Human Breathing and Eye Blink Rate Responses to Airborne Chemicals

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Increased levels of air pollution have been linked with morbidity and mortality, but mechanisms linking physiologic responses to quality of life and productivity issues remain largely unknown. Individuals often report irritation of the nose and/or eyes upon exposures to environmental contaminants. Evaluation of these self-reports would be greatly aided by the development of valid physiological markers. Chamber studies (unencumbered exposures) of nonsmoker responses to environmental tobacco smoke offer two candidate end points: *a*) Tidal volume increases and breathing frequency declines with stimuli that elicit only moderate irritation. *b*) Eye blink rate increases only with a concentration sufficiently high to cause progressive worsening of eye irritation with prolonged exposure. Experiments with very brief nasal-only presentations also suggest the value of breathing changes as sensitive markers of irritation: *a*) Tidal volume is inversely related to perceived nasal irritation (NI) intensity in both normal and anosmic (lacking olfactory input) individuals, although normals exhibit greater NI sensitivity. *b*) Inhalation duration, in both groups, declines only with trigeminal activation sufficient to cause readily perceptible NI in anosmics. Changes in eye blink rate and breathing may be useful in the investigation of irritation and other effects of air pollution, and could be quite useful in investigations of mixtures of volatile organic compounds. *Key words*: anosmic, breathing, environmental chamber, ETS, eye blink, human, olfactometer, olfactory, psychophysics, trigeminal. — *Environ Health Perspect* 109(suppl 4):507–512 (2001).
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Much research on the effects of environmental chemicals on individuals is designed to estimate the mortality or morbidity that has occurred because of a given pollutant. A much smaller number of laboratory studies focus on short-term effects of environmental chemicals. The end points measured may not predict risk of traditional diseases, but they clearly do lessen quality of life and are quite likely to diminish work performance. Compared to effects studied in epidemiological or other more traditional environmental health investigations, these short-term effects are much less severe for a given individual, may require only seconds or minutes of exposure to appear, and affect a far greater proportion of the population.

Headache, eye/nose irritation, malodor, and difficulty concentrating are so common that they may be viewed as unavoidable effects of exposures encountered in everyday life. Medical intervention is seldom deemed appropriate, and the effects are typically attributed to the individual rather than the environment. Credible estimates of the economic costs of these effects have not been available until recently. Fisk and Rosenfeld (*1*) recently concluded that improvements in indoor air environments could be expected to save $10–20 billion annually in reduced sick building symptoms and $12–125 billion because of improvements in worker productivity.

Companies that manufacture chemicals face much more serious legal and regulatory challenges associated with toxicology than those concerning the less severe effects noted above, and they may be scientifically ill-equipped to rigorously investigate complaints in this area. These companies and other stakeholders may claim, with some validity, that no clear course of action is warranted, given considerable uncertainty as to underlying mechanisms and the lack of sound, standardized test protocols. Funding for research in this area has been scant, partly because of the lack of a regulatory mandate that such effects be considered. Much of the reason for the lack of mandate may lie, in turn, with the inadequate research standards attributable to scant funding.

It is our thesis that the uncertainties and issues highlighted above would be largely resolved by marked improvements in the methodologies applied to the study of short-term effects. We bring a psychobiological perspective to this area and focus on a better understanding of the interplay among stimulus, organismic, and response variables. With regard to stimulus variables, it is noteworthy that much prior work has not presented pollutants at levels representative of those encountered in actual environments. In addition, imprecise control over concentration and other physical or chemical aspects of the pollutant(s) of interest has hindered interpretation of results and integration of findings from different laboratories. Organismic variables refer to those attributes of the individuals being studied that are known, or suspected, to influence some aspect of the response. Examples include demographic variables, psychological states and traits, preexisting medical conditions (e.g., asthma), and chemical exposure history. Under the heading of organismic variables would also be included all those as yet poorly defined biological and psychological factors that constitute extreme sensitivity or susceptibility to chemical pollutants. Two key issues may be noted in this area: *a*) Because there is inadequate quantitative information regarding the responses of individuals considered normal, operational definitions of marked deviations are not presently possible. Oft-repeated claims, for example, that women or children or minorities are more sensitive or susceptible than the general population may prove to be true, but they do not presently rest on empirical findings. *b*) Many studies ostensibly designed to investigate the possibility of unusual sensitivity to environmental chemicals enroll experimental participants on the basis of self-report, fail to incorporate matched controls, and/or do not employ response measures that are minimally subject to various cognitive biases. Unequivocal conclusions from such studies are not possible.

