and SB. Values of C and D obtained for a given compound using different delivery techniques are not necessarily the same. We can allow for this by assigning 'indicator variables' as follows. There is no variable for VDD which is taken as a standard. Compounds studied by GV are assigned an indicator variable Igv that takes the value Igv = 1 and compounds studied by SB are assigned an indicator variable Isb = 1. If the coefficients of these indicator variables in the MLRA are very small, then they can be removed (this means that if Igv is very small, for example, then the GV delivery technique leads to the same values of C or D as the VDD technique). Results in terms of equation (3) and equation (4) are almost exactly the same, and the statistics using equation (4) are as follows: N is the number of data points, SD is the regression standard deviation, R is the correlation coefficient and F is the F-statistic. In order to assess the predictive capability of a given equation, the relevant data set should be divided into a training set and a test set – an equation is then obtained for the training set and used to predict values for the test set. These predicted values will normally be larger than the equation SD, but should not be very much larger. There are not enough points in any of our data sets to carry out a training/test set analysis, and so we used a procedure in which a predictive standard deviation, PSD, is obtained from the 'leave-one-out' statistics of an equation (Abraham *et al.* 2009). Just as for the SD values in the training/test set analysis, the values of PSD should be larger than the corresponding values of the equation SD, but not very much larger; PSD indicates the predictive power of the corresponding equation.

C(odor) = -0.397 – 0.815 **E –** 2.154 **B** – 0.199 **L** + 0.492 **Igv** + 1.226 **Isb** (5)

N = 45, SD = 0.919, R^2 = 0.349, F = 4.2, PSD = 1.035

D(odor) = 0.299 + 0.247 **E** – 0.220 **S** - 0.117 **A** + 0.325 **B** - 0.018 **L** + 0.220 I**gv** + 0.170 **Isb** (6)

N = 44, SD = 0.082, R^2 = 0.719, F = 13.1, PSD = 0.106

In the case of equation (5) there were two large outliers, butyl acetate (7c) and ethyl butanoate (11a) that were omitted, and for equation (6) ethyl butanoate (11a), toluene (18b) and butyl acetate (7b) were left out. The statistics of equation (5) are not very good, but those of equation (6) are quite reasonable. It is possible that, despite our strategy to introduce indicator variables to account for the use of different techniques in obtaining the functions, parameter C for odor is more susceptible to technique-dependent variations.

We give in Table 3 values of C and D for psychometric functions for nasal pungency (NP), nasal localization (i.e., lateralization) (NL), eye irritation (EI), and for the three previous endpoints taken all together as trigeminal chemesthesis (Trigem). There are not enough values for any one of the first three data sets to carry out a MLRA, and so we used again the stratagem of assigning indicator variables. We took eye irritation as the standard and defined Iloc = 1 for nasal localization data and Iloc = 0 for all others, and Inp = 1 for nasal pungency data and Inp = 0 for all others. In addition we took the delivery technique GV as a standard and used Ivd = 1 for the VDD delivery technique and Ivd = 0 for all others, and Isb = 1 for the SB delivery technique and Isb = 0 for all others. Of course, not all the independent variables, including the indicator variables, will

be statistically significant. We found, as before, that the MLRA equations using the variables **L** and **V** are almost the same. Equations using **L** are as follows.

C(Trigem) = 5.936 + 0.690 **E** – 4.273 **S** - 2.290 **A** - 0.229 **L** + 0.527 **lloc** – 1.574 **lvd** (7)

N = 37, SD = 0.339, R^2 = 0.933, F = 69.3, PSD = 0.421

D(Trigem) = 0.130 + 0.253 **B** - 0.009 **L** - 0.038 **lloc** – 0.054 **lvd** (8)

N = 37, SD = 0.062, R^2 = 0.378, F = 4.9, PSD = 0.072

There were no outliers at all to equation (7) and equation (8). The statistics of equation (7) are excellent, with R^2 = 0.933, but R^2 for equation (8) is only 0.378. However, the equation standard deviation is very low, SD = 0.062, and the reason why R^2 is only 0.378 is due to the very low spread of values of D, from 0.026 to 0.380. Scatter plots of experimental vs. fitted values of C and D for odor and chemesthesis (Trigem), not shown, reveal no more than random scatter about the line of identity. Thus equation (7) and equation (8) could be used to estimate values of C and D and hence the entire psychometric function for further compounds that have not been experimentally examined for nasal pungency, nasal localization or ocular chemesthesis sensitivity.

We have summarized here by using a common, uniform methodology, human dose-response functions gathered from the literature depicting the olfactory and chemesthetic trigeminal detectability at the integrated (psychophysical) level of more than three dozen compounds. As previously discussed (Cometto-Muñiz and Abraham 2008; Cometto-Muñiz and Abraham 2010a), comparing such functions with those obtained, for the same compounds, at other levels (e.g., molecular, receptor, cellular) e.g., (Saito *et al.* 2009) and stages (e.g., peripheral, central) of the two chemosensory

pathways will play a key role to fully understand the underlying sensory processes determining the sensitivity range and characteristics of both human chemosenses. To facilitate these comparisons we present in Supplementary Tables 1 and 2, and Supplementary Figures 1 and 2, all odor and trigeminal chemesthetic threshold concentrations reported here, now expressed in Molar units (nM or μM) in the gas phase but also in their corresponding equivalent Molar concentrations in physiological saline solution (liquid phase) at 37°C. The latter representing a common media used to test olfactory and trigeminal responses to chemicals in molecular/receptor/cellular preparations.

4. Conclusions

- All olfactory and nasal/ocular trigeminal chemesthetic detectability functions are very well fitted and described by the sigmoid (logistic) equation (2).
- Odor functions are in the ppb (and lower) range whereas trigeminal chemesthetic functions are typically in the ppm range (with the exception of glutaraldehyde and chloropicrin, as noted).
- Odor functions cover the range between almost chance (P=0.05) and almost perfect (P=0.95) detection within an average (±SD) span of 2.01 (±0.83) orders of magnitude, whereas trigeminal chemesthetic functions do it within an average (±SD) span of 1.07 (±0.44) orders of magnitude.
- Across 16 compounds having each at least one olfactory and one trigeminal chemesthetic function, chemesthetic functions emerge on average (±SD) at concentrations 4.6 (±1.2) orders of magnitude higher than odor functions.
- A quantitative structure-activity relationship (QSAR) (Abraham *et al.* 2007) shows great promise as a tool to describe and, ultimately, predict in humans not only just

odor and chemesthetic thresholds but also complete olfactory and trigeminal chemesthetic detectability functions by calculating the C (threshold) and D (function steepness) parameters from untested odorants and irritants.

References

Abraham MH, Acree Jr. WE, Leo AJ and Hoekman D. 2009. The partition of compounds from water and from air into wet and dry ketones. New J Chem. 33: 568-573.

Abraham MH, Hassanisadi M, Jalali-Heravi M, Ghafourian T, Cain WS and Cometto-Muniz JE. 2003. Draize rabbit eye test compatibility with eye irritation thresholds in humans: a quantitative structure-activity relationship analysis. Toxicol Sci. 76: 384-391.

Abraham MH, Sánchez-Moreno R, Cometto-Muñiz JE and Cain WS. 2007. A quantitative structure activity analysis on the relative sensitivity of the olfactory and the nasal trigeminal chemosensory systems. Chem Senses. 32: 711-719.

Abraham MH, Sánchez-Moreno R, Cometto-Muñiz JE and Cain WS. 2012. An algorithm for 353 odor detection thresholds in humans. Chem Senses. 37: 207-218.

Abraham MH, Sánchez-Moreno R, Gil-Lostes J, Acree Jr. WE, Cometto-Muñiz JE and Cain WS. 2010. The biological and toxicological activity of gases and vapors. Toxicology in Vitro. 24: 357-362.

Acosta MC, Tan ME, Belmonte C and Gallar J. 2001. Sensations evoked by selective mechanical, chemical, and thermal stimulation of the conjunctiva and cornea. Invest Ophthalmol Vis Sci. 42: 2063-2067.

Amoore JE and Hautala E. 1983. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol. 3: 272-290.

Bruning T, Bartsch R, Bolt HM, Desel H, Drexler H, Gundert-Remy U, Hartwig A, Jackh R, Leibold E, Pallapies D, Rettenmeier AW, Schluter G, Stropp G, Sucker K, Triebig G, Westphal G and van Thriel C. 2014. Sensory irritation as a basis for setting occupational exposure limits. Arch Toxicol. 88: 1855-1879.

Bryant B and Silver WL. 2000. Chemesthesis: The common chemical sense. In: Finger TE, Silver WL and Restrepo D, editors. The Neurobiology of Taste and Smell 2nd Edition. New York: Wiley-Liss. pp. 73-100.

Cain WS. 1989. Testing olfaction in a clinical setting. Ear Nose Throat J. 68: 316-328.

Cain WS, Cometto-Muñiz JE and de Wijk RA. 1992. Techniques in the quantitative study of human olfaction. In: Serby MJ and Chobor KL, editors. Science of Olfaction. New York: Springer-Verlag. pp. 279-308.

Cain WS, de Wijk RA, Jalowayski AA, Pilla Caminha G and Schmidt R. 2005. Odor and chemesthesis from brief exposures to TXIB. Indoor Air. 15: 445-457.

Cain WS, Jalowayski AA, Schmidt R, Jeon J, Bruff TC and Butala JH. 2006a Human chemosensory and physiological responses to chloropicrin vapor. The Toxicologist 45th Annual Meeting of the Society of Toxicology. San Diego, CA: pp. 478-479 (Abstract # 2340).

Cain WS, Lee NS, Wise PM, Schmidt R, Ahn BH, Cometto-Muñiz JE and Abraham MH. 2006b. Chemesthesis from volatile organic compounds: Psychophysical and neural responses. Physiol Behav. 88: 317-324.

Cain WS, Schmidt R and Behan JM. 2015 Perceptual antagonism in odor mixtures: Independence form odor quality. Abstracts of the 37th Annual Meeting of the Association for Chemoreception Sciences. Bonita Springs, FL, April 22-25, Abs.#P15: pp. 32-33.

