Title

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Journal

Chemical Senses, 20(2)

ISSN

0379-864X 1464-3553

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Publication Date

1995

DOI

10.1093/chemse/20.2.191

Data Availability

The data associated with this publication are within the manuscript.

Peer reviewed

Chemical Senses **20**(2):191–198, 1995

Relative sensitivity of the ocular trigeminal, nasal trigeminal, and olfactory systems to airborne chemicals

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Running head: Eye irritation and odor thresholds

[1] Research performed while J.E.C.-M. was a member of the Carrera del Investigador Científico, Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), República Argentina.

Abstract

We measured thresholds for eye irritation and odor in homologous series of alcohols (ethanol, 1-butanol, 1-hexanol, and 1-octanol), ketones (2-propanone, 2-pentanone, 2-heptanone, and 2-nonanone), and alkylbenzenes (toluene, ethyl benzene, and propyl benzene). Eye irritation thresholds were well above odor thresholds for all series. Both sensory thresholds declined with carbon chain length, a trend that has implicated lipophilicity in the potency of these and related stimuli. Eye irritation thresholds were remarkably close to nasal pungency thresholds obtained previously in persons lacking olfaction (i.e., anosmics). The agreement between the two thresholds implies that, despite differences in the mucus layer at the two sites and in the epithelial tissue itself, there is remarkable similarity at the site of stimulation. As a practical matter, the eyes could serve as the sites to assess potency for induction of nasal pungency, an assessment previously limited to testing anosmics. Presumably — for our brief stimulus presentations (1-3 sec) — the differences between ocular and nasal mucosae have little relevance to chemical sensitivity. Studies of the ability of homologous chemical series to evoke threshold eye irritation, nasal pungency, and odor not only have practical value but also can help to define the physicochemical properties of the receptor and perireceptor biophases.

Introduction

Study of the sensory properties of airborne chemicals has included, principally, olfaction, and, to a lesser extent, the nasal common chemical sense (CCS) (Green et al., 1990). Much less common has been the investigation of the response of the ocular CCS to gas-phase stimuli (Walker et al., 1990). Free nerve endings from the trigeminal nerve constitute the CCS receptors for both the nasal and ocular mucosae. A pioneer study by Moncrieff (Moncrieff, 1955) compared the sensitivity of the ocular CCS, the nasal CCS, and olfaction, but employed relatively reactive chemicals and a very crude methodology that included no measurement of concentrations at all.

Research assessing the ocular irritation potential of substances has typically used stimuli in liquid phase instilled into the eye of an animal preparation (Guillot et al., 1982; Kobel and Gfeller, 1985). Results are usually reported on the Draize scale (Draize et al., 1944), despite the widespread criticisms of lack of reproducibility of the subjective scoring procedure (Burton, 1972; Weil and Scala, 1971). Most of the suggested alternatives to the Draize test involve *in vitro* assays (Booman et al., 1989), though *in vivo* assays have also been proposed (e.g., Kennah II et al., 1989). One *in vivo* approach explored in animals has consisted of recording electrophysiological responses to instilled compounds from the sensory nerve fibers innervating the eye (Belmonte et al., 1991; Beuerman et al., 1992; Gallar et al., 1993).

The Draize test has been used principally to screen individual compounds and some mixtures that might appear in personal products and other products that may come into contact with the eyes of humans. Neither the Draize test nor the recordings from fibers of the eyes of animals have addressed the important issue of sensitivity to airborne irritants. Just as one might wish to screen ingredients in personal products, one

might wish to screen ingredients for inclusion in materials and furnishings used in indoor environments. The high frequency of complaints of irritation in some new and refurbished spaces, and in other spaces, such as new cars, can motivate such screening (see Cain and Cometto-Muñiz, 1993; Cometto-Muñiz and Cain, 1992). Manufacturers could possibly change ingredients or formulation of their products if tests revealed likely problems with irritation when ingredients off-gas from a finished product.

Some human studies of ocular sensitivity to airborne chemicals and particles have emerged lately as new methods of evaluation and stimulus presentation have evolved (Douglas and Coe, 1987; Kjærgaard and Pedersen, 1989; Kjærgaard et al., 1989; Kjærgaard et al., 1992; Kjærgaard et al., 1990). The emphasis has been on the development of objective changes, such as redness of the eyes and alterations of the tear film. Continued development of the techniques will require psychophysical measurements in order to correlate subjective reactions to irritating vapors with objective signs.

