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Authors

Cometto-Muniz, J. Enrique
Cain, William S.
Abraham, Michael H.

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Detection of Single and Mixed VOCs by Smell and by Sensory Irritation

J. Enrique Cometto-Muñiz¹, William S. Cain¹, and Michael H. Abraham²

¹Chemosensory Perception Laboratory, Department of Surgery (Otolaryngology), University of California, San Diego, La Jolla CA 92093-0957, USA.

²Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK.

Address for correspondence:

J. Enrique Cometto-Muñiz, Ph.D.
Chemosensory Perception Laboratory,
Department of Surgery (Otolaryngology),
University of California, San Diego
9500 Gilman Dr. – Mail Code 0957
La Jolla, CA 92093-0957

Phone: (858) 622-5832

FAX: (858) 458-9417

e-mail: ecometto@ucsd.edu

Running head: Chemosensory Detection of VOCs

Abstract

We have measured complete concentration-detection (i.e., psychometric or detectability) functions to study the olfactory and ocular/nasal chemesthetic (a term that includes sensory irritation) impact of VOCs presented singly and in various binary mixtures. Such functions provide considerably more information than that provided by measuring only a “threshold”. The outcome for single VOCs confirmed the much higher absolute sensitivity of olfaction compared to chemesthesis, but also demonstrated that the detection of ocular and nasal sensory irritation increases as a function of vapor concentration at a much higher rate than that for the detection of odor. The outcome for the binary mixtures revealed that, for both olfaction and chemesthesis, complete additivity of detection of individual components held at relatively low levels of detectability but broke down at higher levels. The breakdown for odor detection, compared to that for sensory irritation detection, was, first, more extensive, and, second, dependent to a larger extent on the degree of structural and chemical similarity/dissimilarity between the mixed VOCs.

Key words: Concentration-detection functions — Odor detection — Eye irritation detection — Nasal pungency detection — VOC Mixtures — Chemosensory additivity.

Introduction

Complaints about the quality of the air in indoor environments very often involve symptoms of eye, nose, and throat irritation (Hodgson, 2002; Tsai and Gershwin, 2002), and sometimes perception of odors (Engvall et al., 2002). To understand and attempt to eliminate complaints based on these reactions, we need to know the levels at which chemicals present indoors begin to produce an olfactory response and those at which they begin to produce a chemesthetic response, such as sensory irritation. Chemesthetic responses in the mucosae of the face are principally mediated by the trigeminal nerve. There are a number of compilations of human odor thresholds (AIHA, 1989; Devos et al., 1990; Fazzalari, 1978; van Gemert, 1999) but the variability of reported values is so high, often 3 or more orders of magnitude, that it hampers the practical applicability of the data. Regarding ocular and nasal chemesthetic thresholds, it is crucial to control for odor biases since almost all irritants also evoke an odor sensation and, as a rule, do so beginning at lower concentrations than those producing irritation. Such control has not been common in compilations of sensory irritation thresholds (Ruth, 1986).

In 1989 we started to measure odor, nasal pungency, and eye irritation thresholds along homologous chemical series using a uniform procedure. The approach included vapor-phase measurements via gas chromatography, a simple but practical static-dilution delivery system (cf. Cain et al., 1992), and a sensory technique based on a forced-choice procedure that controlled for biases and for differences in response criterion across participants (Cometto-Muñiz and Cain, 1990). To control for odor biases in measurements of nasal pungency thresholds, we tested subjects lacking a functional sense of smell (called anosmics), as determined by a standardized clinical olfactory test

(Cain, 1989). This strategy to separate trigeminal from olfactory detection of volatile organic compounds (VOCs) was later followed by two additional strategies (Cometto-Muñiz and Cain, 1998): 1) measuring eye irritation thresholds in both anosmics and normosmics (i.e., subjects with normal olfaction) and 2) measuring, also in anosmics and normosmics, nasal localization or lateralization thresholds, that is, the ability to determine whether a VOC was presented to the right or left nostril when clean air is simultaneously inhaled via the contralateral nostril. Previous research determined that such localization is mediated by trigeminal, not olfactory, input (Kobal et al., 1989). The various strategies produced a similar outcome: olfactory thresholds for homologous VOCs typically lay between 1 and 5 orders of magnitude below trigeminal thresholds (see review in Cometto-Muñiz, 2001).

