Acute Sensory Irritation from Exposure to Isopropanol (2-Propanol) at TLV in Workers and Controls: Objective versus Subjective Effects

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Objectives. Phlebotomists occupationally exposed to isopropanol (IPA) (2-propanol) and naïve controls (n = 12 per group) were exposed to the time-weighted average threshold limit value of 400 p.p.m. IPA for 4 h in an environmental chamber to investigate: (i) acute effects of sensory irritation using subjective health symptom reports and objective, physiological end-points; and (ii) differences in measured effects in relation to exposure history.

Methods. Before, during and after exposure subjects gave self-reports of health complaints. During exposure subjects rated the intensity of the odor, sensory irritation and annoyance. Objective end-points of ocular hyperemia, nasal congestion, nasal secretion and respiration were obtained at various times before, during and after exposure. Results were compared with exposure to phenylethyl alcohol (PEA), a negative control for irritation, and to clean air (CA), a negative control for odor and irritation, using a within-subjects design.

Results. Significantly higher intensity ratings of odor, irritation and annoyance were reported during the exposure to IPA, when compared with exposure to CA or PEA. Nevertheless, the overall level of reported sensory irritation to IPA was low and perceived as ‘weak’ on average. Health symptom ratings were not significantly elevated for IPA as compared with PEA or CA exposure. The only physiological end-point that showed a change exclusively in the IPA condition was respiration frequency: relative to baseline, respiration frequency increased in response to IPA in both groups. No differences were encountered between the occupationally exposed and the control groups.

Conclusions. The increase in respiration frequency in response to IPA may reflect either a reflexive change due to sensory irritation (an autonomic event) or a voluntary change in breathing in response to perception of an unpleasant, solvent-like odor (a physiological event caused by cognitive mediation). Our findings on objective end-points, including nasal and ocular sensory irritation, did not confirm subjective irritation reports. Irritation reports and odor intensity decreased, rather than increased, over time, lending credence to the cognitive argument and suggesting that the elevated subjective responses to IPA may be mediated by responses to its odor.

Keywords: exposure assessment; isopropanol; occupational exposure; sensory irritation; threshold limit value; nasal congestion; ocular hyperemia; nasal secretion; respiration; phlebotomy

INTRODUCTION

Isopropanol (IPA) is a volatile solvent that is widely encountered in many industrial environments (e.g. primarily acetone production, inks, coatings, cosmetics and pharmaceuticals) and to a lesser extent in consumer products (e.g. rubbing alcohol). Extensive studies of IPA exposure revealed a low order of acute and chronic toxicity through the major routes of human exposure (dermal or inhalation) (Nelson et al., 1943; Kapp et al., 1996); scant evidence has been found to suggest clinically significant neurological or behavioral impairments from either one-time or extended occupational exposures (Maizlish et al., 1985; Sethre et al., 2000).
Consistent with the sensory properties of other short chain alcohols, IPA at sufficiently high concentrations is capable of producing sensory irritation in the upper respiratory airways and eyes (Cometto-Muniz and Cain, 1993). However, since there is little reliable data to indicate the concentration of IPA at which irritation will occur (Nelson et al., 1943; Ukai et al., 1994), we investigated the subjective and objective aspects of odor and irritation in a rigorous and controlled manner. Based on observations and recent research, the concentration at which irritation onset occurs is likely to be significantly different for occupationally exposed workers and the general public (Dalton et al., 1997; Wysocki et al., 1997). Reports of sensory irritation and associated symptoms from chemical exposure are important endpoints in the determination of occupational exposure levels. For many regulated compounds reports of irritation to the eyes, mucous membranes and upper respiratory tract during chamber or field studies, as well as complaints of central nervous system (CNS) symptoms, such as headache and dizziness, have been used to establish occupational exposure limits (Paustenbach et al., 1997; American Conference of Governmental Industrial Hygienists, 1998). Unfortunately, in many instances such reports are often ill-defined, subjective evaluations that differ greatly between one individual and another and, for a single individual, from one occasion to another (Matsushita et al., 1969; Dick et al., 1989). One approach to address the subjectivity has been to use animal models to assess the irritancy of airborne chemicals (Alarie, 1966). With the recent development of more objective and thorough assays for sensory irritation in humans, however, more accurate estimates of exposure concentrations that will be protective of sensory irritation effects can be determined. Using these methods, two studies have recently been conducted to determine the odor detection and intra-nasal irritation threshold for IPA vapor and the development of sensory irritation from a 4 h whole body exposure to IPA at the current time-weighted average (TWA) threshold limit value (TLV) (400 p.p.m.) in an environmental chamber.

The present study was designed to evaluate the sensory irritancy of IPA and the contribution of odor and response bias to the reports of sensory irritation. Because sensitivity and responsivity to a volatile compound can be dramatically altered by an individual’s previous exposure, we tested two groups of participants: volunteers who had regular occupational exposure to IPA vapor in their function as phlebotomists and naïve controls who did not. All participants received a whole body exposure to the current TWA TLV of 400 p.p.m. IPA vapor for 4 h, in order to determine whether it produced any ocular, nasal or respiratory irritation symptoms or self-reported complaints.

More specifically, the study sought to address the following aims:

1. to determine if higher levels of symptoms or perceived irritation are reported during exposure to 400 p.p.m. IPA than during exposure to phenylethyl alcohol (PEA) (a negative control for irritation) or during exposure to clean air (CA);
2. to compare objective measures of ocular, nasal and respiratory irritation with self-reported symptoms and perceived irritation, both during and following exposure to IPA vapor;
3. to evaluate whether the objective physiological end-points or subjective responses differ between occupationally exposed workers and naïve controls.

**MATERIALS AND METHODS**

**Subjects**

A total of 24 subjects (n = 12 per group) were tested in this study: 12 phlebotomists, who reported daily occupational exposure to IPA vapor in their workplace, and 12 naïve controls. All subjects had participated in a previous study (M.A. Smeets and P. Dalton, unpublished data) in which odor and lateralization thresholds for IPA were measured. Both groups consisted of five males and seven females. Ethnic/racial background of the participants was predominantly African-American (n = 14); the remaining subjects (n = 10) were Caucasian (n = 5), Asian-American (n = 4) or Hispanic (n = 1). The average age of the control group was 40.8 ± 6.7 yr, and of the phlebotomist group 43.9 ± 9.3 yr. In the phlebotomist group there were two current smokers and four ex-smokers, compared with three current smokers and three ex-smokers in the control group.

Subject recruitment. After a survey of occupations in which regular exposure to IPA occurred, a suitable exposed population was identified as phlebotomists who worked in a laboratory or hospital and who spent most of their time in the process of collecting blood samples. All subjects in the phlebotomist group received exposure to IPA primarily through the use of 70% IPA swabs, reporting an average use of 90 wipes (between 25 and 300) a day.

