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Odor and chemesthesis from brief exposures to TXIB

Abstract An experiment explored ability of subjects to detect vapors of the plasticizer TXIB (2,2,4-trimethyl-1,3-pentanediol diisobutyrate) and ethanol via olfaction and via ocular and nasal chemesthesis, i.e. chemically stimulated feel. Testing, tailored to the sensitivity of each subject, produced psychometric functions for individuals. Olfactory detection of TXIB began at concentrations below 1 ppb (v/v), with 50% correct detection at 1.2 ppb. (Comparable detection for ethanol occurred almost two orders of magnitude higher.) Chemesthetic detection of TXIB began at about 500 ppb, with 50% correct detection at 2.1 ppm for the eye and 4.6 ppm for the nose, both close to saturated vapor concentration. (Comparable detection for ethanol occurred essentially three orders of magnitude higher.) Suggestions that TXIB plays a role in generation of irritative symptoms at concentrations in the range of parts-per-billion need to reckon with a conservatively estimated 200-fold gap between the levels putatively 'responsible' for the symptoms and those even minimally detectable via chemesthesis. Neither the variable of exposure duration nor that of mixing offers a likely explanation. Inclusion of ethanol in the study allowed comparisons pertinent to issues of variability in human chemoreception. An interpretation of the psychometric functions for individuals across materials and perceptual continua led to the conclusion that use of concentration as the metric of detection in olfaction inflates individual differences.

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Practical Implications
This study indicated that the plasticizer TXIB could contribute odor at concentrations in the range of parts-per-billion, but could hardly contribute sensory irritation *per se*, as alleged in reports of some field studies where TXIB has existed amongst many other organic compounds.

Introduction

The chemical TXIB (2,2,4-trimethyl-1,3-pentanediol diisobutyrate) serves principally as a plasticizer and may appear in vinyl, urethanes, and various other polymers for inclusion in such consumer goods as polyvinyl chloride (PVC) flooring, wallpaper, water-based paints, and artificial leather products. With a molecular weight of 286.42 Da, a boiling point of 281.5°C, and a vapor pressure of 0.004 mbar (± 100%) at 25°C (Eastman Chemical Material Safety Data Sheet, 2005), TXIB lies outside the category of volatile organic compounds (VOCs) by the EU definition (the European Parliament and the Council of the European Union, 2004).

Field measurements of TXIB

Samples of air and dust from commercial, institutional, and residential buildings in Europe have commonly contained quite low concentrations of TXIB (e.g. Ribéron et al., 2002; Wilkins et al., 1993; Wolkoff and Wilkins, 1994, but see Gasking, 1988). Concentration in air samples from Swedish homes did not generally exceed 1 ppb (v/v, 11.9 $\mu g/m^3$), though did systematically exceed it in homes with recent painting with water-base paint. In most of those cases, the concentration did not exceed 10 ppb, but in one case, with all rooms recently painted and PVC floor covering, concentration reached 31.4 ppb (Wieslander et al., 1997). Concentration in more than 800 English homes yielded a similar picture, with 95% below 1.2 ppb and a maximum below 10 ppb (Raw et al., 2004). Some of the English homes had apparently undergone recent painting.

Although no comparably large set of data exists for American homes, a small group of months-old, unfurnished, never-occupied American manufactured ($n = 4$) and site-built ($n = 7$) demonstration homes yielded geometric mean concentrations of 0.8 and 1.8 ppb, respectively (Hodgson et al., 2000). All but one of the 11 contained vinyl sheet flooring that

comprised an average of 19% of floor area. Samples of air from large commercial buildings in the US, including the 100 buildings of the well-known BASE study, generally yielded <1 ppb (Apte and Erdmann, 2002; Girman et al., 1999; Shields et al., 1996).

Symptoms and TXIB

The presence of PVC flooring, more common in Europe than in the US, and recent painting lie among numerous risk factors, including, for example, water damage, a family history of atopy, living in a multi-unit building, presence of high emitting sources of VOCs, and poor ventilation, for respiratory symptoms in occupants (Sundell, 2004; Wälinder et al., 2001). TXIB will almost inevitably occur at some level where PVC flooring occurs. Studies suggest that emission of TXIB does not decay as fast as that from some other materials from flooring or floor installation (Wilke et al., 2002). We can note, however, that rates of emission in new product seemed to have declined in response to implicit or explicit demands for lower emissions in the 1990s (Lundgren et al., 1999).

Although considered low in human systemic and acute dermal toxicity (Astill et al., 1972; David et al., 2003), TXIB has come under suspicion as a contributor to odor or to symptoms of occupants in indoor spaces (Kostianinen, 1995). The concern has arisen because of associations between levels of measured TXIB and frequency or magnitude of principally upper respiratory symptoms. When Metiäinen et al. (2002) analyzed symptoms of complainants in flats in Helsinki, they found higher risk of symptoms of nose and eye irritation, of throat symptoms, and of the symptom 'heavy head' in flats with concentrations of TXIB over 2.5 ppb ['Normal' average concentration in the Finnish VTT Material Emission and Indoor Air Database equals about 1.2 ppb, according to Järnström and Saarela (2002).] Such associations neither prove nor disprove a causative role for TXIB among the many chemicals in a space, even assuming a chemical cause. Metiäinen et al. reported that replacement of the old, and apparently somewhat deteriorated, PVC carpeting with low-emitting PVC carpeting glued with low-emitting glue reduced the symptoms. The investigators apparently did not measure the levels of chemicals after the renovation.

With respect to any chemical implicated, correctly or incorrectly, in the occurrence of upper respiratory symptoms, the question arises: Does the material cause irritation at concentrations of environmental relevance? For a material of otherwise low toxicity to play a role in such symptoms, irritation would seem a likely mediator. Villberg et al. (2000) reported, without elaboration, that symptoms of eye irritation and nasal allergies associated positively with concentration of 'esters (especially TXIB)' (p. 423).

Determinants of chemesthesis

Most airborne organic chemicals can evoke sensations of feel, now commonly called chemesthetic sensations, at concentrations a variable distance above their odor thresholds (Cain and Cometto-Muñiz, 1995). For materials with low odor thresholds, however, the threshold for chemesthesis usually lies three or more orders of magnitude higher (Cometto-Muñiz and Cain, 1994).

Although various reports indicate that TXIB has odor, there apparently exist no data on its odor threshold, not to mention its chemesthetic thresholds in the nose and eye. In general, chemesthetic thresholds for the two sites correlate strongly (Cometto-Muñiz and Cain, 1995, 1997).