In a study of nasal localization of the neat chemicals benzaldehyde and eucalyptol, Hummel and colleagues found that normosmics (n=17) outperformed anosmics and hyposmics (n=35) in terms of the total sum of correct lateralizations, but no vapor concentrations were quantified and no thresholds were measured (Hummel et al., 2003). Another investigation of nasal localization in anosmics (n=5) and normosmics (n=4) for 1-propanol, 1-butanol, and 1-hexanol included measurement of thresholds and vapor quantification of all stimuli by gas chromatography, and found higher thresholds (i.e., lower sensitivity) in anosmics by a factor of 1.27, but the difference failed to achieve significance perhaps due to the small number of subjects (Cometto-Muñiz and Cain, 1998). Even if the difference in nasal trigeminal sensitivity between anosmics and normosmics is real, it pales compared with the differences between olfactory and trigeminal sensitivity mentioned above.

The absolute value of odor and sensory irritation thresholds measured under these standardized conditions might not directly represent thresholds obtained under actual whole-body exposures, but their consistency and the wide variety of VOCs tested proved to be extremely useful to establish robust quantitative structure-activity relationships (QSARs) between potency for odor (Abraham et al., 2002), for nasal pungency (Abraham et al., 1996; Abraham et al., 1998a), and for eye irritation (Abraham et al., 2003; Abraham et al., 1998b) and associated physicochemical characteristics.

A further step in understanding which VOCs might evoke sensations of smell and sensory irritation and under which conditions this might be expected to occur entails studying the detection of mixtures of chemicals. Occupants of buildings are exposed to dozens, perhaps hundreds, of chemicals at low concentrations. In the series of experiments described here we have begun to address the issue of chemosensory perception of mixtures by focusing on the simplest case: binary mixtures. The approach shared important features with our previous studies of single VOCs: vapor quantification by gas chromatography, a static vapor-delivery technique, and a forced-choice procedure. Rather than measuring a “threshold” value under some performance criterion we measured complete concentration-detection (also called psychometric or detectability) functions. These functions describe the probability of chemosensory detection as a function of concentration. They range from where detection occurs at chance, i.e., subthreshold level, to where detection becomes virtually perfect, i.e., beginning of the suprathreshold level (Cometto-Muñiz et al., 2002). Knowledge of the psychometric function for individual VOCs presented in mixtures facilitates a comprehensive and dynamic quantitative understanding of the rules of dose- and response-additivity in mixtures that the simple measure of a “threshold” value cannot

provide (Cometto-Muñiz et al., 1997). For example, these functions are quite revealing in terms of investigating the level-dependency of such rules.

At this early stage in our understanding of the rules for chemosensory detection of chemical mixtures, selection of the compounds to test is somewhat arbitrary. We have chosen the following VOC pairs: 1) 1-butanol/2-heptanone, 2) butyl acetate/toluene, and 3) ethyl propanoate/ethyl heptanoate. These specific compounds or their chemical class (e.g., ethyl esters) are commonly found in indoor air (e.g., Knudsen et al., 1999; Kostianen, 1995; Rothweiler and Schlatter, 1993; Wolkoff and Wilkins, 1994) and in model mixtures thought to be representative of indoor environments (Mølhave et al., 1991). The selected three pairs present varying contrasts. The first pair comprised two aliphatic, lineal, flexible molecules, with oxygen-containing but different chemical functionalities, and capable of interacting via hydrogen-bonds. The second pair presented a sharper contrast between components from a structural-chemical criterion: aliphatic vs. aromatic, lineal vs. cyclic, flexible vs. rigid, with little possibility of interacting via hydrogen-bonds. The third pair included chemically-similar components but allowed us to probe the role of a contrasting carbon chain length, within a homologous series, on the rules for detectability of mixtures.