Potential exposed subjects were contacted through advertisements placed in local newspapers and through word-of-mouth at area hospitals. Naïve control subjects were recruited through newspaper advertisements and the Monell subject database. All individuals responding to the advertisements were administered a screening questionnaire over the telephone to verify their health status and occupational exposure history. In addition to being in good general health, control subjects had to confirm that they had no history of significant or prolonged exposure to any
volatile chemicals, including IPA. Exposed subjects were accepted into the study if they met the same general health criteria, were currently employed as a full-time phlebotomist and had a minimum of 1 yr experience. Phlebotomists reported an average of 11 ± 8 yr of work experience in this occupation (min. 2 yr, max. 26 yr). Approval for the experiment was obtained from the Committee on Studies Involving Human Beings of the Institutional Review Board of the University of Pennsylvania.

Procedure
Prior to the first session all subjects came in for a separate information and screening session. They were provided with information about the study, they reviewed questions on general health, and read and signed informed consent forms. Since information about the odor given prior to exposure may bias or alter a person’s reactions to that odor, care was taken to provide all subjects with the same information (Dalton et al., 2000). The subjects were told that one or several sessions would involve an exposure to isopropanol vapor at levels allowed in the workplace and that several health measures would be taken. They were not told that the other exposures would be to CA or an odor compound. Thus, assuming they expected to be exposed to IPA or something else on each occasion, we presume expectations were comparable across exposures. The order of exposure sessions was counterbalanced across each group, with six possible orders yielding two volunteers per order in each group. Prior to each exposure baseline measures of nasal cross-sectional area (CSA), ocular hyperemia and nasal secretion were taken. Subjects then entered the exposure chamber with the chemical (either IPA or PEA) at its respective target concentration. Volunteers wore a half-face mask with an activated charcoal filter (3M-type) upon entering the chamber to prevent inhalation exposure to the chemical until they were comfortably seated and 5 min baseline respiratory measurements had been made.

During the 4 h exposure the subjects watched educational videos. In order to maintain vigilance, and standardize cognitive activity, they periodically completed questions about the visual and verbal content of the videos, which they believed to be part of the task. At regular intervals, according to the timetable shown below, the subjects were prompted by the computer to make their ratings of odor, irritation and health symptoms on a laptop computer. After 2 h exposure all subjects were given a 20 min break, during which they were allowed to use the restroom facilities and obtain some liquid refreshment (e.g. water or juice) and a snack. During this period mid-point assessments of nasal CSA, ocular hyperemia and nasal secretion were obtained. At the end of the break the subjects returned to the chamber for the second half of the exposure session, again using a respirator to prevent exposure to the chemical until they were comfortably seated and 5 min of baseline respiratory recording had been collected.

During all exposures subjects were constantly monitored via a video system. A two-way intercom system allowed for communication between investigator and subject at all times. Physiological measures of heart rate and respiration were monitored on a computer screen in the investigator’s booth. No adverse events were encountered during any of the testing.

Chemical exposures
All sessions were conducted in a sound-attenuated chamber measuring 10 × 10 × 7 feet. Temperature was maintained at 70 ± 2°F, relative humidity at 50 ± 10% and airflow at 50 ± 5 feet³/min. Airflow through the chambers was on a one-pass system and was exhausted without recirculation. IPA (≥99.5%, ACS reagent; Aldrich) was vaporized using a VOC generator. The liquid was pumped at a controlled and metered rate from a storage reservoir to the vapor generator. IPA was diluted with preheated nitrogen gas and then transferred via a heated line to the air plenum of the chamber. From the air plenum it was injected through multiple outlets to promote uniform mixing before entry into the chamber. The target exposure concentration for IPA sessions was 400 p.p.m. IPA concentrations inside the chamber were sampled every 3 s. On-line samples were collected from a sampling point within the breathing zone of each subject and measured on-line, using a Thermoquest Hydrocarbon Analyzer with FID; readings were averaged and recorded at 15 min intervals throughout exposure. Mean concentration of IPA during exposure was 406 p.p.m. (SD 9 p.p.m.) and did not vary more than 10% during any exposure (min 362, max 439 p.p.m.).

The odor of PEA was dispersed using a carboy that contained a mixture consisting of 225 ml of polyethylene glycol (PEG 200), 150 ml of PEA and 75 ml of ethanol (which served as the tracer compound for on-line monitoring with the hydrocarbon analyzer) over a layer of glass beads to increase evaporative surface area. For convenience we will further refer to this mixture as simply PEA. The odor, contained in the headspace over the liquid, was pumped into the chamber at a rate of 10 l/min. Based on data obtained prior to the study, the PEA mixture was refreshed halfway through the session to prevent a drop in concentration towards the end of the exposure. During PEA exposures the hydrocarbon analyzer measured the concentration of ethanol, since the low levels of PEA used were below the detection limits of the FID. Mean concentration of ethanol during exposure was 26 p.p.m. (SD 5 p.p.m.), with a minimum average exposure of 14 and a maximum of 40 p.p.m. As this concentration is just above the odor threshold
for ethanol and well below the irritation threshold, no sensory impact of ethanol was anticipated. Sampling was also carried out during clean air sessions; at no time did the readings exceed the normal background of 0.4–0.8 p.p.m. Three-point calibrations of the hydrocarbon analyzer were conducted weekly or bi-weekly (depending on testing frequency) for both IPA and ethanol.

**Dependent measures**

**Intensity ratings and health symptom reports.** Self-reported levels of odor, annoyance and irritation intensity in the eyes, nose and throat (the sites of trigeminal innervation indexed by the respiratory marker of sensory irritation in the RD50 assay) were obtained every 2 min during the first 20 min of exposure, followed by one rating after 1 and 2 h exposure, both prior to and following the break.

All intensity ratings were obtained using the labeled magnitude scale (Green et al., 1996), a category–ratio scale that yields ratio data but, because it uses verbal descriptors to rate perceived intensity, can also provide absolute intensity estimates. The scale has been validated for use with olfactory stimuli that produce irritation. Volunteers rated the intensity of odor, irritation and annoyance by marking the appropriate place on a scale ranging from ‘no sensation’ to ‘strongest imaginable sensation’. Previous research (Dalton et al., 2000) has revealed that the sensory evaluation of irritation can be elevated by affective evaluations (e.g. of unfamiliarity and annoyance). Thus, concurrent ratings of annoyance intensity were obtained to tease out the affective irritation response (annoyance) from the sensory component (perceived irritation). In addition, subjects rated the intensity of the perceived odor.

