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Journal

Experimental Brain Research, 182(1)

ISSN

0014-4819

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Publication Date

2007

Data Availability

The data associated with this publication are within the manuscript.

Peer reviewed

Experimental Brain Research **182**:71-79, 2007

Concentration-detection functions for eye irritation evoked by homologous n-alcohols and acetates approaching a cut-off point

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Running head: Eye Irritation functions near a cut-off

Abstract

We measured concentration-detection (i.e., psychometric) functions for the eye irritation evoked by three homologous n-alcohols (1-nonanol, 1-decanol, and 1-undecanol) and two homologous acetates (nonyl and decyl acetate). A vapor delivery device based on a dynamic dilution of stimuli in nitrogen served to present various concentrations of each compound, including the undiluted vapor, to the subjects (n≥26). Delivered concentrations were quantified by gas chromatography. Detection probability (P) was assessed via a three-alternative, forced-choice procedure, and quantified on a scale ranging from P = 0.0 (chance detection) to P = 1.0 (perfect detection). Flowrate to the eye equaled 2.5 L/min and time of exposure was 6 sec. The functions for 1-undecanol and decyl acetate plateau at P ≈ 0.5 and P ≈ 0.25, respectively, such that further increases in concentration failed to increase detection notably. Thus, both series reached a break-point, or cut-off, in detection of ocular irritation. The present outcome provides additional evidence that the cut-off does not rest on the low vapor concentration of the homolog but, more likely, on the homolog exceeding a critical molecular dimension(s) which prevents it from interacting effectively with the appropriate receptors.

Keywords: Eye Irritation Psychometric Functions – n-Alcohols – Acetates – Ocular Chemesthesis – Eye Irritation cut-off

Introduction

Human sensitivity to airborne chemicals rests principally on two chemosensory systems: olfaction and chemesthesis. The latter (Green et al. 1990; Bryant and Silver 2000) is also known as chemically-induced somesthesis (Green and Lawless 1991) or chemical nociception (Hummel et al. 2003; Kwan et al. 2006). Environmental vapors producing chemesthetic sensations impinge preferentially on exposed mucosae such as the nasal, ocular, and, to a lesser extent, oral mucosa (Doty et al. 2004). Chemical nociceptors within free nerve endings of the trigeminal nerve (cranial nerve V) that innervate these mucosae respond to a wide variety of chemical vapors if the concentration of the vapors is high enough (Doty and Cometto-Muñiz 2003). In the nose, many chemicals presented at relatively low concentrations will activate exclusively the sense of smell, but will also begin to activate chemesthesis at higher concentrations (Cometto-Muñiz 2001). Perceptual differentiation between a strong smell and a weak nasal “feel” or irritation could prove difficult for a subject, and is likely to be biased by individual criterion (Cometto-Muñiz and Cain 1990). The task of nasal lateralization (or localization), whereby the subject seeks to identify the nostril (right or left) receiving the chemical stimulus when the other nostril simultaneously receives an identical puff of blank air, has proven a convenient tool to probe into detection of nasal chemesthesis unbiased by smell (Wysocki et al. 1997; Cometto-Muñiz and Cain 1998; Dalton et al. 2000). The approach relies on the observation that nasal lateralization is only achieved through trigeminal chemesthetic activation, not through olfactory stimulation (Schneider and Schmidt 1967; Kobal et al. 1989). In the eyes, chemical stimulation with vapors exclusively activates chemesthesis, resulting in eye irritation (Belmonte et al. 2004), and olfactory cues can be easily avoided by plugging the nose of the subject.

Information on ocular chemesthesis from vapors is scarce although it represents a convenient approach to investigate the physicochemical and structural determinants of the sensory irritation potency of airborne chemicals, particularly volatile organic compounds (VOCs) (Abraham et al. 1998a; Abraham et al. 1998b; Abraham et al. 2003). In comparison, more information is available on eye irritation from liquid chemicals (see review in (Gerner et al. 2005). Nevertheless, developing quantitative structure-activity relationships (QSARs) to understand the basis for the production of barely noticeable to very mild human eye irritation from environmental vapors is central to solve widespread problems related to sensory complaints regarding indoor air quality (Wolkoff et al. 2005; Wolkoff et al. 2006).