Cain WS, Schmidt R and Jalowayski AA. 2007a. Odor and chemesthesis from exposures to glutaraldehyde vapor. Int Arch Occup Environ Health. 80: 721-731.

Cain WS, Schmidt R and Wolkoff P. 2007b. Olfactory detection of ozone and D-limonene: reactants in indoor spaces. Indoor Air. 17: 337-347.

Cometto-Muñiz JE. 2001. Physicochemical basis for odor and irritation potency of VOCs. In: Spengler JD, Samet J and McCarthy JF, editors. Indoor Air Quality Handbook. New York: McGraw-Hill, pp. 20.1-20.21.

Cometto-Muñiz JE and Abraham MH. 2008. Human olfactory detection of homologous n-alcohols measured via concentration-response functions. Pharmacol Biochem Behav. 89: 279-291.

Cometto-Muñiz JE and Abraham MH. 2009a. Olfactory detectability of homologous n-alkylbenzenes as reflected by concentration-detection functions in humans. Neuroscience. 161: 236-248.

Cometto-Muñiz JE and Abraham MH. 2009b. Olfactory psychometric functions for homologous 2-ketones. Behav Brain Res. 201: 207-215.

Cometto-Muñiz JE and Abraham MH. 2010a. Comparison of dose-response functions at the behavioral and at the cell/receptor levels. Chem Senses. 35: A70-A71 (Abstract).

Cometto-Muñiz JE and Abraham MH. 2010b. Odor detection by humans of lineal aliphatic aldehydes and helional as gauged by dose-response functions. Chem Senses. 35: 289-299.

Cometto-Muñiz JE and Abraham MH. 2010c. Structure-activity relationships on the odor detectability of homologous carboxylic acids by humans. Exp Brain Res. 207: 75-84.

Cometto-Muñiz JE and Cain WS. 1993. Efficacy of volatile organic compounds in evoking nasal pungency and odor. Arch Environ Health. 48: 309-314.

Cometto-Muñiz JE and Cain WS. 1998. Trigeminal and olfactory sensitivity: comparison of modalities and methods of measurement. Int Arch Occup Environ Health. 71: 105-110.

Cometto-Muñiz JE, Cain WS and Abraham MH. 2003. Dose-addition of individual odorants in the odor detection of binary mixtures. Behav Brain Res. 138: 95-105.

Cometto-Muñiz JE, Cain WS and Abraham MH. 2004. Chemosensory additivity in trigeminal chemoreception as reflected by detection of mixtures. Experimental Brain Research. 158: 196-206.

Cometto-Muñiz JE, Cain WS and Abraham MH. 2005. Odor detection of single chemicals and binary mixtures. Behav Brain Res. 156: 115-123.

Cometto-Muñiz JE, Cain WS, Abraham MH and Gil-Lostes J. 2008. Concentration-detection functions for the odor of homologous n-acetate esters. Physiol Behav. 95: 658-667.

Cometto-Muñiz JE, Cain WS, Abraham MH and Gola JM. 1999. Chemosensory detectability of 1-butanol and 2-heptanone singly and in binary mixtures. Physiol Behav. 67: 269-276.

Cometto-Muñiz JE, Cain WS, Abraham MH and Gola JMR. 2001. Ocular and nasal trigeminal detection of butyl acetate and toluene presented singly and in mixtures. Toxicol Sci. 63: 233-244.

Cometto-Muñiz JE, Cain WS, Abraham MH and Gola JMR. 2002. Psychometric functions for the olfactory and trigeminal detectability of butyl acetate and toluene. Journal of Applied Toxicology. 22: 25-30.

Cometto-Muñiz JE, Cain WS, Abraham MH and Sánchez-Moreno R. 2007. Concentration-detection functions for eye irritation evoked by homologous n-alcohols and acetates approaching a cut-off point. Exp Brain Res. 182: 71-79.

Cometto-Muñiz JE, Cain WS, Abraham MH, Sánchez-Moreno R and Gil-Lostes J. 2010. Nasal chemosensory irritation in humans. In: Morris JB and Shusterman DJ, editors. Toxicology of the Nose and Upper Airways. New York: Informa Healthcare USA, Inc. pp. 187-202.

Cometto-Muñiz JE, Cain WS, Hiraishi T, Abraham MH and Gola JMR. 2000. Comparison of two stimulus-delivery systems for measurement of nasal pungency thresholds. Chem Senses. 25: 285-291.

Cometto-Muñiz JE and Simons C. 2015. Trigeminal Chemesthesis. In: Doty RL, editor. Handbook of Olfaction and Gustation (3rd Edition). Hoboken, NJ: Wiley Blackwell. pp. 1091-1112.

Devos M, Patte F, Rouault J, Laffort P and van Gemert LJ. 1990. Standardized Human Olfactory Thresholds. IRL Press, Oxford.

Fazzalari FA, editor 1978. Compilation of odor and taste threshold values data. Baltimore: American Society for Testing and Materials.

Green BG. 2012. Chemesthesis and the chemical senses as components of a "chemofensor complex". Chem Senses. 37: 201-206.

Green BG and Lawless HT. 1991. The psychophysics of somatosensory chemoreception in the nose and mouth. In: Getchell TV, Doty RL, Bartoshuk LM and Snow Jr. JB, editors. Smell and Taste in Health and Disease. New York: Raven Press. pp. 235-253.

Knudsen HN, Clausen G and Fanger PO. 1997. Sensory characterization of emissions from materials. Indoor Air. 7: 107-115.

Knudsen HN, Valbjørn O and Nielsen PA. 1998. Determination of exposure-response relationships for emissions from building products. Indoor Air. 8: 264-275.

Laing DG. 1982. Characterisation of human behaviour during odour perception. Perception. 11: 221-230.

Laing DG. 1983. Natural sniffing gives optimum odour perception for humans. Perception. 12: 99-117.

Lee Y, Lee CH and Oh U. 2005. Painful channels in sensory neurons. Mol Cells. 20: 315-324.

Macmillan NA and Creelman CD. 1991. Detection theory: A user's guide. Cambridge University Press, Cambridge.

Nagata Y. 2003. Measurement of odor threshold by triangle odor bag method. Odor measurement review. Tokyo: Office of Odor, Noise and Vibration. Environmental Management Bureau, Ministry of Environment. pp. 118-127 (see also: https://www.env.go.jp/en/air/odor/measure/102_113_112.pdf).

Ruth JH. 1986. Odor thresholds and irritation levels of several chemical substances: a review. Am Ind Hyg Assoc J. 47: A142-151.

Saito H, Chi Q, Zhuang H, Matsunami H and Mainland JD. 2009. Odor coding by a Mammalian receptor repertoire. Sci Signal. 2: ra9.

Schmidt R and Cain WS. 2010. Making scents: dynamic olfactometry for threshold measurement. Chem Senses. 35: 109-120.

Schmidt R, Rohde AM, Daughtrey WC and Cain WS. 2008. Odor and Irritation from Complex Mixtures of Aromatic Hydrocarbons and their Main Constituents. Chem Senses. 33: S116-S117.

van Gemert LJ. 2003. Odour Thresholds. Compilations of odour threshold values in air, water and other media. Oliemans, Punter & Partners BV, Utrecht.

Viana F. 2011. Chemosensory properties of the trigeminal system. ACS Chem Neurosci. 2: 38-50.

Table 1. Chemicals tested, delivery techniques, chemosensory endpoints, number of subjects (# S's), their average age (±SD) and range, gender distribution (Females(F)/Males(M)), number of trials per subject/ concentration, total number of trials per concentration, and reference source. Delivery techniques include: vapor delivery device (VDD and VDD2), glass vessel (GV), and squeeze bottle (SB). Chemosensory endpoints include: odor (O), nasal pungency (NP), nasal localization or lateralization (NL), and eye irritation (EI).

