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Odor detection by humans of lineal aliphatic aldehydes and helional as gauged by dose-response functions

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Running head: Odor Detectability of Aldehydes

Abstract

We have measured concentration-detection (i.e., psychometric) functions to determine the odor detectability of homologous aliphatic aldehydes (propanal, butanal, hexanal, octanal, and nonanal) and helional. Subjects ($16 \leq n \leq 18$) used a three-alternative forced-choice procedure against carbon-filtered air (blanks), under an ascending concentration approach. Generation, delivery, and control of each vapor were achieved via an 8-station vapor delivery device. Gas chromatography served to quantify the concentrations presented. Group and individual functions were modeled by a sigmoid (logistic) equation. Odor detection thresholds (ODTs) were defined as the concentration producing a detectability (P) half-way (P=0.5) between chance (P=0.0) and perfect detection (P=1.0). ODTs decreased with carbon chain length: 2.0, 0.46, 0.33, and 0.17 ppb, respectively, from propanal to octanal, but the threshold increased for nonanal (0.53 ppb), revealing maximum sensitivity for the 8-carbon member. The strong olfactory-receptor ligands octanal and helional (0.14 ppb) showed the lowest thresholds. ODTs fell at the lower end of previously reported values. Inter-individual variability (ODT ratios) amounted to a factor ranging from 10 to 50, lower than typically reported, and was highest for octanal and hexanal. The behavioral dose-response functions emerge at concentrations 2 to 5 orders of magnitude lower than those required for functions tracing the activation of specific human olfactory receptors by the same aldehydes in cell/molecular studies, after all functions were expressed as vapor concentrations.

Keywords: Olfactory detection functions, odor thresholds, homologous aldehydes, helional, odor potency, olfactory structure-activity relationships.

Introduction

Available data indicate that the detection of odorants by the olfactory sense is based on a combinatorial code of activated olfactory receptors (**ORs**) (Buck 2004). That is, each odorant activates a pattern of ORs and, conversely, each OR responds to a number of odorants (Firestein 2004). In addition, each olfactory sensory neuron (**OSN**) is thought to express one type of OR (Malnic 2007). Humans have a total of 800 olfactory genes of which about 380 code for intact protein receptors (Olender *et al.* 2008). The rest are pseudogenes, albeit some pseudogenes might still be functional (Lai *et al.* 2008). Thus, there are close to 400 types of human ORs, although very few from any species, with the exception of Drosophila, have been linked to their respective odorant ligands, i.e., have been de-orphanized (Malnic 2007).

A few de-orphanized ORs from mammals have been found to be strongly responsive to aldehydes, in particular homologous aliphatic aldehydes, e.g., butanal (Mizrahi *et al.* 2004), heptanal (Krautwurst *et al.* 1998), octanal (Araneda *et al.* 2000; Araneda *et al.* 2004; Benbernou *et al.* 2007; Hall *et al.* 2004; Peterlin *et al.* 2008; Zhao *et al.* 1998) and nonanal (Benbernou *et al.* 2007; Sanz *et al.* 2005), as well as bulkier and/or more rigid aldehydes, e.g., helional (Hatt *et al.* 1999; Jacquier *et al.* 2006; Wetzel *et al.* 1999), lilial (Cook *et al.* 2009; Doszczak *et al.* 2007), lyral (Grosmaitre *et al.* 2006; Singer and Shepherd 1994; Touhara *et al.* 1999), citronellal (Krautwurst *et al.* 1998; Schmiedeberg *et al.* 2007; Shirokova *et al.* 2005; Stary *et al.* 2007) and bourgeonal (Spehr *et al.* 2004). Some of these ORs are human ORs (Doszczak *et al.* 2007; Hatt *et al.* 1999; Jacquier *et al.* 2006; Sanz *et al.* 2005; Schmiedeberg *et al.* 2007; Wetzel *et al.* 1999). In principle, one can predict that the particular aldehyde(s) shown to be the most potent ligands in cell/receptor assays employing human ORs could also turn out to be

the most potent odorants (i.e., those with the lowest threshold) in human psychophysical detection tasks. Obviously, many other factors beyond the bare odorant ligand/OR interaction can modulate this outcome. These factors not only include the influence of neural processing at higher levels of the olfactory pathway but also include events happening even before the ligand/receptor interaction, for example, the influence of odorant binding proteins (**OBPs**) (Ko *et al.* 2009; Vidic *et al.* 2008). In this regard, a human OBP has been shown to posses binding specificity for aldehydes (Tcatchoff *et al.* 2006), and a rat OBP was shown to increase the odorant detection sensitivity of the rat ORI7 to its specific odorant ligand octanal (Ko and Park 2008). These findings illustrate the need to complement the study of olfactory structure-activity relationships at the cell/receptor level (Araneda *et al.* 2004; Hall *et al.* 2004; Saito *et al.* 2009; Singer 2000) with those at the psychophysical odor detection level (Abraham *et al.* 2002; Abraham *et al.* 2007b; Cometto-Muñiz and Abraham 2008a; 2009a) to gain a comprehensive understanding of the olfactory system sensitivity as a whole.

In the present study we measure human concentration-detection (i.e., psychometric) functions for the odor of selected aliphatic aldehydes and for helional, both at the individual and group ($16 \leq n \leq 18$) levels. The research is part of a broader effort to establish quantitative structure-activity relationships (**QSARs**) for the human olfactory detection of airborne chemicals, under an apparatus and methodology aimed to minimize sources of chemico-analytical and psychophysical variability and uncertainty, while enhancing speed and efficiency of subject testing (Cometto-Muñiz *et al.* 2003; Cometto-Muñiz and Abraham 2008a; Cometto-Muñiz *et al.* 2008; Cometto-Muñiz and Abraham 2009a; b). The obtained dose-response functions can be compared to equivalent functions from receptor and olfactory neuron measurements (at the

peripheral, olfactory bulb, and/or higher neural levels) to gain novel insights into the detection and processing of chemical signals via olfaction.

Materials and Methods

An institutional review board at the University of California, San Diego, approved the protocol for all experiments described here. All participants provided written informed consent.

Stimuli. We tested the following aldehydes (purity or source and CAS number in parenthesis, FCC: Food Chemical Codex quality): propanal (97%) (CAS 123-38-6), butanal (≥99%) (CAS 123-72-8), hexanal (98%) (CAS 66-25-1), octanal (99%) (CAS 124-13-0), nonanal (95+%, FCC) (CAS 124-19-6), and helional, i.e., alpha methyl-1,3-benzodioxole-5-propanal (International Flavors and Fragrances, IFF) (CAS 1205-17-0).

Subjects. A total of 43 participants (19 female) ranging from 18 to 37 years of age were recruited. They were nonsmokers and all performed in the normosmic (normal sense of smell) range in a clinical olfactory test (Cain 1989). Not all subjects were available to be tested with every aldehyde but 2 participants (female) were tested with all six stimuli. Table 1 presents the characteristics of the various subgroups of participants.

Insert Table 1 about here

Apparatus and Procedure. We used an olfactometer especially designed with the aim of optimizing the generation, delivery, and control of odorant vapors, as well as the efficiency of subject testing in human chemosensory detection tasks. The instrument is

an 8-station vapor delivery device (VDD8) that has been described in detail in recent publications (Cain *et al.* 2007; Cometto-Muñiz and Abraham 2008a; Cometto-Muñiz *et al.* 2008; Cometto-Muñiz and Abraham 2009a; b). Briefly, each station consists of three sniffing cones: two presenting blanks (carbon-filtered air) and one presenting the odorant (active cone), randomly selected in each trial. Participants move sequentially from station 1 (lowest concentration) to station 8 (highest concentration), selecting in each station the cone that smells different, and rating their confidence in the decision on a scale ranging from "1" (not confident at all, just guessing) to "5" (extremely confident). Thus, we employ a three-alternative, forced-choice procedure with an ascending concentration approach. Local extraction of air above the cones and a very high room ventilation rate (18 air changes per hour, ach) with 100% fresh air (no recirculation) maintain an environment with negligible odor background. Dilutions are achieved in the VDD8 by changing ratios between the odorant-line flow and the (carbon-filtered) air-line flow, both tightly monitored. The dilution occurs at the base of the active cones. A speaker system instructs subjects to sniff from each cone in a 5-sec window and to wait 15 sec before continuing to the next station. After finishing with all 8 stations (what we call a "round"), participants leave the room. The experimenter sets a new random order of active cones and waits for at least 5 min. Then, the subjects are called back and perform another round. During the course of a day (session), participants complete 35 rounds. Sessions with a particular aldehyde continue until at least 16 subjects have finished testing. The order of testing of aldehydes was randomized.