Previous human psychophysical studies on QSARs for the detection of ocular chemesthesis from VOCs revealed that the outcome is largely accounted for by selective, rather than specific, processes driving the action of these irritants on the ocular mucosa (Abraham et al. 2003). By selective we mean processes in which the key step is the transfer of the irritant from the air where the eye is exposed, through the various biophases in the ocular mucosa, to the receptor(s) biophase(s). By specific we mean processes in which the key step relies on the irritant possessing a narrowly tuned chemical structure, functionality, or conformation that when even slightly modified produces a dramatic change in activity. There are some prototypical irritants, usually active at much lower concentrations than general VOCs, that fit tightly and activate strongly a particular receptor, e.g., nicotine (Alimohammadi and Silver 2000; Thuerauf et al. 2006), capsaicin (Bae et al. 2004; Silver et al. 2006), isothiocyanates and thiosulfinates (Bautista et al. 2006), and menthol (Bandell et al. 2006), but even these “specific” receptors often display broad chemical selectivity (Trevisani et al. 2002; Macpherson et al. 2006).

Despite the prevalence of selective mechanisms to account for eye irritation potency from vapors, recent studies of homologous chemical series have shown the emergence of a cut-off point in chemesthetic detection (Cometto-Muñiz et al. 2005b; Cometto-Muñiz et al. 2006). In other words, a homolog is reached in the series that cannot be detected by eye irritation, even at vapor saturation. All larger homologs cannot be detected either. The outcome of these studies suggested that the cut-off rested on the irritant exceeding some critical molecular dimension(s) to fit the appropriate receptor(s) rather than on a low vapor concentration. If this is the case, a new parameter could be added to the QSAR model mentioned above to account for the dimension effect, similarly to what has already been accomplished for olfactory potency (Abraham et al. 2002). Cut-offs based on molecular size are well known and described for other biological effects of VOCs, namely anesthesia (Franks and Lieb 1985), where it has been shown that they can be used to define the features of target sites (Katz 2003). Interestingly, we note that volatile anesthetics were shown to directly stimulate olfactory receptors (Peterlin et al. 2005).

In the present investigation we set out to measure concentration-detection (i.e., psychometric or detectability) functions for ocular chemesthesis from homologous n-alcohols and acetates approaching a recently described cut-off point (Cometto-Muñiz et al. 2005b). We aim to determine whether, as these homologs reach (and pass) the cut-off point, gradual increases in concentration begin to fail to produce corresponding increases in detectability, as would be expected if a critical molecular dimension had been reached and started to hamper chemesthetic detection. In contrast, homologs situated before the cut-off point should still show corresponding increases in detectability with increasing vapor concentration.

Materials and Methods

The protocol for all experiments described here was approved by a Committee from the Human Research Protections Program of the University of California, San Diego. All subjects gave written informed consent on forms approved by the Committee.

Experiment 1: n-Alcohols

Subjects. We recruited 31 subjects (18 females) with an average age (±SD) of 24 (±8) years, ranging from 18 to 56 years old. All subjects were given a clinical olfactory test (Cain 1989) to assess smell sensitivity (no standardized test is available for either nasal or ocular chemesthetic sensitivity). Most subjects (n=26, 15 females) scored in the normosmic range, very few (n=4, 2 females) scored in the mildly hyposmic range, and one subject (a female) scored moderately hyposmic for one nostril. The eye irritation results from hyposmic subjects did not differ from that of normosmics, so their data was included. Three subjects (males) were smokers but their data was within the range of that for nonsmokers. Most subjects (n=22, 10 females) did not use contact lenses. Those who did (n=9, 8 females) refrained from using them on testing days; their data was not different from that of non-users.

A subset of 21 participants (11 females) from the pool described above had available time to complete, each, at least 20 trials per concentration (half with each eye) for **all three** chemicals. Data presented below for individual subjects refers to this more comprehensively tested group.

Stimuli. The chemicals tested (purity in parenthesis, FCC: Food Chemical Codex quality) included: 1-nonanol (98%), 1-decanol (98+%, FCC), and 1-undecanol (97%). Humidified medical grade air served as blank. Table 1 presents, for each chemical, the vapor concentrations tested, as determined by gas chromatography, and as determined by the ratio of stimulus flow / total (air+stimulus) flow (see Apparatus below).