Response variables are those conditions of the test situation that may alter any aspect of the response being recorded. In this category one might also place considerations as to the kind of response being measured. As noted above, few studies in this category have investigated candidate physiological measures that could be used to validate and help explain the mechanistic bases of various self-reported effects of airborne chemicals. The related need to better understand relationships among different response measures should also be considered.

Our recent olfactometer-based and environmental chamber–based research to address some of the issues and problems highlighted above may be of use in both providing

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a more coherent methodological framework and indicating promising research directions. Both types of studies were sanctioned by Institutional Review Boards at the University of North Carolina at Chapel Hill, and R.J. Reynolds Tobacco Company (Winston-Salem, North Carolina, USA). Written informed consent was obtained from all experimental participants. We summarize recent evidence that breathing or eye blink rate may be valuable nonverbal correlates of irritation. We then outlined the ideal steps to be taken in our laboratory and those of other researchers.

Methods of Olfactometer-Based Research

We employ an automated air-dilution olfactometer, originally developed by Walker et al. (*2*), which controls total flow rate as well as odorant/irritant concentration. Stimuli from the olfactometer are presented to the experimental participant via a facemask with a snug fit that ensures the participant breathes only air from the olfactometer (Figure 1).

Because the volume flow rate of air sent from the olfactometer to the participant is held constant, our approach also allows for the precise measurement of breathing. As depicted in Figure 2, both prestimulus (PRE) and stimulus (DUR) periods begin with the onset of an inhalation. This facilitates valid comparisons of breathing made just before, then during chemical stimulation.

Because we are interested in addressing the need for nonverbal objective correlates of self-reported effects, our experimental participants quantify the intensity of their perception of odor and irritation after each trial. Participants evaluate each stimulus relative to their memory of sensations of odor and irritation experienced prior to a given study. They place a mark on an unstructured line scale labeled to indicate the point corresponding to no sensation and that corresponding to the most intense sensation experienced prior to beginning the study. We have used this approach in laboratory studies of human responses to environmental tobacco smoke (ETS) (*3,4*) and single odorants (*5–8*). In each experiment, 50–75 trials are typically given during a test session, and at least four such sessions are conducted for each participant.

Is Tidal Volume a Marker of Irritation?

We highlight here the perceptual and breathing findings of a recent study in which 31 normal and 4 anosmic individuals were tested repeatedly with a range of four concentrations of propionic acid (PA). Methods and results of the perceptual findings are presented in detail elsewhere (*8*); breathing results have been summarized recently (*9*). In brief, an automated air-dilution olfactometer (*5,10,11*) was used to present a set of four concentrations of PA. During each session, 10 air trials and 10 trials at each of the four odorant concentrations were presented during a period of about 2.5 hours. For 20 of the 31 normals and all four anosmics, all conditions of stimulus presentation and recording of breathing data were identical. Data from this subset of participants was then used to evaluate the utility of breathing as an objective correlate of irritation.

Our analysis of breathing data began with an examination of the time course of responses. Raw (instantaneous rate of inhalation or exhalation) data for the PRE and DUR segments of each trial were converted to cumulative inhaled volumes (CIVs). The mean CIV for clean air trials for each session was then calculated, and CIV data for each of the concentrations for that session were expressed as a proportion of the mean CIV for clean air. Thus, the mean CIV over the course of the PRE or DUR rose monotonically from 0 to 1, whereas the CIV for the odorant concentrations rose to a number almost always less than 1. Data could then be collapsed over trials within session, then over sessions for each participant, and finally across all participants within each of the two groups (normal, anosmic). Figures 3 and 4 show the temporal pattern of breathing changes during the first 2 sec of stimulus presentation.