Gas chromatography. Quantification of the concentrations delivered was confirmed by gas chromatography (GC) (flame ionization detector, FID) by means of a calibration curve for mass, specific for each odorant (Cometto-Muñiz *et al.* 2003). On every testing day, before subjects started the session and one or two times per hour thereafter, we

took vapor samples from the odorant-line and injected them into the GC instrument for reading against the calibration curve. The samples were taken from a sampling port in the path of the metered odorant-line flow, centimeters before it enters the base of the cone and is diluted to its final concentration by the metered air-line flow. (Sampling right before the final dilution at the cone provided odorant concentrations that are just high enough to be read by direct injection into the GC). The average coefficient of variation of these vapor concentrations across testing sessions (i.e., days) equaled 28% for propanal, 13% for butanal, 15% for hexanal, 22% for octanal, 23% for nonanal, and 32% for helional. The range of final concentrations tested for each aldehyde, in seven binary steps, was: 0.12 to 15 parts per billion by volume (ppb) for propanal, 0.056 to 7.1 ppb for butanal, 0.049 to 6.2 ppb for hexanal, 0.018 to 2.3 ppb for octanal, 0.029 to 3.7 ppb for nonanal, and 0.020 to 2.6 ppb for helional.

Data analysis and modeling. The outcome is summarized as plots of detection probability corrected for chance, i.e., detectability, (P) vs. vapor concentration in log ppb (called psychometric functions), and as confidence rating vs. vapor concentration (log ppb). Correction for chance produced a number between P = 0.0 (chance detection) and P = 1.0 (perfect detection) according to (Macmillan and Creelman 1991):

$$P = (m \cdot p(c) - 1) / (m - 1) \qquad \text{Equation (1)}$$

where P = detection probability corrected for chance, m = number of choices per trial (here, three), and p(c) = proportion correct (i.e., number of correct trials / total number of trials).

A sigmoid (logistic) equation served to model psychometric functions for the group and for each individual as follows:

$$P = P_{max} / (1 + e^{(-(x-C)/D)}) \qquad \text{Equation (2)}$$

where P = detection probability ($0 \leq P \leq 1$), $P_{max} = 1.0$, x = vapor concentration (log ppb by volume), and C and D are constants (fitted parameters). C is the value of x when P=0.5, that is, when detection probability is half-way (P=0.5) between chance (P=0.0) and perfect (P=1.0) detection. Constant C was taken as the odor detection threshold (**ODT**) expressed in log ppb. In turn, the constant D defines the steepness of the function such that the smaller the value of D, the steeper the function. Statistical significance was established by analysis of variance (**ANOVA**) (SuperANOVA v.1.11, Abacus Concepts, Inc., Berkeley, CA).

Results

Figure 1 (left) presents the group psychometric functions for homologous aldehydes and helional. Along homologs, functions shifted progressively to the left (i.e., towards lower concentrations) from propanal to octanal, indicating an increase in olfactory potency, that is, a decrease in odor threshold, with increasing carbon chain length. This trend ended with nonanal, whose function shifted to the right (higher threshold), close to that of butanal. Helional, the aldehyde outside the homologous series, was the most potent odorant, slightly more so than octanal. Its psychometric function was shifted to the extreme left and, consequently, had the lowest threshold. As expected, these patterns of odor detectability were closely mirrored by those of confidence ratings (Figure 1, right). Table 2 quantifies the key parameters of the group function for each aldehyde, including: ODT (in ppb), C(±SE) (in log ppb), D(±SE), and two measurements of goodness of fit: R^2 and Chi Square. The sigmoid, equation (2), provided a very adequate fit to the experimental data. The lower section of Table 2 shows the same key parameters but for the 2 common subjects tested with all 6 odorants. The close similarity between the outcome for all subjects and that for the

common subjects indicates that differences in threshold among compounds are not due to differences in subject samples.

Insert Figure 1 and Table 2 about here

Supplementary Figures S1 to S6 present the individual psychometric functions for all aldehydes. Each subject was assigned a unique number so the performance of participants tested with more than one aldehyde can be followed across odorants. Table 3 quantifies each of these individual functions in terms of C, D, and R^2. We see that the sigmoid, equation (2), also provided a very close fit to individual data, with 90 of the 100 individual functions having an R^2 of 0.90 or higher.

Insert link to Supplementary Figures S1 to S6 and Table 3 about here

The results of a two-way ANOVA for the factors gender and aldehyde on the individual values of C (i.e., the ODT in log ppb) revealed a significant effect for aldehyde {$F(5,88) = 20.8$, $p < 0.0001$} but not for gender or the interaction gender X aldehyde. A follow-up contrast within the aldehyde factor showed that ODTs for the two odorants reported to be the most potent ligand for a specific olfactory receptor (octanal and helional) were significantly lower than those for the rest of the aldehydes ($F = 63.6$, $p < 0.0001$), giving statistical support to the results shown in Figure 1 (left), and Tables 2 and 3. As mentioned, the value of D reflects the steepness of the psychometric function. D can be calculated from the group function (Table 1) or from the average of individual Ds (Table 2). The values of D from the group functions ranged from 0.20 to 0.44 (Table 1), and were higher than those averaged from individual functions which ranged from 0.11 to 0.26 (Table 2). In any case, neither set of D values showed a consistent trend

among homologs, or between aldehydes that have been shown to be the most potent ligand for a specific olfactory receptor and those that have not.

Discussion

Group odor detectability

Olfactory potency along homologous aldehydes increased consistently (i.e., thresholds decreased) between propanal and octanal. This trend has been observed before in a study that delivered the aldehydes via a "squeeze bottle" system and measured ODTs using a fixed-performance criterion (Cometto-Muñiz *et al.* 1998) rather than the comprehensive psychometric function approach employed here. Still, two important differences emerge between present and previous aldehydes data. The first difference is that the present ODTs are lower than those obtained previously, although the gap between the two sets of ODTs decreases with increasing carbon chain length. For the three aldehydes common to both studies, we find that the gap equals 3.8 orders of magnitude for butanal, 2.4 for hexanal, and 1.4 for octanal. In fact, using the present approach, we consistently found lower ODTs than previously observed (and also found a decreasing gap) for all series tested: n-alcohols (Cometto-Muñiz and Cain 1990; Cometto-Muñiz and Abraham 2008a), acetates (Cometto-Muñiz and Cain 1991; Cometto-Muñiz *et al.* 2008), 2-ketones (Cometto-Muñiz and Cain 1993; Cometto-Muñiz and Abraham 2009b), and alkylbenzenes (Cometto-Muñiz and Cain 1994; Cometto-Muñiz and Abraham 2009a). As discussed in the recent papers just cited, the improvements in olfactometric and psychophysical techniques led to lower ODTs by removing various sources of uncertainty and variability (i.e., "noise"). The second difference between the present and previous aldehydes data resulted from expanding

the range of homologs tested by adding propanal and nonanal at each end. We now find that the trend in decreasing thresholds is reversed upon reaching the 9-carbon homolog, whose ODT now increases. The result alters the trend that showed monotonically decreasing ODTs as a function of carbon chain length into one that shows an incipient U-shape (Figure 2). In fact, two additional recently study series, acetates and alkylbenzenes, also show this U-shape trend (Cometto-Muñiz *et al.* 2008; Cometto-Muñiz and Abraham 2009a) (Figure 2). The outcome suggests that human olfactory sensitivity measured at the integrated, behavioral, level reaches an optimum molecular dimension (or size) within homologous series such that odor detectability peaks at a certain chain length, declining for smaller or larger homologs. The phenomenon is somewhat reminiscent of the cut-off effect observed for trigeminal chemosensory irritation (i.e., chemesthesis) (Cometto-Muñiz *et al.* 2007a). Nevertheless, the chemesthetic cut-off is quite more drastic than the effect in olfaction since homologs beyond a certain size do not just increase their irritation threshold (becoming less potent) but loose altogether their ability to evoke chemesthesis, even when one increases vapor concentration by heating the liquid chemical (Cain *et al.* 2006; Cometto-Muñiz *et al.* 2005a; b; Cometto-Muñiz *et al.* 2006; Cometto-Muñiz *et al.* 2007a; b; Cometto-Muñiz and Abraham 2008b). Although the two remaining series: n-alcohols and 2-ketones reached a plateau in ODTs rather than showing a U-shaped trend (Figure 2), the possibility remains that subsequent homologs beyond 1-octanol and 2-nonanone might show an increase in ODTs. The issue is open for further investigation. We note that the aldehydes have the lowest thresholds among all the tested series (Figure 2). This might be related to the existence of specific ORs for the aldehydes, as discussed below, and/or to their particular chemical reactivity (Abraham *et al.* 2007b). Within the aldehydes tested, those that were found to be the most potent ligands for specific ORs

(cases of octanal and helional) also were the ones with the lowest ODTs by, at least, a factor of 2 (Table 2).