For both olfaction and chemesthesis, threshold shows an inverse association with molecular size, up to a point (Abraham et al., 2001, 2002). The association holds loosely across homologous series, though more tightly within them. To illustrate, in aliphatic series both olfactory and chemesthetic thresholds generally decline monotonically, often at different rates, as length of the carbon-chain increases. So, octanol has lower odor and chemesthetic thresholds than ethanol, even though it has lower vapor pressure (Cometto-Muñiz and Cain, 1990). Curiously, then, thresholds go down as vapor pressure goes down, such that the materials with low vapor pressure have the higher potency. At a certain point in a series, however, threshold may become indeterminate. That is, even when neat, substances with molecules of certain chain-lengths may evoke no chemesthesis or odor (Cometto-Muñiz et al., 2005).

The chain-length where the chemesthetic threshold becomes indeterminate usually lies below where the odor threshold becomes indeterminate (Cometto-Muñiz and Cain, 1997). In the terminology of receptor pharmacology, chemesthesis has a cut-off at a smaller molecular size than odor (Franks and Lieb, 1986a,b). Accordingly, some larger molecules have discernible odor but no chemesthetic potency. This makes sense on physical grounds as chemesthetic thresholds require much higher concentrations than odor thresholds. A material may have enough activity for its airborne concentration to reach an odor threshold, though not the chemesthetic threshold (Abraham et al., 2001). Moreover, it may make sense on biological grounds, as well. Both olfaction and chemesthesis mediate their respective sensations via receptors, presumably proteins in both cases (Belmonte et al., 2004; Doty et al., 2004; Malnic et al., 2004; Nielsen, 1991). Size requirements for odorants to stimulate olfaction may vary considerably among the more than 300 types of olfactory proteins. The requirements for the chemesthetic proteins will vary little as only a few such proteins probably mediate all chemesthesis to VOCs and other materials, such as TXIB, that may not fit a formal definition of VOC but may still become

airborne in low concentration (Doty et al., 2004). It would seem improbable that the size requirements for olfactory and chemesthetic stimulation would fall exactly in register.

Because of the size of its molecule and its low vapor pressure, TXIB seemed to lie at the edge of where materials may evoke odor or chemesthesis. A sniff of neat TXIB establishes in an instant that it evokes a mild odor of a quality one might associate with plastic. A fragrance chemist or perfumer would undoubtedly call its odor character indistinct. Both in terms of its mildness and indistinct character, its odor threshold might seem likely to lie not far below saturated vapor concentration. That is, only moderate dilution would seem necessary for the odor to sink below detectability. Experience with other large molecules with similar perceptual characteristics teaches otherwise (Cain, 1988). The thresholds for these mild odors might lie orders of magnitude below saturated vapor.

Molecules near the cut-off often have dull chemesthetic impact (Cain and Cometto-Muñiz, 1995). The aliphatic alcohols can serve once more to illustrate. Whereas the chemesthetic threshold for octanol lies orders of magnitude below that for ethanol, octanol creates a dull, vague feel and ethanol a sharp prickle (Cometto-Muñiz and Cain, 1990).

Because odor can interfere with the appreciation of feel, measurement of chemesthetic thresholds in the nose needs to circumvent the effects of olfaction. One circumvention has entailed reliance upon perceptions of subjects with no sense of smell, anosmics (e.g. Cometto-Muñiz and Cain, 1990). Measurement of the lowest detectable concentration of VOC in such subjects yields their chemesthetic thresholds. The second circumvention has entailed measurement of the lowest concentration where subjects can tell whether the VOC has entered the right or the left nostril. At levels below the chemesthetic threshold, subjects with normal smell may perceive the odor but fail to discern the nostril through which the vapor entered. At approximately the chemesthetic threshold, subjects can lateralize the nostril of entry (e.g. Cometto-Muñiz and Cain, 1997; Kobal et al., 1989).

The distribution of sensitivity

This experiment concerned the ability of subjects to detect odor and feel from TXIB. The focus went beyond specification of the point of 50% detection, i.e. the traditional threshold concentration, to specification of the entire psychometric function, from low to high probability of detection. This approach allows statements about the underlying distributions of sensitivity for the sensory continua of interest. (The psychometric function is the integral of the distribution.) The function makes it possible to ask, for example, whether a phenomenon might occur only 5% of the time, i.e. to examine extremes in a distribution. Because the ability of TXIB to evoke any chemesthesis remained uncertain, the investigation included ethanol as a positive control, a material with indisputable ability to do so.

Ethanol can evoke both nasal and ocular chemesthesis, though no investigators have specified its psychometric functions. As a material that lies, in a manner of speaking, at the other end of the chemesthetic continuum, i.e. with low molecular weight, high vapor pressure, distinct odor, and sharp pungency, ethanol can provide a contrast regarding the distribution of sensitivity. The inclusion of these two materials may also shed light on one of the more persistent questions about olfaction, namely, why people may differ so much in sensitivity.

Method

Subjects

Thirty-three subjects (14 males and 19 females) aged between 18 and 43 years, and screened for health participated in the study. A subset of 19–20 participated per task. The subjects gave written informed consent in accordance with a protocol approved by the Human Subjects' Committee of the University of California, San Diego, CA, USA.

Materials

The materials consisted of:

1. TXIB (CAS No. 6846-50-0, Eastman Chemical Co., Kingsport, TN, USA, Lot 6023340);
2. Ethanol (CAS No. 64-17-5, Sigma-Aldrich, St. Louis, MO, USA, 99.5 + %);
3. Silicone oil (CAS No. 63148-62-9, Dow Corning 200 Fluid, Dow Corning Co., Midland, MI, USA, Food Grade, 350 cs);
4. Distilled water (CAS No. 7732-18-5, Arrowhead, Nestlé Waters North America Inc., Greenwich, CT, USA).

The silicone oil served to dilute the TXIB into two series of concentrations, a higher and a lower, and the distilled water served to dilute the ethanol into two series, also a higher and a lower. For each material, the higher series probed the range where chemesthetic detection occurred and the lower series probed the range where odor detection occurred.

Apparatus

Teflon®-topped glass vessels previously described by Cometto-Muñiz et al. (2000) served as the means to present vapors. A vessel, with volume 1.9 l, contained 200 ml of test solution, leaving 1.7 l of headspace as a reservoir. The lid of a vessel had three openings, one

for air to enter and two for air to exit the headspace. A long Teflon® tube that extended from the lid down just to the surface of the liquid provided the conduit for the incoming air. When air flowed down this tube, it generated a weak gurgling sound.