For irritation ratings volunteers were provided with detailed instructions on the types of sensations that are indicative of sensory irritation in the upper airways. They were also provided with a schematic diagram of the upper respiratory airways to assist them in localizing the relevant areas from which to report symptoms. These procedures are effective ways to allow individuals to differentiate odor-mediated reports from true sensory irritancy and their use has been shown to reduce levels of reported irritation (but not odor) (see Dalton et al., 2000). Additional health symptoms (see Appendix 1) were obtained at seven intervals, at 0, 55, 115, 140, 195, 255 min during exposure and 30 min following cessation of exposure at 290 min, as shown in Table 1.

**Acoustic rhinometric assessment of nasal congestive changes.** The congestive and decongestive changes that can accompany exposure were measured using a computerized system (Eccovision) using sound waves passed into the nose (Kesavanathan et al., 1996). A silastic probe nose piece was placed on a wave tube and lubricating jelly was applied liberally to the tip of the nose piece. The wave tube was placed on a flat surface and, while seated, the subject leaned over the wave tube and affixed his/her nostril on the top of the nose piece. Nasal changes were evaluated immediately prior to exposure, at the midpoint break and following exposure on each day of testing.

**Nasal secretion volume.** One of the most common complaints from exposure to VOCs is increased mucus secretion or rhinorrhea (Samet and Cheng, 1994). Mucus secretion was measured using pre-weighed filter paper discs. Small 8 mm discs were punched out of Whatman filter paper 1 using a biopsy punch. Each disc was placed in a 3 ml polypropylene tube, labeled and pre-weighed on a Mettler AC 100 electronic balance. Weights were recorded. During measurement a filter paper disc was positioned on the anterior end of the inferior turbinate for 1 min, after which the disc was placed back in its vial. This procedure was repeated twice more. Measurements were obtained from one nostril only. Subject’s nasal secretion rate was evaluated at baseline and after 2 and 4 h exposure for each condition.

### Table 1. End-points to evaluate sensory irritation

<table>
<thead>
<tr>
<th>End-point</th>
<th>Frequency of assessment</th>
<th>Pre-exposure</th>
<th>1st half-session</th>
<th>2nd half-session</th>
<th>Post-exposure</th>
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<td></td>
<td></td>
<td>Baseline</td>
<td>0</td>
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<td>115</td>
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<tr>
<td>Odor intensity</td>
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<td>X*</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Symptoms</td>
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<tr>
<td>Nasal cross-sectional area</td>
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<td>Ocular hyperemia</td>
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<td>Nasal secretion volume</td>
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<td>Respiratory rate/volume</td>
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*Odor intensity was rated every 2 min for the first 20 min of exposure.
Respiratory measurements. Respiration during exposure was measured using the Colbourn LabLincV System, a biological monitoring system interfaced with a computer for data acquisition, reduction and analysis of respiration rate and tidal volume. These measures can be used to assess both voluntary and spontaneous changes in breathing rates in response to odors/irritants. Waveforms were recorded using data acquisition software (Windaq/Dataq Instruments). Waveforms were sampled at a rate of 25 Hz by transthoracic impedance, i.e. passing a 4 µA, 50 kHz constant current through the thorax and measuring the voltage across two electrodes placed between the sixth and seventh ribs laterally.

Baseline respiration measures were recorded for 5 min while the subject was seated in the chamber with the chemical at the target concentration; for this they wore a respirator to preclude their being able to smell the chemical. After 5 min the actual session was begun by removing the respirator, thus exposing the subject to the stimulus. During the break electrode leads were detached from the electrodes that remained attached to the subject’s skin. After the break the calibration procedures were repeated and an additional 2 min of baseline recorded with the respirator in place. Respiration was monitored continuously throughout the exposure, but data were collapsed into smaller epochs for analysis.

Ocular hyperemia. It has been hypothesized that exposure to VOCs causes a disruption of the eye’s protective tear film and thus allows the chemical environment to contact the epithelium and cause dryness and irritation. Hyperemia, or red eye, is the most consistent clinical sign of eye irritation and is caused by blood vessel dilation. A procedure for quantitating the change in redness from photographic images before and after an experimental intervention has been established (Kjaergaard et al., 1992).

Before exposure, during the mid-point break and immediately after completion of the exposure period volunteers’ eyes were examined for hyperemia (redness). Hyperemia was evaluated by photographing the conjunctiva with the eye turned inward and outward (nasally and temporally) using a Nikon F3 camera with a 105 mm MicroNikkor lens, 4× magnification and a flash. Slides (35 mm) were developed and, under the assumption that both eyes should be equally reactive to VOC exposure, slides of only one eye per subject/condition and time point were selected for further analysis. Slide pairs were analyzed by a panel of four trained judges, who were blind to the conditions. These judges received training intended to standardize their evaluations on the relevant dimensions of ocular hyperemia, involving a set of calibration slides showing varying degrees of redness and a small set of practice trials. For each subject in each condition four pairs of slides were compared: nasal baseline versus 2 and 4 h exposure and temporal baseline versus 2 and 4 h exposure. Each pair combination was judged twice. During evaluation sessions slide pairs were projected one above the other. Judges were asked to evaluate the target slide in comparison with the reference slide (the positions of which were counterbalanced) using an optical scan sheet and the following response categories: definitely more red, probably more red, probably less red or definitely less red than the reference slide. To ensure that no significant differences in reactivity were found for any exposure conditions across ‘eyes’, a separate session was conducted in which the judges evaluated differences, selected from all conditions and times between the left and right eyes (100 pairs total). This revealed no significant differences in ‘left’ versus ‘right’ judgements (P = 0.80).

The scores for each subject by condition were compared with their self-reports of ocular irritation during and following exposure.

Statistical analysis

To determine whether any of the end-points were elevated by exposure to IPA compared with PEA or CA exposure, all end-points were analyzed with exposure history as the between-group factor and odorant (IPA, PEA and CA) and time of assessment as within-group factors. First, main effects and interactions were evaluated using repeated measures multivariate analysis of variance (MANOVA Repeated Measures, Statistica for PC) and Greenhouse–Geisser corrections for sphericity. Significant interactions were evaluated with univariate ANOVAs. Post hoc testing was conducted using Tukey’s HSD test. Bonferroni corrections were applied where necessary to control for multiple comparisons. Analyses focused mainly on two questions: (i) whether the measured end-points during exposure to IPA were significantly different from the control conditions (an effect of, or interaction involving, the factor condition); (ii) whether the measured end-points revealed any significant differences between controls and phlebotomists (an effect of, or interaction involving, the factor group).

In general, outliers were identified as being >2.5 SD removed from the mean for any given dataset and were subsequently eliminated from the dataset. In the case of missing data cells, the mean for that given variable was substituted by the mean for that time point and group to prevent loss of the entire row of data during analyses, unless the majority of data was missing for a given subject, in which case that subject’s data were eliminated from the data set.