Chemical Stimulus	Delivery Technique	Chemo-sensory Endpoint	# S's	Average Age (±SD)	Age Range	F/M	Trials per Subject	Total trials	Reference
1a. Ethanol	VDD	O	14	35(±14)	20-59	6/8	21	294	(Cometto-Muñiz and Abraham 2008)
1b. Ethanol	GV	O	19		18-43		30-40	570-760	(Cain *et al.* 2005)
1c. Ethanol	GV	NL	18	26(±6)	19-40	11/7	28	504	(Schmidt *et al.* 2008)
1d. Ethanol	GV	NL	19		18-43		30-40	570-760	(Cain *et al.* 2005)
1e. Ethanol	GV	EI	19		18-43		30-40	570-760	(Cain *et al.* 2005)
2a. 1-Butanol	VDD	O	17	33(±14)	19-57	8/9	30-40	570-760	(Cometto-Muñiz and Abraham 2008)
2b. 1-Butanol	SB	O	4	36(±13)	24-54	3/1	16	64	(Cometto-Muñiz *et al.* 1999)
2c. 1-Butanol	SB	NP	4	40(±14)	28-59	3/1	16	64	(Cometto-Muñiz *et al.* 1999)
2d. 1-Butanol	SB	EI	4	36(±13)	24-54	3/1	16	64	(Cometto-Muñiz *et al.* 1999)
3. 1-Hexanol	VDD	O	17	31(±13)	18-56	8/9	21	357	(Cometto-Muñiz and Abraham 2008)
4. 1-Octanol	VDD	O	14	32(±13)	19-56	6/8	21	294	(Cometto-Muñiz and Abraham 2008)
5. 1-Nonanol	VDD2	EI	26	24(±8)	18-56		≤20	≥420	(Cometto-Muñiz *et al.* 2007)
6a. Ethyl acetate	VDD	O	16	25(±5)	18-32	8/8	35	560	(Cometto-Muñiz *et al.* 2008)
6b. Ethyl acetate	GV	NL	10		18-36	6/4	28	280	(Cain *et al.* 2006b)
7a. Butyl acetate	VDD	O	17	25(±5)	18-38	9/8	35	595	(Cometto-Muñiz *et al.* 2008)
7b. Butyl acetate	GV	O	12	27(±12)	18-56	6/6	≥18	222	(Cometto-Muñiz *et al.* 2003)
7c. Butyl acetate	SB	O	4	37(±14)	25-56	3/1	16	64	(Cometto-Muñiz *et al.* 2002)
7d. Butyl acetate	GV	NP	5	51(±15)	34-71	3/2	≥19	96	(Cometto-Muñiz *et al.* 2001)
7e. Butyl acetate	SB	NP	4	44(±13)	29-60	3/1	16	64	(Cometto-Muñiz *et al.* 2002)
7f. Butyl acetate	GV	NL	10		18-36	5/5	28	280	(Cain *et al.* 2006b)
7g. Butyl acetate	GV	EI	12	28(±10)	19-51	6/6	≥14	176	(Cometto-Muñiz *et al.* 2001)
7h. Butyl acetate	SB	EI	4	37(±14)	25-56	3/1	16	64	(Cometto-Muñiz *et al.* 2002)
8a. Hexyl acetate	VDD	O	16	26(±5)	19-35	8/8	35	560	(Cometto-Muñiz *et al.* 2008)
8b. Hexyl acetate	GV	NL	10		18-36	5/5	28	280	(Cain *et al.* 2006b)
9. Octyl acetate	VDD	O	16	26(±4)	19-35	8/8	35	560	(Cometto-Muñiz *et al.* 2008)
10a. Ethyl propanoate	GV	O	22	26(±10)	18-50	10/12	≥27	610	(Cometto-Muñiz *et al.* 2005)
10b. Ethyl propanoate	GV	NP	5	44(±20)	20-64	2/3	20	100	(Cometto-Muñiz *et al.* 2004)
10c. Ethyl propanoate	GV	NL	10		18-36	6/4	28	280	(Cain *et al.* 2006b)
10d. Ethyl propanoate	GV	EI	18	25(±20)	19-53	10/8	20	360	(Cometto-Muñiz *et al.* 2004)
11a. Ethyl butanoate	VDD	O	4	22(±2)	20-25	2/2	100	400	(Schmidt and Cain 2010)
11b. Ethyl butanoate	GV	NL	10		18-36	5/5	28	280	(Cain *et al.* 2006b)
12a. Ethyl heptanoate	GV	O	22	26(±10)	18-50	10/12	≥29	658	(Cometto-Muñiz *et al.* 2005)
12b. Ethyl heptanoate	GV	NP	5	44(±20)	20-64	2/3	20	100	(Cometto-Muñiz *et al.* 2004)
12c. Ethyl heptanoate	GV	EI	18	25(±20)	19-53	10/8	20	360	(Cometto-Muñiz *et al.* 2004)
13. Butyl propanoate	GV	NL	10		18-36	3/7	28	280	(Cain *et al.* 2006b)
14. 2-Propanone (acetone)	VDD	O	17	24(±5)	18-35	9/8	35	595	(Cometto-Muñiz and Abraham 2009b)
15. 2-Pentanone	VDD	O	22	25(±4)	20-35	11/11	35	770	(Cometto-Muñiz and Abraham 2009b)
16a. 2-Heptanone	VDD	O	18	27(±5)	19-35	9/9	35	630	(Cometto-Muñiz and Abraham 2009b)
16b. 2-Heptanone	SB	O	4	36(±13)	24-54	3/1	16	64	(Cometto-Muñiz *et al.* 1999)
16c. 2-Heptanone	SB	NP	4	40(±14)	28-59	3/1	16	64	(Cometto-Muñiz *et al.* 1999)
16d. 2-Heptanone	SB	EI	4	36(±13)	24-54	3/1	16	64	(Cometto-Muñiz *et al.* 1999)
17. 2-Nonanone	VDD	O	19	24(±4)	19-35	10/9	35	665	(Cometto-Muñiz and Abraham 2009b)

Chemical Stimulus	Delivery Technique	Chemo-sensory Endpoint	# S's	Average Age (±SD)	Age Range	F/M	Trials per Subject	Total trials	Reference
18a. Toluene	VDD	O	16	23(±6)	18-36	9/7	35	560	(Cometto-Muñiz and Abraham 2009a)
18b. Toluene	GV	O	10	29(±12)	19-56	5/5	≥22	224	(Cometto-Muñiz *et al.* 2003)
18c. Toluene	SB	O	4	37(±14)	25-56	3/1	16	64	(Cometto-Muñiz *et al.* 2002)
18d. Toluene	GV	NP	5	51(±15)	34-71	3/2	≥19	96	(Cometto-Muñiz *et al.* 2001)
18e. Toluene	SB	NP	4	44(±13)	29-60	3/1	16	64	(Cometto-Muñiz *et al.* 2002)
18f. Toluene	GV	EI	12	28(±10)	19-51	6/6	≥14	176	(Cometto-Muñiz *et al.* 2001)
18g. Toluene	SB	EI	4	37(±14)	25-56	3/1	16	64	(Cometto-Muñiz *et al.* 2002)
19. Ethylbenzene	VDD	O	17	25(±5)	20-36	8/9	35	595	(Cometto-Muñiz and Abraham 2009a)
20. Butylbenzene	VDD	O	16	24(±5)	18-36	7/9	35	560	(Cometto-Muñiz and Abraham 2009a)
21. Hexylbenzene	VDD	O	16	24(±5)	19-36	8/8	35	560	(Cometto-Muñiz and Abraham 2009a)
22. Octylbenzene	VDD	O	17	24(±5)	18-36	9/8	35	595	(Cometto-Muñiz and Abraham 2009a)
23a. Naphthalene	GV	O	20	25(±6)	19-40	10/10	28	560	(Schmidt *et al.* 2008)
23b. Naphthalene	GV	NL	6	26(±7)	19-38	2/4	28	168	(Schmidt *et al.* 2008)
23c. Naphthalene	GV	EI	19	27(±8)	18-44	10/9	20	380	(Schmidt *et al.* 2008)
24a. 1-Methyl Naphthalene	GV	O	20	25(±6)	19-40	10/10	28	560	(Schmidt *et al.* 2008)
24b. 1-Methyl Naphthalene	GV	NL	8	27(±9)	19-44	4/4	28	224	(Schmidt *et al.* 2008)
24c. 1-Methyl Naphthalene	GV	EI	22	26(±7)	19-44	11/11	20	440	(Schmidt *et al.* 2008)
25a. 2-Methyl Naphthalene	GV	O	20	25(±6)	19-40	9/11	28	560	(Schmidt *et al.* 2008)
25b. 2-Methyl Naphthalene	GV	NL	8	29(±8)	19-44	5/3	28	224	(Schmidt *et al.* 2008)
25c. 2-Methyl Naphthalene	GV	EI	19	26(±8)	18-44	9/10	20	380	(Schmidt *et al.* 2008)
26. Propanal	VDD	O	16	26(±5)	19-37	8/8	35	560	(Cometto-Muñiz and Abraham 2010b)
27. Butanal	VDD	O	18	22(±5)	18-37	9/9	35	630	(Cometto-Muñiz and Abraham 2010b)
28. Hexanal	VDD	O	16	23(±5)	18-37	7/9	35	560	(Cometto-Muñiz and Abraham 2010b)
29. Octanal	VDD	O	16	24(±5)	19-37	9/7	35	560	(Cometto-Muñiz and Abraham 2010b)
30. Nonanal	VDD	O	17	25(±6)	19-37	10/7	35	595	(Cometto-Muñiz and Abraham 2010b)
31. Helional	VDD	O	17	24(±5)	19-37	10/7	35	595	(Cometto-Muñiz and Abraham 2010b)
32a. Glutaraldehyde	VDD	O	40	22(±3)	18-35	40/0	28	1120	(Cain *et al.* 2007a)
32b. Glutaraldehyde	VDD	NL	25	22(±3)	18-27	25/0	32	800	(Cain *et al.* 2007a)
32c. Glutaraldehyde	VDD	EI	34	22(±4)	18-35	34/0	21	714	(Cain *et al.* 2007a)
33. Formic acid	VDD	O	18	24(±5)	19-37	12/6	35	630	(Cometto-Muñiz and Abraham 2010c)
34. Acetic acid	VDD	O	16	22(±3)	19-29	10/6	35	560	(Cometto-Muñiz and Abraham 2010c)
35. Butyric acid	VDD	O	14	24(±5)	19-37	9/5	35	490	(Cometto-Muñiz and Abraham 2010c)
36a. Hexanoic acid	VDD	O	18	24(±5)	19-37	9/9	35	630	(Cometto-Muñiz and Abraham 2010c)
36b. Hexanoic acid	VDD	O	5	28(±5)	22-32	4/1	30	150	(Cain *et al.* 2015)
37. Octanoic acid	VDD	O	14	23(±3)	20-30	8/6	35	490	(Cometto-Muñiz and Abraham 2010c)
38. D-Limonene	VDD	O	13	23(±3)	20-26	6/7	38	494	(Cain *et al.* 2007b)
39a. Chloropicrin	VDD	O	43	23(±4)	19-34	18/25	30	1290	(Cain *et al.* 2006a)
39b. Chloropicrin	VDD	EI	50	23(±4)	19-34	23/27	21	1050	(Cain *et al.* 2006a)
40. Ozone	VDD	O	10	22(±2)	20-26	4/6	43	430	(Cain *et al.* 2007b)
41a. 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TXIB)	GV	O	19		18-43		30-40	570-760	(Cain *et al.* 2005)
41b. 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TXIB)	GV	NL	19		18-43		30-40	570-760	(Cain *et al.* 2005)
41c. 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TXIB)	GV	EI	19		18-43		30-40	570-760	(Cain *et al.* 2005)

Table 2. Value (±standard error) of parameters C and D, and estimates of goodness of fit for **odor (O)** psychometric functions modeled via the simplified sigmoid equation (2). Stimuli listed in ascending value of D.