Two tubes that extended 3 cm out from the lids provided the conduit for flow from the headspace. Teflon®-lined PVC tubing extended these tubes to Teflon® nose-pieces that fit snuggly into the nares. When the subject sniffed, the gurgling would indicate the presence of a tight connection, with air just from the headspace entering the nostrils. For testing of odor, the subject sniffed from both tubes. For testing of nasal chemesthesis via localization, the subject sniffed from just one tube per vessel, but from two vessels, one to the right nostril and one the left. One vessel contained stimulus material, the other just solvent. For testing of ocular chemesthesis, compressed air that flowed at 3 l/min for 5 s carried the vapor to one eye via a glass eye cup attached to a vessel via Teflon®-lined PVC tubing.

Analysis of concentration

Calibration of the concentration of vapor in the headspace over the solutions required two steps: (1) injection of liquid samples of test material in order to establish a response factor from the instrument, an HP5890 gas chromatograph (GC; Hewlett Packard, Palo Alto, CA, USA) with a flame ionization detector, and (2) injection of vapor samples (0.2 ml) from the headspace. For measurement of liquid samples, ethanol was diluted to 1% (v/v) in 1-propanol and injected at volumes 0.1–1.0 μl (0.79–7.89 μg ethanol), and TXIB was diluted to 0.005% in ethanol for low concentrations of interest and 0.1% for higher concentrations of interest and injected at volumes 0.1–1.0 μl (0.0047–0.047 μg TXIB for the lower range and 0.095–0.98 μg TXIB for the upper range). Injections were made onto an HP19095F-123 column (30 m $\times$ 0.53 mm) held at 50°C for ethanol and 150°C for TXIB. The coefficient of variation of the response averaged 5% for the liquid samples.

Starting with the headspace over neat material, measurement headspace concentration covered a span of 300 to 1 for ethanol (CV = 4% for samples in quintuplicate) and 17 to 1 for TXIB (CV = 21%), in the latter case the lowest detectable via the GC. The results from the lower portion of these functions were extrapolated to obtain the lowest concentrations in the series.

Procedure

Each subject participated in many hours of testing, distributed over as many as 12 sessions. In a session, a subject judged one continuum: odor, nasal chemesthesis, or ocular chemesthesis, sometimes for one material and sometimes for both.

The first session entailed range-finding to establish where the subject would begin to perform above the level of chance. This enabled the experimenter to focus the testing subsequently on concentrations within the region of interest for that subject. Accordingly, different subjects had somewhat different series. By the end of the testing for a given continuum, the experimenter sought to have about 30–40 judgments per concentration for each subject. For testing of odor, adjacent concentrations in the liquid series varied by a factor of three. The vapor phase concentrations covered the range 7 ppt to 67 ppb for TXIB and 1 ppb to 80 ppm for ethanol, each with 11 members in a series. For testing of ocular and nasal chemesthesis, adjacent concentrations in a series varied by a factor of two. The vapor phase concentrations covered the range 280 ppb to 7.1 ppm for TXIB and 457 ppm to 32,280 ppm for ethanol, each with eight members in a series.

Odor. The experimenter placed three vessels, one with test material and two blanks, into a slotted box-shaped opaque plastic sleeve, with only the spouts in view. The subject sniffed from the vessels successively and chose the one with the strongest odor (three-alternative forced choice). Order varied randomly from trial to trial. The experimenter then withdrew the sleeve and changed the vessels out of sight of the subject. The next trial began after 90 s. Testing followed an irregular order with respect to concentration of the test material, i.e. the method of constant stimuli (Gescheider, 1997).

Ocular chemesthesis. The experimenter placed three vessels into the sleeve, as for testing of odor. One tube at the top of a vessel connected to the eye-cup, with the other tube capped. The experimenter connected the compressed air source to the tube for inflow and pressed a button to trigger flow toward the eye for 5 s. The linear flow rate at the eye equaled 8 cm/s, a flow common in an ordinary room and not distracting. After he had delivered stimulus from the first vessel, experimenter repeated the procedure for the other two. The subject then judged which vessel caused the strongest sensation. Other details followed that for testing odor.

Nasal localization (chemesthesis). The experimenter placed two vessels into the sleeve, one with stimulus material and one without (blank). A tube at the top of each vessel held a spout, with the other tube capped. The subject placed the tube from one vessel to the left nostril and that from the other vessel to the right nostril. The subject sniffed and sought to decide which side gave the stronger sensation. The order with respect to left and right varied randomly from trial to trial. Other details of testing followed that for testing of odor.

Results

The psychophysical procedure allowed different, though largely overlapping, spans of concentrations among the subjects, such that a lower span would probe the performance of a more sensitive subject and a higher span the performance of a less sensitive subject. In general, the experimenter calculated probabilities of correct performance at detection or localization for four to six concentrations. Occasionally, a subject who showed high sensitivity one day would show low sensitivity on another day and vice versa. In such cases, the experimenter might switch from the low to the high series and develop probabilities over a wider than customary range.

A psychometric function in the form of a log-normal distribution fitted to each subject's probabilities became the datum for computation of averages. Figures A1–A6 of Appendix A show linear regression functions for individual subjects in normal-deviate coordinates, z vs. log concentration. The median r^2 for the 119 functions in the appendix equaled 0.86 ($r = 0.93$). Figure 1 shows the average proportions detected, corrected for chance, for each task and chemical over the range explored. The standard errors represent the variability of the functions fitted to the data for individuals. As expected, the subjects could smell the materials at much lower concentrations than they could feel them. In addition, the subjects could smell TXIB at much lower concentrations than they could smell ethanol.

Subjects could detect the odor of TXIB on half of trials above chance at 1.2 ppb (geometric standard deviation, GSD = 7.1) and the odor of ethanol on half of trials at 91 ppb (GSD = 7.5). Hence, TXIB exceeded ethanol in olfactory stimulating efficiency by almost two orders of magnitude. Comparable performance for ocular detection of TXIB occurred at 2.1 ppm (GSD = 2.5) and of ethanol occurred at 2784 ppm (GSD = 2.0). Therefore, the gap of about a 100-fold in potency between the odors of ethanol and TXIB became a 1000-fold between their ocular chemesthetic effects. Approximately the same held true between their nasal chemesthetic effects. Subjects could localize TXIB on half of trials at 4.6 ppm (GSD = 2.5) and could localize ethanol at 2443 ppm (GSD = 1.1).