In the present study we measured eye irritation and odor thresholds for homologous series of alcohols, ketones, and alkylbenzenes — presented as vapors — and used a simple, though efficient, squeeze bottle delivery technique that served well in the past to measure eye irritation, odor, and nasal pungency (irritation) thresholds for homologous acetates (Cometto-Muñiz and Cain, 1991). Our aim in studying series is to obtain results that will eventually permit prediction of sensitivity from knowledge of key physicochemical properties of individual stimuli and mixtures.

Use of the same delivery system and procedure to gather thresholds for the three sensory reactions should allow standardized comparison of the relative sensitivity of each sensory channel. Particular reasons to compare eye irritation and nasal pungency

include: 1) study of the effect of different mucus layers, 2) study of the effect of different epithelial layers, and 3) possibility that eye irritation might be a good assay of trigeminal chemical sensitivity and one that would have no interference from smell.

Materials and Methods

Stimuli. All chemicals were analytical grade reagents. The alcohols studied were ethanol, 1-butanol, 1-hexanol, and 1-octanol. The ketones were 2-propanone (acetone), 2-pentanone, 2-heptanone, and 2-nonanone. The alkylbenzenes were toluene, ethyl benzene, and propyl benzene. Deionized water served as solvent for ethanol and 2-propanone, and mineral oil served as solvent for the rest.

Dilution series for each compound were prepared in duplicate. Each series consisted of the undiluted substance (i.e., 100 % v/v), labeled dilution step 0, and subsequent three-fold liquid dilutions (i.e., 33, 11, 3.7, etc., %v/v), labeled dilution steps 1 to 16.

Stimuli were presented in 250 ml, squeezable, high density polyethylene bottles, containing 30 ml of solution. The bottle caps used for odor testing had a pop-up spout that fitted into the nostril being tested, allowing each nostril to be tested separately (Amoore and Ollman, 1983; Cain, 1989). The bottle caps used for eye irritation testing had a 25-ml measuring chamber (of the type used in variable volume dispensers), the rim of which was placed around the eye (Cometto-Muñiz and Cain, 1991). The chamber was connected by a tube to the headspace of the bottle (inside the bottle, the tube ended well above the level of the liquid solution). A squeeze of the bottle with this cap in place delivered a puff of vapor into the measuring chamber where the eye was being

exposed. A polyethylene dust cover closed the open end of the measuring chamber when the bottle was not in use.

The concentration of the compound in the **headspace** of each bottle was measured by a gas chromatograph (photoionization detector) equipped with a gas sampling valve, allowing direct sampling of the headspace. For every substance, repeated chromatographic readings were taken from each dilution step, including the bottle containing the pure chemical. The headspace of the bottle with undiluted chemical contains vapor saturated with the chemical at room temperature (23 °C). Knowledge of saturated vapor concentration (at 23 °C) and its associated average chromatographic reading allowed conversion of the readings from the other bottles into concentration units (ppm by volume), and a calibration curve was derived.

Subjects. In the study of the alcohols, ten subjects (five males and five females) participated. Their ages ranged between 19 and 38 years (average ± SD: 24.9 ± 5.6). These subjects and those in the studies of the ketones and alkylbenzenes were all nonsmokers.

In the study of the ketones also ten subjects (six males and four females) participated. Their ages ranged between 19 and 30 years (average ± SD: 21.5 ± 3.6).

In the study of the alkylbenzenes eight subjects (four males and four females) participated. In this case, participants covered a much broader age range in order to match a group of available anosmic subjects (i.e., persons lacking a functional sense of smell) who would be tested for nasal pungency (irritation) thresholds (results from the anosmics are cited but not described in detail here). The age of the subjects ranged from 21 to 60 years, and consisted of a male and a female in the following categories:

early twenties, early thirties, early forties, and late fifties/sixty. A 21-year-old male became unavailable after being tested for odor thresholds and was replaced by a 22-year-old male tested only for eye irritation thresholds to complete the group.