Normal participants (Figure 3) exhibited CIV declines of 39 and 14%, beginning at 500 and 710 msec, with presentations of 59.15 and 8.22 ppm, respectively. With anosmics (Figure 4), 59.15 ppm caused a 19% decline in CIV that began at 730 msec. Differences between normal and anosmic CIV patterns indicate that the olfactory system contributes to breathing responses to airborne chemicals. The presence of an intact olfactory system either increases the magnitude of the breathing change or causes one to be seen with stimulus levels that are ineffective in anosmics. This is consistent with the greater nasal irritation sensitivity of normals (*8,12*), a difference most reasonably attributed to the presence of the olfactory nerve.

Based on the temporal pattern of breathing changes observed, the percentage changes from the PRE period to the first complete inhalation after stimulus onset were calculated. This approach also allowed us to investigate explicitly the degree to which normal and anosmics decrease breathing by a lessening of breath volume (InVol) as opposed to a shortening of inhalation duration (InDur). Finally, these changes in breathing were compared to odor and nasal irritation ratings, to assess the possibility that breathing patterns may be sensitive and reliable correlates of perception. In this evaluation we focused on nasal

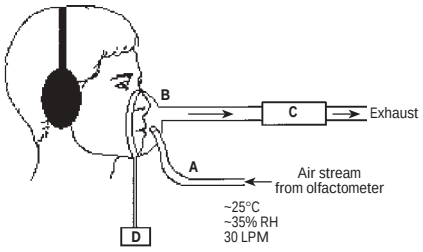

Figure 1. Key components of system used to present odorants generated by an air-dilution olfactometer. LPM, liters per minute; RH, relative humidity. Odorized or clean air (*A*) from the olfactometer is warmed and humidified, then directed at a constant volume flow rate to a facemask (*B*) equipped with an inflatable rim that produces a comfortable but snug seal with the participant's face. Breathing is unobtrusively measured with a pneumotachograph (*C*) mounted downstream of the participant and out of view. Pressure in the facemask rim is monitored by a transducer (*D*) to verify that only air from the olfactometer is available to the participant. Reproduced from Walker et al. (*9*) with permission of Oxford University Press.

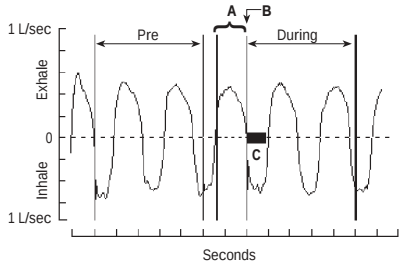

Figure 2. Measurement of breathing in relation to stimulus presentation. The participant receives only clean, warmed, and humidified air during the "Pre" period, after which a flow valve rapidly operates with the subsequent exhalation onset. Odorant concentrations reach full value before the first inhalation of the "During" period, during which breathing responses to either an odorant concentration or clean air are recorded. CIV analyses were conducted for the first 2 sec (thick bar) of the "During" period. Sensory ratings were entered immediately after stimulus offset. Reproduced from Walker et al. (*9*) with permission of Oxford University Press.

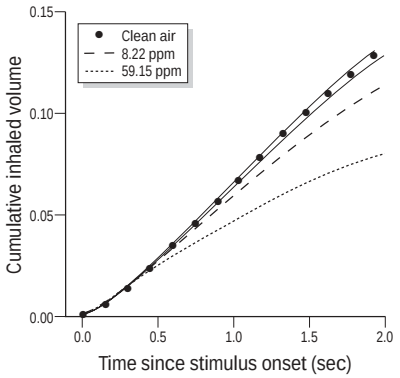

Figure 3. CIVs for normal participants in response to four concentrations of PA and, for comparison, clean air. Reproduced from Walker et al. (*9*) with permission of Oxford University Press.

irritation because of prior work indicating that considerable odor sensation, and even some weak nasal irritation, may be present without any reduction in inhalation volume (*7*).

