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Does Haber's Law Apply to Human Sensory Irritation?

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Irritation of the eyes, nose, and throat by airborne chemicals—also referred to as "sensory irritation"—is an important endpoint in both occupational and environmental toxicology. Modeling of human sensory irritation relies on knowledge of the physical chemistry of the compound(s) involved, as well as the exposure parameters (concentration and duration). A reciprocal relationship between these two exposure variables is postulated under Haber's law, implying that protracted, low-level exposures may be toxicologically equivalent to brief, high-level exposures. Although time is recognized as having an influence on sensory irritation, the quantitative predictions of Haber's Law have been addressed for only a handful of compounds in human experimental studies. We have conducted a systematic literature review that includes a semiquantitative comparison of psychophysical data extracted from controlled human exposure studies versus. the predictions of Haber's law. Studies containing relevant data involved exposures to ammonia (2), chlorine (2), formaldehyde (1), inorganic dusts such as calcium oxide (1), and the volatile organic compound 1-octene (1). With the exception of dust exposure, varying exposure concentration has a proportionally greater effect on sensory irritation than does changing exposure duration. For selected time windows, a more generalized power law model ($c^n \times t = k$) rather than Haber's law per se ($c \times t = k$) yields reasonably robust predictions. Complicating this picture, however, is the frequent observation of intensity–time "plateauing," with time effects disappearing, or even reversing, after a relatively short period, depending on the test compound. The implications of these complex temporal dynamics for risk assessment and standard setting have been incompletely explored to date.

Irritation of the eye, nose, and throat ("sensory irritation") can occur with exposures to irritant gases, vapors, dusts, and smokes (Alarie, 1973). This constellation of symptoms is frequently reported by individuals exposed to industrial chemicals or environmental tobacco smoke (ETS), by occupants of "problem buildings" and residents living near industrial emission sources, and after emergency chemical releases (CDC, 1991; Dalton, 2001; Fisk et al., 1993; Kharrazi et al., 1994; Kreutzer et al., 1996; Mendell, 1993; Schaper, 1993; Shusterman et al., 1991). Although generally less incapacitating than lower respiratory tract responses such as bronchospasm, sensory irritation and related upper respiratory tract symptoms together account for significant decrements in economic productivity in indoor environments and act as a warning against more protracted and deleterious exposure (Fisk & Rosenfeld, 1997).

The neurological modality involved in sensory irritation has been referred to as "chemesthesis," and is conveyed by the fifth cranial (trigeminal) nerve in the case of ocular and nasal irritation, and by a combination of the fifth and ninth (glossopharyngeal) in the case of pharyngeal irritation (Bryant & Silver,

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2000). The larynx and lower respiratory tract are also sensitive to chemical irritants and are innervated by the tenth cranial, or vagus, nerve. Molecular and neurologic mechanisms of chemesthesis in the upper airway/mucous membranes are at least partially understood. Nociceptive nerves of the C and Aδ class express molecular receptors for heat/acid/capsaicin (TRPV1), acid (ASIC/DRASIC), nicotine (nAChR), purines released by tissue damage (P2X), and possible nonspecific membrane alterations in response to high-level volatile organic compound (VOC) exposures (Cometto-Muniz et al., 2005a, 2005b; Julius & Basbaum, 2001; Keiger et al., 2003; Waldmann et al., 1999; Spehr et al., 2004). Irritant-induced upper airway reflexes include sneezing, cough, nasal congestion, rhinorrhea, sinus and middle ear dysfunction, and laryngospasm (Widdicombe, 1988; Raphael et al., 1991). Upper airway irritants can also exacerbate asthma, possibly through a "naso-bronchial reflex" (Berger & Nolte, 1979). In the context of acute, high-level exposures, sensory irritation may precede and warn of potential lower respiratory tract health effects such as tracheitis, bronchitis, bronchospasm, and chemical pneumonitis (Shusterman, 1999). Predicting sensory irritation from airborne chemicals is therefore an important goal for toxicologists and risk assessors.