RESULTS

Subjective end-points of sensory irritation, etc., will be reported first, to be followed by the objective,
the 4 h exposure was not rated as significantly more weak) and CA exposure (m
performed on LMS ratings to normalize frequency and annoyance were collected per session (for an overview see Table 2). A log transformation was performed on LMS ratings to normalize frequency distributions. Intensity ratings of odor, irritation and annoyance differed significantly as a function of exposure condition (P < 0.0001).

The mean rating across both groups of odor intensity during IPA exposure (m = 17.5, moderate) was significantly higher (P values less than the Bonferroni corrected α of 0.017) than during PEA (m = 5.5, weak) and CA exposure (m = 3.2, barely detectable/weak). Although PEA odor was initially rated as 17.5 and CA as 8.6, which constitutes a significant difference (P < 0.01), average odor intensity of PEA across the 4 h exposure was not rated as significantly more intense than CA (P > 0.017, the Bonferroni corrected α), due to olfactory adaptation.

IPA was perceived as more irritating than PEA and CA (P < 0.001). However, it should be noted that the absolute irritation ratings for IPA averaged across the entire exposure duration were quite low: for IPA 3.35 (between ‘barely detectable’ and ‘weak’), for PEA 0.9 and for CA 0.8. Similarly, IPA (m = 3.1) was rated as more annoying than PEA (m = 0.8) or CA (m = 0.7, P < 0.001).

Although phlebotomists tended to give lower ratings for odor intensity in all conditions than did the control subjects, this difference did not reach significance. Similarly, apparent tendencies of phlebotomists to provide lower irritation and annoyance ratings during control exposures than controls but higher ratings during IPA exposure did not turn out to be statistically significant.

As expected, odor intensity changed over time as did irritation and annoyance during control exposures than controls but higher ratings during IPA exposure did not turn out to be statistically significant.
Acute sensory irritation from exposure to isopropanol

This primarily reflects a significantly higher rating during the first 2 min of the pre- and post-break sessions than during the remainder of the session ($P < 0.0001$). Average ratings were higher before the break than after the break for odor intensity ($P < 0.01$), irritation intensity ($P = 0.02$) and annoyance intensity ($P < 0.01$), which indicates that the subjects had not completely recovered from the adaptation and habituation that occurred during the first pre-break trial.

Health symptom reports

Perceived intensity for a total of 36 symptoms was rated on a 5 point scale, ranging from ‘not at all’ (0) to ‘extremely’ (4). The 36 symptoms were categorized according to the symptom types: CNS, autonomic nervous system (ANS), cognition/mood, sham, sensory irritation, sensory, respiratory and gastrointestinal (GI) (see Appendix for symptoms that correspond to each of the categories). Symptoms were rated seven times throughout an exposure session.

The mean ratings of health symptoms as a function of group, condition and category are displayed in Table 3. Overall, on a scale of 0–4, symptom ratings for all conditions, including IPA, were quite low (overall mean 0.08 ± 0.22), indicating a negligible impact of exposure on symptom perception. No differences in symptom ratings were observed among the different exposure conditions or groups and there were no significant interactions involving the factor condition. On the level of separate symptom categories, the only symptom category that came close to demonstrating an effect of condition was the CNS category, indicating higher CNS symptom ratings (i.e. ‘drowsiness’) in the IPA condition than in the control conditions. It should be noted, though, that the overall effect of condition (involving all symptom categories) did not reach statistical significance.

The frequency/intensity of symptom reports differed across symptom categories ($F(7,147) = 5.36, P < 0.01$), but no differences were observed between exposure to IPA and the control conditions. Post hoc testing revealed significantly higher symptom ratings for CNS symptoms ($m = 0.19$) than for sensory ($m = 0.03, P < 0.001$) and GI ($m = 0.03, P < 0.001$). Cognition/mood ($m = 0.09$) and sham ($m = 0.09$) received intermediate ratings and did not differ significantly from any other symptom category. In general, symptom ratings varied across time ($P = 0.03$) and increased during exposure, but returned to baseline at the end of the break and following exposure.

Acoustic rhinometry assessment of nasal congestive changes

During each session measurements were taken at baseline, after 2 h (during the break) and after 4 h. Replicate measurements for each nostril were obtained at each time point. Analyses were performed on the area between 0 and 5 cm, which includes the structures of the nasal valve and the septal and erectile tissue while excluding measurement anomalies associated with the nasopharynx and paranasal sinuses (Silkoff et al., 1999). The two readings for each nostril were averaged and analyses performed on the average minimal distance area and nasal volume for each nostril. One subject’s data were eliminated due to loss of data. Results are reported for minimal nasal CSA, because this measure is considered to be more sensitive and robust than nasal volume (Fisher, 1997). Mean CSA as a function of group, exposure

| Table 3. Symptom ratings per group, condition and category (averaged over time) |
|---------------------------------|-------|-------|-------|-------|
| CA Mean       | SD    | PEA Mean | SD    | IPA Mean | SD    |
| Controls      | CNS   | 0.24   | 0.09  | 0.26   | 0.11  | 0.28  | 0.11  |
|                | ANS   | 0.14   | 0.04  | 0.13   | 0.04  | 0.16  | 0.05  |
|                | Cognition | 0.12 | 0.05  | 0.16   | 0.06  | 0.20  | 0.16  |
|                | Sham  | 0.04   | 0.02  | 0.05   | 0.02  | 0.10  | 0.06  |
|                | Sensory | 0.25  | 0.06  | 0.23   | 0.08  | 0.33  | 0.13  |
|                | Sensory | 0.08  | 0.07  | 0.04   | 0.04  | 0.06  | 0.04  |
|                | Respiratory | 0.11 | 0.05  | 0.08   | 0.04  | 0.15  | 0.05  |
|                | GI    | 0.02   | 0.03  | 0.04   | 0.05  | 0.07  | 0.07  |
| Phlebotomists  | CNS   | 0.09   | 0.07  | 0.11   | 0.1   | 0.19  | 0.11  |
|                | ANS   | 0.01   | 0.01  | 0.03   | 0.04  | 0.01  | 0.05  |
|                | Cognition | 0.03  | 0.02  | 0.02   | 0.06  | 0.04  | 0.16  |
|                | Sham  | 0.09   | 0.03  | 0.15   | 0.02  | 0.10  | 0.06  |
|                | Sensory | 0.04  | 0.03  | 0.06   | 0.08  | 0.09  | 0.13  |
|                | Respiratory | 0.03  | 0.01  | 0.02   | 0.04  | 0.03  | 0.05  |
|                | GI    | 0.01   | 0.02  | 0.04   | 0.05  | 0.01  | 0.07  |
Statistical testing of CSA is based on the assumption that baseline areas vary in a non-significant fashion between groups and conditions. However, a significant effect of condition on baselines areas was found \( F(2,42) = 4.22, P = 0.02 \). As can be seen in Fig. 2a, baseline levels appear higher for the IPA and PEA conditions than in the CA condition. At the post hoc level, with Bonferroni corrections applied (\( \alpha = 0.017 \)), baseline levels in the IPA and PEA conditions were higher than in the CA condition with marginal significance at \( P = 0.02 \). We are unable to account for these differences, since assessment conditions were counterbalanced over sessions, groups and seasons. Consequently, a MANCOVA was performed on area, using the baseline values as the covariate to correct for any variation in the data as a result of variation in baseline values. The results of this analysis showed a significant group \( \times \) time interaction \( F(1,21) = 4.69, P = 0.04 \) in the presence of a main effect of time \( F(1,21) = 8.8, P < 0.01 \). Separate analyses per group revealed that the interaction was due to a change in CSA among the controls: CSA was lower after 4 h than after 2 h exposure for controls (\( P < 0.001, 0.51 \) versus 0.56 cm\(^2\), respectively), while area measures among phlebotomists did not vary with time (see Fig. 2b).