Procedure. Both eye irritation and odor thresholds were measured using squeeze bottles and a two-alternative, forced-choice procedure with an ascending method of limits. This means that on each trial the subject had to choose the stronger of two stimuli: one was a blank and the other a certain concentration of the substance studied (e.g., dilution step 16). A correct choice entailed the presentation of the same concentration (from another set) also paired with a blank. An incorrect choice entailed the presentation of the next step — a liquid concentration three times higher — (following the previous example, dilution step 15). Hence, correct choices led to another presentation of the same concentration whereas errors triggered increments in concentration. The procedure continued until the participant got five correct choices of the same concentration (step) in a row. That level was taken as the threshold. Testing always started with the use of a high dilution (low concentration) — clearly below threshold — and, as mistakes were made, proceeded to increasing concentrations.

Once the threshold was measured for one nostril or eye, the other nostril or eye was tested. After that, testing began with another substance in identical manner.

For the ketones and alkylbenzenes, each participant provided a total of eight thresholds per compound and sensory modality (half with the right nostril/eye and half with the left nostril/eye). For the alcohols, each participant provided a total of four thresholds per compound and sensory modality (half with the right nostril/eye, and half with the left nostril/eye). Sessions typically lasted between 1 and 2 hours and were repeated until the specified number of measurements was reached. Order of

presentation of the chemicals differed among subjects. The number of times that the right or left nostril/eye was tested first for a certain substance was counterbalanced for each subject.

Data analysis. Individual thresholds were converted into headspace concentration (ppm) through the calibration curve and averaged geometrically since they tend to follow a log normal distribution (Amoore, 1986; Brown et al., 1968; Cain and Gent, 1991).

Results

Figure 1 shows eye irritation and odor thresholds as a function of carbon chain length for each of the three homologous series.

Insert Figure 1 about here

For all compounds, eye irritation thresholds lay well above odor thresholds. The substance with the smallest difference between thresholds was 2-propanone, for which the nose (olfactory sensitivity) was only 15 times more sensitive than the eyes. The substance with the largest difference was propyl benzene, for which the nose was approximately 2700 times more sensitive than the eyes. Table 1 shows the ratio eye irritation threshold/odor threshold for each compound studied.

Insert Table 1 about here

Both sensory thresholds declined with increasing carbon chain length in all three series. For ketones and alkylbenzenes, the decline in odor thresholds was steeper than

that for eye irritation thresholds. Thus, the gap between them became larger as the series progressed. For the ketones, however, eye irritation and odor showed a tendency to plateau when the series reached 2-heptanone. For the alcohols, on the contrary, eye irritation declined faster than odor, though between 1-hexanol and 1-octanol there was a disproportionate reduction in odor threshold compared with that observed for the previous members.

Discussion

Knowledge of the sensory properties of homologous series of airborne chemicals provides an important tool to understand the basis of their action on the receptive structures. This is so since physicochemical properties in such series change in an orderly and systematic fashion. This approach has been coupled in previous studies with the testing of clinically diagnosed anosmic subjects. Anosmics provide "true" nasal pungency thresholds, unbiased by any odor sensation (Cometto-Muñiz and Cain, 1990; Cometto-Muñiz and Cain, 1991; Cometto-Muñiz and Cain, 1993; Cometto-Muñiz and Cain, 1994). In all these studies thresholds for odor and nasal pungency were found to decline with increasing carbon chain length for all series tested.

Odor thresholds for the alcohols, ketones, and alkylbenzenes selected here have been measured before in the above cited studies, using the same technique and procedure but, of course, with a different group of subjects. Figure 2 shows the correlation between the present and previous odor thresholds for these 11 chemicals. For reasons we cannot explain, the present group of subjects showed less olfactory sensitivity to butanol, hexanol, and octanol than did subjects in previous experiments. The departure from previous results was especially striking for octanol (lower left point

on Figure 2). For the ketones, alkylbenzenes, and the remaining alcohol (ethanol), mean thresholds all fell within one standard deviation of the line of identity.

Insert Figure 2 about here

As illustrated in Figure 1, eye irritation thresholds lay orders of magnitude above odor thresholds. In the acetate series, eye irritation and nasal pungency thresholds were found to fall very close to each other, and both well above odor thresholds (Cometto-Muñiz and Cain, 1991). Figure 3 depicts a comparison between the present eye irritation thresholds for homologous alcohols, ketones, and alkylbenzenes and the previously obtained nasal pungency thresholds (from anosmics) for the same substances. The overall outcome resembles that obtained before for the acetates: common chemical sensitivity in the eyes and the nose is very similar, with some advantage (lower thresholds) for the nose in the case of ethanol and 2-pentanone. The extent to which the result for these two compounds is particular to the group of subjects tested or is a more general phenomenon is as yet unanswered.