Several approaches have been developed for modeling human sensory irritation. Animal data documenting changes in breathing patterns in rodents (the RD_{50}) generally correlate with human observations for irritants, implying that cross-species extrapolation may be valid under some circumstances (Alarie, 1984). The RD_{50}, however, does not take into consideration exposure time. Human psychophysics provides a more direct method for evaluating sensory irritation. Psychophysicists employ a variety of techniques for separating the closely associated modalities of olfaction and sensory irritation, both at and above the threshold of perception. Relevant psychophysical techniques include use of anosmic subjects (who will not be biased by odor), use of an odorless model irritant (carbon dioxide), use of the "lateralization threshold" among normosmics, and use of subjective rating scales (Cometto-Muniz & Cain, 1998; Doty et al., 2004). Subjective stimulus rating (denoted ψ), in turn, may employ ordered category scales, visual analog scales (with or without linguistic anchors), or dimensionless comparison of test stimuli versus. reference stimuli (method of magnitude estimation) (Lawless & Malone, 1986; Gescheider, 1985; Stevens, 1975). The fact that the existing experimental literature on concentration–time relationships employs varying exposure protocols, psychophysical scaling methods, and statistical approaches renders the task of summary analysis challenging, as becomes apparent in the following.

The human psychophysics and animal experimental literature also contains a number of works addressing structure–activity and dose-response relationships of sensory irritants. (Abraham et al., 1998; Alarie et al., 1998; Schaper, 1993) Notwithstanding the value of these models, which are based on empirical observations, available data for a given airborne chemical seldom cover the entire range of exposure conditions of interest to regulators. A more comprehensive model would allow risk assessors to extrapolate across different exposure conditions (i.e., concentrations and durations), in order to predict human sensory irritation by airborne chemicals. One element of such a model would address the degree to which protracted exposures at lower levels act (biologically) like briefer, higher level exposures.

The formulation $c \times t =$ constant for a given toxicologic endpoint (where c is exposure concentration and t is time) was proposed by Fritz Haber (1868–1934) and Ferdinand Flury (1877–1947) to describe the behavior of war gases (Witschi, 1999). According to Haber's law, equivalent biological effects can result from both brief, high-level and more protracted, low-level chemical exposures. Initial experimental validation involved the endpoint of pulmonary edema and mortality in experimental animals exposed to phosgene gas, although this endpoint has subsequently been modeled for chlorine and other pulmonary irritants (Gelzleichter et al., 1992; Rinehart & Hatch, 1964; ten Berge, 1986; Zwart & Woutersen, 1988). Experimental data from this system suggest that c and t are interchangeable within specified time limits, but that for protracted exposures, concentration becomes more important than time in predicting toxicity (i.e., a "dose-rate effect" is apparent).

Miller et al. (2000) point out that Haber's law ("rule") is a special case of the power function:

$$c^{\alpha} t^{\beta} = k$$
$$(\text{or}: \quad \alpha \log c + \beta \log t = k')$$

for which $\alpha = \beta = 1$ and the analysis is restricted to a single effect level. (For constant effect levels, either α *or* β, but not both, should be allowed to differ from 1, lest the model run the risk of being overparameterized.) Of importance, this more general formulation allows for modeling, not only of dose-rate effects but also of data pertaining to varying effect levels, yielding three-dimensional graphical presentations. The authors therefore argue that in order to achieve progress in toxicologic modeling, Haber's law as applied to descriptive and regulatory toxicology should be replaced with more generalized power function models. Consistent with this proposal, the California Environmental Protection Agency (Cal/EPA, 1999) followed ten Berge (1986) in recommending a power function including the exponent α (described as "modified Haber's law") for time extrapolation when using toxicity data to develop acute reference exposure levels.

Of note, the field of psychophysics (from which is derived most of the source material for this review) also relies on power functions to summarize psycho(ψ)–physical (ϕ) data:

$$\psi = k\phi^{\alpha}$$
$$(\text{or}: \quad \log \psi = \alpha \log \phi + k')$$

Since psychophysics initially dealt with vision, hearing, or tactile sense, rather than the chemical senses (smell, taste, and trigeminal chemoreception), it is understandable that ϕ, or steady-state intensity, would be the sole exposure parameter incorporated into what is referred to as Stevens's power

law (Stevens, 1957, 1975; Gescheider, 1985). For the chemical senses, however, mass effects are possible, and incorporation of both concentration and time into the exposure parameter ϕ is appropriate, that is, $\phi = f(c, t)$:

$$\psi = k(c, t)^{\alpha}$$

where c and t are combined in a manner to be determined.

One specific formulation of Stevens's power law (assuming chemesthesis involves perfect mass integration) would be:

$$\psi = k(c \times t)^{\alpha}$$
$$(\text{or}: \quad \log\psi = \alpha \log c + \alpha \log t + k')$$

which, in turn, could be generalized to:

$$\log \psi = \alpha \log c + \beta \log t + k'$$

if one assumed that varying c and t had unequal effects on ψ. For a fixed ψ this would translate to:

$$\alpha \log c + \beta \log t = k''$$

an identical formulation to that of Miller et al. shown earlier.