Chemical Stimulus	Chemosensory Endpoint	Delivery Technique	C	±SE-C	D	±SE-D	Chi Square	R2
36b. Hexanoic acid	O	VDD	-2.830	0.0280	0.150	0.0260	0.017	0.99
35. Butyric acid	O	VDD	-3.584	0.0190	0.160	0.0200		0.99
31. Helional	O	VDD	-3.868	0.0240	0.200	0.0210	0.0096	0.99
27. Butanal	O	VDD	-3.334	0.0170	0.200	0.0150	0.0045	>0.99
37. Octanoic acid	O	VDD	-3.066	0.0260	0.200	0.0200		0.99
26. Propanal	O	VDD	-2.695	0.0160	0.210	0.0140	0.0039	>0.99
20. Butylbenzene	O	VDD	-2.610	0.0120	0.210	0.0100	0.0021	>0.99
39a. Chloropicrin	O	VDD	-0.320	0.0120	0.210	0.0140	0.0009	>0.99
36a. Hexanoic acid	O	VDD	-2.992	0.0230	0.220	0.0200		0.99
22. Octylbenzene	O	VDD	-1.050	0.0180	0.220	0.0160	0.0049	>0.99
19. Ethylbenzene	O	VDD	-2.220	0.0340	0.230	0.0300	0.0162	0.98
15. 2-Pentanone	O	VDD	-1.000	0.0130	0.230	0.0120		>0.99
18a. Toluene	O	VDD	-1.100	0.0250	0.240	0.0220	0.0086	0.99
30. Nonanal	O	VDD	-3.274	0.0280	0.250	0.0250	0.0106	0.99
21. Hexylbenzene	O	VDD	-2.360	0.0300	0.250	0.0260	0.0116	0.99
34. Acetic acid	O	VDD	-2.284	0.0210	0.250	0.0200		0.99
16a. 2-Heptanone	O	VDD	-2.320	0.0240	0.270	0.0220		0.99
9. Octyl acetate	O	VDD	-1.690	0.0160	0.270	0.0140		1.00
40. Ozone	O	VDD	-1.540	0.0400	0.270	0.0390	0.033	0.95
14. 2-Propanone (acetone)	O	VDD	-0.080	0.0240	0.270	0.0220		0.99
7a. Butyl acetate	O	VDD	-2.370	0.0210	0.290	0.0180		0.99
17. 2-Nonanone	O	VDD	-2.260	0.0180	0.290	0.0170		>0.99
41a. TXIB	O	GV	-2.870	0.0075	0.300	0.0066	0.00032	1.00
33. Formic acid	O	VDD	-0.289	0.0620	0.300	0.0600		0.95
38. D-Limonene	O	VDD	-1.320	0.0380	0.310	0.0390	0.024	0.96
6a. Ethyl acetate	O	VDD	-0.610	0.0250	0.320	0.0230		0.99
4. 1-Octanol	O	VDD	-2.360	0.0250	0.330	0.0230	0.0064	0.99
8a. Hexyl acetate	O	VDD	-2.540	0.0220	0.350	0.0200		0.99
3. 1-Hexanol	O	VDD	-2.090	0.0140	0.360	0.0140	0.0018	>0.99
29. Octanal	O	VDD	-3.759	0.0190	0.370	0.0180	0.0034	>0.99
32a. Glutaraldehyde	O	VDD	-3.560	0.0350	0.410	0.0340	0.0098	0.99
2a. 1-Butanol	O	VDD	-2.100	0.0320	0.410	0.0320	0.008	0.99
2b. 1-Butanol	O	SB	-0.450	0.0490	0.410	0.0450	0.023	0.98
1b. Ethanol	O	GV	-0.940	0.0077	0.430	0.0070	0.00033	1.00
1a. Ethanol	O	VDD	-0.480	0.0200	0.430	0.0200	0.0028	>0.99
28. Hexanal	O	VDD	-3.482	0.0500	0.440	0.0490	0.0185	0.98
7c. Butyl acetate	O	SB	-3.990	0.0830	0.450	0.0760	0.099	0.94
16b. 2-Heptanone	O	SB	-1.130	0.0840	0.450	0.0810	0.061	0.93
10a. Ethyl propanoate	O	GV	-0.530	0.0290	0.480	0.0300	0.0019	>0.99
11a. Ethyl butanoate	O	VDD	-4.910	0.0440	0.500	0.0450	0.012	0.98
18c. Toluene	O	SB	-1.010	0.1100	0.570	0.1070	0.119	0.90
24a. 1-Methyl Naphthalene	O	GV	-2.780	0.0770	0.580	0.0810	0.018	0.96
12a. Ethyl heptanoate	O	GV	-1.370	0.0280	0.600	0.0330	0.002	>0.99
23a. Naphthalene	O	GV	-3.140	0.0640	0.700	0.0630	0.011	0.98
25a. 2-Methyl Naphthalene	O	GV	-2.770	0.0800	0.750	0.0830	0.016	0.97
18b. Toluene	O	GV	-1.530	0.2500	1.370	0.2750	0.045	0.87
7b. Butyl acetate	O	GV	-2.680	0.1820	1.590	0.2030	0.031	0.93
Average	**O**		**-2.160**		**0.389**			
SD	**O**		**1.160**		**0.272**			
Maximum	O		-0.080		1.590			
Minimum	O		-4.910		0.150			

Chemical Stimulus	Chemosensory Endpoint	Delivery Technique	C	±SE-C	D	±SE-D	Chi Square	R2
Average (w/out 7b.ButAc & 18b.Tol)	**O**		**-2.163**		**0.341**			
SD (w/out 7b.ButAc & 18b.Tol)	**O**		**1.180**		**0.142**			
Maximum (w/out 7b.ButAc & 18b.Tol)	O		-0.080		0.750			
Minimum (w/out 7b.ButAc & 18b.Tol)	O		-4.910		0.150			

Table 3. Value (±standard error) of parameters C and D, and estimates of goodness of fit for **nasal pungency (NP), nasal localization (i.e., lateralization) (NL) and eye irritation (EI)** psychometric functions modeled via the simplified sigmoid equation (2). Stimuli listed in ascending value of D.

Chemical Stimulus	Chemosensory Endpoint	Delivery Technique	C	±SE-C	D	±SE-D	Chi Square	R2
18e. Toluene	NP	SB	3.690	0.230	0.026	17.600	0.079	0.93
18d. Toluene	NP	GV	4.000	0.005	0.044	0.005	0.00025	1.00
12b. Ethyl heptanoate	NP	GV	2.510	0.010	0.170	0.010	0.0008	1.00
7e. Butyl acetate	NP	SB	2.280	0.063	0.190	0.056	0.063	0.95
16c. 2-Heptanone	NP	SB	2.370	0.043	0.200	0.039	0.027	0.97
7d. Butyl acetate	NP	GV	2.340	0.030	0.220	0.032	0.009	0.99
2c. 1-Butanol	NP	SB	2.910	0.048	0.250	0.045	0.015	0.97
10b. Ethyl propanoate	NP	GV	2.760	0.042	0.350	0.050	0.0046	0.98
Average NP	**NP**		**2.858**		**0.181**			
SD NP	**NP**		**0.651**		**0.106**			
Maximum NP			4.000		0.350			
Minimum NP			2.280		0.026			
7f. Butyl acetate	NL	GV	3.360	0.028	0.120	0.025	0.013	0.98
25b. 2-Methyl Naphthalene	NL	GV	2.170	0.017	0.130	0.018	0.0032	0.99
1c. Ethanol	NL	GV	3.590	0.011	0.130	0.011	0.0023	1.00
24b. 1-Methyl Naphthalene	NL	GV	1.940	0.019	0.140	0.020	0.0079	0.98
11b. Ethyl butanoate	NL	GV	3.500	0.009	0.140	0.007	0.0021	1.00
13. Butyl propanoate	NL	GV	3.090	0.020	0.150	0.016	0.011	0.99
1d. Ethanol	NL	GV	3.380	0.004	0.180	0.003	0.00042	1.00
10c. Ethyl propanoate	NL	GV	3.680	0.030	0.180	0.027	0.0096	0.98
6b. Ethyl acetate	NL	GV	4.010	0.050	0.180	0.045	0.027	0.95
32b. Glutaraldehyde	NL	VDD	-0.330	0.030	0.190	0.034	0.008	0.96
23b. Naphthalene	NL	GV	1.970	0.041	0.210	0.043	0.0079	0.97
8b. Hexyl acetate	NL	GV	2.870	0.007	0.210	0.008	0.0009	1.00
41b. TXIB	NL	GV	0.670	0.005	0.220	0.006	0.00022	1.00
Average NL	**NL**		**2.608**		**0.168**			
SD NL	**NL**		**1.284**		**0.034**			
Maximum NL			4.010		0.220			
Minimum NL			-0.330		0.120			
18g. Toluene	EI	SB	3.450	0.002	0.065	0.003	0.00005	1.00
23c. Naphthalene	EI	GV	1.870	0.031	0.091	0.041	0.0064	0.99
24c. 1-Methyl Naphthalene	EI	GV	1.800	0.011	0.120	0.009	0.0022	1.00
18f. Toluene	EI	GV	3.680	0.030	0.130	0.029	0.032	0.96
39b. Chloropicrin	EI	VDD	-0.110	0.013	0.140	0.013	0.0023	>0.99
25c. 2-Methyl Naphthalene	EI	GV	2.000	0.016	0.140	0.016	0.0046	0.99
5. 1-Nonanol	EI	VDD2	0.760	0.027	0.150	0.037	0.018	0.94
32c. Glutaraldehyde	EI	VDD	-0.410	0.010	0.170	0.011	0.0012	>0.99
12c. Ethyl heptanoate	EI	GV	2.190	0.020	0.180	0.021	0.0031	0.99
41c. TXIB	EI	GV	0.340	0.003	0.210	0.003	0.00018	1.00
1e. Ethanol	EI	GV	3.480	0.004	0.220	0.004	0.00054	1.00
7h. Butyl acetate	EI	SB	2.240	0.039	0.240	0.035	0.022	0.98
2d. 1-Butanol	EI	SB	2.690	0.033	0.240	0.030	0.01	0.99
16d. 2-Heptanone	EI	SB	2.020	0.055	0.280	0.052	0.03	0.96
10d. Ethyl propanoate	EI	GV	2.790	0.049	0.310	0.050	0.012	0.97
7g. Butyl acetate	EI	GV	1.980	0.085	0.380	0.074	0.054	0.95
Average EI	**EI**		**1.923**		**0.192**			
SD EI	**EI**		**1.234**		**0.084**			
Maximum EI			3.680		0.380			
Minimum EI			-0.410		0.065			