As the GSDs showed, the chemesthetic effects had lower relative variability than the olfactory effect, a common outcome. Whereas the span of uncertainty between the point where the average subject could just barely perceive odor to where he/she could perceive it almost perfectly equaled two to three orders of magnitude, the same span for chemesthesis equaled little more than one order of magnitude. A similar difference in span reflected itself in individual differences (Figure 1).

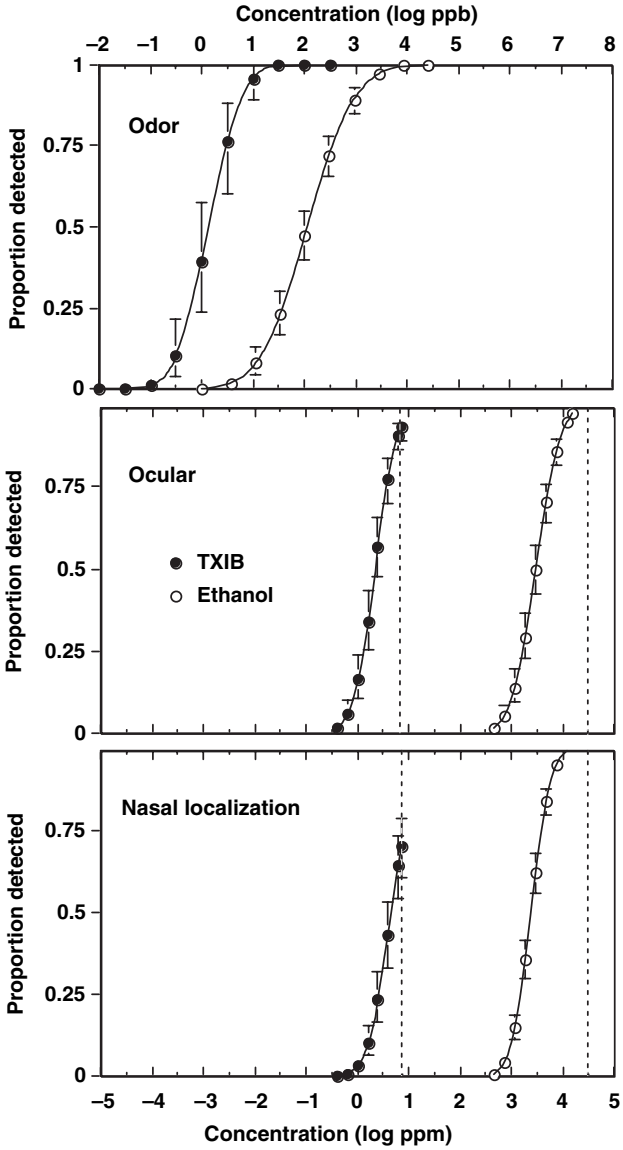

Fig. 1 Psychometric functions for the odor, ocular chemesthesis, and nasal localization (chemesthesis) for ethanol and TXIB. Concentration is expressed in log ppb at the top and log ppm at the bottom. Bars show standard errors from functions fitted to the data of individuals (see Appendix A). Dashed lines show saturated vapor concentrations for the two materials. All results were corrected for chance performance via the formula, $P = [p(c)-1]/(m-1)$, where P = detection probability corrected for chance, $p(c)$ = proportion correct, and m = number of choices in the forced-choice procedure, 3 for detection and 2 for localization (see Gescheider, 1997)

As the distributions for ocular and nasal chemesthetic effects for TXIB indicated, subjects on average failed to reach perfect performance at the saturated vapor concentration of 7.2 ppm. The chemesthetic effects of TXIB, such as they were, occurred at concentrations just below saturation. In contrast, the chemesthetic effects for ethanol approached perfect detection at concentrations in the vicinity of 6–8% of saturation.

Discussion

The results of the psychophysical experiment demonstrated that TXIB can evoke both olfactory and chemesthetic responses. Hence, this large molecule, as airborne chemicals go, does not exceed a cut-off where chemosensory activity disappears. As Figure 3 shows, both TXIB and ethanol follow the general trend of the relationship between odor and nasal chemesthesis for materials studied earlier (Cain and Cometto-Muñiz, 1995).

As noted in the Introduction, the concentration of TXIB measured in most dwellings and offices studied lay below 1 ppb. In the study of English homes, Raw et al. (2004) found the median, i.e. 50th percentile, at 0.15 ppb, close to what Kostiainen (1995) reported, 0.14 ppb, in normal buildings in Finland some years earlier. Järnström and Saarela (2002) indicated 1.2 ppb as average (not median) for 'normal' Finnish housing (their quotes). This corresponds to the 95th percentile in English dwellings.

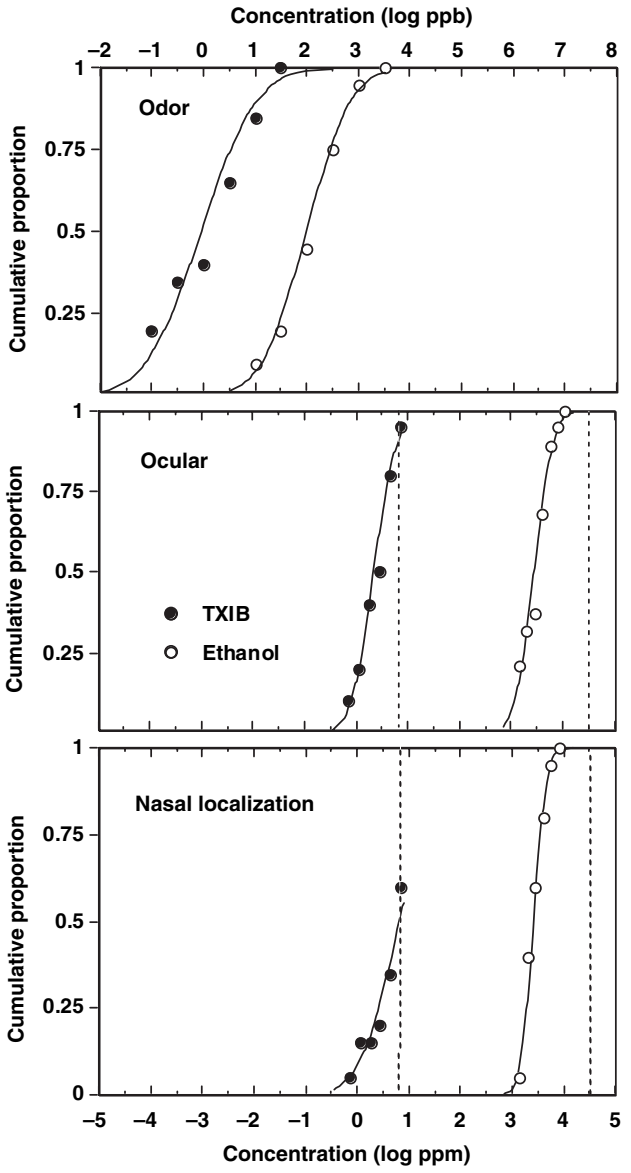

Fig. 2 Cumulative distributions of subjects who achieved the point of 50% detection (corrected for chance) for ethanol and TXIB. Concentration is expressed in log ppb at the top and log ppm at the bottom