Insert Figure 2 about here

One could argue that if the present and other recent work did indeed succeed in minimizing various sources of interfering "noise" in sensory and chemico-analytical measurements, then the obtained ODTs should appear at the low end of reported values from odor threshold compilations (Devos *et al.* 1990; van Gemert 2003). Figure 3 shows that this is precisely the case. Our ODTs are close to those recently reported by Nagata (Nagata 2003) using a triangle odor bag method (Iwasaki 2003).

Insert Figure 3 about there

In terms of the steepness of the functions (quantified by the value of D), we have not found a consistent trend among aldehydes. Other series have produced mixed results. n-Alkylbenzenes and 2-ketones have shown no or partial trends (Cometto-Muñiz and Abraham 2009a; b) whereas n-alcohols and acetate esters have shown a significant decrease in the value of D (i.e., functions became steeper) with increasing carbon chain length (Cometto-Muñiz and Abraham 2008a; Cometto-Muñiz *et al.* 2008). Perhaps the uniformity of D values across aldehydes reflects the fact that they might activate quite specifically a narrower range of ORs that the other series. This would agree with: 1) the relative narrow overall range of ODTs from highest to lowest seen for the aldehydes compared to the other series tested (Figure 2), and 2) the considerably higher odor potency (i.e., lower ODTs) of aldehydes compared to other series (Figure 2).

Individual odor detectability and intersubject variability

The considerable amount of odor detection data gathered per subject allowed us to examine individual psychometric functions for each aldehyde (Supplementary Figures S1 to S6, and Table 3). As was the case for the group data, the sigmoid equation (2) also provided a very adequate description of individual data. A question of interest among our group of normosmic, nonsmoker, young adults was the extent of performance variability across subjects for each aldehyde. The ratio of ODTs (in ppb) between the least and the most sensitive subject equaled 6 for propanal, 8 for butanal, 53 for hexanal, 55 for octanal, 15 for nonanal, and 7 for helional. The outcome is illustrated in Figure 4. If the behavioral detection of odorants that are the most potent ligand for a specific OR is assumed to be heavily dependent on the integrity of mainly that OR, one could speculate that: 1) the ODT for such odorants would be lower than those for chemically-related, less-potent ligands, and 2) due to genetic variation in ORs, the spread in ODTs among individuals (Figure 4) would be larger for odorant ligands activating mainly one critical OR than for those activating a wide pattern of ORs where no single receptor type is critical. The first expectation was met for octanal, among the most potent ligands for human OR1A1 and OR1A2 (Schmiedeberg *et al.* 2007) and for helional, the most potent ligand for human OR 17-40 (Hatt *et al.* 1999; Jacquier *et al.* 2006; Wetzel *et al.* 1999), but was not met for nonanal, a strong ligand of human OR1G1 (Sanz *et al.* 2005) (Figure 1, Table 2). The second expectation was met for octanal and, to some extent, nonanal but not for helional (Figure 4). A recent investigation found hexanal to be even more potent than octanal and nonanal as a ligand of human OR2W1 (Saito *et al.* 2009). If, based on these findings, hexanal is also considered a most potent odorant for some specific OR, then both expectations (particularly the second one) were met for hexanal (Figure 1, Table 2, Figure 4).

Insert Figure 4 about here

Comparison of olfactory dose-response functions for aldehydes tested at the behavioral and at the cell/receptor level

A number of investigations using preparations from mouse, rat, and human origin have measured dose-response functions for specific olfactory receptors, employing, among other odorants, some of the aldehydes tested here: hexanal, octanal, nonanal, and helional. These studies are summarized in Table 4, where the parameter of interest is the "effective concentration 50" (EC_{50}). The EC_{50} is the concentration of the odorant producing half (50%) of the maximum response obtained for that particular preparation (when all sources of unspecific responses have been discounted). The EC_{50} can be compared with our constant C, i.e., the odor detection threshold concentration. We recognize that there are differences between the concepts underlying each measurement and that there are several limitations in the comparison of the two. As mentioned below, cell/receptor functions could also be compared to suprathreshold odor functions. Furthermore, since human ORs are far from having been completely sampled and characterized, the comparison of EC_{50}s and ODTs is preliminary. Using the limited data presently available, we deemed worthwhile to probe for a tentative comparison between olfactory responses emerging at the two neural levels, particularly as it relates to issues of structure-activity within the selected aldehydes. Both parameters, EC_{50} and C, are obtained from dose-response functions modeled by sigmoid equations. We note that in all cell/receptor studies cited in Table 4, with one exception (Sanz *et al.* 2005), the odorant stimulus is presented as a **liquid** solution ($Conc_{liquid}$), whereas in all our experiments, and in the noted exception, the odorant is presented as a **vapor**, i.e., a gas

($Conc_{gas}$). Thus, in order to make meaningful comparisons of olfactory potency between the two parameters for any given odorant, we must first express both values in the same physical state, e.g., vapor. We have done precisely that by establishing, for each odorant, the partition coefficient between the gas and liquid media, according to:

$K_{gas\ to\ liquid} = Conc_{liquid}/Conc_{gas}$ Equation (3)

The method to obtain these coefficients (K) has been described in detail in a recent publication (Abraham *et al.* 2007a). It does not make much difference whether the liquid phase is water (K_w) or some variation of physiological saline (K_{sal}), typically at 37°C, as commonly used in cell/receptor studies. To strengthen comparability between data sets we chose K_{sal} at 37°C (Table 4). Once the partition coefficients are taken into account, we find that, with one exception, ODTs calculated from constant C are quite lower than the corresponding EC_{50}s for the same odorants, by a factor ranging from 1 to 6 orders of magnitude. The factor ranges from 2 to 5 orders of magnitude if we consider only human ORs: OR2W1 (Saito *et al.* 2009) and OR1G1 (Sanz *et al.* 2005) (Table 4). The exception is the study by Wetzel et al. (1999) on the response of OR17-40 to helional, although this paper does not report an EC_{50}. It only reports a ”threshold” response that emerges within a concentration range whose upper boundary (0.007 nM, vapor phase) is very close to our ODT for helional (0.006 nM).

Insert Table 4 about here

A straightforward explanation for the much higher sensitivity shown by the behavioral response rests on the stimulation of the intact olfactory epithelium, including relevant peri-receptor factors, e.g., OBPs (Ko and Park 2008), and on the various degrees of signal sharpening and contrast provided by progressively higher stages of the olfactory pathway (Christie and Westbrook 2006; Vogt 2006). In any case, we suggest that there is merit in attempting further systematic comparisons of dose-

response functions, measured at different processing levels, for both strong specific-ligands of particular ORs and broader-acting odorants. For example, comparing functions obtained in unicellular vs. multicellular recordings, peripheral vs. central locations, and “in vitro” vs. “in vivo” conditions. As an integral part of these comparisons, one could also include another behavioral endpoint: suprathreshold concentration-response (i.e., psychophysical) functions. The outcome will help to increase our understanding of how the chemical information contained in odorants is detected and subsequently processed by the sense of smell.

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Table 1. Number and characteristics of subjects in the various subgroups, and of the two common subjects tested with all 6 aldehydes.

Subject subgroups	Number of subjects	Average age (years ±SD)	Age range	Number of males	Number of females
Propanal	16	26 ±5	19-37	8	8
Butanal	18	22 ±5	18-37	9	9
Hexanal	16	23 ±5	18-37	9	7
Octanal	16	24 ±5	19-37	7	9
Nonanal	17	25 ±6	19-37	7	10
Helional	17	24 ±5	19-37	7	10
Common subjects	2		20-37	-	2

Table 2. Upper section. Quantification of the group psychometric odor function for each aldehyde, including number of subjects (n), odor detection threshold (ODT), constant C (i.e., the ODT in log ppb) (±standard error, SE), constant D (±SE), R^2, and Chi Square. Lower section. Same data but for the two common subjects tested with all 6 aldehydes.

	n	ODT (ppb)	C (log ppb)	SE (C)	D	SE (D)	R^2	Chi Square
All subjects								
Propanal	16	2.0	0.305	±0.016	0.21	±0.014	0.997	0.0039
Butanal	18	0.46	-0.334	±0.017	0.20	±0.015	0.996	0.0045
Hexanal	16	0.33	-0.482	±0.050	0.44	±0.049	0.975	0.0185
Octanal	16	0.17	-0.759	±0.019	0.37	±0.018	0.996	0.0034
Nonanal	17	0.53	-0.274	±0.028	0.25	±0.025	0.991	0.0106
Helional	17	0.14	-0.868	±0.024	0.20	±0.021	0.992	0.0096
Common subjects								
Propanal	2	1.8	0.265	±0.036	0.17	±0.033	0.979	0.0265
Butanal	2	0.55	-0.259	±0.028	0.12	±0.023	0.988	0.0212
Hexanal	2	0.41	-0.389	±0.062	0.41	±0.058	0.964	0.0303
Octanal	2	0.28	-0.554	±0.061	0.42	±0.058	0.964	0.0292
Nonanal	2	0.74	-0.129	±0.077	0.29	±0.070	0.930	0.0670
Helional	2	0.18	-0.734	±0.030	0.07	±0.032	0.987	0.0204

Table 3. Values of C, D, and R^2 for each individual psychometric odor function for the aldehydes.