Examination of the first inhalation after stimulus onset shows that the CIV declines in normals (Figure 5) were achieved by a progressive decline in InVol, beginning with a slight drop at 1.14 ppm, and a marked decline in InDur with only the highest concentration. Anosmics (Figure 6) exhibited declines in InDur and InVol with only the 59.15-ppm (highest) concentration, and these declines were much more modest than the changes seen in normals. Comparison of these breathing results with sensory ratings from this same experiment (*8*) demonstrates that: *a*) in normals, odor perception rises slightly, but breathing does not change, with the lowest concentration; *b*) the higher breathing sensitivity (greater declines in InVol) of normals is paralleled by the higher nasal irritation of these individuals, suggesting a common neural basis; *c*) InDur is decreased in normals only with a stimulus concentration sufficient to cause marked nasal irritation in anosmics; and *d*) in anosmics, modest but reliable declines in both InDur and InVol are closely correlated with the marked elevation in nasal irritation magnitude seen with only the highest PA concentration.

It must be acknowledged that the results for this olfactometer-based study involve only a single compound presented to the nose alone and for a much briefer period of time than is representative of chemical exposures in everyday life. In interpreting these results and evaluating how they might be applied to better understand various aspects of environmental health, two dichotomous positions may be envisioned. An extremely skeptical view might hold that the results are specific to PA presented briefly to only the nose.

In direct contrast one could take the perhaps simplistic view that the relationship between breathing parameters and nasal irritation is fixed regardless of the subset of afferents of the trigeminal nerve that are stimulated, the stimulus complexity (single compound vs mixtures), the duration of stimulation, whether the eyes are also stimulated, and the relative olfactory-trigeminal stimulatory effectiveness of the compound(s) being tested. We suggest the most reasonable prediction is that breathing responses will be sensitive measures of perceived irritation but that the relationship between the two end points will depend on some or all variables just noted.

Based on this view, at least four next steps may be offered that will greatly reduce uncertainty:

- On the basis of prior comparisons of normal and anosmic sensitivities, PA may be described as intermediate in terms of trigeminal stimulatory effectiveness relative to that of the olfactory system. Because the olfactory system clearly contributes to the perception of nasal irritation, it is important to determine if the inverse relationship between InVol and nasal irritation is seen with stimuli varying widely in relative olfactory–trigeminal potency.
- Because the olfactometer-based data suggesting InVol as a marker for nasal irritation derive from a single compound, it would be useful to replicate the PA study with multicomponent mixtures.
- The postulated link between InVol and NI is based on nasal-only presentations. It would be useful to determine the degree, if any, to which the relationship is altered when stimuli are presented to the eyes and nose simultaneously.
- Finally, the proposed use of InVol as a marker for NI in normal and anosmic participants is based on very brief stimulations. Thus, it would be informative to investigate breathing changes using experimental protocols that incorporate much longer (minutes to tens of minutes or hours) exposures.

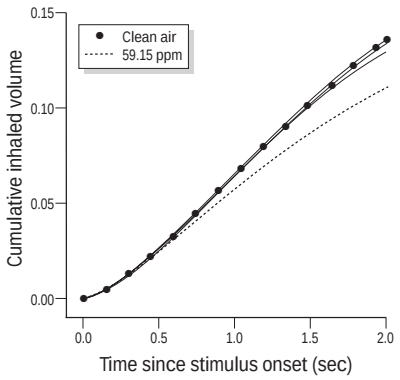

Figure 4. CIVs for anosmic participants in response to four concentrations of PA and, for comparison, clean air. Reproduced from Walker et al. (*9*) with permission of Oxford University Press.

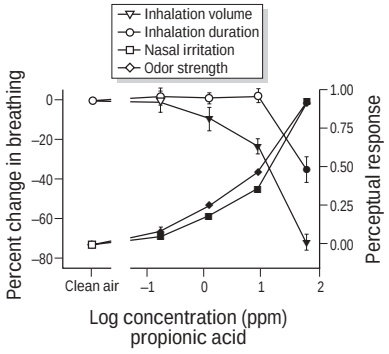

Figure 5. Comparison between two inhalation measures and sensory ratings of odor magnitude and nasal irritation in normal participants. The negative correlation between nasal irritation and InVol (r = –0.99) was greater than that between nasal irritation and InDur (r = –0.91). In Figures 5 and 6, filled symbols indicate a statistically significant difference (α level of 0.05) from clean air. Reproduced from Walker et al. (*9*) with permission of Oxford University Press.