Chemical Stimulus	Chemosensory Endpoint	Delivery Technique	C	±SE-C	D	±SE-D	Chi Square	R2
All Chemesthesis Average	NP, NL, and EI	VDD, VDD2, GV, SB	**2.366**		**0.181**			
All Chemesthesis SD	NP, NL, and EI	VDD, VDD2, GV, SB	**1.195**		**0.075**			
All **Chemesthesis** Maximum	NP, NL, and EI	VDD, VDD2, GV, SB	4.010		0.380			
All **Chemesthesis** Minimum	NP, NL, and EI	VDD, VDD2, GV, SB	-0.410		0.026			

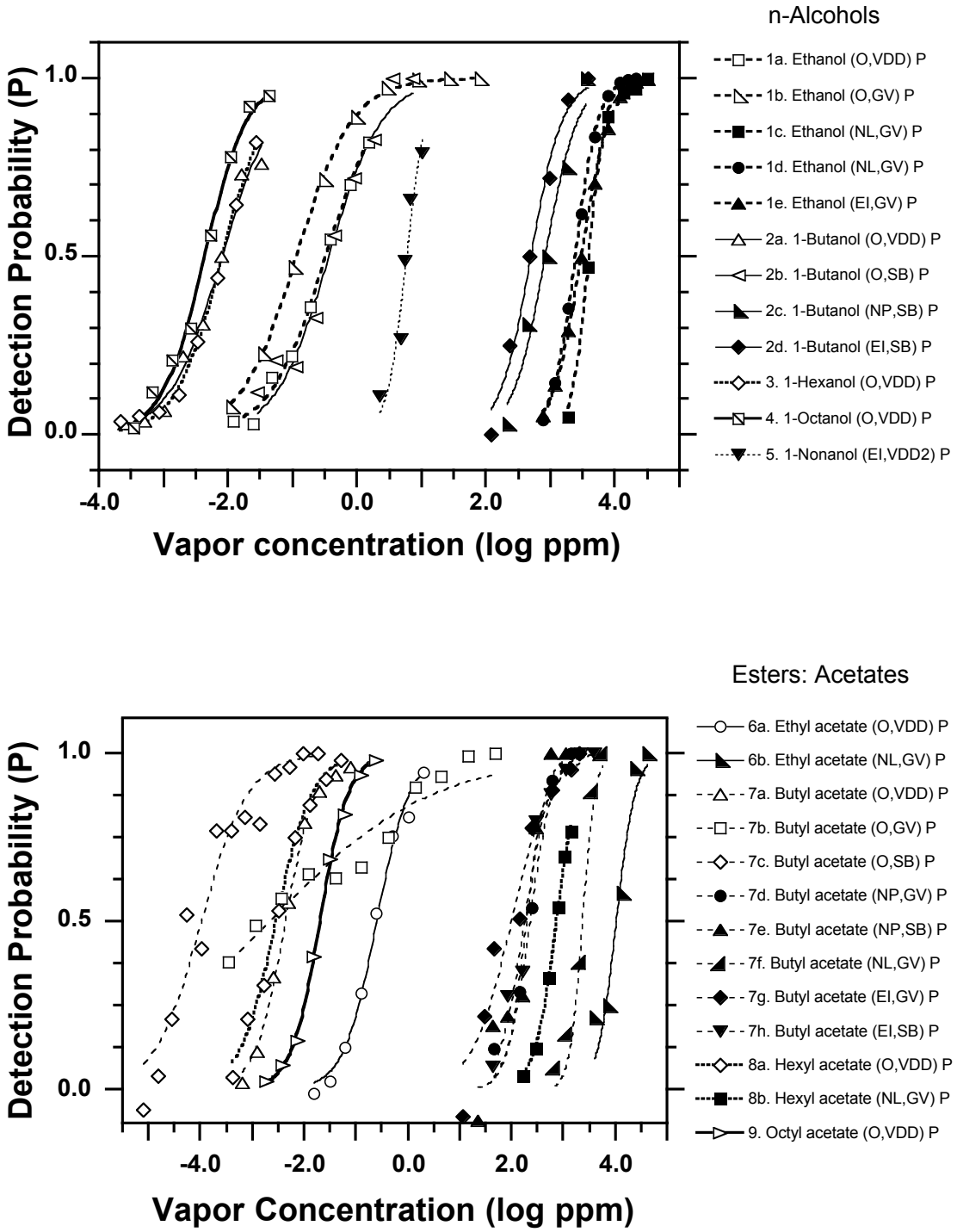
Figure Legends

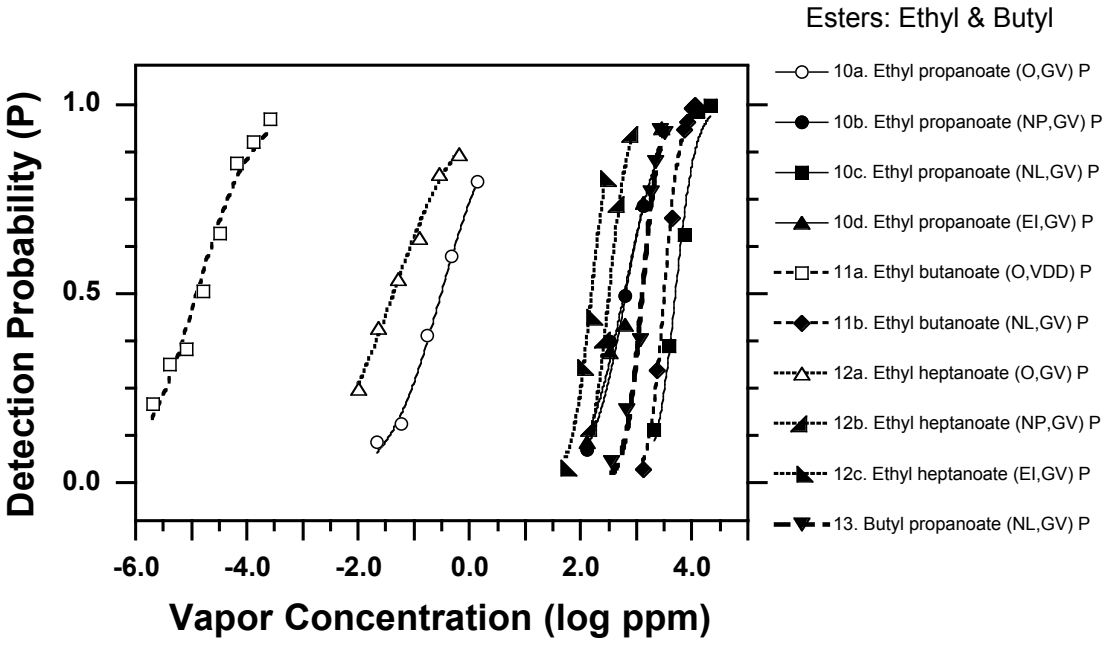
Figure 1. Detectability functions for the odor (O), nasal pungency (NP), nasal localization (NL), and eye irritation (EI) evoked by the 41 chemicals listed in Table 1. They include: n-alcohols, acetate esters, ethyl and butyl esters, 2-ketones and carboxylic acids, alkylbenzenes, naphthalenes, aldehydes, and miscellaneous chemicals. All functions are modeled by the sigmoid equation (2). Olfactory functions are depicted by empty symbols and chemesthetic functions (NP, NL, and EI) are depicted by filled symbols. Stimulus delivery techniques included: vapor delivery device (VDD and VDD2), glass vessels (GV), and squeeze bottles (SB).

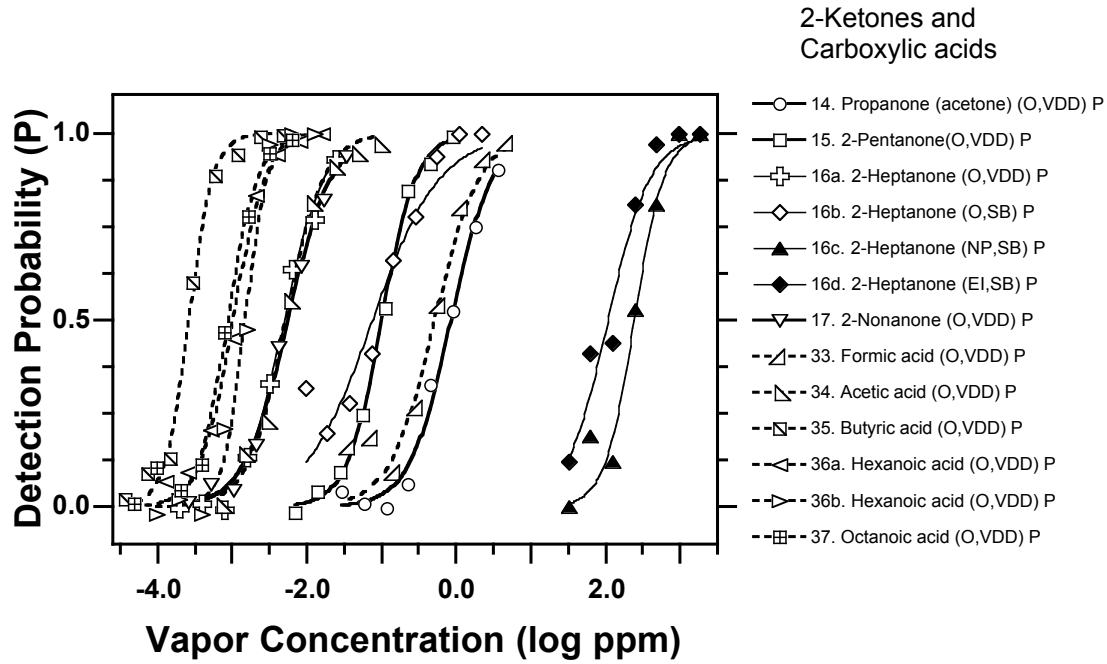
Supplementary Figure 1. Illustrating the comparison of ODT concentrations measured in the gas phase and their equivalent concentrations in physiological saline solution (liquid phase) at 37 °C. All concentrations expressed as nM.