Concern about a contribution of TXIB to symptoms has arisen for concentrations about 20-fold or more above the median, 2.5–3 ppb (Järnström and Saarela, 2002; Metiäinen et al., 2002). According to the present results (Figure 1), the typical young person could possibly notice odor from TXIB about three-quarters of the time at such concentrations. We say 'possibly' because TXIB would be just one of perhaps one to two hundred airborne chemicals in a space that would likely endow it *en masse* with a characteristic odor. (Every place has an odor if one chooses to attend to it upon entering.) The quality of this blend will depend upon the relative potencies of the chemicals, but according to rules not yet deciphered. At concentrations below those detected 100% of the time, i.e. below approximately 10 ppb for TXIB, little of the quality of any given chemical would emerge. Not surprisingly, many spaces have a vague odor of 'home,' 'office,' and so on.

Although occupants may sometimes cite odor as the source of their dissatisfaction with a space, the principal issue raised with respect to TXIB concerns irritation. According to the present results, the typical person would not feel the presence of TXIB even a fraction of the time below about 500 ppb (Figure 1). Nor, as far as we can tell, would any fraction of persons detect TXIB by feel at a concentration below 500 ppb (Figure 2). To 'explain' a chemesthetic response to TXIB at 2.5 ppb would require some way to make up for at least a 200-fold disparity.

Could the presence of other chemicals explain the disparity? At concentrations of very low chemesthetic detectability, airborne chemicals show perceptual independence (Cometto-Muñiz et al., 2004). Accordingly, cumulative mass, weighted by chemosensory effectiveness, across materials in a mixture might evoke feel well below the mass required of a single material. If, however, the combined effect of all airborne chemicals in a space caused irritative symptoms, then TXIB would earn no particular distinction as the cause. Although the quantity TVOC, defined in the customary way, seems to account for symptoms reliably only at high levels, TVOC weighted to reflect the relative biological potency of the constituents may fare better predictively (Cometto-Muñiz et al., 1997).

Could duration of exposure account for the disparity? An irritating vapor will tend to become more irritating the longer a person has exposure to it, up to a point (Cain et al., 1986). The feel may then subside

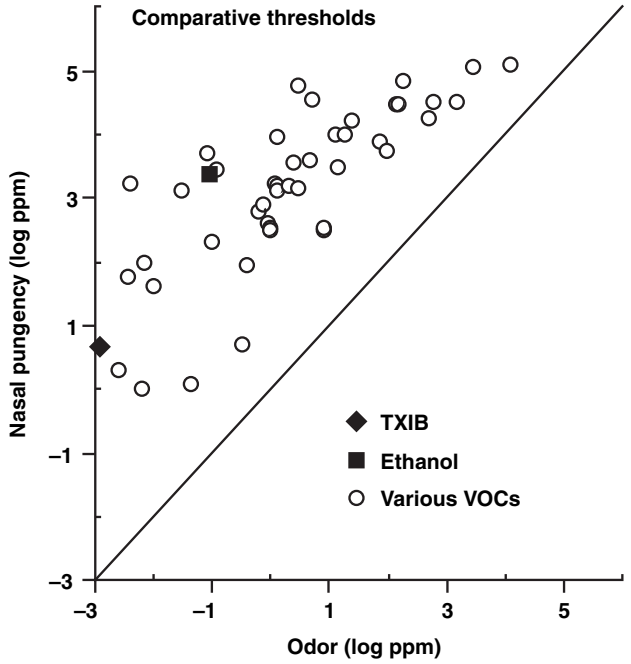

Fig. 3 Comparative thresholds for odor and nasal pungency for ethanol and TXIB, and for various VOCs studied previously

(Cain, 1990; Cain and Cometto-Muñiz, 1995). No studies have yet addressed whether a vapor that evokes no feel at first may eventually become perceptible. Beyond that issue, one can ask whether such a phenomenon would vary from one chemical to another. Hence, would TXIB, but not other airborne chemicals, show the phenomenon? The possibility seems remote. The relevant time-scale for the phenomenon, and hence for relevant studies, could range from minutes to days.

Although limited in terms of the duration of exposure, this investigation offers no encouragement for the conclusion that TXIB should cause irritation at the concentrations measured in the relevant studies of occupied spaces. This in no way refutes the symptoms expressed, but suggests a need to look more broadly for an answer to why they might occur.

Individual differences in olfaction and chemesthesis

The outcome of this investigation afforded a perspective on individual differences in chemoreception. The findings and analysis have enough importance to merit discussion, though their placement in Appendix B acknowledges that only some readers may find the theoretical treatment of interest.

Conclusions

The material TXIB proved detectable both by smell and by nasal and ocular chemesthesis. The material behaved perceptually like that of others of high molecular weight and high lipophilicity that might approach, but have not reached, a chemosensory cut-off.

If present alone in the air, TXIB could trigger some olfactory perception in quite a few spaces where it has been measured. At concentrations just above the median of English homes (0.13 ppb), to use a recent example, the typical person might occasionally detect some presence by smell. At concentrations above those associated statistically with symptoms (2.5–3 ppb) in some studies, the average person would likely detect the presence of TXIB more often than not by smell. Only at such levels might the plastic odor of TXIB begin to become apparent.

As one of more than a 100 airborne materials in a typical space, TXIB might have no separate perceptual identity until present at concentrations considerably above that for essentially perfect olfactory detection, about 10 ppb. Below levels in the tens of ppb, the olfactory contribution of TXIB likely just blends into that of the other VOCs to form *en masse* the characteristic odor of the space.

Detection of any chemesthetic effect of TXIB began above 500 ppb. This held true for both the nose and the eye. Even at 1 ppm, the average person rarely registered any chemesthetic effect, nor did more than a small fraction of people register threshold-level chemesthesis.

Neither the presence of other chemicals nor the passage of time seems adequate to account for the 200-fold span of concentration between where putative irritative symptoms begin and where chemesthetic effects occurred in the brief exposures of this investigation.