Materials and Methods

All participants provided written informed consent on forms approved by the Human Research Protections Program (HRPP) of the University of California, San Diego. HRPP also approved the study protocol.

Subjects. For experiments on odor, all subjects performed in the normosmic range of a standardized clinical olfactory test (Cain, 1989) and were all nonsmokers. They ranged in age from 18 to 56 years. In each experiment we typically tested a group of 10 to 20 normosmics, with an approximately equal number of males and females.

For experiments on eye irritation, the same subject characteristics as above applied and, in addition, participants were not usual wearers of contact lenses.

For experiments on nasal pungency, all subjects were anosmics (Cain, 1989) and nonsmokers. They ranged in age from 20 to 74 years. In each experiment we typically tested 4 to 7 persons, with an approximately equal number of males and females. Most of these participants were either congenital or head-trauma anosmics. We avoided anosmics who might, under certain conditions, regain some of their olfactory ability; for example, those with nasal sinus disease.

Stimuli. Six single chemicals and three pairs of binary mixtures were studied. The mixtures were: 1-butanol (99.8% purity) and 2-heptanone (98%), butyl acetate (99+%) and toluene (99.8%), and ethyl propanoate (97+%) and ethyl heptanoate (98+%). Mineral oil (Light, Food Chemical Codex quality) served as solvent and blank.

All stimuli, single chemicals and mixtures, were quantified in the headspace, i.e., the vapor-phase, of the containers by gas chromatography (GC) (flame ionization detector or FID) (Cometto-Muñiz et al., 2003b). Weekly GC measurements were performed to confirm stability.

Procedure. We employed either a two- or a three-alternative forced-choice procedure against blanks. Detection probability (P) was corrected for chance and standardized by adjusting it to a scale ranging from 0.0 for chance detection to 1.0 for perfect detection according the following formula (Macmillan and Creelman, 1991):

$P = (mp - 1)/(m - 1)$, where P = detection probability corrected for chance, m = number of alternative forced-choices (here, 3), and p = proportion correct. Psychometric functions for single stimuli were obtained by an ascending concentration approach (cf. Cometto-Muñiz et al., 2002). Mixtures were presented in irregular order. The containers were adapted with either two nosepieces (Cometto-Muñiz et al., 2000) or an eyepiece (Cometto-Muñiz et al., 2001) for nasal and ocular stimulation, respectively (see Figure 1).

Insert Figure 1 about here

Preparation of mixtures. The concentration of each component in a mixture was selected based on the detectability of that concentration of the component as measured in its respective psychometric function. In the case of the mixture 1-butanol/2-heptanone, the mixtures were prepared by adding to the concentration series of one chemical (taken from its psychometric function) a fixed concentration of the second chemical corresponding to a known detectability, for example $P=0.20$ (taken from the psychometric function of the second chemical) (cf. Cometto-Muñiz et al., 1999). In this way, three more series were created with increasing fixed concentrations of the second chemical corresponding to $P=0.40$, 0.60 , and 0.80 . The same process was repeated but now using the concentration series of the second chemical to which fixed concentrations of the first chemical (corresponding to $P=0.20$, 0.40 , 0.60 , and 0.80) were added. Testing these stimuli produced families of psychometric functions where the added fixed

concentration of one component (e.g., that corresponding to $P=0.20$) could be transformed into an added “equivalent concentration” of the other component. If these functions for mixtures, based on “equivalent concentrations” of one chemical into the other (and vice versa), follow the same trend as the functions for one or the other single chemical, then it means that the outcome supports a model of dose-addition between the two components of the mixtures.