Insert Figure 3 about here

Taking the data for all homologous series studied so far and the three types of sensory responses, a salient outcome emerges: the appearance of a cut-off point. For odor, this is reflected in thresholds reaching a plateau, and failing to decrease indefinitely. Such a plateau is reached, approximately, with hexyl acetate (Cometto-Muñiz and Cain, 1991), 2-heptanone (Cometto-Muñiz and Cain, 1993), and propyl benzene (Cometto-Muñiz and Cain, 1994), respectively, in the acetate, ketone, and alkylbenzene series. Interestingly, the alcohols do not show the cut-off, at least up to 1-octanol, the highest member studied (Cometto-Muñiz and Cain, 1990).

For nasal pungency, the cut-off is expressed relatively abruptly when a member is reached for which a threshold for pungency cannot be obtained 100 % of the time in all anosmics — not even at vapor saturation — with our criterion of five correct choices in a row. This point is achieved with 1-octanol (Cometto-Muñiz and Cain, 1990), heptyl acetate (Cometto-Muñiz and Cain, 1991), 2-nonanone (Cometto-Muñiz and Cain, 1993), and propyl benzene (Cometto-Muñiz and Cain, 1994) in the respective series.

The cut-off for eye irritation thresholds, depending on the chemical series, shows similarity to nasal pungency or to odor. Similarly to nasal pungency, eye irritation thresholds show an abrupt cut-off in the acetate series (with octyl acetate) and, presumably, in the alkylbenzene series (with propyl benzene), though the latter needs further confirmation by testing higher members in the series. Similarly to odor, eye irritation thresholds in the alcohols fail to show a cut-off (up to 1-octanol), and in the ketones the cut-off shows as a plateau.

In terms of elucidating the properties of the underlying receptor mechanism(s) for the production of eye irritation, nasal pungency, and odor, our data encourage various lines of thought. Increasing lipophilicity enhances the effectiveness of the molecule (lower thresholds) but only up to an optimal molecular size, beyond which no further gain in potency is obtained or effectiveness is even lost. This suggests that the reception process takes place in a hydrophobic environment but with certain size requirements (such as a hydrophobic pocket on a membrane-immersed protein). Alternatively, reception might take place in a hydrophobic site under relatively few spatial restrictions (such as the lipid phase of the cellular membrane) but the aqueous perireceptor medium (tear film, nasal mucus) would *per se* impose a barrier to water insoluble molecules, explaining the appearance of the cut-off. In animal preparations it

might be possible to alter the polarity of the bathing medium surrounding the receptive structures and sort out the effect of the medium itself on the responses to chemicals.

An animal bioassay that uses mice has been developed to assess the upper respiratory tract irritation potency of airborne substances (Alarie, 1966). The response of interest in this bioassay is the concentration of the tested chemical that depresses the respiratory rate of mice by 50% (i.e., RD_{50}). As reported in a previous study (Cometto-Muñiz and Cain, 1994) our human pungency thresholds correlate well with RD_{50}s for a set of 21 compounds (r=0.85). If we include the three lower acetates (methyl, ethyl, and propyl acetate) the correlation is only modest (r=0.63, n=24). We pointed out that a disparity in the time-course function of the respiratory decrease (Kane et al., 1980) for these three acetates — compared to the typical function — could account for these results. Time plays a major role in nasal irritation (e.g., Cain et al., 1986; Cometto-Muñiz and Cain, 1984), and our pungency thresholds are based on a restricted (one nostril only), short term (1-3 sec) exposure, while RD_{50}s are based on exposure of mice (whole head) for at least 10 minutes, sometimes considerably longer.