The results of this investigation have relevance to why olfaction seems particularly variable (see Appendix B). Psychometric functions for individual subjects imply that olfactory detection shows much more variation in time than does chemesthesis. Neurobiological data suggest no particular variability, but strong compression of olfactory input at the first two stages of neural processing. This much-compressed signal flowing centrally means that small differences in performance, some undoubtedly because of variation in time, seem amplified when expressed in terms of concentration. If true for the individual, this needs logically to hold for the differences across people. That is, differences in performance reflect themselves in much larger differences in such measures as the threshold expressed in terms of concentration. The metric inflates the variation.

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Appendix A: Psychometric functions for individual subjects

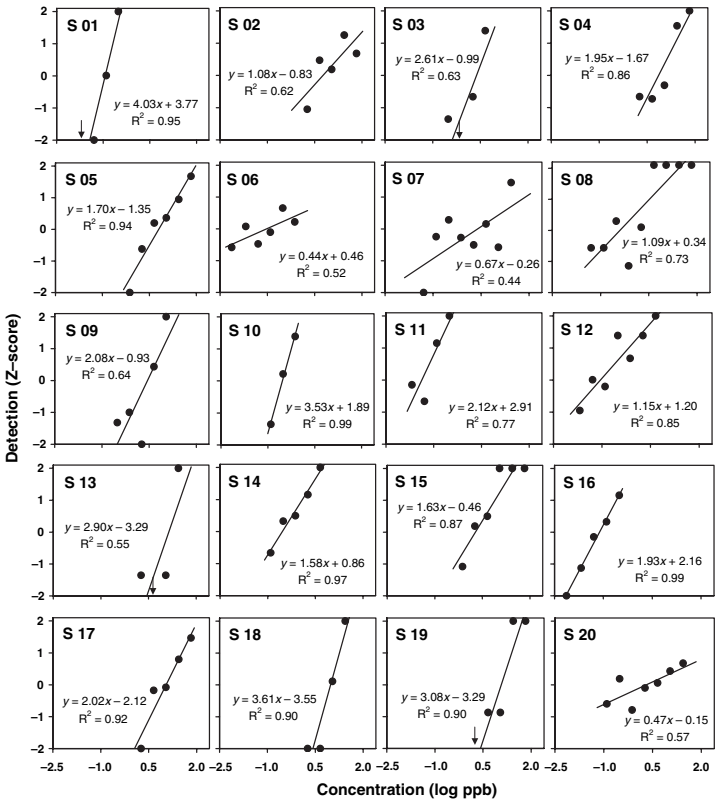

Fig. A1 Showing psychometric functions for detection of the odor of TXIB for individual subjects. The plots show normal deviate, i.e. *z*-transformed scores that correspond to probability of detection vs. log concentration. In such coordinates, data for chemosensory detection customarily approximate a straight line. A *z*-score of 0 corresponds to 50% correct detection. Ninety-five percent of the distribution lies between $z = -2$ and $+2$. Arrowheads in some plots indicate existence of a lower value than $z = -2$. The higher the slope of the regression line, the smaller the variation in a subject's performance

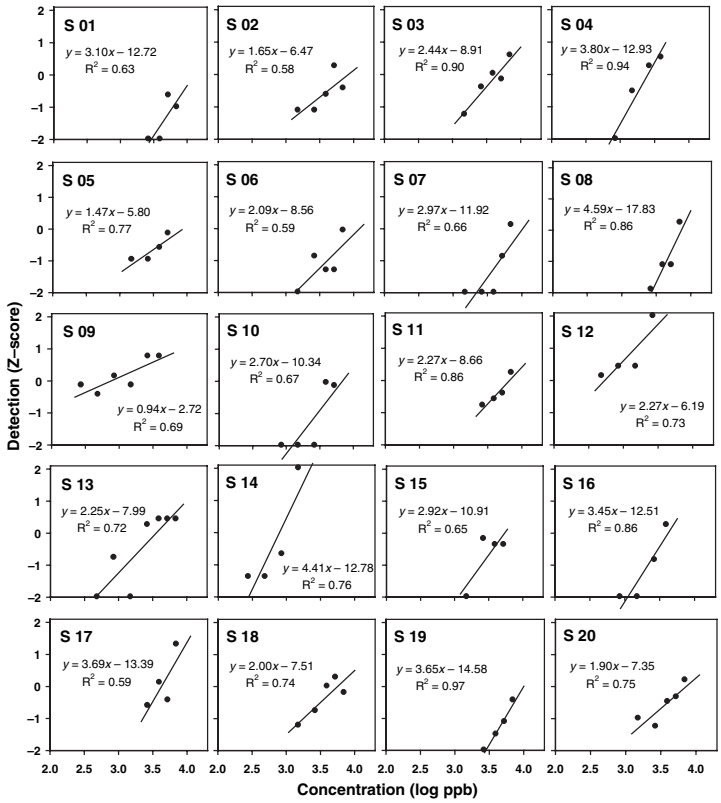

Fig. A2 Psychometric functions for nasal chemesthesis of TXIB for individual subjects

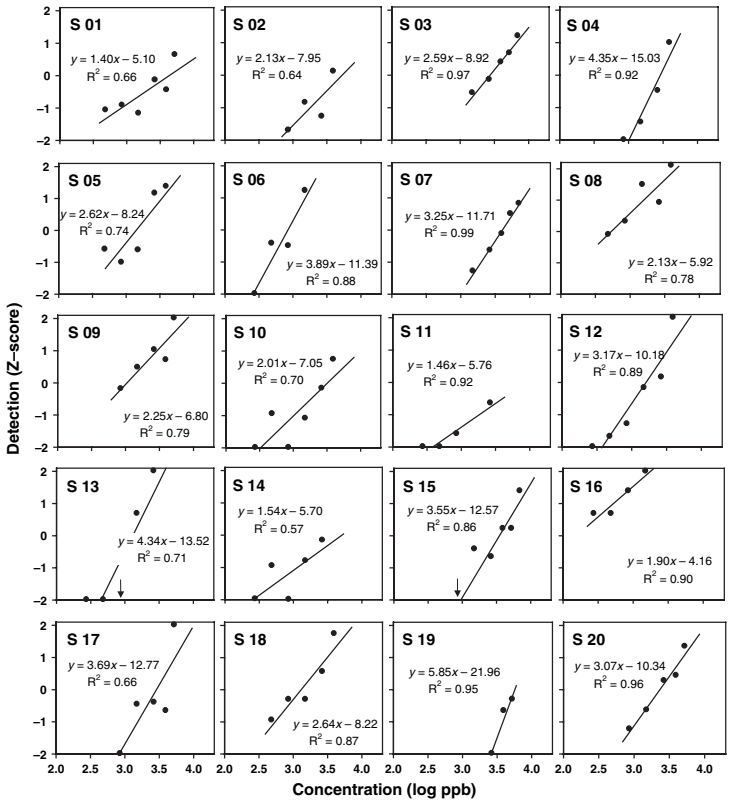

Fig. A3 Psychometric functions for ocular chemesthesis of TXIB for individual subjects