These results would suggest that phlebotomists do not show any congestive changes over time, whereas the controls do. However, when inspecting the mean CSA values in Table 4, this conclusion would seem counter-intuitive. After all, phlebotomists show congestive changes from 0.64 cm\(^2\) at baseline to 0.56 cm\(^2\) after 4 h exposure to PEA and from 0.61 cm\(^2\) at baseline to 0.55 cm\(^2\) after 4 h exposure to IPA. This was

![Fig. 1. Mean (± SEM) (a) odor, (b) irritation and (c) annoyance intensity ratings by condition and group.](image)

![Fig. 2. Mean (± SEM) nasal area by (a) condition and time and (b) group and time.](image)

<table>
<thead>
<tr>
<th></th>
<th>CA</th>
<th>PEA</th>
<th>IPA</th>
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<tbody>
<tr>
<td><strong>Controls</strong></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>0.51 ± 0.13</td>
<td>0.56 ± 0.11</td>
<td>0.57 ± 0.16</td>
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<tr>
<td>+2 h</td>
<td>0.52 ± 0.13</td>
<td>0.57 ± 0.14</td>
<td>0.58 ± 0.16</td>
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<tr>
<td>+4 h</td>
<td>0.47 ± 0.11</td>
<td>0.50 ± 0.14</td>
<td>0.55 ± 0.14</td>
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<tr>
<td><strong>Phlebotomists</strong></td>
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<tr>
<td>Baseline</td>
<td>0.56 ± 0.13</td>
<td>0.64 ± 0.12</td>
<td>0.61 ± 0.11</td>
</tr>
<tr>
<td>+2 h</td>
<td>0.57 ± 0.17</td>
<td>0.60 ± 0.14</td>
<td>0.55 ± 0.12</td>
</tr>
<tr>
<td>+4 h</td>
<td>0.59 ± 0.14</td>
<td>0.56 ± 0.15</td>
<td>0.55 ± 0.13</td>
</tr>
</tbody>
</table>

Table 4. Mean (± SD) nasal minimum cross-sectional area in cm\(^2\) averaged over nostril and time, per condition and group.
Table 5. Mean weight of mucus collections in mg by group, per condition and time of collection

<table>
<thead>
<tr>
<th></th>
<th>CA</th>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>Baseline</td>
<td>1.345</td>
<td>2.218</td>
<td></td>
<td>0.159</td>
<td>0.308</td>
<td>0.032</td>
<td>0.383</td>
</tr>
<tr>
<td></td>
<td>+2 h</td>
<td>1.523</td>
<td>2.069</td>
<td></td>
<td>0.25</td>
<td>0.44</td>
<td>0.49</td>
<td>1.463</td>
</tr>
<tr>
<td></td>
<td>+4 h</td>
<td>1.523</td>
<td>2.172</td>
<td></td>
<td>0.877</td>
<td>2.521</td>
<td>0.186</td>
<td>0.44</td>
</tr>
<tr>
<td>Phlebotomists</td>
<td>Baseline</td>
<td>0.075</td>
<td>0.49</td>
<td></td>
<td>0.733</td>
<td>1.82</td>
<td>0.158</td>
<td>0.229</td>
</tr>
<tr>
<td></td>
<td>+2 h</td>
<td>0.075</td>
<td>0.481</td>
<td></td>
<td>0.15</td>
<td>0.31</td>
<td>0.275</td>
<td>0.432</td>
</tr>
<tr>
<td></td>
<td>+4 h</td>
<td>−1.029</td>
<td>4.511</td>
<td></td>
<td>−0.153</td>
<td>1.31</td>
<td>0.25</td>
<td>0.364</td>
</tr>
</tbody>
</table>

not revealed by the MANCOVA analysis because this analysis only takes into account changes from 2 to 4 h exposure, using the baselines as covariants, but not as an end-point in the actual analysis. In addition, the congestive changes in the phlebotomy group to PEA and IPA are cancelled out by decongestive changes in the CA condition, which may just reflect noise. We therefore decided to conduct an additional analysis including only the actual exposure conditions (PEA and IPA). This revealed no significant differences between baseline values. After performing a MANOVA, no differences of group and condition were found. There were congestive changes over time (P = 0.01), with nasal CSA values of 0.60, 0.57 and 0.54 cm² for baseline, +2 and +4 h, respectively. After conducting post hoc tests the difference between baseline and +4 h was found to be significant (P < 0.01), but the magnitude of these changes did not differ between the PEA and IPA conditions. On average participants’ subjective ratings of nasal patency revealed little congestion (ratings averaged between 4.0 and 5.0 on a scale from 1.0 to 5.0.) Ratings of patency did not differ as a function of exposure condition or exposure history (P > 0.1).

Nasal secretion

Changes in mucus secretion were estimated by recording weight changes of filter paper discs that were placed on the anterior end of the inferior turbinate. During each session measurements were obtained at baseline and again after 2 and 4 h exposure. For each time point the first data point was discarded (F.B. MacGregor, D.N. Roberts, A.G. Robson, J. Cocker, N.B. Pride and R.C. Schroter, unpublished data) and the two remaining data points averaged. One subject’s data was eliminated because of missing data points.