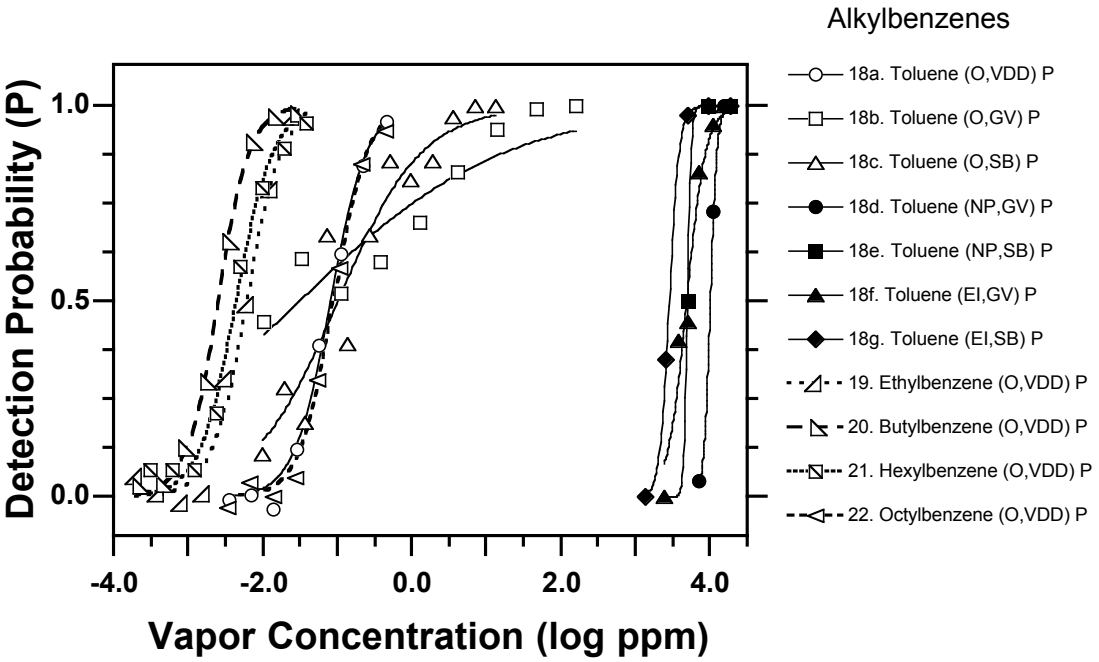
Supplementary Figure 2. Illustrating the comparison of trigeminal chemesthetic threshold (Trigem) concentrations measured in the gas phase and their equivalent concentrations in physiological saline solution (liquid phase) at 37 °C. All concentrations expressed as microM.

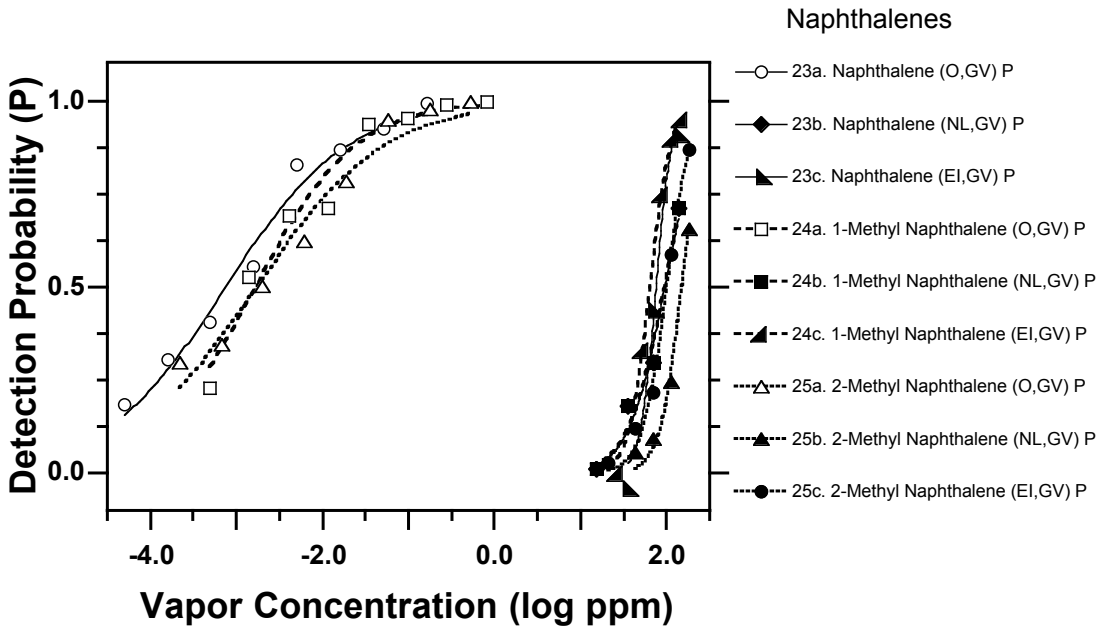
FIGURE 1.

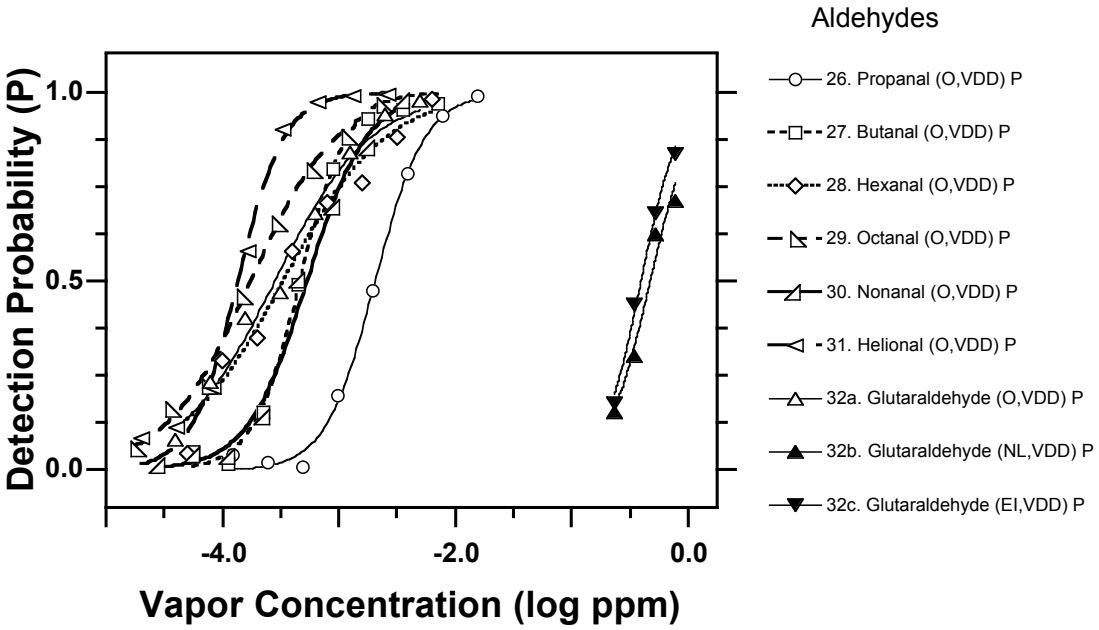

n-Alcohols
1a. Ethanol (O,VDD) P
1b. Ethanol (O,GV) P
1c. Ethanol (NL,GV) P
1d. Ethanol (NL,GV) P
1e. Ethanol (EI,GV) P
2a. 1-Butanol (O,VDD) P
2b. 1-Butanol (O,SB) P
2c. 1-Butanol (NP,SB) P
2d. 1-Butanol (EI,SB) P
3. 1-Hexanol (O,VDD) P
4. 1-Octanol (O,VDD) P
5. 1-Nonanol (EI,VDD2) P
Detection Probability (P)
1.0
0.5
0.0
-4.0
-2.0
0.0
2.0
4.0
Vapor concentration (log ppm)
Esters: Acetates
6a. Ethyl acetate (O,VDD) P
6b. Ethyl acetate (NL,GV) P
7a. Butyl acetate (O,VDD) P
7b. Butyl acetate (O,GV) P
7c. Butyl acetate (O,SB) P
7d. Butyl acetate (NP,GV) P
7e. Butyl acetate (NP,SB) P
7f. Butyl acetate (NL,GV) P
7g. Butyl acetate (EI,GV) P
7h. Butyl acetate (EI,SB) P
8a. Hexyl acetate (O,VDD) P
8b. Hexyl acetate (NL,GV) P
9. Octyl acetate (O,VDD) P
Detection Probability (P)
1.0
0.5
0.0
-4.0
-2.0
0.0
2.0
4.0
Vapor Concentration (log ppm)