In the case of the other two mixtures (butyl acetate/toluene and ethyl propanoate/ethyl heptanoate), preparation of the mixtures was different from the above in the sense that the approach principally tested for response-addition. That is, would the actual detectability of the mixtures be approximated simply by the combination of the detectabilities of the individual components? If so, the following formula based on an assumption of complete additivity of detection for individual chemicals should predict the experimental results (Feller, 1968-1971):

$$P_{\text{det.A,B}} = 1 - [(1-P_{\text{det.A}})(1-P_{\text{det.B}})] \quad (1)$$

where $P_{\text{det.A,B}}$ = probability of detection of the binary mixture of chemicals A and B, $P_{\text{det.A}}$ = probability of detection of A alone, and $P_{\text{det.B}}$ = probability of detection of B alone. In this context, preparation of the mixtures entailed: 1) Choosing two or more detectability levels, e.g. $P=0.8$ and $P=0.4$. 2) From the already measured psychometric function of each component, finding the concentration producing these levels. 3) Testing, within the same experiment and subjects, the detectability of the concentration of the single chemicals A and B producing, for example, $P=0.8$, and that of three binary mixtures: a) one where A is at a concentration producing 3/4 of 0.8 (i.e., $P=0.6$) and B at 1/4 of 0.8 (i.e., $P=0.2$), b) one where A is at a concentration 1/2 of 0.8 (i.e., $P=0.4$) and B also at 1/2 of 0.8 (i.e., $P=0.4$), and c) one where A is at a concentration producing 1/4 of 0.8

(i.e., 0.2) and B at 3/4 of 0.8 (i.e., $P=0.6$). This gives a total of five stimuli: two are single (one per chemical, at $P=0.8$ in our example), and the other three are the mixtures just described. Note that, for the three mixtures, the sum of the individual detectabilities of A and B always equal 0.8, the same detectability as for single stimulus A and single stimulus B. The outcome of the experiment will be compared with that expected from equation (1) to see if there are significant deviations from the model assumed.

Results

Psychometric functions for single chemicals. Figure 2 shows odor, eye irritation, and nasal pungency detectability functions for each single chemical. Confirming previous results, olfactory functions lay at concentrations orders of magnitude lower than trigeminal functions and, within a homologous series (i.e., ethyl propanoate and heptanoate), the longer homolog was more potent than the shorter homolog both in terms of odor and of sensory irritation (Cometto-Muñiz, 2001). Within the chemesthetic modality, the ocular and the nasal mucosa were approximately equally sensitive, with a slightly higher sensitivity for the eye in the cases of 2-heptanone and ethyl heptanoate (interestingly, the largest compounds tested). The rate of growth for chemesthetic functions was higher than that for olfactory functions: It took an increase between 0.5 and 1.5 orders of magnitude in concentration for sensory irritation detectability to rise from chance to virtually perfect but it took an increase between 2 and 4.5 orders of magnitude for the same change to occur for odor detectability.

Insert Figure 2 about here

Detectability of mixtures

A) Mixtures of 1-butanol/2-heptanone. The straightforward “detection probability corrected for chance”, or ‘P’, that we have used in Figure 2, and that ranges from 0.0 (i.e., chance detection) to 1.0 (i.e., perfect detection), can be converted into what is called a Z-score. A normal distribution table is used to convert P values into Z-scores. This transformation assumes that the measured values are normally distributed against the independent variable, in this case log ppm. Under this assumption, concentration-detection functions that are shaped like an ogive, such as those in Figure 2, have the convenient feature of becoming linear when the P for each concentration is transformed into a Z-score via the normal distribution table (see Gescheider, 1997). Figure 3 illustrates that detectability (expressed as Z-scores) plotted as a function of butanol concentration (actual or equivalent) follows a similar trend whether the stimulus consists of butanol alone, heptanone alone (converted to butanol-equivalent concentrations) or mixtures of the two (where the heptanone component was converted to butanol-equivalent). Comparable results are obtained if detectability is plotted as a function of heptanone concentration, actual or equivalent (results not shown). The outcome gauged across this broad range of detectability suggests that, as a first approximation, dose-addition holds for the detection of odor, eye irritation, and nasal pungency from mixtures of butanol and heptanone.