In more than one aspect the topic of the nature of the receptive biophase for these sensory endpoints (thresholds) can be compared to the phenomena of anesthesia. The mechanisms underlying general anesthesia have been studied for well over a century, with still no broadly accepted agreement among investigators. One of the few known facts (known since as early as the 1890s) is the good correlation between anesthetic potency and lipophilicity, as expressed, for example, in olive oil/water, or more recently octanol/water (Franks and Lieb, 1978) partition coefficients. This fact and that of the wide chemical diversity of anesthetic agents (comparable to the diversity of odorants and irritants) led to the conclusion that the primary targets are lipid portions of nerve membranes. Recent data, however, point to particularly sensitive

proteins as target sites (see reviews in Franks and Lieb, 1982; Franks and Lieb, 1990). Interestingly, one line of evidence suggesting that anesthetics act on specific proteins rests upon the cut-off effect for anesthesia seen in homologous series (e.g., alcohols) (Franks and Lieb, 1985).

With regard to olfaction, evidence gathered relatively recently is mounting in the direction of the existence of many specific odor receptors (Buck and Axel, 1991; Firestein, 1991; Korsching, 1991). Much less is known about the sensory irritant (pungency) receptor, though a protein model with broad tuning has been suggested (Nielsen, 1991).

Studies of detection thresholds for eye irritation, nasal pungency, and odor in airborne mixtures of known substances, compared to those of the individual components at equivalent concentrations, can also add valuable information to understand the degree of specificity involved in the reception processes underlying the sensory effects. Any screening of individual compounds would determine realistic irritation potency only insofar as the total environment of volatile organic compounds (VOCs) does not add greatly to potency. Even if a specific irritation receptor exists, it might indeed be very broadly tuned, which would mean a strong chance for broad integration of potency across substances.

In our previous efforts in the current series of papers (Cometto-Muñiz and Cain, 1990; Cometto-Muñiz and Cain, 1991; Cometto-Muñiz and Cain, 1993; Cometto-Muñiz and Cain, 1994) we have defined a zone in which one can study smell with minimal interference or confounding influence from irritation. This zone is defined as the concentration range above the odor threshold (measured in normosmics) but below the nasal pungency threshold (measured in anosmics). In this respect, the work goes well

beyond any categorical classification of a chemical as a trigeminal stimulant vs. olfactory stimulant. Nevertheless, ongoing experiments on our lab indicate that normosmics report nasal pungency at levels below the pungency threshold in anosmics. This suggests that the presence of an intact olfaction might drive down the threshold for nasal pungency. The extent to which this might be true could be established with an "objective" measurement of nasal pungency in normosmics and anosmics (e.g., an electrophysiological recording such as the negative mucosal potential, NMP, see Kobal, 1985).

As far as we can tell, most VOCs could trigger trigeminal reactions if present in high enough concentration. In some instances, the vapor pressure of a substance at room temperature may be a limiting factor. Hence, a substance that may not trigger a response at 23°C might trigger one at 28°C. In other instances, a molecule may lie beyond the lipophilic cut-off point discussed above. Because such molecules have very low vapor pressures, it will be difficult to show that they would still trigger a trigeminal response if enough molecules could become airborne. A molecule such as 2-decanone, for example, may seem incapable of triggering a trigeminal response because it elicits no response at vapor saturation for it (348 ppm), even when this value is close to the pungency threshold for 2-nonanone (339 ppm). If the number of molecules of 2-decanone that could be made airborne could be increased continuously, they might well reach a value were they would indeed trigger a trigeminal response. The need for more molecules of 2-decanone than of 2-nonanone would be determined by the apparent existence of a cut-off point beyond 2-nonanone which would make 2-decanone a relatively less effective trigeminal stimulus though not a completely ineffective one. In this respect, the term cut-off point seems itself too categorical, but has nevertheless taken hold in the literature.

Irritation sensitivity may very well be modulated by parameters of stimulation, such as duration (Cometto-Muñiz and Cain, 1984), flowrate, temperature, and humidity. Hence, a threshold measured at 5 sec may fall below that measured at 0.5 sec. Our data, obtained with sniffs of usually 1-2 sec describe the boundaries between no effect, a pure olfactory effect, and an olfactory-trigeminal effect. In our experience, persons with normal olfaction provide rather unreliable estimates of a nasal trigeminal threshold. For this reason, it seemed necessary to rely strictly on the data from anosmic subjects who would have no distraction from accompanying odor. Another possibility now seems open: the eye irritation threshold can substitute for the nasal irritation threshold. Accordingly, if an investigator wants to know the possibility of evoking nasal pungency (irrespective of odor) for any particular airborne stimulus of interest, our data suggest that a fair approximation to the answer can be gained by testing the airborne compound on the eyes.