Insert Table 1 about here

Apparatus. Stimuli vapors were presented to subjects from a dynamic dilution, vapor delivery device (VDD) controlled by a computer via LabView (National Instruments Corporation, Austin, Texas) software. In brief, the VDD generates a humidified (~50% RH) medical grade air, or blank, line and a stimulus-saturated (in nitrogen, N_2) line. Loading chemical vapor to the stimulus line is achieved by sparging N_2 through the neat liquid stimulus and filtering the output flow through an aerosol filter (model 33G, Parker, Metamore, Ohio) to remove any aerosol that might have been formed. The VDD includes four sparging bottles, and corresponding aerosol filters to use with up to four chemicals. A fifth sparging bottle contains distilled water and is used to humidify the air line. A vacuum system analogous to that devised by Kobal (Kobal 1985), and previously described (Jalowayski et al. 2001), allowed the experimenter to present blank air, a certain stimulus dilution (e.g., 60% v/v) or neat stimulus vapor (i.e., 100% v/v) to the subject's eye, virtually seamlessly. Closing a solenoid valve connected to a vacuum source added stimulus to the air line, while the simultaneous opening of another solenoid removed an equal amount of air. In any trial, the total flowrate to the eye equaled 2.5 L/min and time of exposure equaled 6 sec. Thus, if the concentration desired on a trial was 50% saturated vapor, a stimulus-line stream of 1.25 L/min entered the air line for 6 sec, while simultaneously 1.25 L/min of air exited for 6 sec. Identical

switching noises from solenoid valves were produced for each trial whether presenting stimulus or blank.

Procedure. One chemical was tested per session and the order of presentation of chemicals across sessions and subjects was randomized. Within a session, each trial entailed a three-alternative, forced-choice procedure against two blanks. Order of stimulus and blanks was also randomized. Wearing noseclips to avoid odor cues, subjects had to decide which of the three presentations felt different (typically stronger) to the tested eye. They also had to rate their confidence in the decision on a scale from 1 (not confident at all) to 5 (extremely confident). The experimenter started the session by presenting a trial including the lowest concentration of the particular chemical to one eye and then to the other. The procedure continued in ascending concentration (always alternating the tested eye) until the highest tested concentration was reached. (For 1-decanol and 1-undecanol, the highest concentration was the full stimulus strength, i.e., 100% v/v.) A rest period of at least 3 minutes followed before the whole process started again (beginning with the other eye) until, typically, 20 trials per concentration (half with each eye) were completed. Sessions lasted between 2 and 3 hours and included two 5-10 min breaks.

Data analysis. Results are summarized as either probability of eye irritation detection (i.e., detectability) or confidence rating as a function of vapor concentration for each chemical. Detectability (P) was corrected for chance (Macmillan and Creelman 1991) by adjusting it to a scale ranging form P = 0.0, i.e., chance detection, to P = 1.0, i.e., perfect detection, according to:

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

where P = detectability corrected for chance, m = number of choices per trial (in our case, three), and p(c) = proportion correct (i.e., number of correct trials / total number of trials).

Experiment 2: Acetates

Subjects. We recruited 26 subjects (15 females) with an average age (±SD) of 25 (±11) years, ranging from 18 to 56 years old. Four of them (3 females) had participated in Experiment 1. All subjects were given a clinical olfactory test (Cain 1989) to assess smell sensitivity (no standardized test is available for either nasal or ocular chemesthetic sensitivity). Most subjects scored in the normosmic range (n=21, 13 females), 3 (1 female) scored in the mildly hyposmic range for one nostril, and 2 (1 female) scored in the moderately hyposmic range for both nostrils. Eye irritation data from the few hyposmics was within the range observed for normosmics. Most subjects were nonsmokers (n=22, 13 females). Eye irritation data from the few smokers (n=4, 2 females) was within the range observed for nonsmokers. Most subjects (n=22, 12 females) did not wear contact lenses. Those who did (n=4, 3 females) refrain from wearing them on testing days; their eye irritation data was within the range observed for non-wearers.

Stimuli. The chemicals tested (purity in parenthesis, FCC: Food Chemical Codex quality) included: nonyl acetate (97+%, FCC) and decyl acetate (98%). Humidified medical grade air served as blank. Table 2 presents, for each chemical, the vapor concentrations tested, as determined by gas chromatography of samples taken at the outlet of the VDD, and as determined by the ratio of stimulus flow / total (air+stimulus) flow (see Apparatus, Experiment 1).