Insert Figure 3 about here

B) Mixtures of butyl acetate/toluene. As described above, the strategy here tested whether mixtures of the two compounds in complementary proportions departed significantly or not from a model of response-additivity of individual components, as expressed in equation (1). The outcome for chemesthetic detectability at both sites (eyes and nose) revealed a common feature: At relatively high detectability levels, the mixtures

tended to fall short of complete additivity. This tendency was more pronounced for eye irritation than for nasal pungency. Figure 4 (top) illustrates the outcome for eye irritation, where three levels of detectability were probed, and Figure 4 (bottom) illustrates it for nasal pungency, where four levels of detectability were probed. An analysis of variance (ANOVA) gave statistical support to the observed trends: For eye irritation, there were significant differences among the three levels of detectability ($p < 0.001$) and among the five types of stimuli ($p < 0.02$), but not for their interaction. For nasal pungency, there were significant differences among the four levels of detectability ($p < 0.01$), no significant differences for the five types of stimuli but a significant interaction between the two factors ($p = 0.05$). The significance of the interaction indicates that the trend seen across type of stimulus is not uniform among the four levels of detectability. Such trend is relatively flat for the two lower detectability levels but it is shaped like a “U” for the two higher levels (Cometto-Muñiz et al., 2001).

Insert Figure 4 about here

The outcome for olfactory detectability revealed a qualitative similarity with the outcome for chemesthesis: Additivity of detection in olfaction also held at relatively low levels of detectability and decreased significantly at relatively high levels (Figure 5). Nevertheless, in quantitative terms, the outcome differed from that of chemesthesis: The decrease in additivity was more pronounced for olfactory than for trigeminal detection (Cometto-Muñiz et al., 2003a).

Insert Figure 5 about here

C) Mixtures of ethyl propanoate/ethyl heptanoate. Testing of this mixture followed the same strategy as with the previous one, i.e., a direct test of response-addition. The outcome for ocular and nasal chemesthetic detection paralleled that obtained with the butyl acetate/toluene pair in that: 1) at low detectability levels, eye irritation and nasal pungency did not depart from the values calculated from a model assuming complete additivity of detection (equation (1)), and 2) at high detectability levels, departure from complete additivity was more pronounced for eye irritation than for nasal pungency (Figure 6). In fact, for the present mixture, nasal pungency at high detectability levels did not depart from complete additivity. Even when the approach adopted to test the ethyl propanoate/ethyl heptanoate mixture directly tested response-addition, it is possible to use the detectability obtained for the single compounds at low and at high detectability to attempt calculation of “equivalent concentration” and look at dose-addition as done for 1-butanol/2-heptanone. When this is done, the same trends as observed in Figure 6 and mentioned above are obtained (Cometto-Muñiz et al., 2004).

Insert Figure 6 about here

In terms of olfactory detectability, the mixture of ethyl propanoate and heptanoate showed the same general trends observed so far: Complete additivity at relatively low levels of detectability that breaks down at higher levels (Figure 7). For this mixture, though, the departure of odor detection from complete additivity at high levels of detectability was far less dramatic than that observed for the mixture butyl acetate/toluene (compare Figure 7 with Figure 5).

Insert Figure 7 about here

Discussion

Measurement of psychometric functions for odor and sensory irritation detectability of VOCs provides us with a more comprehensive understanding of the olfactory and chemesthetic sensory modalities than that gained by measuring a “threshold” response. In terms of detection of single VOCs we have confirmed that, for any given compound, odor detection occurs at concentrations orders of magnitude lower than sensory irritation detection (Cometto-Muñiz, 2001), but also we have shown that the rate of growth for chemesthetic detectability, ocular or nasal, is much steeper than that for olfactory detectability (Cometto-Muñiz et al., 2002). As a direct practical consequence, we can state that any fixed reduction in the concentration of VOCs polluting an environment (e.g., a 2-times, 5-times, or 10-times reduction) will have a much more dramatic effect on detection of sensory irritation than in detection of odor. Thus, odors are much more difficult to eliminate by dilution.