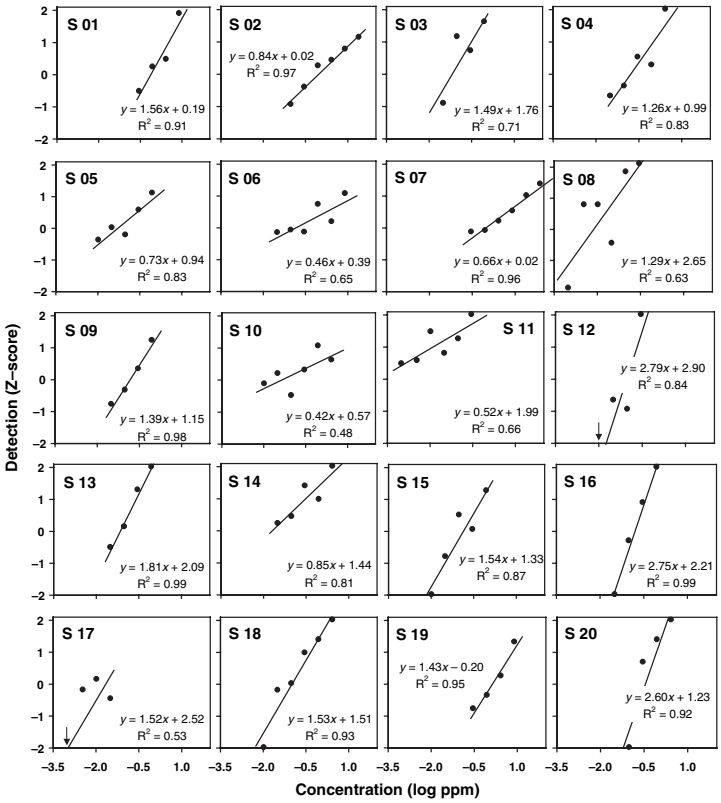

Fig. A4 Psychometric functions for detection of the odor of ethanol for individual subjects

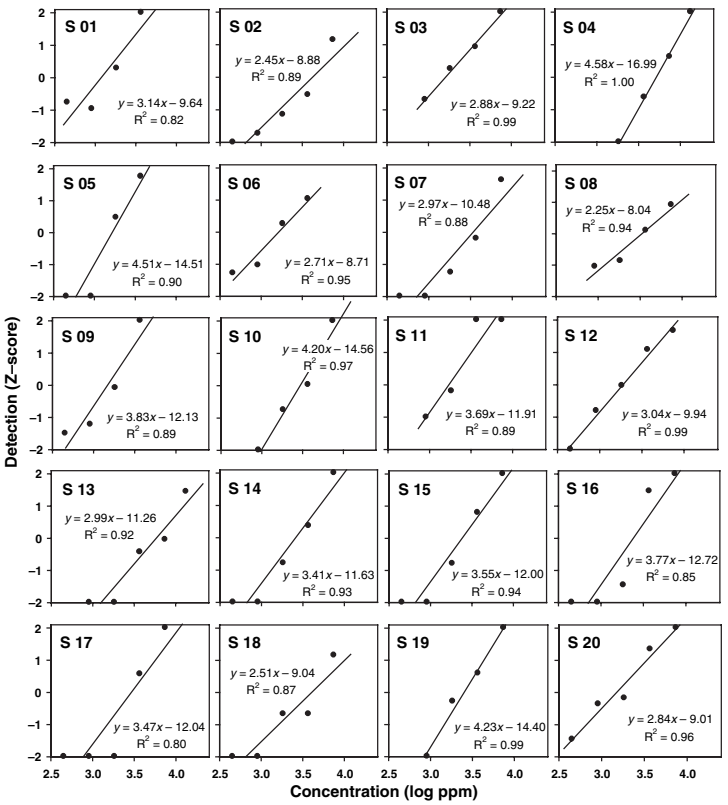

Fig. A5 Psychometric functions for nasal chemesthesis of ethanol for individual subjects

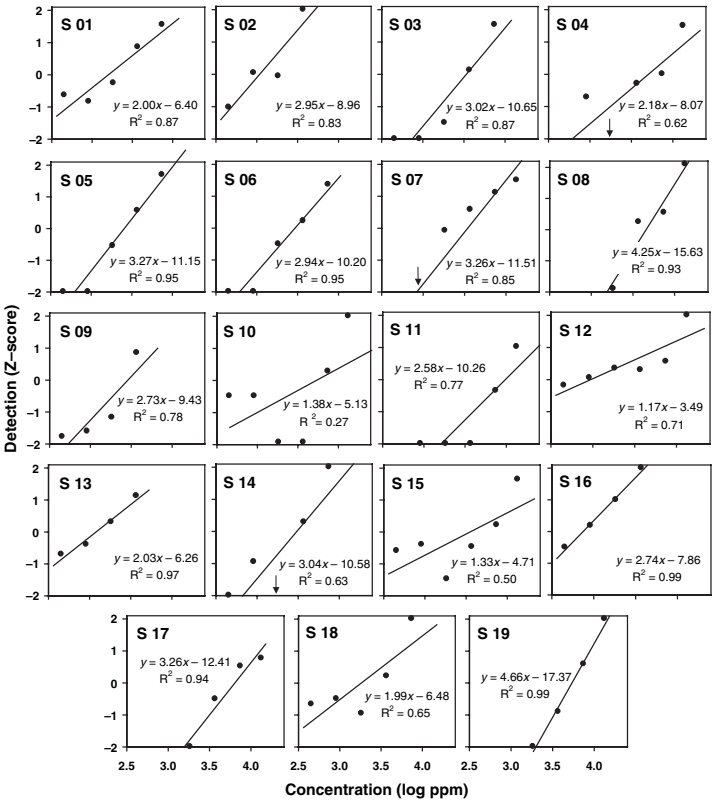

Fig. A6 Psychometric functions for ocular chemesthesis of ethanol for individual subjects

Appendix B: Discussion of individual differences in olfaction and chemesthesis

Olfaction has long had the reputation as the modality with the largest individual differences in sensitivity. People will often remark about how they know someone with a remarkable nose or they themselves may claim such superiority. Some will profess the opposite. Not uncommonly, studies will measure differences of three, four, or even five orders of magnitude (see Cain and Gent, 1991). Some of this variation may come from fluctuations in the magnitude of the stimulus, i.e. poor stimulus control, or from unreliable measurement of threshold, e.g. too few trials. Measurement of the psychometric function obviates at least the latter problem, for psychometric functions would show little regularity if based upon too few trials (see Appendix A). Choice of how to present the stimulus can minimize the former. The system used here sought to provide very stable stimulation, providing a tight seal between the nostrils and the spouts, and providing a large enough volume that a subject would not exhaust it with a sniff (see Cometto-Muñiz et al., 2000).