Thus, although toxicologists and psychophysicists have been studying related phenomena using different methods and vocabularies, convergent analysis of data is imminently practical. However, in order to test the predictions of Haber's law (or more generalized power law models), some standardization of experimental design and procedures is required (discussed later).

To date, neither Haber's law nor other more generalized power law models have been systematically evaluated with respect to their predictions regarding human sensory irritation, a frequent critical endpoint for exposure standards, under varying conditions of concentration and duration. Discussion has taken place regarding the (explicit or implicit) use of Haber's law in occupational standard setting in relation to "time-weighted average" exposures (Atherly, 1985; Brodeur et al., 2001). Concentration–time trade-offs are also subsumed in some environmental exposure standards (Doull & Rozman, 2000; Gaylor, 2000). In light of these common concerns, evaluation of Haber's law and other power law models could assist risk assessors in addressing such exposure guidelines as permissible exposure limits (PELs) for occupational settings and reference exposure levels (RELs) for environmental public health protection purposes. In this context, this report was initially commissioned by the Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency, with the objective being to review available published human experimental literature relevant to the validity of Haber's Law (and other power law formulations) as applied to human sensory irritation.

METHOD

A literature review was conducted, beginning with a search of the National Library of Medicine's *PubMed* database, as well as a review of secondary references, in order to identify controlled human exposure studies in which airborne exposure to the eyes, nose, and/or throat was conducted and the following conditions satisfied: (1) *subjective mucous membrane irritation was rated* using psychophysical methods (category scales, visual analog scales, or method of magnitude estimation); and (2) *exposure concentration (c) and time (t) were varied* such that equivalent (or overlapping) c × t products were achieved with different exposure conditions. Time, in turn, could be varied by having multiple experimental trials with varying exposure times, or by obtaining multiple sensory ratings during a single continuous exposure. The literature search was conducted with the following logic: "(eye OR nose OR throat OR sensory) AND irritation AND human AND concentration AND time." In addition, secondary references were reviewed in order to identify primary studies fulfilling the criteria described.

As a result of this exercise, we systematically reviewed the health literature for three compounds: ammonia, chlorine, and formaldehyde. The rationale for this selection included: (1) the availability of at least three controlled human exposure studies for each (published in the English language), which, in turn, (2) documented at least one upper respiratory tract/mucous membrane irritative endpoint, and (3) occupational or environmental relevance of the agent in question.

Subjective upper respiratory tract endpoints examined in these studies included eye, nose, and throat irritation. In addition to studies of ammonia, chlorine, and formaldehyde, a single study of eye irritation was identified utilizing the test compounds *n*-butanol and 1-octene (Hempel-Jorgensen et al., 1999), as well as a single study involving exposure to alkaline mineral dusts (Cain et al., 2004). These studies were deemed of value because they included both multiple exposure times and concentrations, and hence were included in the review.

For each agent we tabulated potentially relevant studies and abstracted data from those with designs adequate to compare with the predictions of Haber's law (i.e., in which comparison were made of valid sensory endpoints for multiple $c \times t$ combinations). In order to present data in a consistent manner from studies utilizing differing methodologies, we tabulated ψ (defined here as either mean sensory rating or percent of subjects achieving a given criterion sensory rating) as a function of $(c \times t)$ integral with the expectation that the ratio of ψ to $(c \times t)$ would be constant for a given health endpoint if Haber's law (and not a more generalized power function model) were applied. Depending on the source study design and data presentation, we preferentially abstracted data (1) for fixed $c \times t$ products; if this was not possible, we abstracted data for (2) a fixed ψ. If neither of these was practical we (3) abstracted data cross-sectionally such that comparisons of $\psi/(c \times t)$ reflect neither a fixed exposure nor outcome parameter.