An important observation made regarding the comparative chemesthetic potency of members of homologous chemical series relates to the appearance of a cut-off effect. Within such series, the vapor concentration threshold necessary to evoke mucosal sensory irritation decreases (i.e., potency increases) with carbon chain length, but only up to a certain size (Cometto-Muñiz et al., 1998). Eventually, a homolog is reached that lacks the ability to evoke chemesthesis reliably, even at vapor saturation. The failure extends to all ensuing homologs. Two mechanisms may account for the cut-off (Franks and Lieb, 1990). One rests on a physical restriction whereby the saturated vapor pressure of the VOC at room temperature falls below the threshold. The other rests on a biological restriction whereby a molecule lacks a key property to trigger transduction; for example, it could exceed the size that allows it to interact effectively with a target site or

to fit into a binding pocket in a receptive macromolecule. We are at present investigating whether the cut-off effect observed within a number of homologous series is likely to rest on a physical or on a biological mechanism. Our strategy rests on: 1) Heating the liquid source of the vapor stimulus from 23 °C (room temperature) to 37 °C (body temperature), thus substantially increasing the available vapor concentration. If the cut-off persists despite the increased concentration, a physical cut-off is unlikely. 2) Measuring psychometric functions, not just a “threshold”, for the 2-3 homologs bracketing the cut-off point and quantifying how chemesthetic detectability deteriorates with carbon chain length. 3) Sorting out the dimensional commonalities among the various biological cut-off homologs, and selected rigid comparison molecules, in order to develop a model of the maximum molecular dimensions beyond which any VOC vapor will fail to evoke sensory irritation. Our initial work with the acetate and n-alcohol homologous series suggests decyl acetate and 1-undecanol as the cut-off homologs.

Information gathered via psychometric functions can be especially revealing in terms of understanding the detection of mixtures. In particular, in terms of the role that detectability level of individual components might play on the degree of response-addition seen in the mixtures. We have made use of these functions to study the olfactory and trigeminal detectability of three types of binary mixtures, made of diversely contrasting chemical components, focusing on a dose-addition approach and on a response-addition approach. Within the context of this small number of examples, some interesting trends begin to emerge. At relatively low levels of detectability of the mixture components, e.g. $0.0 < P < 0.5$, both odor and sensory irritation (ocular and nasal) are characterized by complete additivity of detection (i.e., response-addition), irrespective of whether the components share considerable (ethyl propanoate/heptanoate) or little (butyl acetate/toluene) structural/chemical similarity. At relatively high levels of

detectability of the mixture components, e.g. $0.5 < P < 1.0$, complete additivity of detection tended to break down only slightly for nasal pungency, more for eye irritation, and most for odor. Nevertheless, only for olfactory detectability was it possible to attenuate this breakdown by switching from a quite dissimilar chemical pair (i.e., butyl acetate/toluene) to a relatively similar one (i.e., ethyl propanoate/heptanoate) (compare Figures 4 and 6). Overall, the outcome from these mixture studies corresponds to that of structure-activity studies of single VOCs (Abraham et al., 2001) in suggesting a broader chemical tuning in chemesthesis than in olfaction.

What might be the physiological basis for the observed level-dependence of chemosensory additivity? Virtually all sensory systems employ neural inhibition in the processing of information. In the simplest and probably most common instance, the information traveling along one line will modulate information traveling along an adjacent line, a phenomenon called lateral inhibition. Commonly, inhibitory influences exhibit level dependency. Research on processing of chemosensory information has shown the existence of strong inhibitory effects, some lateral, some feed-forward, and some feed-backward (e.g., Aungst et al., 2003; Halabisky and Strowbridge, 2003). The outcome of the present research suggests level dependence in such inhibition. At very low levels of stimulation the systems integrate the multiple signals from the environment. We can view this as the information-hungry level of processing, where fine differences get little emphasis. At progressively higher levels of stimulation, inhibition also increases progressively and sharpens differences in “kind” of stimulation. In the extreme case in olfaction, a strong odor will inhibit the apparent presence of weaker odors, masking them.

At this stage of understanding, we see the operation of level-dependent inhibition both for olfaction and chemesthesis, though more so for olfaction. This would mean that the strongest odor would dominate perception and, to a smaller extent, the most irritating source would dominate perception. The matter requires more study, particularly regarding chemesthesis, where both the eye and the nose may contribute to sensory irritation. If the present results on mixtures can be generalized, they lead to conclude that the stronger components make a disproportionately large contribution to total chemosensory impact.