Acknowledgements

The research described in this article was supported by NIH Grant DC00284, and by the United States Environmental Protection Agency through Cooperative Agreement Nº CR816362-020 awarded to the John B. Pierce Laboratory. It has been reviewed by the Agency and cleared for publication, but does not necessarily reflect the views of the Agency and no official endorsement should be inferred. Mention of trade names or commercial products does not constitute endorsement or recommendation for use. Thanks are due to Mr. Todd O'Hearn for excellent technical assistance.

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Table 1. Ratio eye irritation threshold/odor threshold for each substance investigated.

Stimuli	Ratio eye irritation threshold/odor threshold
ethanol	1,276
1-butanol	153
1-hexanol	42
1-octanol	96
2-propanone	15
2-pentanone	344
2-heptanone	759
2-nonanone	622
toluene	226
ethyl benzene	1,133
propyl benzene	2,695

Figure legends

Figure 1. Threshold eye irritation (triangles) and threshold odor (squares) for the 11 compounds studied. Results are expressed as geometric means across subjects ± standard deviation.

Figure 2. Odor thresholds obtained in the present study as a function of the odor thresholds obtained in previous studies — using identical procedure and delivery system — for the same 11 substances. Standard deviations across each of the two axes are indicated by pairs of dots. The dashed line represents the identity line.

Figure 3. Comparison of eye irritation thresholds (triangles) obtained in the present study and nasal pungency thresholds (squares), from anosmic subjects, obtained previously (Cometto-Muñiz and Cain, 1990; Cometto-Muñiz and Cain, 1993; Cometto-Muñiz and Cain, 1994). Dots indicate standard deviations.