RESULTS

Ammonia

We reviewed four controlled human exposure studies (Table 1): one examined multiple exposure levels only, another

TABLE 1
Controlled human exposure studies of ammonia

First author (year)	Study type	Level(s) (ppm)	Duration (s)	Endpoints (lower respiratory tract)	Endpoints (upper respiratory tract)	Conclusions with regard to Haber's law
Cometto-Muniz (1984)	Controlled exposure	99, 434	1.25, 2.50, and 3.75 s	None	Nasal irritation (suprathreshold rating)	Linear relationships between quantitative sensory rating and both concentration and duration. *c* and *t* vary reciprocally for given sensory rating. Consistent with Haber's law for very brief (<4 s) exposures.
Ferguson (1977)	Semicontrolled exposure	25, 50, 100	6h/day × 6 wk	Spirometry	Eye, nose, throat examination	Crude control of exposures and unconventional analysis purports to show decreased irritation over period of weeks. Not interpretable with regrard to Haber's law.
McLean (1979)	Controlled exposure	100	5, 10, 15, and 20 s	None	Nasal airway resistance (change from baseline)	Dose-response for duration of exposure is roughly linear, but single exposure level. Limited utility with regard to Haber's law.
Wise (2005)	Controlled exposure	37, 48, 52, 67, 98, 131, 289, 721	0.1–10 s	None	Nasal irritation (lateralization threshold + suprathreshold rating)	*Detection:* 2.5-fold increase in duration compensated for 50% reduction in concentration. *Suprathreshold irritation*: 3.1-fold increase in duration compensated for 50% decrease in concentration. Consistent with power law (<4 s) exposure.

multiple exposure times, and two employed both multiple exposure concentrations and times. The study that examined multiple exposure times with a single (100 ppm) exposure level (McLean, et al., 1979) showed progressive increases in nasal airway resistance (from baseline) that were more or less linearly related to exposure time over the range of 5 to 20 s. The study in question did not include symptom ratings per se, although nasal airway resistance is significant as a reflex response to nasal irritation. Ferguson et al. (1977) described a semiexperimental study that involved multiple exposure levels (25, 50, and 100 ppm) in an occupational setting over a protracted (6-wk) exposure period. However, the study was of insufficient quality to derive useful data—either subjective or objective. Only two controlled exposure studies (Cometto-Muniz & Cain, 1984; Wise et al., 2005) described ammonia-induced sensory irritation with both multiple exposure concentrations and times and used rigorous psychophysical methods.

Cometto-Muniz and Cain (1984) documented psychophysical measures of nasal "pungency" (irritation) and total nasal sensation (odor + irritation) for combinations of exposure times spanning 1.25 to 3.75 s., and exposure levels from 47 to 434 ppm ammonia. Data for nasal pungency alone were abstracted from the article, and an index was derived consisting of mean sensory rating intensity (method of magnitude estimation) divided by the product of $c \times t$ (in ppm $\cdot$ s), with the expectation under Haber's law that this index would be constant (Table 2). The observed range was 0.049 to 0.074, with a trend toward slightly higher values with higher exposure levels. Because the $c \times t$ product varied across experimental conditions, direct testing of Haber's law predictions was not possible with this data set. Notwithstanding this limitation, given the relatively narrow distribution of values this study can be considered as providing limited support for Haber's law for the endpoint of subjective nasal irritation involving very short-duration (<4 s.) exposures.

Wise et al. (2005) examined both irritant detection (by nasal lateralization) and suprathreshold rating of nasal irritation (method of magnitude estimation) utilizing ammonia vapor with various combinations of concentration (37 to 721 ppm) and time (0.1 to 10 s). For the endpoint of irritant detection, a 2.5-fold increase in duration was necessary to offset a 50% reduction in concentration. For suprathreshold rating, a 3.1-fold increase in exposure time offset a 50% reduction in concentration. Concentration–time trade-off for suprathreshold ratings was not studied beyond 4 s because stimulus detectability did not increase significantly in that range, likely predicting a plateau in the ψ–time relationship. Estimated stimulus durations to achieve equivalent intensity ratings appear in Table 3; as in the previous analysis, an index was derived consisting of ψ divided by mean ($c \times t$) integral. For each criterion ψ (63%, 100%, or 158% intensity relative to the reference stimulus), $c \times t$ became smaller ($\psi / c \times t$ became larger) as the stimulus concentration became greater. The authors concluded that an "imperfect mass integrator model" describes short-term temporal integration of irritation in the nose. Borrowing the slopes from the authors' regression formulas for log(c) versus. log(t) at fixed outcome, we obtained power-law exponents ("n" in $c^n \times t = k$) of 1.30 for irritant detection (lateralization) and 1.64 for suprathreshold rating (ψ). These regression formulae explained >95% of the observed variance in the data within this very limited time window (<4 s.).

TABLE 2
Nasal irritation data: Ammonia exposure (Cometto-Muniz & Cain, 1984)

Concentration (ppm)	Duration (s)	$c \times t$ (ppm-s)	Sensory rating[a] (0–infinity)	Sensory rating/ $c \times t$
99	1.25	124	8	0.065
99	3.75	371	18	0.049
434	1.25	543	40	0.074
434	3.75	1628	104	0.064

[a]Method of magnitude estimation.