Insert Table 2 about here

Apparatus. Same as in Experiment 1.

Procedure. Same as in Experiment 1.

Data Analysis. Same as in Experiment 1.

Results

Experiment 1: n-Alcohols

Figure 1 (left) shows the concentration-detection functions for the three alcohols. Only 1-nonanol approached ($P \approx 0.80$) perfect detection ($P = 1.00$), and did it at a nominal concentration (90%v/v) below full vapor strength (100%v/v) (see Table 1). Both 1-decanol and 1-undecanol barely reached $P \approx 0.5$ at full strength. In fact, 1-undecanol reached a ceiling of detectability that could not be increased with a further increase in vapor concentration. Thus, a cut-off in eye irritation detectability emerged at the level of the 10-carbon n-alcohol and became clearer for the 11-carbon homolog. Confidence ratings closely followed the trends observed for detectability (Figure 1, right).

Insert Figure 1 about here

A look at the single subject data revealed that, despite individual variability, the trends were common to most subjects (Figure 2). A closer look at the individual graphs showed that: a) on one end, three subjects failed to detect almost all concentrations of the three chemicals whereas, on the other end, one subject detected almost perfectly all concentrations of the three chemicals, b) the most sensitive and the least sensitive subjects tended to include the same individuals across the three alcohols, and c) the distribution of sensitivities was quite continuous and did not separate sharply into discrete groups of subjects.

Insert Figure 2 about here

Experiment 2: Acetates

Figure 3 presents the psychometric functions for eye irritation obtained for nonyl and decyl acetate. The function for nonyl acetate grew continuously with concentration, and reached a detectability of $P \approx 0.5$. In contrast, the function for decyl acetate was much shallower, showed a tendency to plateau, and even at the highest concentration (100% v/v) only reached a detectability of $P \approx 0.25$. For each chemical, the trend in confidence ratings across concentration closely followed the trend observed in detectability, including the continuous increase for nonyl acetate and the flatness for decyl acetate (Figure 3).

Insert Figure 3 about here

A look at the outcome for individual subjects provided a picture of the variability across participants and of their common trends (Figure 4). The results were very

comparable to those for the alcohols. In general, the most sensitive and the least sensitive subjects were the same for the two acetates. A small group of three subjects performed at chance detection level for all concentrations of both acetates. For nonyl acetate, a number of subjects consistently increased detection with concentration. For decyl acetate, most subjects failed to increase detection consistently with concentration. One subject showed an uncommonly high detectability for decyl acetate, detaching from the group, but even in this case there was no consistent increase with concentration, admittedly, perhaps due to a ceiling effect. Interestingly, this participant was also the most sensitive for nonyl acetate, but for this compound the individual did show a trend of increased detection with concentration.

Insert Figure 4 about here

Discussion

The present outcome provides additional support to the existence of a cut-off in the ocular chemesthetic detection of homologous n-alcohol and acetate vapors at the levels of 1-undecanol and decyl acetate, respectively (Cometto-Muñiz et al. 2005b). In previous studies, only one or two concentrations per chemical were tested (Cometto-Muñiz et al. 2005b; Cometto-Muñiz et al. 2006). These corresponded to the saturated vapor at 23°C (room temperature), at 37°C (body temperature) or both. Here, by measuring psychometric functions, we have explored the detectability of a range of concentrations for each stimulus, often reaching up to the neat vapor (100 %v/v).

The cut-off points reported along these and previous series studied (ketones, alkylbenzenes, aldehydes, and carboxylic acids) (Cometto-Muñiz et al. 2005b; Cometto-

Muñiz et al. 2006; Cometto-Muñiz et al. 2007) represent the average at the group level. Nevertheless, in all investigations, the precise boundary for the cut-off has shown some variability across subjects. How can this individual variability be compatible with the argument of a cut-off based on a molecular size limit? One explanation considers the existence of genetic diversity regarding the exact structure and dimension(s) of chemesthetic receptors. Studies in animals have shown that genetic variability explains differences among individuals in their ability to detect nociceptive stimuli (Elmer et al. 1998; Mogil et al. 1999). Human psychophysical experiments on detection of nasal chemesthesis from VOCs showed that individual subjects might vary by one or two carbon units in the exact position of the cut-off homolog along a series but, once a subject reaches his or her cut-off, he or she never comes back to detect a larger molecule again (Cain et al. 2006). It is then possible that these differences in the point of cut-off rest on genetic variability among individuals in terms of the maximum homolog dimension(s) that their array of chemesthetic receptors can effectively accommodate. We note that even those participants who detect a cut-off homolog above chance reach a detectability plateau below perfect detection (i.e., below P = 1.0) such that further increases in concentration fail to increase detection (Figures 2, right, and 4, right) (see below).