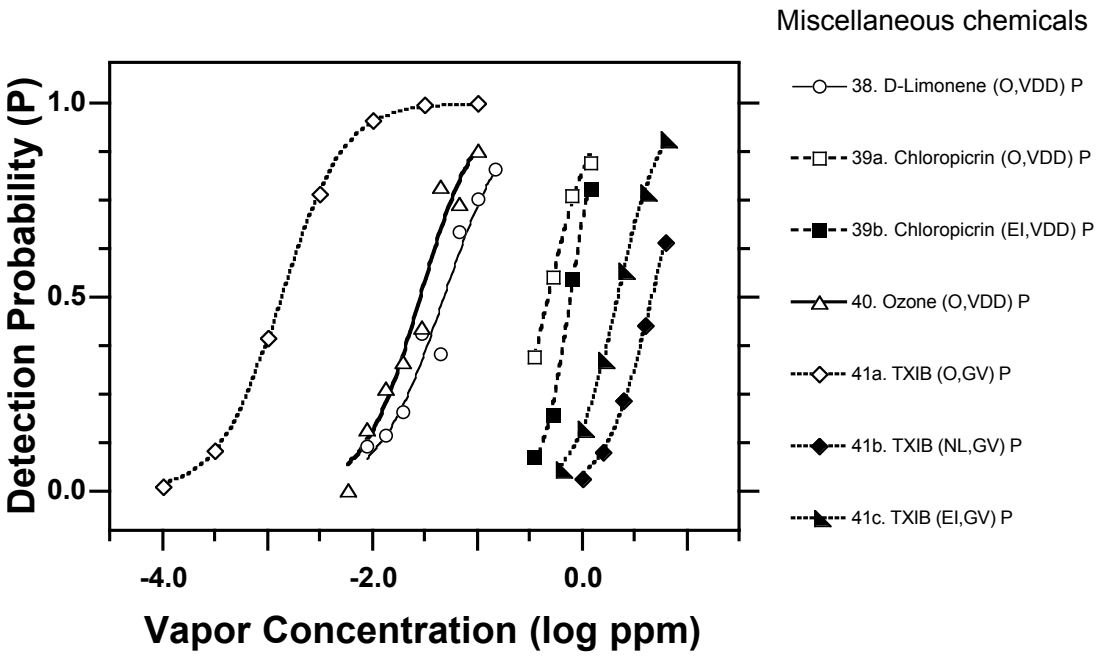

Esters: Ethyl & Butyl
Detection Probability (P)
1.0
0.5
0.0
-6.0
-4.0
-2.0
0.0
2.0
4.0
Vapor Concentration (log ppm)
10a. Ethyl propanoate (O,GV) P
10b. Ethyl propanoate (NP,GV) P
10c. Ethyl propanoate (NL,GV) P
10d. Ethyl propanoate (EI,GV) P
11a. Ethyl butanoate (O,VDD) P
11b. Ethyl butanoate (NL,GV) P
12a. Ethyl heptanoate (O,GV) P
12b. Ethyl heptanoate (NP,GV) P
12c. Ethyl heptanoate (EI,GV) P
13. Butyl propanoate (NL,GV) P

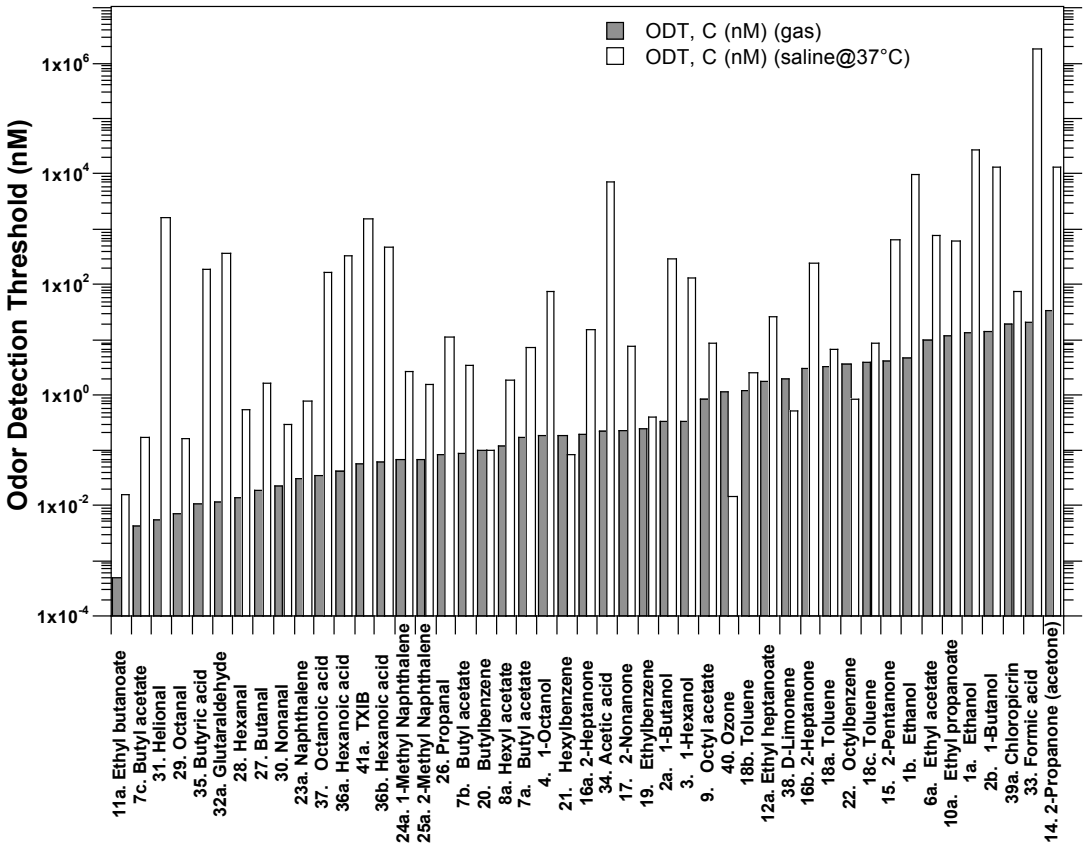

2-Ketones and
Carboxylic acids
Detection Probability (P)
1.0
0.5
0.0
-4.0
-2.0
0.0
2.0
Vapor Concentration (log ppm)
14. Propanone (acetone) (O,VDD) P
15. 2-Pentanone(O,VDD) P
16a. 2-Heptanone (O,VDD) P
16b. 2-Heptanone (O,SB) P
16c. 2-Heptanone (NP,SB) P
16d. 2-Heptanone (EI,SB) P
17. 2-Nonanone (O,VDD) P
33. Formic acid (O,VDD) P
34. Acetic acid (O,VDD) P
35. Butyric acid (O,VDD) P
36a. Hexanoic acid (O,VDD) P
36b. Hexanoic acid (O,VDD) P
37. Octanoic acid (O,VDD) P


Alkylbenzenes
Detection Probability (P)
1.0
0.5
0.0
-4.0
-2.0
0.0
2.0
4.0
Vapor Concentration (log ppm)
18a. Toluene (O,VDD) P
18b. Toluene (O,GV) P
18c. Toluene (O,SB) P
18d. Toluene (NP,GV) P
18e. Toluene (NP,SB) P
18f. Toluene (EI,GV) P
18g. Toluene (EI,SB) P
19. Ethylbenzene (O,VDD) P
20. Butylbenzene (O,VDD) P
21. Hexylbenzene (O,VDD) P
22. Octylbenzene (O,VDD) P

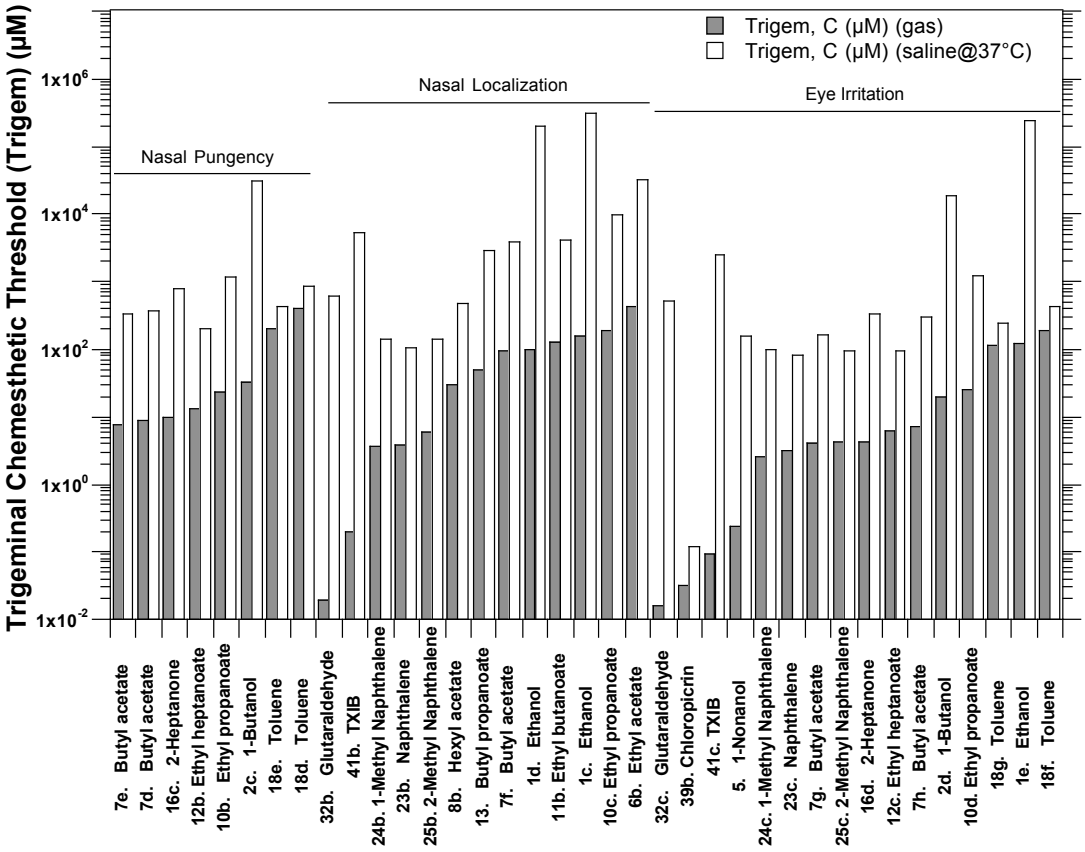

Naphthalenes
Detection Probability (P)
1.0
0.5
0.0
-4.0
-2.0
0.0
2.0
Vapor Concentration (log ppm)
23a. Naphthalene (O,GV) P
23b. Naphthalene (NL,GV) P
23c. Naphthalene (EI,GV) P
24a. 1-Methyl Naphthalene (O,GV) P
24b. 1-Methyl Naphthalene (NL,GV) P
24c. 1-Methyl Naphthalene (EI,GV) P
25a. 2-Methyl Naphthalene (O,GV) P
25b. 2-Methyl Naphthalene (NL,GV) P
25c. 2-Methyl Naphthalene (EI,GV) P


Aldehydes
Detection Probability (P)
1.0
0.5
0.0
-4.0
-2.0
0.0
Vapor Concentration (log ppm)
26. Propanal (O,VDD) P
27. Butanal (O,VDD) P
28. Hexanal (O,VDD) P
29. Octanal (O,VDD) P
30. Nonanal (O,VDD) P
31. Helional (O,VDD) P
32a. Glutaraldehyde (O,VDD) P
32b. Glutaraldehyde (NL,VDD) P
32c. Glutaraldehyde (EI,VDD) P


Miscellaneous chemicals
Detection Probability (P)
1.0
0.5
0.0
-4.0
-2.0
0.0
Vapor Concentration (log ppm)
38. D-Limonene (O,VDD) P
39a. Chloropicrin (O,VDD) P
39b. Chloropicrin (EI,VDD) P
40. Ozone (O,VDD) P
41a. TXIB (O,GV) P
41b. TXIB (NL,GV) P
41c. TXIB (EI,GV) P



Supplementary Figure 1. Illustrating the comparison of ODT concentrations measured in the gas phase and their equivalent concentrations in physiological saline solution (liquid phase) at 37 °C. All concentrations expressed as nM.