Changes in mucus secretion volume as a function of group, condition and time are presented in Table 5. Comparison of baseline values for non-random distributions between groups and conditions revealed a marginally significant group × condition interaction [F(2,42) = 3.34, P = 0.06]. As can be seen in Table 5, the control group had much higher secretion levels at baseline during the CA sessions than did controls (m = 1.35 mg for controls versus 0.075 mg for phlebotomists), although this difference did not reach significance (P > 0.07). Because baseline differences were marginally significant across group and condition, a MANCOVA was conducted using baseline as the covariant. A significant group difference was found [F(1,18) = 6.66, P = 0.02], with m = 0.07 versus 0.8 mg for phlebotomists and controls, respectively. Mean negative weights were observed for phlebotomists, indicating that weights were lower after insertion into the nostril than before. In theory residual moisture from the filter paper may have been absorbed onto the relatively dryer mucous membranes of the phlebotomists. Consistent group differences in the baseline volume of nasal secretions raised the possibility of chronic differences in nasal mucosal dryness among phlebotomists, due to environmental exposure. However, this explanation cannot account for the magnitude of the weight loss (1.029 mg), which indicates a greater loss of water than is actually contained in the filter paper. It is possible that some type of methodological error (systematic scale problem or filter placement problem) contributed to this result. Nasal secretion volumes did not differ among any of the exposure conditions. Overall, levels of secretion were fairly low: consistent with the objective measurements, none of the subjects reported a feeling of ‘runny nose’.

Respiration frequency

Data reduction was performed using the Windaq Waveform Browser (Dataq Instruments). For each session the following epochs were selected for further analysis for both the pre- and post-break recordings: 2–5 min of baseline; six 1 min segments at equal intervals during the first 20 min of exposure; 2 min segments after 1 and 2 h exposure; resulting in a total of 18 segments per session/condition. These times were selected to concur with the times when ratings of odor intensity and health symptoms were provided. Motion artifacts were identified and either corrected using mean substitution (for the segment, group and condition) or excluded from the segment being analyzed. Selected segments were further analyzed using Advanced CODAS (Dataq Instruments), using a peak–peak analysis algorithm, resulting in an average cycles per minute measure for...
Baseline respiration rates differed significantly between exposure conditions \(F(92,40) = 4.09, P = 0.02\). Post hoc testing revealed that baseline respiratory rates were higher in the CA condition \((m = 19.1)\) than the IPA condition \((m = 17.1, P = 0.02)\). Accordingly, respiration frequency was adjusted for differences in baseline by dividing individual respiration frequency by the individual’s baseline for that condition and session. Figure 3a and b displays the ratio levels for the CA and IPA conditions. A MANOVA performed on the normalized rates revealed a significant effect of condition \(F(2,40) = 3.86, P = 0.03\). With a mean ratio of 1.16 (exposure/baseline), respiration rate was higher in the IPA condition than the control conditions (1.05 and 1.06 for the CA and PEA conditions, respectively). At the post hoc level there was a marginal difference in normalized ratios between IPA and CA \((P = 0.04, \alpha = 0.017\) after Bonferroni correction for multiple comparisons). Although the
Table 6. Mean difference scores (± SD) for eye redness evaluation by condition, time point (+2 versus +4 h) and group

<table>
<thead>
<tr>
<th></th>
<th>CA</th>
<th>PEA</th>
<th>IPA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+2 h</td>
<td>+4 h</td>
<td>+2 h</td>
</tr>
<tr>
<td>Controls</td>
<td>0.33 ± 0.53</td>
<td>0.20 ± 0.54</td>
<td>0.07 ± 0.84</td>
</tr>
<tr>
<td>Phlebotomists</td>
<td>-0.06 ± 0.44</td>
<td>-0.27 ± 0.65</td>
<td>-0.06 ± 0.57</td>
</tr>
</tbody>
</table>

Since a mean of 2.5 denotes no difference from baseline, difference scores were calculated by subtracting 2.5 from the evaluation. A difference score >0 indicates an increase in redness with regard to baseline, <0 a decrease in redness with regard to baseline.

normalized respiration rates appear elevated for the phlebotomists compared with controls, this difference was not statistically significant. In general, respiration rates in all conditions and across all groups were higher after the break than before the break (P = 0.01, ratio of 1.14 versus 1.04).

Ocular hyperemia

Pictures were taken at baseline, during the break and after 4 h exposure, thus yielding 36 pictures per condition and a total of 108 pictures (3 × 36) per subject. Approximately 15% of pairs could not be judged due to problems during development or poor quality of the slides.

Inter-rater reliability was determined to fall between 0.60 and 0.70. Although this level corresponds to the performance of the judges in previous ocular hyperemia assessments (Kjaergaard et al., 1990; see also Ogle and Cohen, 1996), we felt that inter-rater reliability could be improved with additional training. Panel members reported finding the task difficult because differences between most slides were quite subtle. A subset of 70 slide pairs was identified about which the judges had shown the least agreement (e.g. for which opposite response categories had been used: ‘definitely less red’ and ‘definitely more red’). These pairs were presented to the judges again for evaluation after additional training. Inter-rater reliability on the entire set of ratings improved significantly, ranging between 0.75 and 0.81; 22.5% (n = 13) of the problematical slide pairs continued to receive opposite ratings. A mean rating of 2.5 [(1 + 2 + 3 + 4)/4 = 2.5] was used as a reference for no differences in evaluated redness between exposure time point and baseline and difference scores between evaluations and the 2.5 reference were calculated. The difference scores were normally distributed, as evidenced by Kolmogorov–Smirnov testing. Repeated measures MANOVA was conducted on the difference scores averaged over judges, condition and time point (after 2 versus 4 h exposure). A marginally significant condition × time interaction was found [F(2,42) = 3.24, P = 0.05]. Clearly, evaluations in the CA condition revolved around the 0 level, whereas ratings for IPA and PEA showed slightly different patterns. At both 2 and 4 h into exposure to IPA there were small increases in eye redness (+0.3), but these scores were not significantly different from any other condition. The highest evaluations for redness were obtained at 4 h into the PEA exposure (+0.44). This elevation was not significant compared with the CA exposure at 4 h (P = 0.06, which is higher than the Bonferroni corrected level of α = 0.017). No main effects or interactions involving group were found (P > 0.1; see Table 6).

Consistent with a failure to find an effect of exposure condition or exposure history on judged hyperemia, no significant differences between groups or conditions were found for the subjective eye symptom reports (P > 0.05).

**DISCUSSION**

The first goal of the present study was to determine whether higher levels of perceived irritation or subjective health symptoms were reported during exposure to 400 p.p.m. IPA than during exposure to PEA (a negative control for irritation) or exposure to CA (a negative control for odor and irritation). Although perceived irritation was rated as significantly higher during IPA exposure than during either control exposure, overall ratings of irritancy did not exceed ‘weak’ for IPA. In comparison, perceived irritation due to PEA and CA exposure was rated as ‘barely detectable’. In general, irritation ratings for all exposure conditions remained fairly stable throughout the pre-break session, but declined significantly after the break.