FIGURE 1

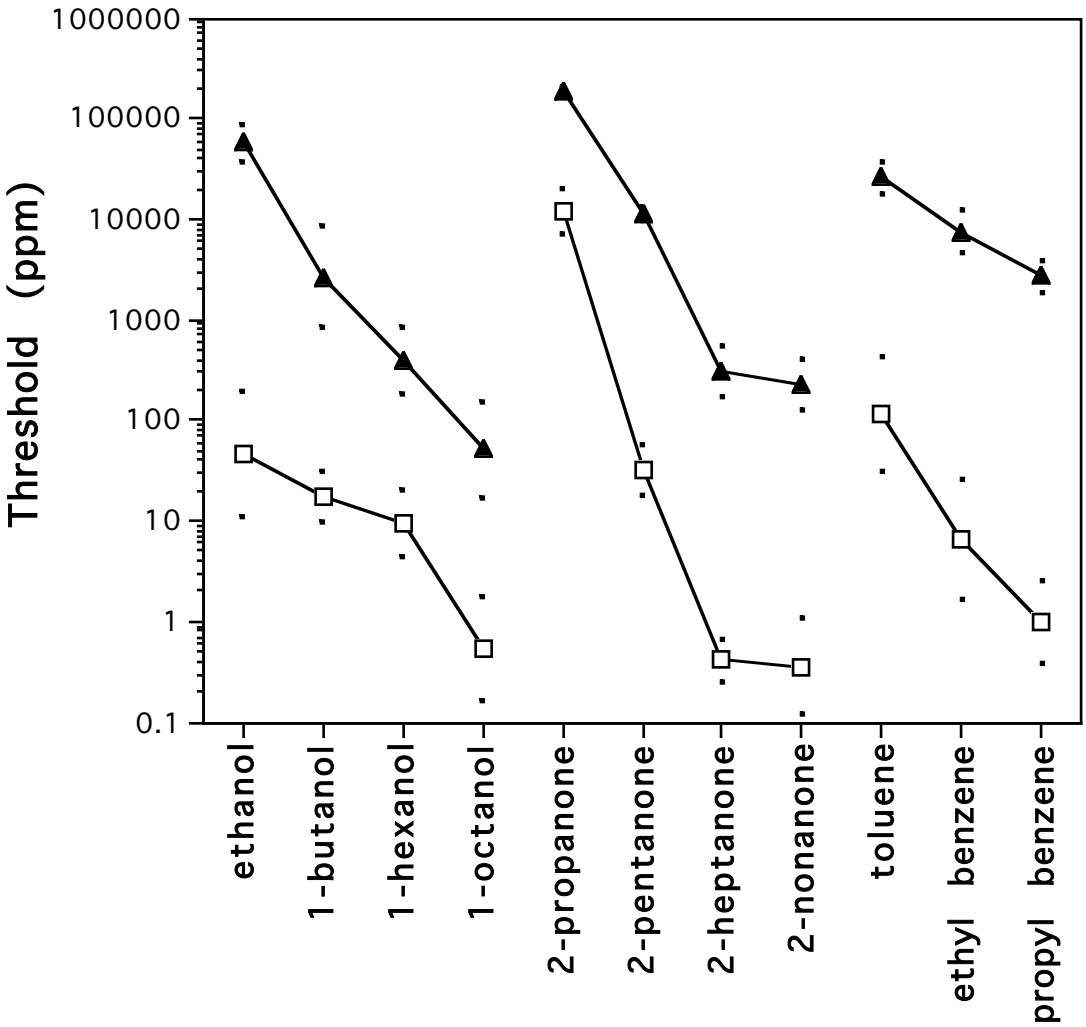

Threshold (ppm)
1000000
100000
10000
1000
100
10
1
0.1
ethanol
1-butanol
1-hexanol
1-octanol
2-propanone
2-pentanone
2-heptanone
2-nonanone
toluene
ethyl benzene
propyl benzene