A further issue concerns whether delivery of lower concentrations has less stability than that of higher concentrations. If so, then one could question whether the higher variability seen for olfactory results vs. chemesthetic results might reflect a physical difference. The study of both the chemesthetic and olfactory outcomes for a more potent and a less potent material over a range of nine orders of magnitude here can, we think, put that issue to rest. Even with overlapping concentrations for the odor detection of ethanol and the chemesthetic detection of TXIB, olfaction produced the broader distribution, i.e. lower slope of the psychometric function, both within and between subjects.

A psychometric function obtained for an individual reflects variation over time (Cain and Gent, 1991; Gescheider, 1997). That is, the person detects a given concentration, by whichever modality, at one moment and not the next. Each concentration becomes a probe for the degree of variation and the probabilities of detection reflect it directly. According to the difference in slope between the functions for olfaction and those for chemesthesis, olfaction would seem to vary in time much more than chemesthesis (Figure 1). Could this represent statistical fluctuation in deposition of molecules in the airway? Unlikely. The difference in slope came out much the same for both ethanol, which required much higher concentrations for detection, and TXIB. No previous study could rule out this factor. Could the larger apparent variation for olfaction occur because of differences in some central process? Unlikely. Candidate central processes would include such phenomena as attention, fatigue, and vigilance, common to input from both modalities. This would seem then to narrow the search for the source of

olfactory variation to that of transduction and first- and second-order neural processing, the level of the olfactory receptor neurons and the mitral-tufted cells of the olfactory bulb.

Is there any neurobiological evidence that olfaction fluctuates widely at these levels, such that the concentration needed to stimulate on one occasion might need to exceed that required on another by two or more orders of magnitude, as the data on detection imply? No. Those who have studied the intensive aspects of olfactory processing at the periphery and the bulb have instead noted stability rather than variation (Duchamp-Viret et al., 2000; Rospars et al., 2003; Sachse and Galizia, 2003). They have, however, also found compression of output vs. input, and herein may lie an illusion that olfaction varies widely in time. Some compression appears in responses of olfactory receptor neurons, but much more appears between the receptor neurons and the second-order neurons (Rospars et al., 2002). The output from the olfactory bulb shows enough compression to make intensity, as an olfactory variable, seem relatively unimportant compared with quality (Duchamp-Viret et al., 1990). Beyond that point, the system can read only this compressed signal (Davison et al., 2003). Accordingly, a modest fluctuation in, say, attention, that would show up as modest difference in probability of detection would reflect itself as a much larger difference in the magnitude of stimulation, expressed as concentration.

The chemesthetic system, unlike olfaction, shows no compression and perhaps even expansion of output vs. input in the peripheral nervous system (Kulle and Cooper, 1975). Barring some compression of the neural signal more centrally, the same modest fluctuation in attention that shows up as a modest difference in probability of chemesthetic detection would therefore reflect itself in a commensurate difference in magnitude of stimulation. To illustrate with normal-deviate scores for ethanol, the equation for detection of odor by the average person (results in Figure 1) equaled $Z_{\text{odor}} = 1.37 \log X_{\text{ppm}} + 1.29$. For the person to go from one standard deviation below his/her own mean ($z = -1$ or $P = 0.16$) to one standard deviation above that mean ($z = +1$ or $P = 0.84$), i.e. a five and a quarter-fold increment in performance, would require a 30-fold increment in concentration. This means that the person would appear 30 times more sensitive at the higher level of performance. The equation for nasal localization equaled $Z_{\text{localization}} = 3.3 \log X_{\text{ppm}} - 11.3$. For the person to go from one standard deviation below his/her mean to one standard deviation above that mean would require just a fourfold increment in concentration. The person would therefore appear only four times more sensitive at the higher level of performance. The difference in apparent sensitivity between olfaction and chemesthesis lies in the metric, viz., concentration. This example concerned differences within an individual. In the absence of evidence of much higher inherent variation over time in olfaction, it seems appropriate to conclude that no variation in time commensurate with the differences in the psychometric function controls performance.

Further evidence that differences between olfaction and chemesthesis lie not in fluctuation in time, but in the relative compression (or expansion) of input, comes from functions for concentration against response at suprathreshold levels. Psychophysical functions for judged odor intensity normally conform more or less to square-root functions, i.e. $Y_{\text{odor}} = k(X_{\text{ppm}})^{1/2}$ (Cain, 1988). In that case, a fivefold change in odor intensity, as per our example regarding detection (actually 5.25), would result from effectively a 30-fold change in concentration. Psychophysical functions for nasal chemesthesis, however, normally conform approximately to square functions, i.e. $Y_{\text{chemesthesis}} = k(X_{\text{ppm}})^2$ (Cain et al., 2004). In that case, determined principally for functions for the tingle of carbon dioxide, the fivefold change in intensity would result from a change in concentration between two- and threefold.

No principle of sensory functioning says that the psychometric functions for detection must agree with suprathreshold psychophysical functions for perceived intensity. In the chemosensory case, they could reflect proportionately the probability that a given density of incident flux of stimulating molecules contacts a given number of receptors. In such a case, the function would perhaps show no compression. At suprathreshold levels, however, they could still show compression.

Although the cumulative probability functions in Figure 2 resemble the psychometric functions for the typical subject in Figure 1, they deserve a fundamentally different interpretation because they reflect a spread among the subjects rather than a spread in performance over time for the average subject. (Incidentally, the use of the criterion of 50% correct has no special relevance to the form of the functions in Figure 1. A different criterion would give a comparable picture.) If we accept that the function for the average subject overstates the variability of performance, then we should accept that the function across subjects does the same. That is, a subject thought to have 30-fold higher sensitivity than another may actually have performed only five times better. This does not make the claim of 30 to 1 false. It merely brings perspective on what individual differences in olfactory sensitivity actually mean.