Propanal (n=16)				Butanal (n=18)				Hexanal (n=16)			
Subject	**C (log ppb)**	**D**	**R^2**	**Subject**	**C (log ppb)**	**D**	**R^2**	**Subject**	**C (log ppb)**	**D**	**R^2**
3	0.25	0.21	0.98	2	-0.08	0.25	0.97	1	-1.08	0.05	1.00
6	0.13	0.25	0.95	4	-0.16	0.15	0.99	7	-0.61	0.11	0.99
7	0.10	0.15	0.98	5	-0.18	0.13	0.97	9	0.51	0.15	0.85
8	0.47	0.12	0.97	7	-0.30	0.15	0.97	14	-0.84	0.48	0.91
12	0.45	0.21	0.90	8	-0.32	0.09	0.96	16	-0.86	0.26	0.95
13	0.39	0.21	0.99	9	-0.45	0.05	0.96	20	-1.22	0.12	0.95
14	0.13	0.18	0.99	10	-0.74	0.11	0.97	21	-0.75	0.26	0.99
19	0.25	0.20	0.96	14	-0.15	0.07	0.99	22	-0.11	0.17	0.96
22	0.36	0.12	0.92	15	-0.27	0.22	0.98	23	-0.35	0.41	0.79
25	0.45	0.23	0.94	17	-0.72	0.17	0.98	24	-0.04	0.24	0.96
28	0.47	0.22	0.92	21	-0.66	0.17	0.97	25	-0.34	0.21	0.98
30	0.27	0.15	0.96	22	-0.39	0.13	0.96	26	-0.48	0.36	0.95
31	0.51	0.06	0.91	23	-0.50	0.11	1.00	27	0.09	0.49	0.82
32	-0.10	0.12	0.99	26	-0.41	0.11	0.96	31	-0.11	0.30	0.96
34	0.09	0.10	0.97	29	-0.41	0.17	0.98	38	0.08	0.42	0.78
35	0.69	0.19	0.99	31	-0.25	0.09	0.97	39	-1.15	0.07	0.99
				37	0.09	0.11	0.97				
				38	0.18	0.67	0.85				
Average	**0.31**	**0.17**			**-0.32**	**0.16**			**-0.45**	**0.26**	
SE	0.05	0.01			0.06	0.03			0.13	0.04	

Octanal (n=16)				Nonanal (n=17)				Helional (n=17)			
Subject	**C (log ppb)**	**D**	**R^2**	**Subject**	**C (log ppb)**	**D**	**R^2**	**Subject**	**C (log ppb)**	**D**	**R^2**
7	-0.24	0.12	0.79	8	-0.58	0.06	0.98	7	-0.91	0.12	0.96
8	-1.21	0.16	0.98	10	-0.66	0.05	0.97	11	-1.27	0.39	0.98
10	-1.10	0.26	0.96	12	0.25	0.14	0.99	12	-0.88	0.09	0.98
11	-1.25	0.17	0.99	13	0.09	0.17	0.93	13	-0.39	0.07	0.90
14	-0.04	0.10	0.91	14	0.21	0.18	0.92	14	-0.63	0.06	1.00
19	-0.27	0.50	0.67	18	-0.43	0.18	0.93	16	-0.76	0.19	0.91
21	-1.17	0.31	0.99	21	-0.55	0.09	0.83	21	-0.96	0.16	0.96
22	-0.93	0.16	0.97	22	-0.41	0.06	0.95	22	-0.80	0.02	0.96
25	-0.48	0.21	0.97	24	-0.27	0.07	0.98	25	-0.92	0.13	1.00
26	-0.95	0.22	0.92	25	0.14	0.11	0.95	26	-0.75	0.22	0.99
28	-0.43	0.13	0.98	26	-0.11	0.06	0.98	27	-1.00	0.11	0.98
29	-1.04	0.23	0.98	28	-0.09	0.10	0.99	28	-0.79	0.01	0.99
30	-0.67	0.20	0.96	29	-0.78	0.19	0.93	31	-0.84	0.06	0.99
33	-1.54	0.12	0.99	30	-0.46	0.13	0.98	40	-0.69	0.08	0.95
36	0.22	0.47	0.73	31	-0.36	0.02	0.97	41	-1.54	0.23	0.97
38	-0.63	0.15	0.97	34	-0.72	0.12	1.00	42	-1.12	0.09	1.00
				36	0.41	0.10	0.88	43	-0.95	0.16	0.99
Average	**-0.73**	**0.22**			**-0.25**	**0.11**			**-0.89**	**0.13**	
SE	0.12	0.03			0.09	0.01			0.06	0.02	

Table 4. Comparison of ODTs form the present study with EC_{50} values, expressed in vapor phase via log K_{sal}, from studies testing olfactory cell/receptor preparations.

Odorant	Species	Stimulus phase	Response level	Receptor(s) tested	Fitting model	EC_{50} (log M)	EC_{50} (nM)	Log Ksal (@37°C)	EC_{50} or ODT (nM) Vapor phase	Reference
Hexanal	Human	Vapor	Behavioral	All	Sigmoid (Eq. 2)			1.67	0.014	This study
Hexanal	Human	Liquid	Cell	OR2W1	Sigmoidal	-5.102	7,907	1.67	168	(Saito *et al.* 2009)
Hexanal	Mouse	Liquid	Cell	MOR4-1	Sigmoidal	-3.231	587,489	1.67	12,509	(Saito *et al.* 2009)
Hexanal	Mouse	Liquid	Cell	MOR271-1	Sigmoidal	-3.322	476,431	1.67	10,144	(Saito *et al.* 2009)
Hexanal	Mouse	Liquid	Cell	MOR1-1	Sigmoidal	-3.987	103,039	1.67	2,194	(Saito *et al.* 2009)
Octanal	Human		Behavioral	All	Sigmoid (Eq. 2)			1.46	0.007	This study
Octanal	Human	Liquid		OR2W1	Sigmoidal	-4.361	43,551	1.46	1,519	(Saito *et al.* 2009)
Octanal	Rat	Liquid	olfactory sensory neurons	OR-I7	Hill function	-5.745	1,800	1.46	63	(Peterlin *et al.* 2008)
Octanal	Rat	Liquid	olfactory sensory neurons	OR-I7	Hill equation	-5.721	1,900	1.46	66	(Araneda *et al.* 2004)
Octanal	Mouse	Liquid	Cell (HeLa/Olf)	Rho-tag-39-Olfr43	Equation	-4.648	22,500	1.46	785	(Shirokova *et al.* 2005)
Nonanal	Human	Vapor	Behavioral	All	Sigmoid (Eq. 2)			1.36	0.022	This study
Nonanal	Human	Vapor	Cell (HEK293)	OR 1G1	No fitting			1.36	1,000	(Sanz *et al.* 2005)
Nonanal	Human	Liquid	Cell	OR2W1	Sigmoidal	-3.598	252,348	1.36	11,046	(Saito *et al.* 2009)
Nonanal	Mouse	Liquid	Cell	MOR40-1	Sigmoidal	-3.194	639,735	1.36	28,002	(Saito *et al.* 2009)
Nonanal	Mouse	Liquid	Cell	MOR37-1	Sigmoidal	-3.295	506,991	1.36	22,192	(Saito *et al.* 2009)
Nonanal	Mouse	Liquid	Cell	MOR33-1	Sigmoidal	-3.234	583,445	1.36	25,538	(Saito *et al.* 2009)
Nonanal	Mouse	Liquid	Cell	MOR30-1	Sigmoidal	-3.914	121,899	1.36	5,336	(Saito *et al.* 2009)
Helional	Human	Vapor	Behavioral	All	Sigmoid (Eq. 2)			5.17	0.006	This study
Helional	Human	Liquid	Cell (HEK293, Xenopus laevis oocytes)	OR17-40	Threshold	-7.000 to -6.000	100 to 1,000	5.17	0.0007 to 0.007	(Wetzel *et al.* 1999)
Helional	Human	Liquid	Cell (HEK293)	h-OR17-40	Equation	-4.006	98,700	5.17	0.67	(Jacquier *et al.* 2006)
Helional	Human	Liquid	Cell (HEK293)	h-OR17-40-EGFP	Equation	-3.942	114,400	5.17	0.78	(Jacquier *et al.* 2006)
Helional	Mouse	Liquid	Cell (HeLa/Olf)	Rho-tag-39-Olfr43	Equation	-5.444	3,600	5.17	0.025	(Shirokova *et al.* 2005)

Figure Legends

Figure 1. Group psychometric odor function (left) and confidence ratings as a function of vapor concentration (right) for each aldehyde. Each point represents the outcome of 560 trials made by 16 subjects for propanal, hexanal, and octanal; 630 trials made by 18 subjects for butanal; and 595 trials made by 17 subjects for nonanal and helional. Bars indicate standard error (SE). Psychometric functions (left) were modeled by the sigmoid equation (2).