FIGURE 2

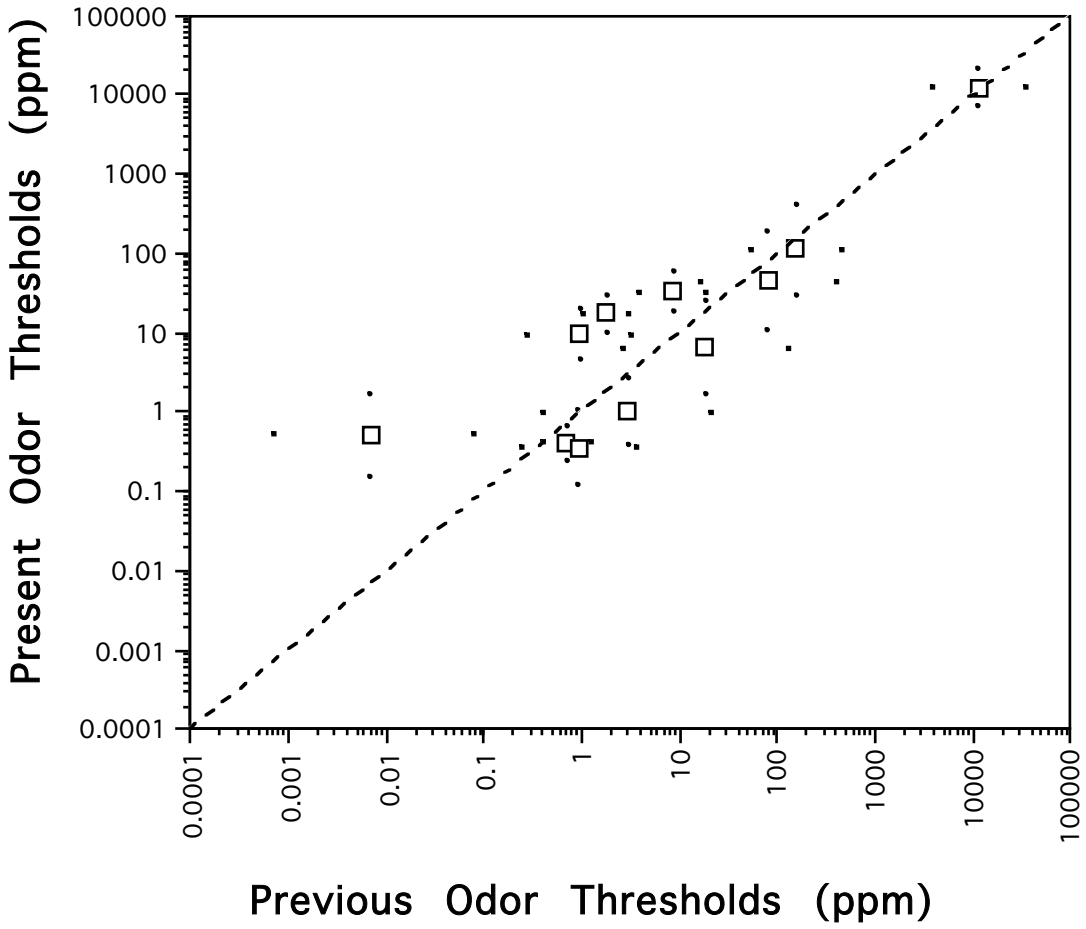
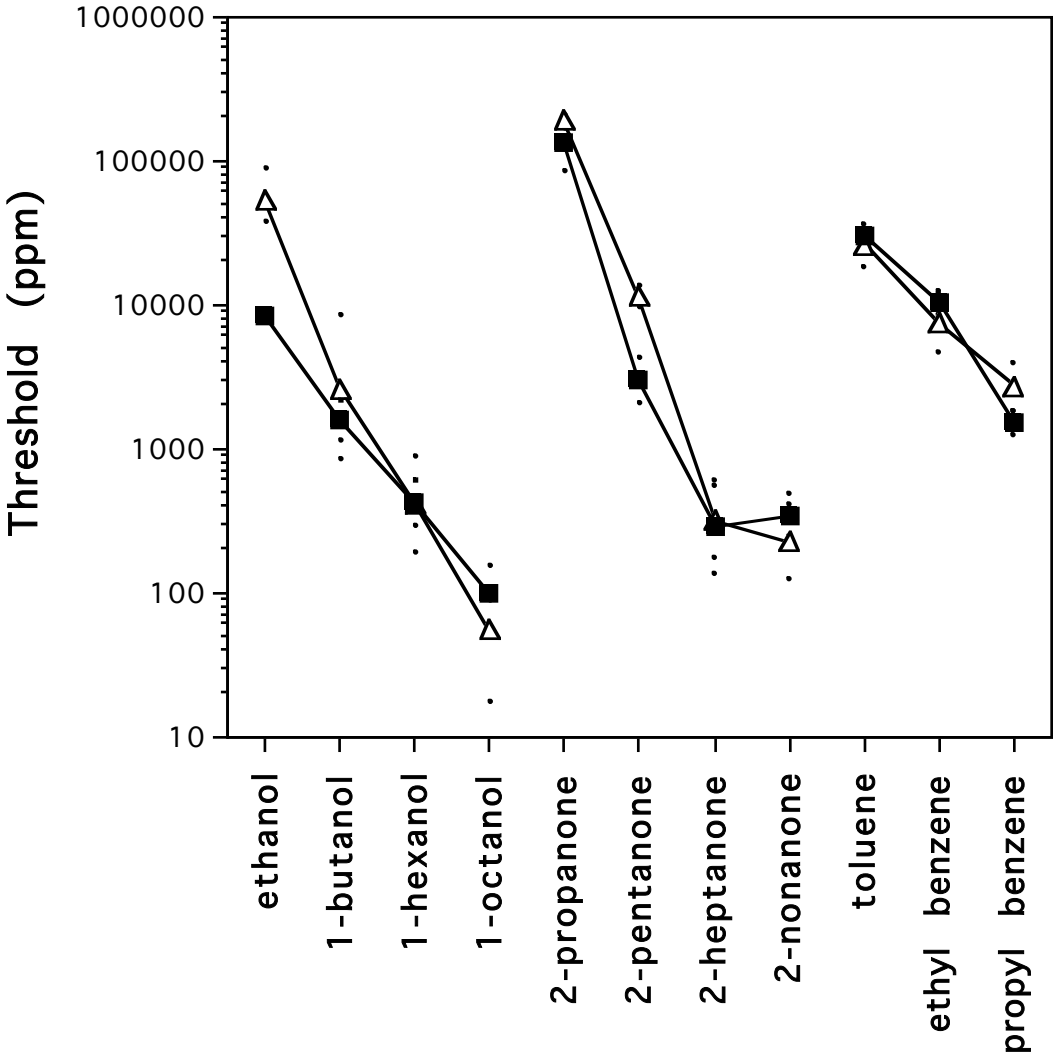

Present Odor Thresholds (ppm)
100000
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
100000
Previous Odor Thresholds (ppm)

FIGURE 3


Threshold (ppm)
1000000
100000
10000
1000
100
10
ethanol
1-butanol
1-hexanol
1-octanol
2-propanone
2-pentanone
2-heptanone
2-nonanone
toluene
ethyl benzene
propyl benzene

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