Practical implications

Concentration-detection functions for the chemesthetic and olfactory detectability of VOCs have shown that, even when nasal pungency and eye irritation begin to be evoked at concentrations orders of magnitude larger than those evoking odor, they sharply increase in detectability to become clearly noticeable. In contrast, odor detectability increases with concentration at a much lower rate. As a result, any fixed reduction (e.g., 10-times) in the concentration of a VOC will reduce detectability of sensory irritation much more dramatically than detectability of odor, within their respective ranges. Concentration-detection functions are particularly informative when employed to probe into the rules of dose- and response-additivity in mixtures. Our results for olfaction, and to a lesser extent for chemesthesis, indicate that additivity of detection of individual VOCs in mixtures is level-dependent: As detectability increases, the degree of additivity decreases. This suggests that a substantial improvement of perceived air quality could follow from control of just the few dominating chemosensory sources.

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Figure legends

Figure 1. Top (Left). Picture of a 1,900-ml glass vessel used for nasal stimulation with chemical vapors. (Right). Picture of a subject being tested birhinally (i.e., both nostrils) via the glass vessels (from (Cometto-Muñiz et al., 2000)). Bottom (Left). Picture of the same glass vessels adapted with an eyepiece for ocular stimulation. (Right). Picture of a subject being tested for eye irritation (from (Cometto-Muñiz et al., 2001)).

Figure 2. Concentration-detection functions for the odor, eye irritation, and nasal pungency of the six chemicals tested singly. (1-Butanol and 2-heptanone are depicted with dashed lines.)

Figure 3. Detectability (expressed as Z-score) of the odor, eye irritation, and nasal pungency of single and mixed stimuli as a function of 1-butanol concentration. All 2-heptanone concentrations were expressed as “butanol equivalent” concentrations. Stimuli included: butanol alone (filled circles joined by dotted lines), heptanone alone (filled squares), and all binary mixtures of four concentrations of butanol with four increasing concentrations of heptanone depicted as crosses, triangles, diamonds, and empty circles, respectively. For each sensory endpoint, the best-fitting equation across all data, with its correlation coefficient, is also shown.

Figure 4. Top. Eye irritation detectability of three mixtures containing varying proportions of butyl acetate and toluene (three middle stimuli on each graph) and of two single stimuli (first and last stimuli on each graph) (filled symbols, continuous line) (see text). Three levels of detectability were probed (one per graph). At each level, the detectability of the mixtures is compared with the detectability calculated under a rule of complete

additivity of single stimuli (empty symbols, dashed line) (see text and equation (1)). Bars indicate standard errors. Bottom. Analogous to Top but for nasal pungency detectability, and probing four levels of detectability (one per graph).

Figure 5. Analogous to Figure 4 but regarding odor detectability of the pair butyl acetate/toluene. Note the profound decrease in detectability of the mixtures at medium and high levels of detectability of the individual compounds (middle and right graph).

Figure 6. *Left*. At relatively low levels of detectability, *eye irritation* evoked by mixtures of ethyl propanoate and heptanoate (filled squares) does not depart significantly from calculated complete additivity (empty squares) (see text and equation (1)), whereas at relatively high levels (filled circles) it falls short of complete additivity. *Right*. *Nasal pungency* evoked by the mixtures (filled symbols) does not depart from complete additivity (empty symbols) at either low (squares) or high (circles) detectability levels. Bars indicate standard errors.

Figure 7. Analogous to Figure 6 but regarding odor detectability of the pair ethyl propanoate/ethyl heptanoate. Note that the decrease in detectability of the mixtures at high levels of detectability of the individual compounds (filled circles) is evident but less profound than for the pair butyl acetate/toluene (Figure 5).

FIGURE 1

FIGURE 2

FIGURE 2

FIGURE 3

FIGURE 4

Top

Bottom

FIGURE 5

FIGURE 6

FIGURE 7

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