Supplementary Figure 2. Illustrating the comparison of trigeminal chemesthetic threshold (Trigem) concentrations measured in the gas phase and their equivalent concentrations in physiological saline solution (liquid phase) at 37 °C. All concentrations expressed as microM.

Supplementary Table 1. For each of the 47 **odor** functions, we list the chemical stimulus tested and its **odor** detection threshold (**ODT**) expressed as the following equivalent concentrations: log ppm by volume in the gas phase, log Molar in the gas phase, and log Molar in a liquid physiological saline solution at 37°C. The equivalence between Molar in gas phase and Molar in liquid saline phase at 37°C was established via the partition coefficient (logK) between the gas and liquid phases, as described earlier (Abraham *et al.* 2007). We note that logKwater and logKsaline at 37°C are essentially the same. Chemicals are listed in increasing value of ODTs expressed as log ppm by volume in the gas phase.

Chemical Stimulus	**ODT (log ppm by vol) (gas phase)**	**ODT (log Molar) (gas phase)**	**LogKw ≈ Log Ksaline solut., both@37°C**	**ODT (log Molar) (saline sol.@37°C)**
11a. Ethyl butanoate	-4.910	-12.315	1.53	-10.785
7c. Butyl acetate	-3.990	-11.395	1.64	-9.755
31. Helional	-3.868	-11.273	5.48	-5.793
29. Octanal	-3.759	-11.164	1.36	-9.804
35. Butyric acid	-3.584	-10.989	4.26	-6.729
32a. Glutaraldehyde	-3.560	-10.965	4.53	-6.435
28. Hexanal	-3.482	-10.887	1.63	-9.257
27. Butanal	-3.334	-10.739	1.96	-8.779
30. Nonanal	-3.274	-10.679	1.15	-9.529
23a. Naphthalene	-3.140	-10.545	1.45	-9.095
37. Octanoic acid	-3.066	-10.471	3.69	-6.781
36a. Hexanoic acid	-2.992	-10.397	3.92	-6.477
41a. TXIB	-2.870	-10.275	4.47	-5.805
36b. Hexanoic acid	-2.830	-10.235	3.92	-6.315
24a. 1-Methyl Naphthalene	-2.780	-10.185	1.61	-8.575
25a. 2-Methyl Naphthalene	-2.770	-10.175	1.38	-8.795
26. Propanal	-2.695	-10.100	2.15	-7.950
7b. Butyl acetate	-2.680	-10.085	1.64	-8.445
20. Butylbenzene	-2.610	-10.015	0.00	-10.015
8a. Hexyl acetate	-2.540	-9.945	1.21	-8.735
7a. Butyl acetate	-2.370	-9.775	1.64	-8.135
4. 1-Octanol	-2.360	-9.765	2.63	-7.135
21. Hexylbenzene	-2.360	-9.765	-0.32	-10.085
16a. 2-Heptanone	-2.320	-9.725	1.92	-7.805
34. Acetic acid	-2.284	-9.689	4.55	-5.139
17. 2-Nonanone	-2.260	-9.665	1.56	-8.105
19. Ethylbenzene	-2.220	-9.625	0.23	-9.395
2a. 1-Butanol	-2.100	-9.505	2.98	-6.525
3. 1-Hexanol	-2.090	-9.495	2.62	-6.875
9. Octyl acetate	-1.690	-9.095	1.04	-8.055
40. Ozone	-1.540	-8.945	-1.88	-10.825

Chemical Stimulus	ODT (log ppm by vol) (gas phase)	ODT (log Molar) (gas phase)	LogKw ≈ Log Ksaline solut., both@37°C	ODT (log Molar) (saline sol.@37°C)
18b. Toluene	-1.530	-8.935	0.35	-8.585
12a. Ethyl heptanoate	-1.370	-8.775	1.19	-7.585
38. D-Limonene	-1.320	-8.725	-0.56	-9.285
16b. 2-Heptanone	-1.130	-8.535	1.92	-6.615
18a. Toluene	-1.100	-8.505	0.35	-8.155
22. Octylbenzene	-1.050	-8.455	-0.63	-9.085
18c. Toluene	-1.010	-8.415	0.35	-8.065
15. 2-Pentanone	-1.000	-8.405	2.22	-6.185
1b. Ethanol	-0.940	-8.345	3.32	-5.025
6a. Ethyl acetate	-0.610	-8.015	1.90	-6.115
10a. Ethyl propanoate	-0.530	-7.935	1.71	-6.225
1a. Ethanol	-0.480	-7.885	3.32	-4.565
2b. 1-Butanol	-0.450	-7.855	2.98	-4.875
39a. Chloropicrin	-0.320	-7.725	0.59	-7.135
33. Formic acid	-0.289	-7.694	4.96	-2.734
14. 2-Propanone (acetone)	-0.080	-7.485	2.60	-4.885

Reference

Abraham MH, Ibrahim A and Acree Jr. WE. 2007. Partition of compounds from gas to water and from gas to physiological saline at 310°K: linear free energy relationships. Fluid Phase Equilib. 251: 93-109.

Supplementary Table 2. For each of the 37 **chemesthetic** functions, we list the chemical stimulus tested and its **trigeminal chemesthetic** threshold (**Trigem.**) expressed as the following equivalent concentrations: log ppm by volume in the gas phase, log Molar in the gas phase, and log Molar in a liquid physiological saline solution at 37°C. The equivalence between Molar in gas phase and Molar in liquid saline phase at 37°C was established via the partition coefficient (logK) between the gas and liquid phases, as described earlier (Abraham *et al.* 2007). We note that logKwater and logKsaline at 37°C are essentially the same. Trigeminal thresholds include nasal pungency (NP), nasal localization or lateralization (NL), and eye irritation (EI). For each of these three threshold endpoints, chemicals are listed in increasing value of Trigem. expressed as log ppm by volume in the gas phase.

Chemical Stimulus	Trigeminal Endpoint	Trigem. (log ppm by vol) (gas phase)	Trigem. (log Molar) (gas phase)	LogKw ≈ Log Ksaline solut., both@37°C	Trigem. (log Molar) (saline sol.@37°C)
7e. Butyl acetate	NP	2.280	-5.125	1.640	-3.485
7d. Butyl acetate	NP	2.340	-5.065	1.640	-3.425
16c. 2-Heptanone	NP	2.370	-5.035	1.920	-3.115
12b. Ethyl heptanoate	NP	2.510	-4.895	1.190	-3.705
10b. Ethyl propanoate	NP	2.760	-4.645	1.710	-2.935
2c. 1-Butanol	NP	2.910	-4.495	2.980	-1.515
18e. Toluene	NP	3.690	-3.715	0.350	-3.365
18d. Toluene	NP	4.000	-3.405	0.350	-3.055
32b. Glutaraldehyde	NL	-0.330	-7.735	4.530	-3.205
41b. TXIB	NL	0.670	-6.735	4.470	-2.265
24b. 1-Methyl Naphthalene	NL	1.940	-5.465	1.610	-3.855
23b. Naphthalene	NL	1.970	-5.435	1.450	-3.985
25b. 2-Methyl Naphthalene	NL	2.170	-5.235	1.380	-3.855
8b. Hexyl acetate	NL	2.870	-4.535	1.210	-3.325
13. Butyl propanoate	NL	3.090	-4.315	1.780	-2.535
7f. Butyl acetate	NL	3.360	-4.045	1.640	-2.405
1d. Ethanol	NL	3.380	-4.025	3.320	-0.705
11b. Ethyl butanoate	NL	3.500	-3.905	1.530	-2.375

Chemical Stimulus	Trigeminal Endpoint	Trigem. (log ppm by vol) (gas phase)	Trigem. (log Molar) (gas phase)	LogKw ≈ Log Ksaline solut., both@37°C	Trigem. (log Molar) (saline sol.@37°C)
1c. Ethanol	NL	3.590	-3.815	3.320	-0.495
10c. Ethyl propanoate	NL	3.680	-3.725	1.710	-2.015
6b. Ethyl acetate	NL	4.010	-3.395	1.900	-1.495
32c. Glutaraldehyde	EI	-0.410	-7.815	4.530	-3.285
39b. Chloropicrin	EI	-0.110	-7.515	0.590	-6.925
41c. TXIB	EI	0.340	-7.065	4.470	-2.595
5. 1-Nonanol	EI	0.760	-6.645	2.850	-3.795
24c. 1-Methyl Naphthalene	EI	1.800	-5.605	1.610	-3.995
23c. Naphthalene	EI	1.870	-5.535	1.450	-4.085
7g. Butyl acetate	EI	1.980	-5.425	1.640	-3.785
25c. 2-Methyl Naphthalene	EI	2.000	-5.405	1.380	-4.025
16d. 2-Heptanone	EI	2.020	-5.385	1.920	-3.465
12c. Ethyl heptanoate	EI	2.190	-5.215	1.190	-4.025
7h. Butyl acetate	EI	2.240	-5.165	1.640	-3.525
2d. 1-Butanol	EI	2.690	-4.715	2.980	-1.735
10d. Ethyl propanoate	EI	2.790	-4.615	1.710	-2.905
18g. Toluene	EI	3.450	-3.955	0.350	-3.605
1e. Ethanol	EI	3.480	-3.925	3.320	-0.605
18f. Toluene	EI	3.680	-3.725	0.350	-3.375

Reference

Abraham MH, Ibrahim A and Acree Jr. WE. 2007. Partition of compounds from gas to water and from gas to physiological saline at 310°K: linear free energy relationships. Fluid Phase Equilib. 251: 93-109.

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