The psychometric function approach introduced here allows us to re-assess the issue of whether vapor concentration alone is driving detection of the chemical or, at some point along the homologous series, some other property(ies), e.g., molecular dimension(s), begins to control detection. Note that the average function for 1-undecanol (Figure 1) and that for decyl acetate (Figure 3), i.e., the cut-off homologs, reach a detectability level where further increases in concentration fail to increase detection noticeably. No such effect is observed for the shorter homologs 1-nonanol (Figure 1) and

nonyl acetate (Figure 3). In fact, as noted above, a look at the individual functions reveals that, for the homologs located at (or beyond) the cut-off point, but not for those before it, almost all subjects reach a detectability level essentially unchanged by further concentration increases (Figures 2 and 4). For most participants, this level is around $0.3 \leq P \leq 0.7$ when it comes to 1-undecanol (Figure 2, right), and around $0.1 \leq P \leq 0.5$ when it comes to decyl acetate (Figure 4, right). These results, in line with previous studies where vapor concentration was increased by a single step via heating the stimulus source (Cometto-Muñiz et al. 2005b; Cometto-Muñiz et al. 2006; Cometto-Muñiz et al. 2007), suggest that the ocular chemesthetic cut-off is not based on a failure of the chemical to reach a sufficiently high concentration but, more likely, on the chemical exceeding some critical dimension(s) to stimulate effectively the relevant receptors.

This leads us to the important question: What are the relevant receptors for chemesthesis from VOCs? The large family of transient receptor potential (TRP) channels that includes the vanilloid, menthol, and other pungent compounds receptors is a likely candidate (Voets and Nilius 2003; Voets et al. 2005). So is the nicotinic receptor (Thuerauf et al. 1999). Chemically reactive VOCs capable of damaging cells can release intracellular nociceptive mediators which, in turn, stimulate endogenous receptors that signal damage to cells (Sutherland et al. 2000; Garle and Fry 2003). The neural substrate for ocular chemesthetic detection rests on unmyelinated C- and thin myelinated A_{delta}- fibers from the trigeminal nerve (Belmonte et al. 2004). Free nerve endings from these fibers function as polymodal nociceptors and have been shown to contain many of the above receptors (Alimohammadi and Silver 2000; Silver et al. 2006). Given the enormous chemical and structural diversity of airborne irritants (Cometto-Muñiz 2001) and the non-reactive nature of many of them, it is quite possible that their chemesthetic action results from the integration of a number of receptors and processes

(Clapham 2003; Inoue and Bryant 2005; Ramsey et al. 2006). This possibility is consistent with the success achieved by a QSAR model based on selective, rather than specific, chemical determinants of human chemesthetic potency (Abraham et al. 2001), as noted in the Introduction. All chemesthetic receptors are thought to be proteins. As such, they would have one or more receptive pockets that could accommodate effectively one or more irritant molecules provided that they do not exceed some critical dimension, similarly to what has been described for anesthetic potency (Eger and Laster 2001).

We pointed out that cut-offs from vapors have also been observed for nasal chemesthesis (Cometto-Muñiz et al. 2005a; Cain et al. 2006). A direct comparison between the ocular and the nasal mucosa in terms of the point of chemesthetic cut-off within and across homologous series awaits further research. If differences are found, it would be interesting to develop strategies that could distinguish between the relative roles played by the perireceptor environment, e.g., tear film vs. nasal mucus, and those played by the presence and relative distribution of particular classes of chemesthetic receptors themselves (Wood and Docherty 1997; Lee et al. 2005). Aside from mucosal site, another revealing variable to explore regarding the cut-off effect is time of exposure. In all the chemesthetic detection studies cited, time of exposure remained in the acute range, between 3 and 24 sec. It has been consistently shown that ocular and nasal chemesthesis change with exposure time such that perceived intensities increase and detection thresholds decrease (Cometto-Muñiz and Cain 1984; Cain et al. 1986; Wise et al. 2004; Wise et al. 2005; Shusterman et al. 2006; Wise et al. 2006). In this context, one would predict that homologs located before the cut-off point will show a trade-off between exposure time and concentration such that a higher level of chemesthetic detectability would be achieved at a fixed concentration if time were increased. In

contrast, those homologs located beyond a cut-off point that rests on molecular dimensions will not show the trade-off. That is, increasing the duration of stimulation will not precipitate detection. Future investigations will need to address these issues.