Subjective health symptoms were not rated as more frequent or more intense in the IPA condition than the control conditions, with very low ratings given to the symptoms aggregated into eight categories (CNS, ANS, cognitive/mood, sham, sensory irritation, sensory, respiratory and GI). The only symptom category that approached statistical significance in the IPA exposure was for CNS symptoms, in particular due to elevated reports of ‘drowsiness’ in the IPA condition when compared with ratings in the control conditions. Finally, no differences were found in the ratings of nasal patency or eye symptoms (dryness, itching) by either the phlebotomists or control subjects during any of the three exposures.

Perceived irritation may have been rated higher in the IPA condition for a variety of reasons. One possibility is that the subjects’ perceptions reflected enhanced levels of sensory irritation, mediated by the trigeminal, glossopharyngeal or vagal nerves, or physiological differences involving other mucosal
tissues. Another possibility, however, is that perceptions of increased irritation may coincide with and be a reflection of more intense odor: odor intensity and annoyance were rated significantly higher in the IPA condition than in all other conditions. Although ratings of irritation and annoyance to PEA (the negative irritant/positive odor control condition) were not significantly different than those experienced during exposure in the CA condition, the less pleasant odor quality of IPA may have played a role in enhancing the overall perception of annoyance and irritation. The tendency for irritation to show a decrease over time (albeit not following the same time course as seen for odor intensity), rather than an increase (see for example Cain et al., 1986), suggests that the rated irritation may be odor mediated. Most studies involving whole body exposure to known sensory irritants have found that (i) irritation tends to increase with exposure duration while (ii) odor-mediated effects tend to decrease, due to olfactory adaptation (Otto et al., 1992). Although it was intended that PEA would serve as a positive odor control for IPA, the odor of PEA over the entire exposure duration was not perceived as iso-intense to the odor of IPA (Fig. 1), thus diminishing their similarity over the course of the 4 h exposure. A pilot study involving 10 participants was conducted to select a concentration of PEA that would be iso-intense with IPA at 400 p.p.m. The average intensity rating of the concentration selected for this study yielded an average rating of ‘intermediate’ during the first minutes of exposure, which was conceived to be equivalent to the perceived intensity from IPA. However, during the actual study PEA received lower intensity ratings and was no longer perceived to be iso-intense. Ideally, the odor of PEA would have been rated as equally intense, in which case any differences in perceived irritation between PEA and IPA could have been potentially explained by either actual irritancy effects of IPA or perceived quality of the odor, not by differences in perceived concentration.

It has been estimated that the odor of IPA can be detected at ~10 p.p.m. (Devos et al., 1990), which is consistent with the geometric mean odor detection threshold obtained for our naïve control group in a related study (M.A. Smeets and P. Dalton, unpublished data). For most volatile chemicals odor detection occurs well below the concentration necessary to evoke sensory irritation. Thus, at concentrations above the odor detection level, but below those known to elicit sensory irritation, it is reasonable to assume that olfactory information is being misinterpreted as integrated with or perhaps elevating perceived eye, nose or throat irritation. The geometric mean level at which intra-nasal sensory irritation for IPA was detected using the lateralization method (see Dalton et al., 2000, for details of this method) was established at 2659 p.p.m. in unexposed controls (M.A. Smeets and P. Dalton, unpublished data), which is well above the odor threshold and TLV level used for exposure in this study.

The second goal of this study was to compare objective measures of nasal, respiratory and ocular irritation with self-reported symptoms and perceived irritation, particularly during and following exposure to 400 p.p.m. IPA vapor. We found that both phlebotomists and controls showed a significant reduction in nasal CSA after 4 h exposure in both the IPA and PEA conditions. It is difficult to establish the clinical significance of this finding, in view of the absence in the literature of concrete changes in nasal CSA measured at similar distances with which our results could be compared. In general, decreases in minimal distance CSA or nasal volumes have been reported in response to nasal provocation with ragweed extract in patients suffering from, for example, ragweed allergies (Roithmann et al., 1997) and following exposure to ethyl -butyl ether (ETBE) (Nihlen et al., 1998a).

Congestive effects occurred not only with IPA but also PEA. The use of PEA was based on reports in the literature that suggest that PEA is not an irritant in the vapor phase (Prah and Benignus, 1984); for example Doty et al. (1978) found that only 1 in 15 anosmics was able to detect PEA at maximum vapor concentration. It is possible that some slight irritation was caused by the ethanol that was mixed with the PEA solution as a tracer. However, maximum concentrations of ethanol were only 40 p.p.m., which is well below the 1000 p.p.m. TLV for ethanol, thus making it unlikely that the congestive effect seen with this exposure was caused by ethanol vapor alone. In a study on various levels of exposure to ETBE Nihlen et al. (1998a) also noticed nasal congestion in the CA condition and only low correlations between the amount of congestion and actual level of ETBE exposure (see also their study on MTBE; Nihlen et al., 1998b) and concluded that the observed nasal swelling was not a direct result of ETBE exposure.

No effects of IPA exposure were found on the volume of nasal secretions obtained following exposure. If anything, subjects’ self-reports were more indicative of enhanced dryness than of enhanced secretion. With regard to eye redness, no evidence of increased eye redness with IPA exposure was encountered in this study. Although evaluations of eye redness were slightly elevated for both groups during exposure to IPA, this effect did not reach statistical significance and was in fact smaller than in the PEA condition (albeit not significantly smaller). The photographic method in combination with panel evaluation is sufficiently sensitive to detect increases in redness, as evident from several earlier studies by Hempel-Jorgenson et al. (1998) and Kjaergaard and Pedersen (1989), where significant increases were observed in photographically measured eye redness to n-butanol and 1-octene and to tobacco dust exposure, respect-
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ovsky. Utilizing similar techniques, however, no significant increases in hyperemia were observed from exposure to nitrous acid (Rasmussen et al., 1995), ETBE (Nihlen et al., 1998a) and MTBE (Nihlen et al., 1998b).

The only objective end-point on which an effect of IPA exposure was observed was respiration rate. Both groups showed marginally significant increases in respiration frequency during exposure to IPA when compared with exposure to CA. However, these increases should be interpreted with caution. Changes in respiration after the onset of exposure may reflect voluntary changes, signaled by the presence of an odor, which serve to regulate inhalation of the odorant. According to the data, immediately upon sensing the presence of IPA during that exposure session breathing rate changed either spontaneously (i.e. as a result of autonomic arousal) or voluntarily (i.e. in order to reduce inhalation of the odor/irritant).