Figure 2. Plot of ODTs as a function of the variable alkyl carbon chain length for homologous aliphatic aldehydes (this study), n-alcohols (Cometto-Muñiz and Abraham 2008a), acetates (Cometto-Muñiz *et al.* 2008), 2-ketones (Cometto-Muñiz and Abraham 2009b) and n-alkylbenzenes (Cometto-Muñiz and Abraham 2009a). Bars (sometimes hidden by the symbol) represent standard error (SE) of the mean.

Figure 3. Values of ODTs for homologous aldehydes (in vapor phase) from studies compiled by van Gemert (van Gemert 2003) (diamonds) and those compiled and standardized by Devos et al. (Devos *et al.* 1990) (circles). Also shown are the ODTs from Nagata (Nagata 2003) (triangles) and from the present study (crosses).

Figure 4. Comparison of psychometric functions between the least and the most sensitive subject for each aldehyde (with their respective ODT). The least and most sensitive subjects for propanal, butanal, hexanal, octanal, nonanal, and helional were, respectively, subjects 35 and 32, 38 and 10, 9 and 39, 36 and 33, 36 and 29, and 13 and 11.

Supplementary Figure Legends

Figure S1. Individual psychometric odor functions for propanal modeled by the sigmoid equation (2). Each point represents the outcome of 35 trials made by that subject. In Figures S1 to S6 and in Table 3, each subject is identified by a unique number so one can follow the performance of participants tested on more than one aldehyde.

Figure S2. Individual functions as in Figure S1 but for butanal.

Figure S3. Individual functions as in Figure S1 but for hexanal.

Figure S4. Individual functions as in Figure S1 but for octanal.

Figure S5. Individual functions as in Figure S1 but for nonanal.

Figure S6. Individual functions as in Figure 2 but for helional.

FIGURE 1

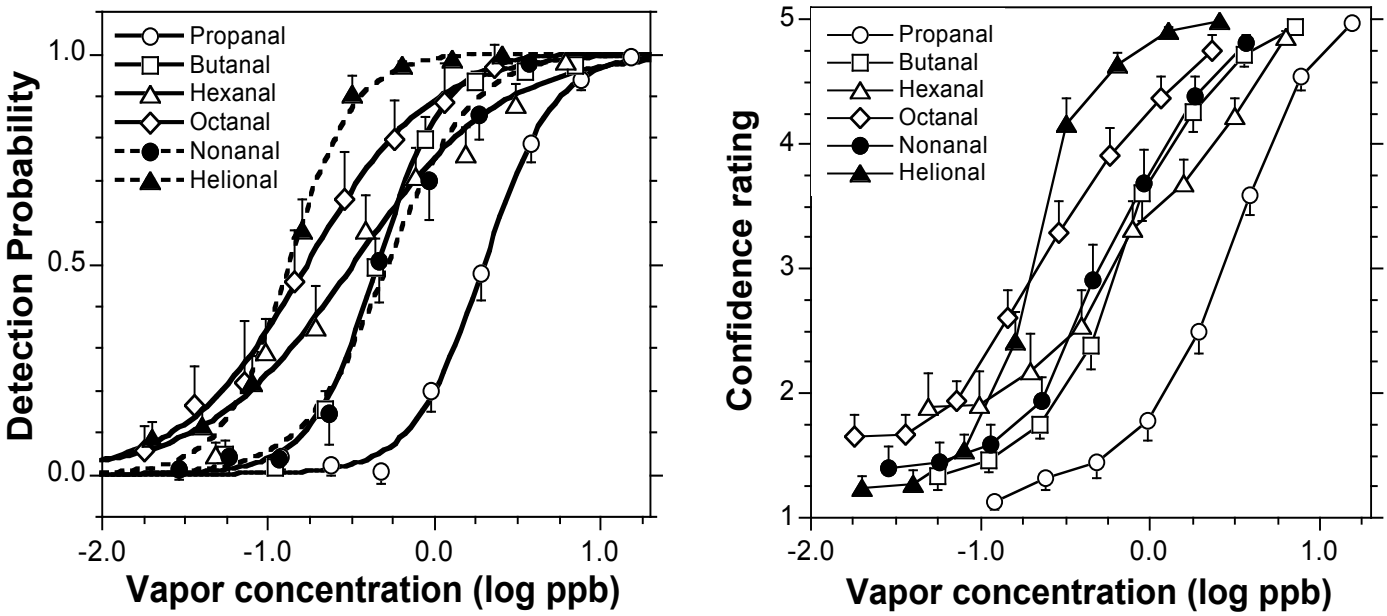

Propanal
Butanal
Hexanal
Octanal
Nonanal
Helional
Detection Probability
1.0
0.5
0.0
-2.0
-1.0
0.0
1.0
Vapor concentration (log ppb)
Confidence rating
5
4
3
2
1
Vapor concentration (log ppb)

FIGURE 2

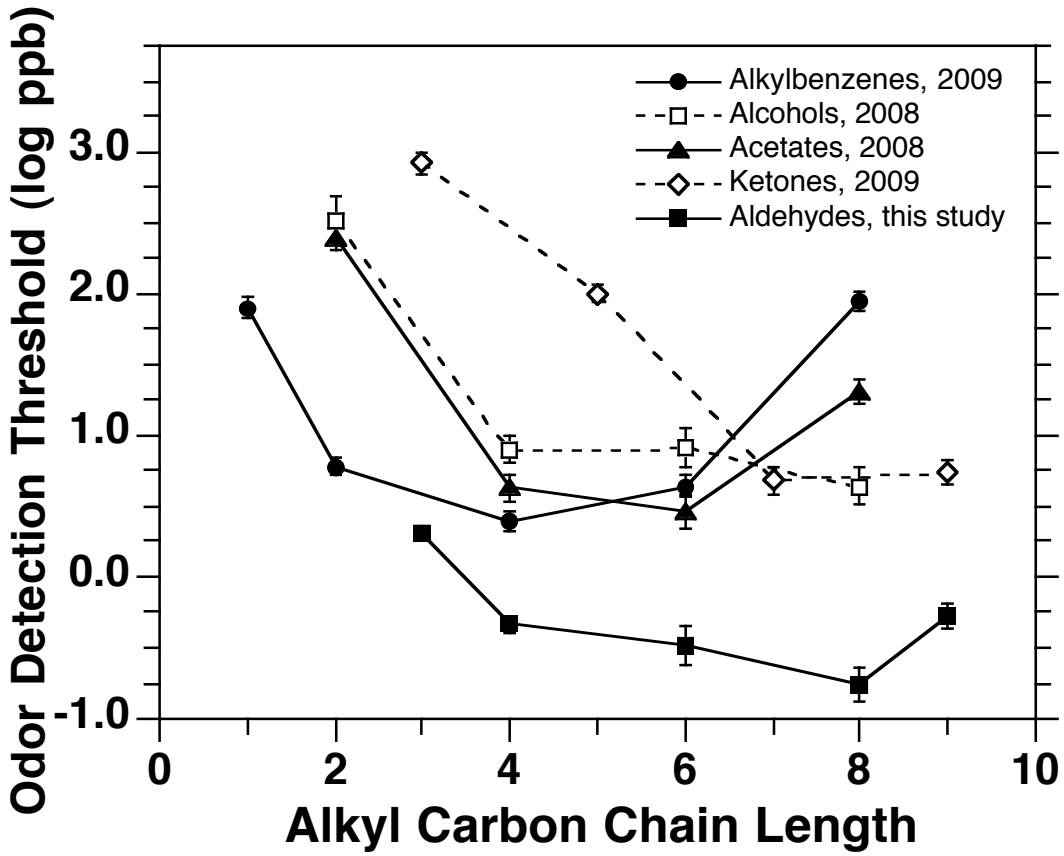

Odor Detection Threshold (log ppb)
3.0
2.0
1.0
0.0
-1.0
0
2
4
6
8
10
Alkyl Carbon Chain Length
Alkylbenzenes, 2009
Alcohols, 2008
Acetates, 2008
Ketones, 2009
Aldehydes, this study