Acknowledgments

The work described in this article was supported by Philip Morris USA Inc. and Philip Morris International, and by research grant number R01 DC 005003 from the National Institute on Deafness and Other Communication Disorders, National Institutes of Health. Thanks are due to K. Balch and J. Keeley for excellent technical assistance. Thanks are also due to Y. Nobumori, J. Liu, and A. Liang for their help in various stages of the study.

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Tables

Table 1. Concentrations tested for each n-alcohol as determined by gas chromatography (flame ionization detector, FID) of samples taken at the outlet of the vapor delivery device (expressed in ppm and in log ppm by volume), and as determined by the ratio of stimulus flow / total (air+stimulus) flow (in % v/v) set with the device (see Apparatus). SD represents standard deviation.

CHEMICAL	ppm ±SD	log ppm ±SD	% v/v
1-Nonanol	2.2 ±0.78	0.350 ±0.130	20
	4.7 ±0.47	0.670 ±0.042	30
	5.5 ±0.51	0.742 ±0.047	50
	6.5 ±1.3	0.812 ±0.087	70
	10 ±0.55	1.009 ±0.023	90
1-Decanol	0.56 ±0.21	-0.252 ±0.169	20
	1.8 ±0.31	0.246 ±0.080	40
	2.4 ±1.3	0.375 ±0.185	60
	3.0 ±1.8	0.471 ±0.302	80
	4.5 ±1.8	0.620 ±0.170	100
1-Undecanol	0.022 ±0.001	-1.658 ±0.022	10
	0.083 ±0.006	-1.081 ±0.032	40
	0.13 ±0.016	-0.897 ±0.054	70
	0.17 ±0.019	-0.761 ±0.049	80
	0.28 ±0.028	-0.549 ±0.044	90
	0.45 ±0.19	-0.347 ±0.120	100

Table 2. Concentrations tested for each acetate as determined by gas chromatography (flame ionization detector, FID) of samples taken at the outlet of the VDD (expressed in ppm and in log ppm by volume), and as determined by the ratio of stimulus flow / total (air+stimulus) flow (in % v/v) set with the VDD (see Apparatus). SD represents standard deviation.

CHEMICAL	**ppm ±SD**	**log ppm ±SD**	**% v/v**
Nonyl acetate	9.4 ±2.5	0.962 ±0.110	20
	17 ±2.6	1.214 ±0.068	40
	33 ±2.1	1.522 ±0.027	60
	43 ±5.7	1.632 ±0.056	80
	51±5.0	1.709 ±0.042	100
Decyl acetate	2.1 ±1.9	0.102 ±0.569	20
	2.7 ±1.1	0.395 ±0.156	40
	4.6 ±1.1	0.656 ±0.107	60
	6.1±1.5	0.773 ±0.109	80
	6.6±1.0	0.815 ±0.066	100

Figure legends

Figure 1. Left. Concentration-detection (i.e., psychometric) functions for eye irritation from 1-nonanol, 1-decanol, and 1-undecanol vapors. Each point represents the average of 100 to 528 trials collected from up to 26 subjects. Bars indicate standard error. Right. Ratings of confidence of detection for eye irritation as a function of concentration for the three alcohols. Bars indicate standard error. Note how closely the trends in confidence (assessed by ratings) follow the trends in detectability in the left graph (assessed by actual performance) across the concentration ranges explored for each of the three alcohols.

Figure 2. Individual functions (dotted lines) for eye irritation detectability of alcohols in 21 subjects. Each small symbol represents the same subject in all three graphs and summarizes the outcome of 20 trials per concentration and chemical. Large symbols represent the group average function (thick, continuous lines) for 1-nonanol (filled circles), 1-decanol (filled squares), and 1-undecanol (filled diamonds).