Breathing Responses to a Very Complex Stimulus Presented Whole Body for Much Longer Durations

Whereas both the chemical stimulus and the interpretation associated with the study just described are rather simple, neither may be said of the second study we highlight. In a controlled laboratory exposure study (*4*), 17 healthy male never-smokers were exposed repeatedly to a no-smoking control condition and each of five concentrations of true ETS: 58, 113, 217, 368, and 765 µg/m^3 of respirable suspended particles (RSP) that were attributable to ETS–RSP. A schematic top view of the chamber layout is shown in Figure 7.

Concentrations were generated by varying smoker activity and ventilation rates. ETS–RSP levels were measured in real time and are summarized in Figure 8.

In addition to the perceptual, breathing, and eye blink rate responses to be highlighted here and below, cognitive and psychological state changes were also recorded and analyzed.

Figures 9 and 10 summarize sensory and breathing results, respectively. Ratings of the intensity of odor and irritation, as a function of ETS–RSP concentration, were generally consistent with earlier work (*13*) in which roughly comparable concentrations of true ETS (as opposed to machine-generated sidestream smoke from only the lit end of the cigarette) were evaluated. Although the magnitude of many sensory responses was quite low, their relationship to ETS–RSP concentration was remarkably systematic. All concentrations elicited odor reliably, but the lowest two caused significant irritation of the nose and eyes for only a few time points.

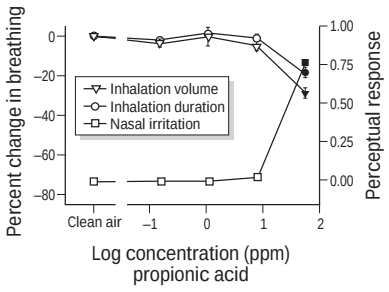

Figure 6. Comparison between two inhalation measures and nasal irritation ratings in anosmic participants. Both breathing measures declined with the rise in nasal irritation (r = –0.99 in both cases). Reproduced from Walker et al. (*9*) with permission of Oxford University Press.

In view of the results in Figure 9 and those of the olfactometer-based study described earlier, the pattern of breathing changes shown in Figure 10 was quite surprising in two ways. First, despite the very modest elevations in nasal and eye irritation with the lowest three concentrations, these stimuli caused significant declines in breathing frequency. These drops were due largely to increases in exhalation duration, shown in the second panel. Although elevations in tidal volume were statistically significant at only a few time points, these changes were sufficient to compensate for the slowed breathing rate and preserve minute ventilation. Minute ventilation was, however, altered significantly by the recording of perceptual, psychological state, and cognitive data even though no experimenter contact was involved. Independent of the presence of ETS, minute ventilation increased approximately 25% during these events. The second striking feature of the data in Figure 10 is the complete lack of a dose–response relationship. The highest and lowest concentrations, which differed by over 13-fold, caused the same degree of change in all parameters.

There appear to be at least three plausible hypotheses to account for these observations. One interpretation, elaborated in the original report (*4*), is that the breathing changes indicate only an awareness of a change in the environment, largely or entirely because of olfactory stimulation. This psychophysiological view is consistent with the apparent all-or-nothing nature of the response. A second view might be that the changes signal a criterion amount of irritation of the nose and/or eyes has been reached. Of course this interpretation would require that breathing be at least as sensitive a measure of irritation as self-report measures. Indeed, comparing Figures 9 and 10 leads to the impression that breathing may be changed at levels of ETS–RSP eliciting no irritation at all. Finally, one might argue that ETS is a sufficiently unusual (not representative of any nonsmoking environment) and complex stimulus that the breathing changes might not be generalizable to other pollutants. Modest mechanistic support for this idea is found in the evidence for specialized nicotinic receptors in the olfactory mucosa and on the endings of ocular and nasal trigeminal afferents (*14–16*).

Experiments to test these hypotheses include those outlined at the end of the previous section. Additionally, one fruitful approach would be to systematically compare the effects of ocular-only, nose-only, and ocular plus nasal presentations of precisely controlled stimuli. Ideally, both normal and anosmic participants would be employed in this effort, which would be conducted in an environmental chamber and incorporate lengthy stimulus exposures. It is also important to include in future work stimuli below one or more response thresholds. For example, it would be valuable to know if stimuli not detected consciously elicit reliable breathing changes.