FIGURE 3

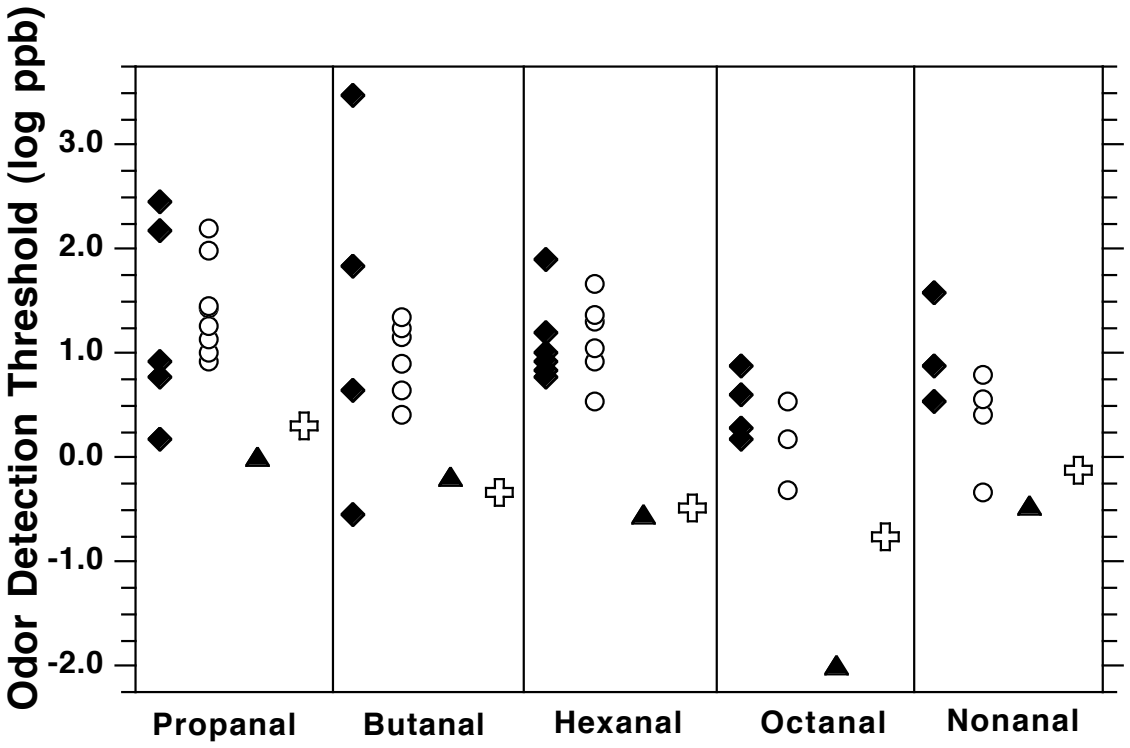
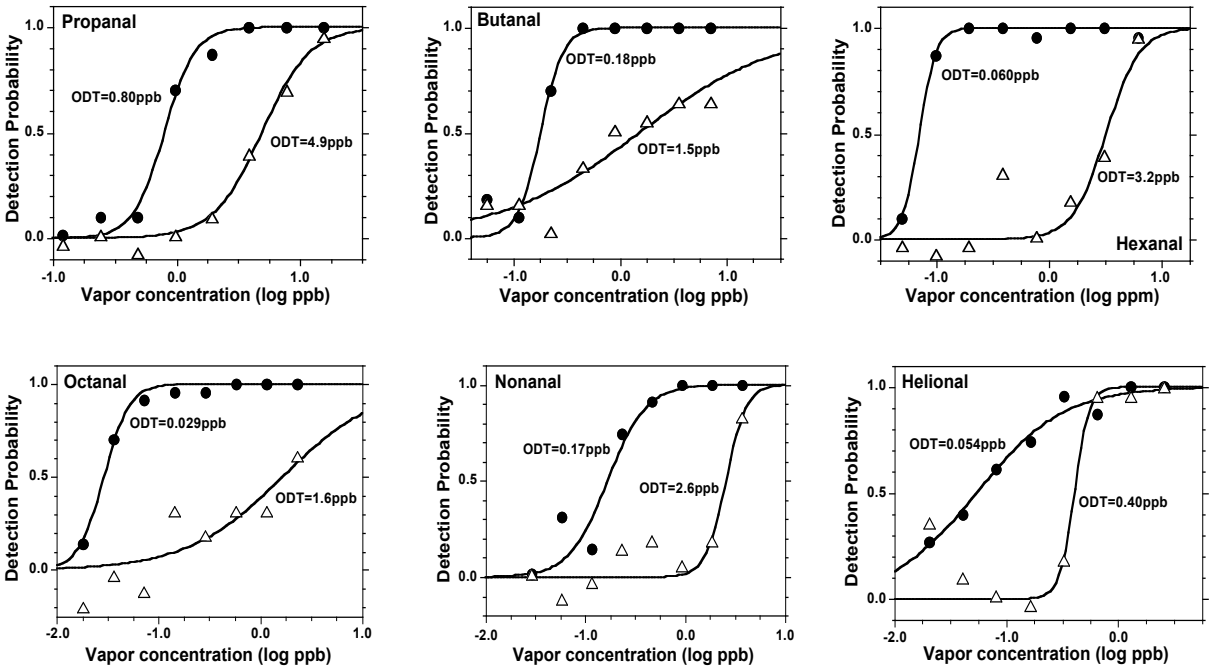
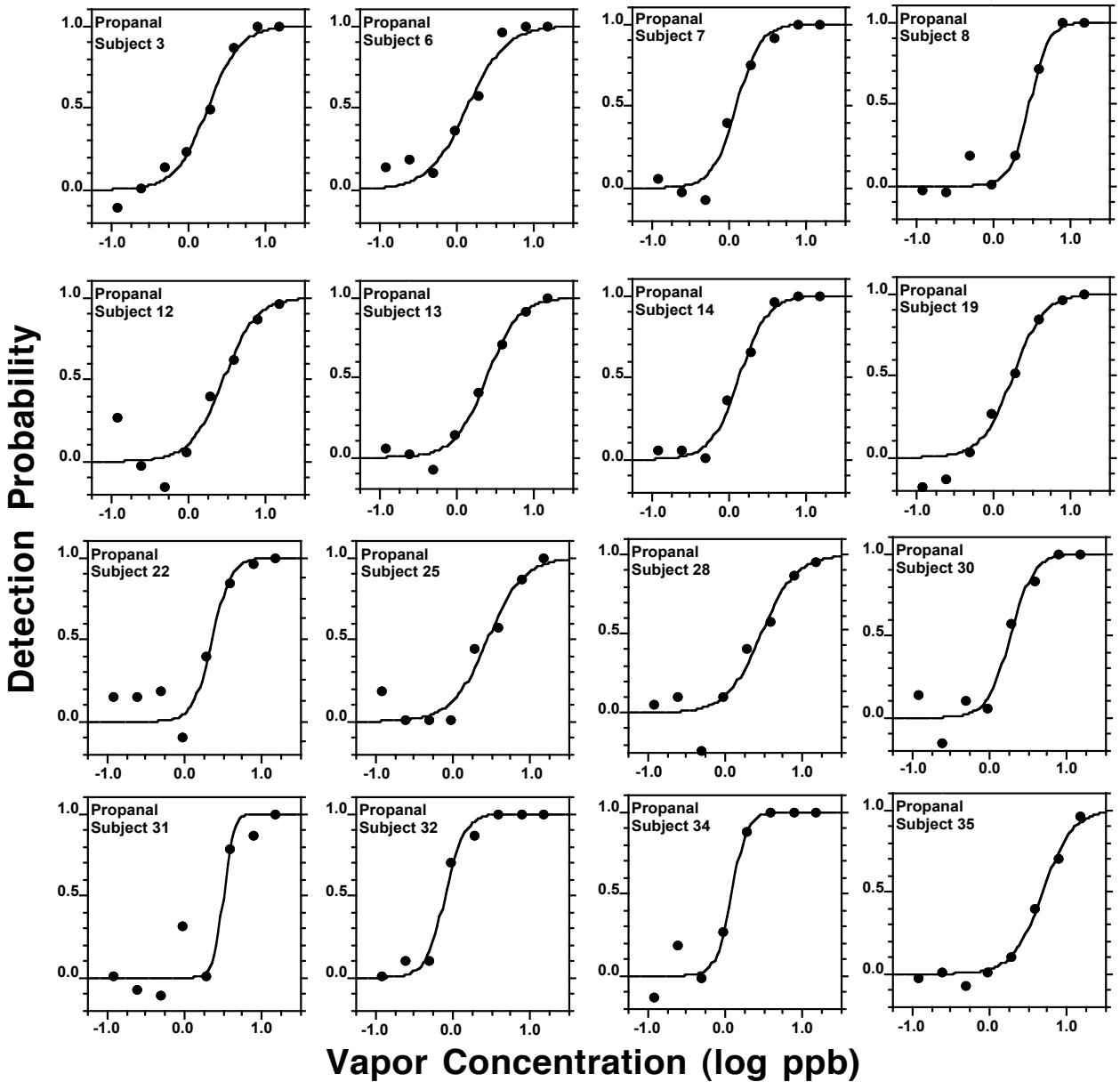