It has been noted by Alarie (personal communication with P.H.D.) and others (our group, anecdotally) that when people smell something they do not like they switch from primarily oro-nasal to oral breathing, which increases the likelihood of throat irritation due to the lack of humidification by the nasal mucosa and the resulting dry air that passes through the oral cavity. This would be apparent even in the absence of an irritant if people were stimulated to breathe differently, but may be enhanced in the presence of an evaporative solvent. An alternative possibility for changes in respiratory frequency could be that they signify reactions to true sensory irritation in either the nose, throat or upper airways. However, in view of the very low levels of reported irritation (average = weak) it seems unlikely that reflexive changes in breathing, mediated by sensory irritation, were responsible for the slight increases in respiration rate we observed.

The third, and final, goal of the study was to evaluate whether the objective physiological end-points or subjective responses differed between occupationally exposed workers (phlebotomists) and naive controls. On subjective symptom reports no differences were encountered between phlebotomists and controls. The phlebotomist group showed a (non-significant) tendency to rate the irritation and annoyance from IPA as higher than the control group, whereas the opposite tendency was observed in the CA and PEA conditions. During the debriefing it became apparent that phlebotomists were more likely to recognize when the exposure condition involved IPA than were the controls. It is reasonable to suggest that this identification may have primed memories of the workplace and thereby mediated the elevation in annoyance and irritation. In a previous study involving the same subjects we found the phlebotomists lateralization thresholds for IPA to be higher than the controls (6720 versus 2659 p.p.m. for phlebotomists and controls, respectively; M.A. Smeets and P. Dalton, unpublished data), supporting the idea that the higher ratings of irritation/annoyance to IPA was cognitively, not sensory, mediated. Across symptom categories and conditions phlebotomists reported lower levels of symptoms, on average, than controls, which tendency is best explained by being accustomed to odorous exposures. However, these differences were once again not statistically significant.

Less (in fact, almost no) nasal secretion was collected from phlebotomists than from controls, regardless of exposure condition. This finding could suggest that phlebotomists experience some chronic changes in dynamic response to volatiles, including IPA, associated with prolonged occupational exposure to IPA. Rhinological changes have been noted in other populations regularly exposed to pollutants and some workplace chemicals, but have mostly involved increased secretion (running nose) rather than the opposite (see for example Edling et al., 1988). However, this finding may have been exaggerated by methodological error (i.e. the findings of negative weight changes of the filter paper from pre- to post-session measurement) and was not paralleled by any between-group differences in nasal congestive changes or ocular hyperemia in reaction to chemical exposures. Finally, phlebotomists showed equivalent changes in respiration frequency during IPA exposure to those of the controls. Hence, no effects from occupational exposure to IPA could be identified using indicators of nasal, or ocular, sensory irritation. It is not possible to reach any conclusions from the present study regarding potential chronic reactivity resulting from long-term occupational exposure to IPA as actual levels and durations of occupational exposure in the worker population were not measured.

Although only a few studies have assessed subjective reports of sensory irritation to IPA and most of those involved exposure to IPA as one component of a complex mixture, our finding that 400 p.p.m. IPA elicited only weak reports of irritation is not surprising. While Ukai et al. (1994) reported increased complaints of local irritation to the eyes and nose in male solvent workers exposed to a mixture of toluene, methyl ethyl ketone, IPA and ethyl acetate, a specific comparison between subgroups exposed to mixtures with and without IPA did not reveal any relative increases in association with the presence of IPA. Reports of mucous membrane (nose and throat) irritation in which IPA exposure occurred in combination with other vapors and dusts (Hiippakka and Samimi, 1987) were more likely to be attributable to other components in the mixture, as measured levels of IPA in these exposures did not exceed 36 p.p.m., which is only slightly above our measured odor detection threshold for non-exposed, naive controls. The early study by Nelson et al. (1943), in which subjects who were exposed to IPA at 400 p.p.m. for brief
controls (Dalton et al., 1997; Wysocki et al., 1997), the present study did not find significant differences either in the sensory (odor, irritation) or somatic (symptom reports, respiration, nasal volume) responses of the phlebotomists when compared with those of the controls. Several factors may account for this discrepancy. First, the concentration to which phlebotomists are regularly exposed may be significantly lower than 400 p.p.m.; our subjects uniformly reported that although the odor of IPA was recognizable, it was quite a bit stronger than they had experienced in their occupational environment. Second, it should be noted that IPA appears to be a weak sensory irritant, which did not elicit strong reactions in either group, thus reducing the range over which differences in sensory or somatic responses could occur. Finally, in a study involving these same subjects in which odor and irritation thresholds were obtained, occupationally exposed phlebotomists had higher thresholds than controls (M.A. Smeets and P. Dalton, unpublished data), but the magnitudes of these differences were smaller than was the case in previous studies involving acetone (Wysocki et al., 1997) or styrene (Dalton et al., 2002). However, the rapid metabolism of IPA to acetone, as measured by blood and breath analysis of these individuals during and following a 4 h exposure, suggests that long-term sensory adaptation of the olfactory and trigeminal system to exhaled volatiles may have been more likely to occur for acetone than for isopropyl alcohol. Thus, multiple factors may have been responsible for the failure to observe substantial differences in response between occupationally exposed and control workers in this study.

CONCLUSION

In conclusion, perceived odor intensity, irritation and annoyance were rated as higher during a 4 h exposure to IPA in both exposed workers and controls than during exposure to an odor or a CA control condition. However, the only physiological end-point that showed a change solely in the IPA condition was respiration rate. The increase in respiration frequency that was observed may reflect either a reflexive change in response to the sensation of irritation or a voluntary change in breathing in response to perception of an unpleasant, solvent-like odor. While the former signifies a more autonomic route of reactive events, the latter implies cognitively mediated behavioral changes. Our findings that objective end-points of either nasal and ocular sensory irritation did not confirm subjective irritation reports and that irritation reports and odor intensity decreased, rather than increased, over time lends credence to the cognitive argument and suggests that the elevated subjective responses to IPA may be mediated by responses to its odor.

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APPENDIX: HEALTH SYMPTOM CATEGORIES

- Central nervous system (CNS): headache; drowsiness; faintness/dizziness; feeling low in energy or slowed; trembling; heavy feelings in your arms or legs.
- Autonomic nervous system (ANS): tightness in your chest; dry mouth/throat; perspiring easily; heart pounding or racing; pains in heart or chest; hot or cold spells; numbness/tingling body parts.
- Cognition: trouble remembering things; feeling confused; feeling irritable; trouble concentrating; feeling depressed; nervousness inside.
- Sham: soreness of your muscles; pains in lower back; joint pains or swelling; feeling weak in body parts; toothache.
- Sensory irritation: nose irritation; throat irritation; eye irritation.
- Sensory: reduced/poor vision; reduced/poor hearing.
- Respiratory: trouble getting your breath; nasal congestion; sneezing; coughing; chest wheezing.
- Gastrointestinal (GI): poor appetite; nausea/upset stomach.

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