For a number of reasons it is unclear how the present breathing and irritation results should be viewed in relation to the considerable number of studies in which rodent respiratory rate depression has been measured in response to various chemicals. Although rats have been used in some of this work, the number of chemicals tested in the mouse is much larger (*17*). Unfortunately, quantitative

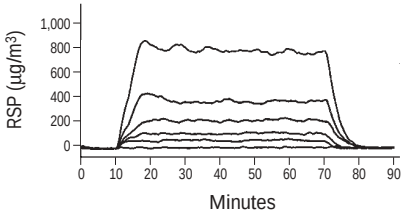

Figure 8. Mean concentrations in micrograms per cubic meter of RSP concentration over the course of the 90-min test session, for each of the five target ETS levels and the no-smoking control condition. Reproduced from Walker et al. (*4*) with permission of Munksgaard International Publishers, Ltd.

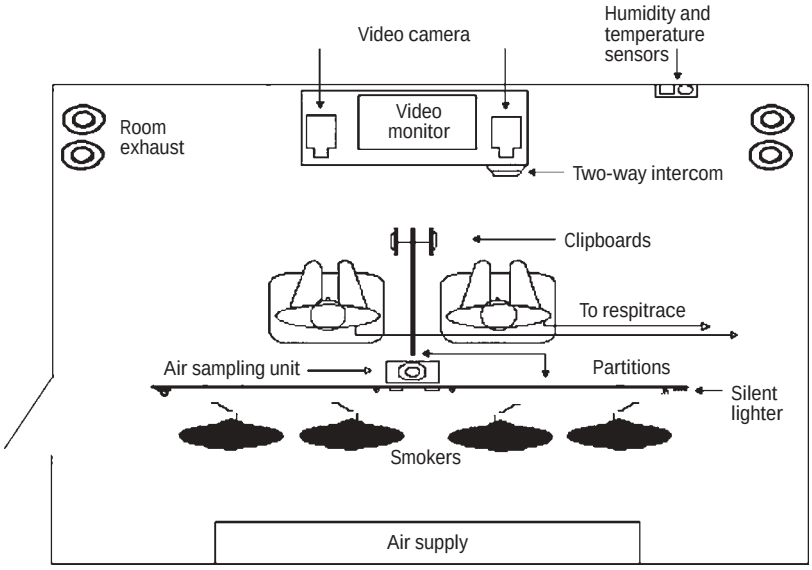

Figure 7. Top view of the environmental chamber and participant locations. Room air was sampled for both real-time and time-weighted average measurements. Temperature and relative humidity were held constant at 22°C and 50%, respectively, but ventilation rates were varied depending on the target ETS level. Video cameras monitored participants throughout a session and intermittently recorded eye blink responses. The television monitor displayed footage of current events and documentary pieces throughout the session except when sensory, cognitive, or psychological state data were being collected. Reproduced from Walker et al. (*4*) with permission of Munksgaard International Publishers, Ltd.

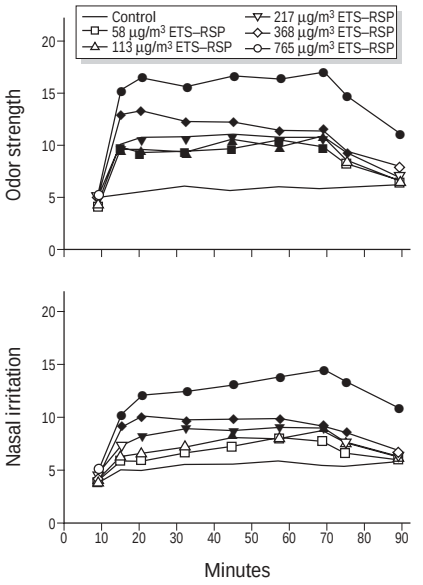

Figure 9. Participant ratings of odor and nasal irritation magnitude as a function of five ETS–RSP concentrations over the course of the test session. The maximum possible value for each rating was 60, with 40 indicating that the sensation magnitude matched the most intense that the participant had experienced prior to the experiment. Filled symbols indicate statistically significant differences, at each time point, between a given ETS concentration and the no-smoking control condition. Reproduced from Walker et al. (*4*) with permission of Munksgaard International Publishers, Ltd.