Odor Detection Threshold (log ppb)
3.0
2.0
1.0
0.0
-1.0
-2.0
Propanal
Butanal
Hexanal
Octanal
Nonanal

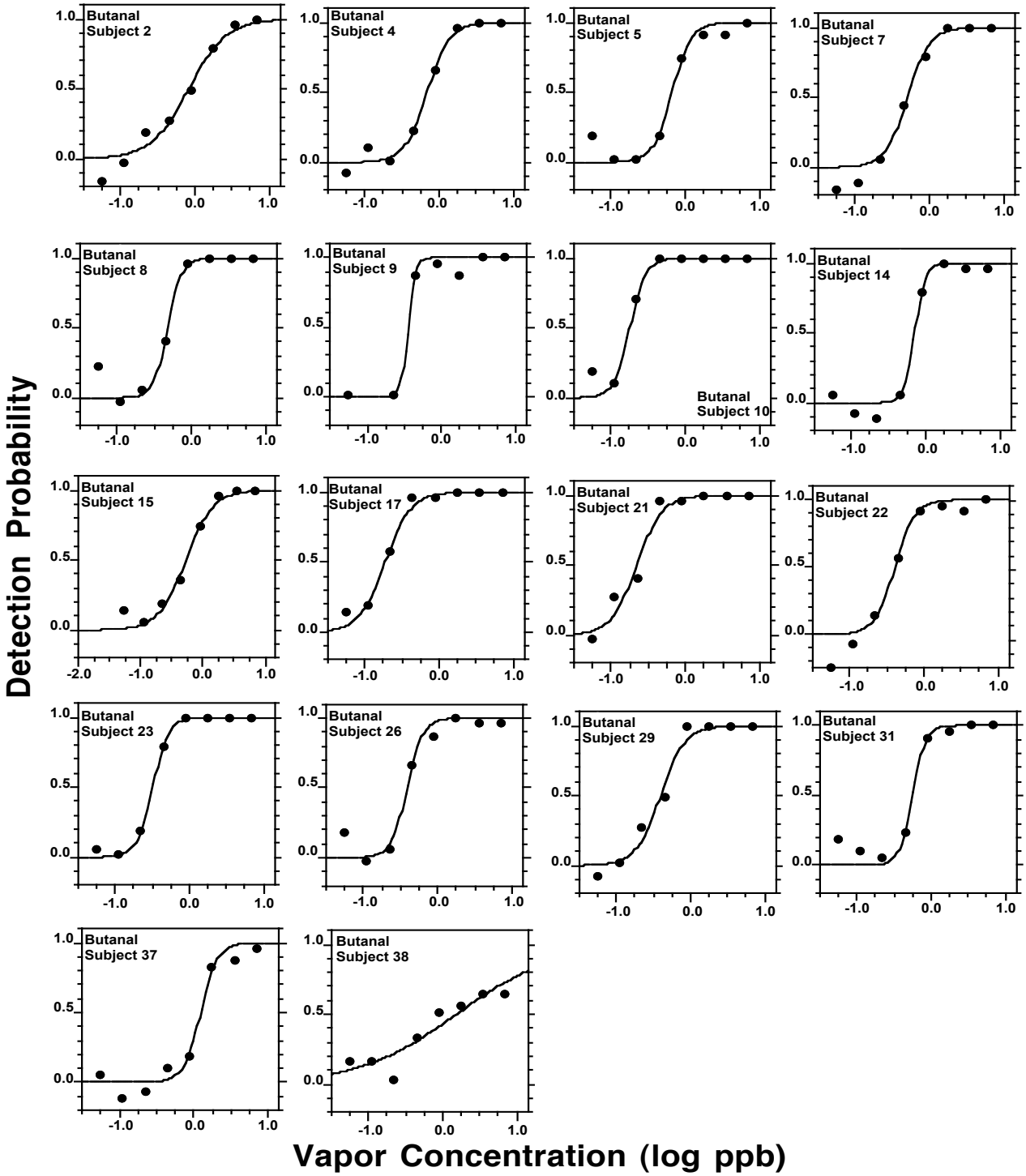
FIGURE 4


Propanal
ODT=0.80ppb
ODT=4.9ppb
Butanal
ODT=0.18ppb
ODT=1.5ppb
ODT=0.060ppb
ODT=3.2ppb
Hexanal
Octanal
ODT=0.029ppb
ODT=1.6ppb
Nonanal
ODT=0.17ppb
ODT=2.6ppb
Helional
ODT=0.054ppb
ODT=0.40ppb
Detection Probability
Vapor concentration (log ppb)
Vapor concentration (log ppm)