Figure 3. Left. Average psychometric functions (left *y*-axis, filled symbols) and confidence ratings (right *y*-axis, empty symbols) for the eye irritation evoked by nonyl acetate. Each point represents the average of 660 trials made by 26 subjects. Bars indicate standard errors. Right. Analogous data but for decyl acetate. Each point represents the average of 600 trials made by 25 subjects.

Figure 4. Individual functions (dotted lines) for eye irritation detectability of acetates in 25 subjects. Each small symbol represents the same subject in both graphs and summarizes the outcome of 20 to 40 trials per concentration and chemical. Large

symbols represent the group average function (thick, continuous lines) for nonyl acetate (filled circles) and decyl acetate (filled squares).

FIGURE 1

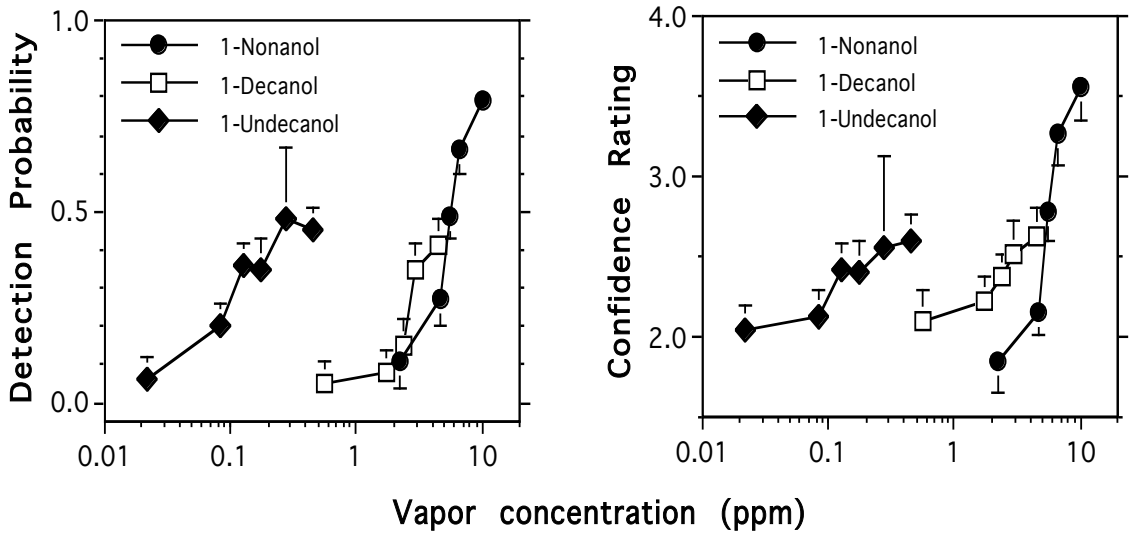


FIGURE 2

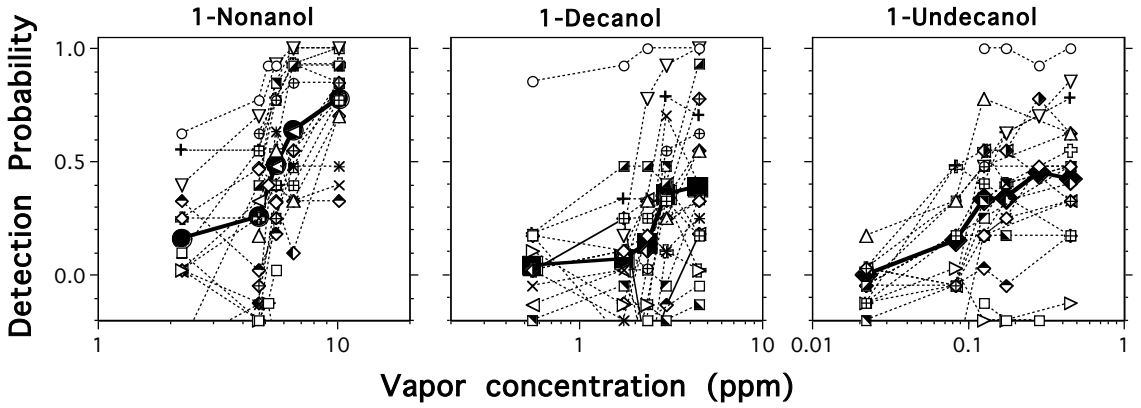


FIGURE 3

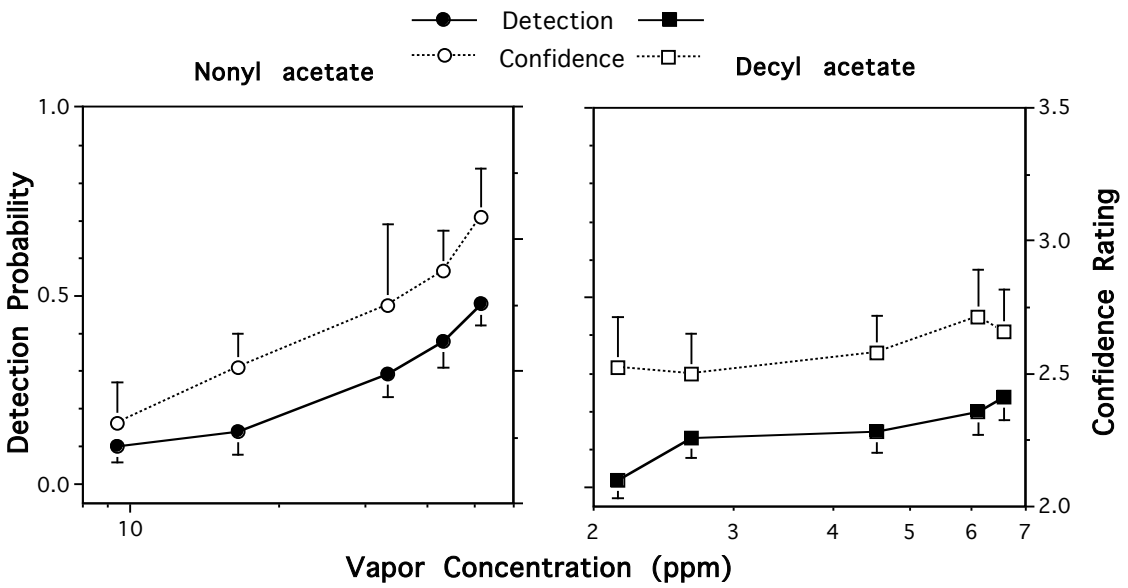
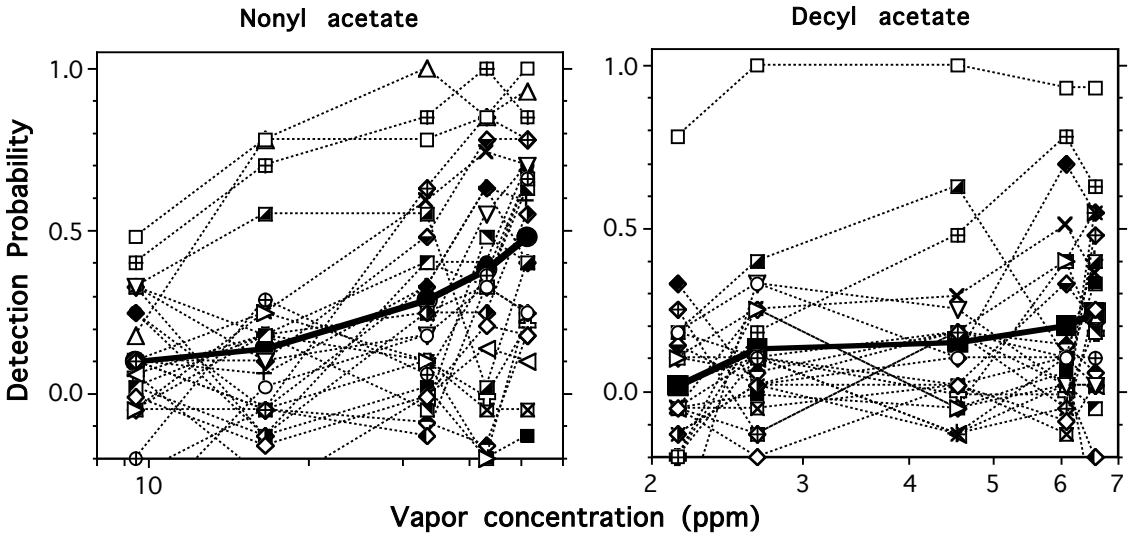


FIGURE 4



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