data exist in normal humans for only a few of the compounds for which mouse respiratory depression data are available. Nasal irritation, but not breathing, responses of anosmic individuals have been reported (*18*,*19*). However, the demonstrated role of the olfactory system in nasal irritation (*8*) and breathing responses (*9*) limits the predictive values of data from anosmics in understanding the effects of actual environments. There are much more data on eye irritation (*20*,*21*) but with rare exceptions (*22*) this work has not included breathing measurements. Even if a database of breathing responses to ocular chemical stimulation in humans were available, we are not aware of a literature on mouse respiratory responses to ocular-only stimulation to which such human data could be compared.

Eye Blink Rate May Be a Simpler, More Directly Sensory, and Less Sensitive Nonverbal Response Than Breathing

The ETS experiment discussed above also provided evidence that eye blink rate may be useful as a marker of moderate to severe eye irritation. Figures 11 and 12 show the eye blink rate changes over the course of the 90-min session and ratings of eye irritation, respectively. The general pattern of results from the two measures are similar, although owing partly to the greater "noise" seen with eye blink rate, the sensory end point is more sensitive (statistically significant with lower concentrations). We suggest the simplest interpretation is that these are two manifestations of the same underlying event: activation by chemicals within ETS of corneal afferents of the ophthalmic branch of the trigeminal nerve. On the basis of this interpretation, eye blink rate would have value as a test of whether the contamination level is sufficient to cause progressive worsening of symptoms over time (with prolonged exposure to a constant input). Our findings in this area are in reasonably good agreement with those of Muramatsu et al. (*23*) and Weber et al. (*24*,*25*), who studied the effects of various levels of sidestream smoke.

Although the eye blink rate and eye irritation results seem attributable solely to the effects of airborne chemicals on the ocular surface, it would be useful to verify that this is the case. This is best done by within-individual comparisons of the magnitude of both responses under conditions where only