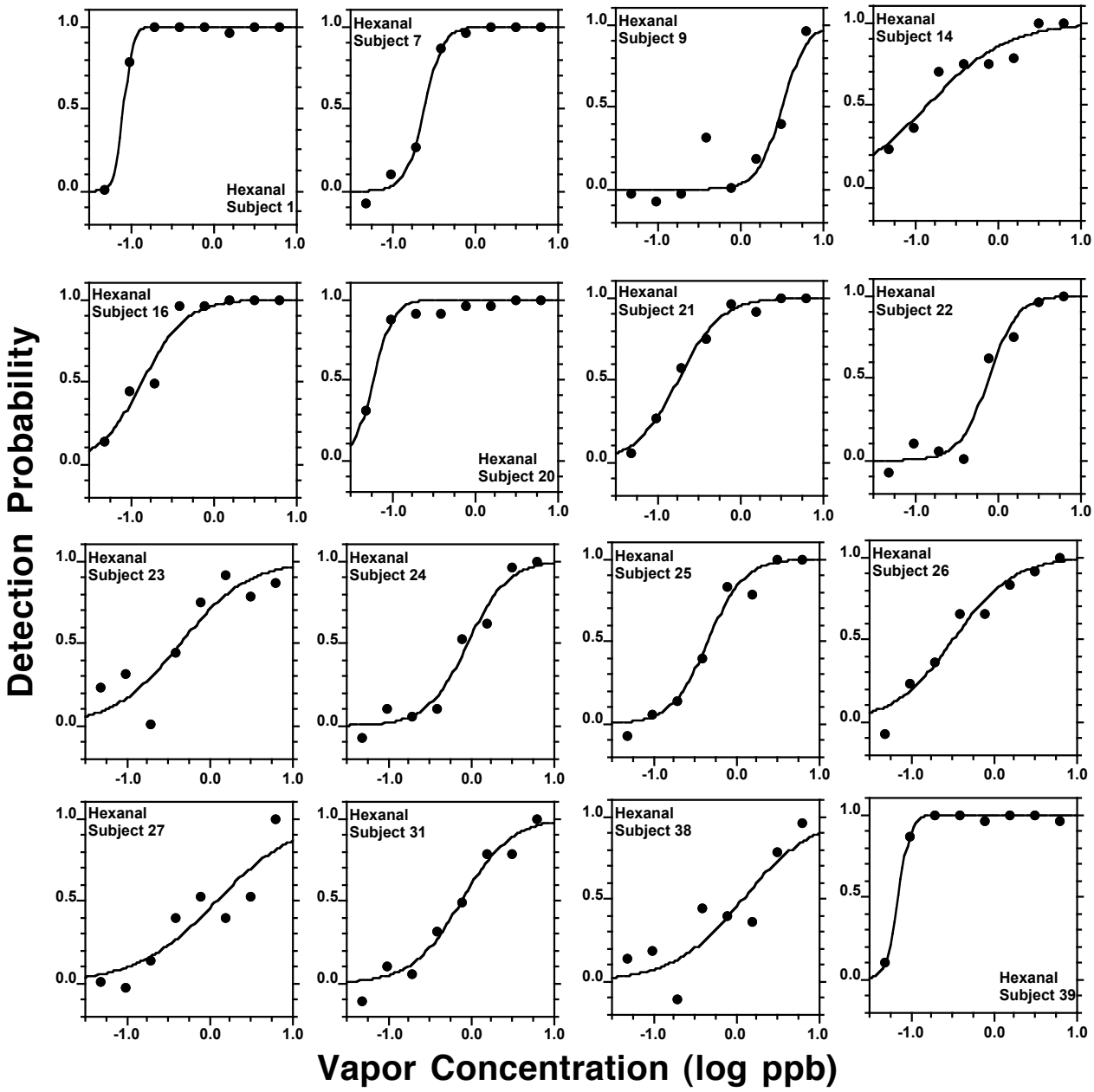
SUPPLEMENTARY FIGURE S1



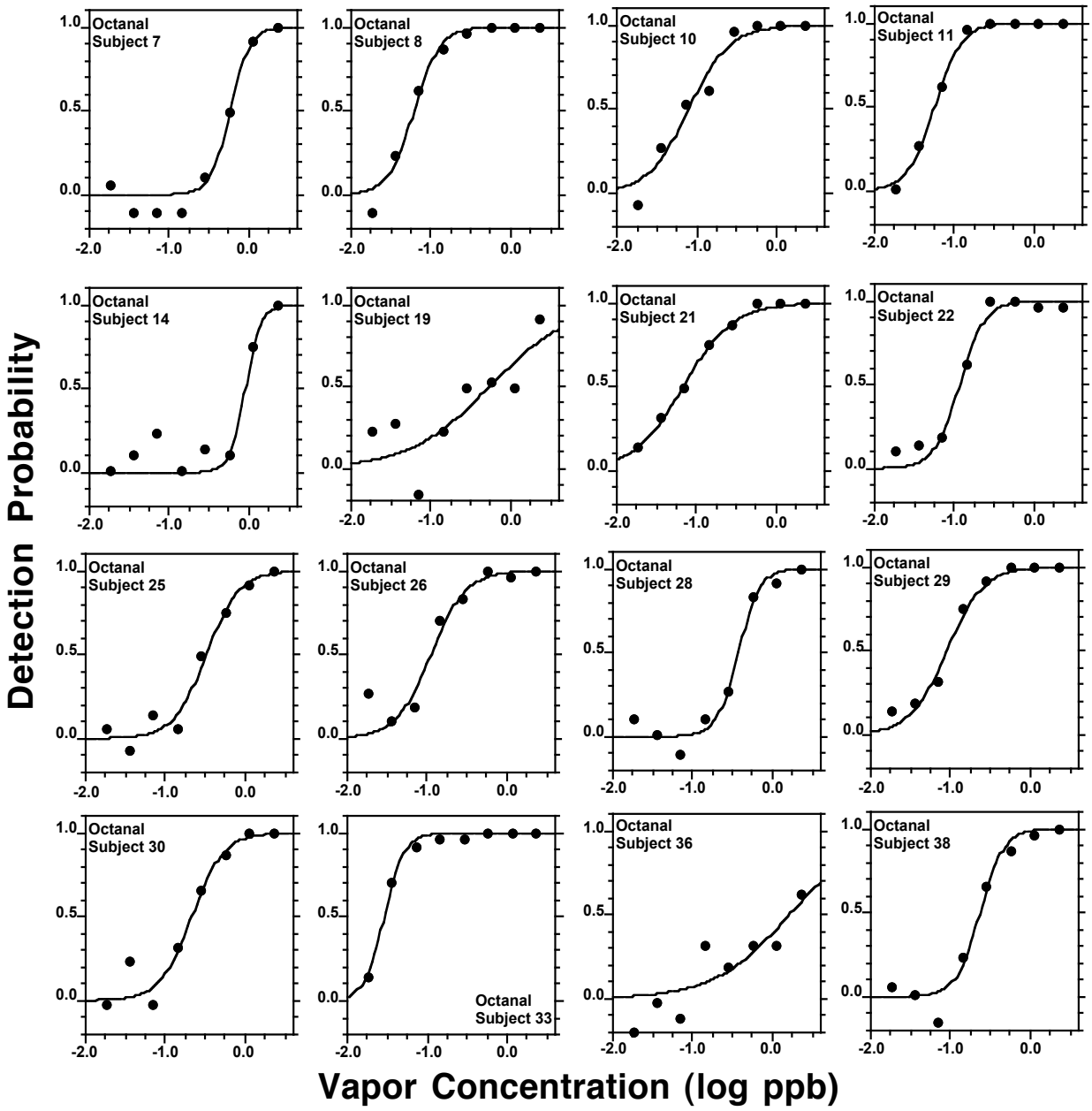
SUPPLEMENTARY FIGURE S2



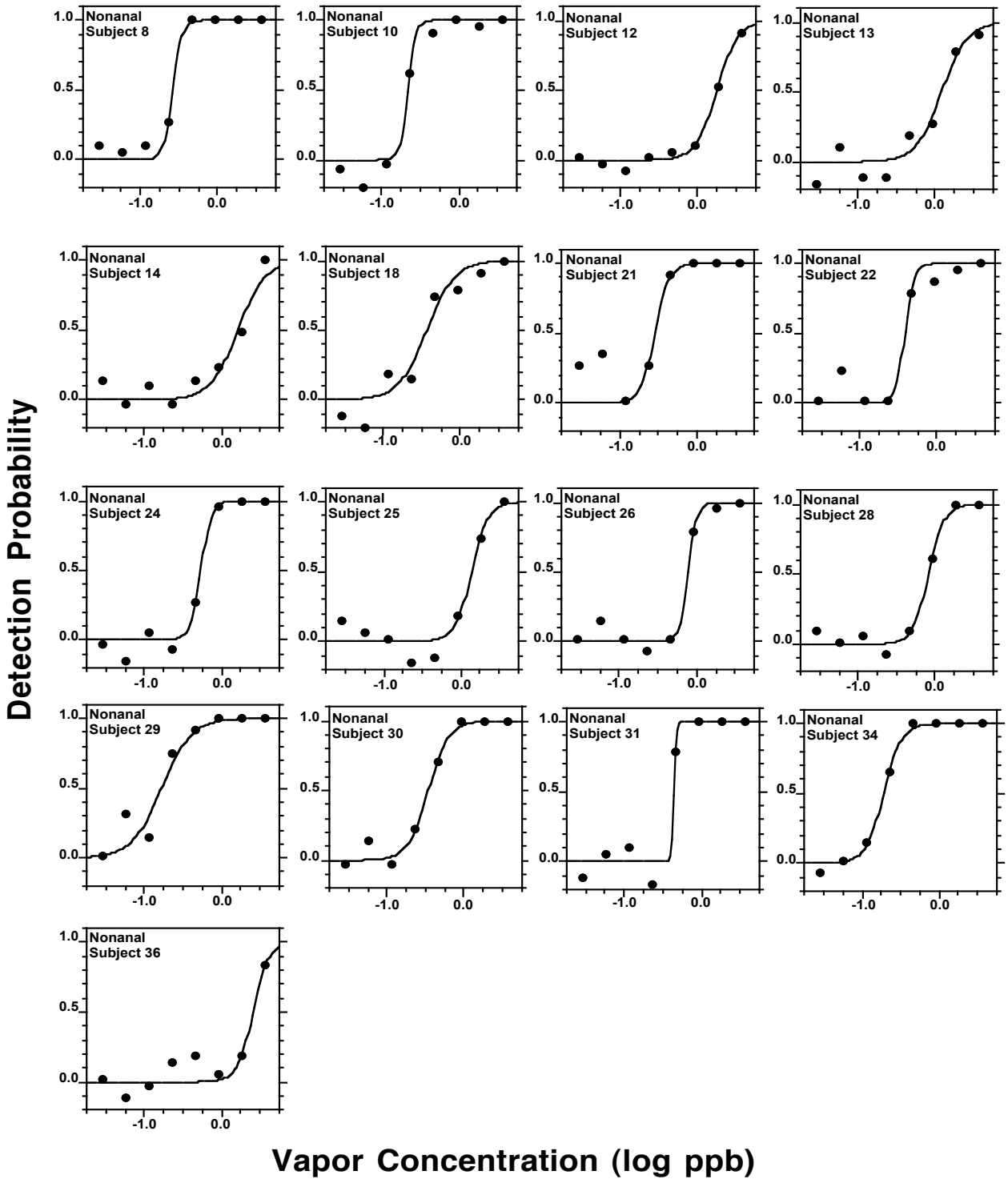
SUPPLEMENTARY FIGURE S3



SUPPLEMENTARY FIGURE S4



SUPPLEMENTARY FIGURE S5



SUPPLEMENTARY FIGURE S6