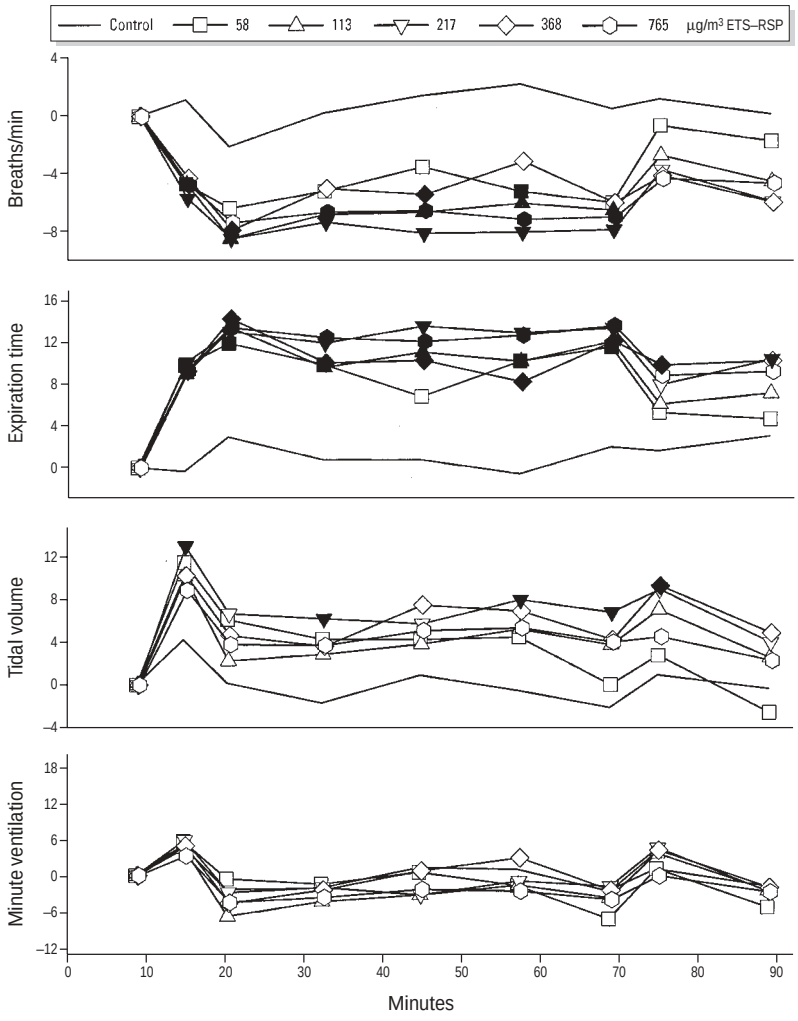

Figure 10. Breathing parameter changes over the course of the test session as a function of the same five ETS–RSP concentrations examined in Figure 9. Plotted values represent mean percentage changes from the first 10 min of the session (when no ETS was ever present) to each of the eight subsequent 10-min time blocks after smokers began to puff on unlit (control) or lit cigarettes. Filled symbols indicate statistically significant differences, at each time point, between a given ETS concentration and the no-smoking control condition. Reproduced from Walker et al. (*4*) with permission of Munksgaard International Publishers, Ltd.

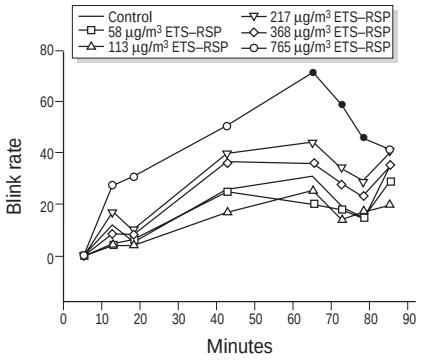

Figure 11. Eye blink rates in response to five ETS concentrations and the control condition. Rates during each of eight 3-min periods were expressed as percentage changes from the rate observed during the presmoking baseline period. Because the reference rate for the first of the eight periods was compared to itself, all initial values are zero. Filled symbols indicate statistically significant differences, at each time point, between a given ETS concentration and the no-smoking control condition. Reproduced from Walker et al. (*4*) with permission of Oxford University Press.

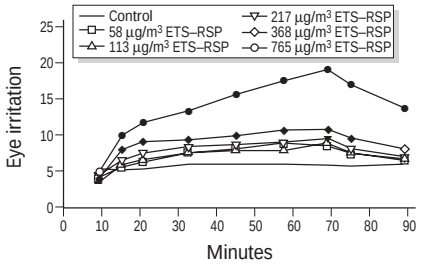

Figure 12. Eye irritation ratings, over the course of the test session, in response to five ETS concentrations and the no-smoking control condition. As in Figure 9, the maximum possible value for each rating was 60. Filled symbols indicate statistically significant differences, at each time point, between a given ETS concentration and the no-smoking control condition. Reproduced from Walker et al. (*4*) with permission of Munksgaard International Publishers, Ltd.

the eyes are stimulated versus those where the whole body is stimulated. This would reveal whether either response was affected by olfactory or nasal trigeminal stimulation. Chemical stimuli much simpler than ETS should be included in such an effort. This feature would shed light on the generality of any relationships between blinking and eye irritation and would facilitate comparisons between ocular and nasal trigeminal chemosensitive afferents.

Conclusions

Within the realm of environmental health, a long-neglected area has been those effects that occur over time frames of a few seconds up to the duration of a workday. Although the detriment to a given individual is seldom great, the much greater prevalence somewhat compensates; as a result, the impact is considerable when viewed from a population perspective. From a technical standpoint at least, accelerated progress is possible. Recent advancements in instrumentation, experimental design, and statistical procedures have provided researchers with straightforward research tools for quantifying a wide range of short-term responses. Stimuli of varying chemical complexity may be confidently presented, for varying durations, to experimental participants in a whole- or partial-body manner. Methods have been developed for collecting and interpreting a wide variety of responses, at least some of which have known biological bases. Future work need not, and we would argue, should not be conducted from a conceptual stance overly driven by standard-setting or range-finding priorities. To the contrary, recent findings demonstrate that careful attention to stimulus, organismic, and response variables yields important insights concerning the biological underpinnings of impacts increasingly being recognized as constituting measurable decrements to quality of life and productivity.

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