TABLE 3
Nasal irritation data: Ammonia exposure (Wise et al., 2005)

Concentration (ppm)	Duration (s)	$c \times t$ (ppm-s)	Sensory rating[a] (0–infinity)	Sensory rating $c \times t$
165	1.26	208	63	0.30
304	0.501	152	63	0.41
478	0.251	120	63	0.53
165	2.75	454	100	0.22
304	0.993	302	100	0.33
478	0.447	214	100	0.47
165	6.31[b]	1041	158	0.15
304	1.70	517	158	0.31
478	0.794	380	158	0.42

[a]Method of magnitude estimation.
[b]Extrapolated from beyond the range of experimental data.

Chlorine

We reviewed four controlled human exposure studies for chlorine (Table 4). Of these, one utilized a single exposure concentration (0.5 ppm) with serial ratings (by VAS) of subjective nasal irritation at 5-min intervals; its utility was confined to evaluating nonlinearities in the time effect. In this latter regard, the "downward" concavity in the ψ–time curve after 5 min could be corrected for by log-transforming time, thereby explaining 99% of the observed variance in the rating data (Shusterman et al., 2003). Another study exposed subjects to 3 different exposure levels (0.1, 0.3, and 0.5 ppm) for 6 h/day for 3 days. However, symptom data from this study were filtered by the

TABLE 4
Controlled human exposure studies of chlorine

First author (Year)	Study type	Level(s) (ppm)	Duration (s)	Endpoints (lower respiratory tract)	Endpoints (upper respiratory tract)	Conclusions with regard to Haber's law
Joosting (1975)	Controlled exposure	0.5, 1, 2, 4	2 h (multiple rating times)	Cough; spirometry	Eye, nose, and throat irritation	Both concentration and time trends seen in eye, nose, and throat irritation. Higher symptom ratings with 2 ppm × 1 h than 1 ppm × 2 h. Consistent with power law model $c^n \times t = k$.
Anglen (1981)	Controlled exposure	0.5, 1.0	4 h (multiple rating times)	Urge to cough	Eye, nose, and throat irritation; rhinorrhea	Both concentration and time trends seen. Higher symptom ratings with 1.0 ppm × 2 h than 0.5 ppm × 4 h (i.e., dose-rate effect). Consistent with power law model $c^n \times t = k$.
Shusterman (2003)	Controlled exposure	0.5	15 min (multiple rating times)	Spirometry	Nasal irritation, congestion, rhinorrhea, postnasal drip Nasal airway resistance (NAR)	Modest (< "slight") subjective nasal irritation; increased NAR among allergic rhinitic subjects only. Initial increase in self-rated nasal irritation between 0 and 5 m. followed by decreasing time effect. Not directly applicable to Haber's law.
Schins (2000)	Controlled exposure	0, 0.1, 0.3, 0.5	6 h/d × 3 d	Spirometry	Nasal lavage markers (albumin, IL-6, IL-8, cell counts); "adverse events"	Symptom data unusable because of report "filtering." No chlorine-related changes in nasal lavage markers. Not directly applicable to Haber's law.

TABLE 5
Sensory irritation data: Chlorine exposure (Anglen, 1981)

Type of irritation	Concentration (ppm)	Duration (h)	$c \times t$ (ppm-h)	Percent responding $\geq 1^a$	Percent responding/ $(c \times t)$
Eyes	0.5	4	2	42%	21
Eyes	1	2	2	58%	29
Nose	0.5	4	2	58%	29
Nose	1	2	2	78%	39
Throat	0.5	4	2	62%	31
Throat	1	2	2	83%	42

[a]Leikert scale: 0 = "no sensation"; 1 = "just perceptible"; 2 = "distinctly perceptible"; 3 = "nuisance"; 4 = "offensive"; 5 = "unbearable."

TABLE 6
Sensory irritation data: Chlorine exposure (Joosting & Verberk, 1974)

Type of irritation	Concentration (ppm)	Duration (h)	$c \times t$ (ppm-h)	Sensory rating[a] (0–5)	Sensory rating/ $(c \times t)$
Eyes	1	2 h	2	1.1	0.55
Eyes	2	1 h	2	1.4	0.70
Nose	1	2 h	2	0.4	0.20
Nose	2	1 h	2	1.7	0.85
Throat	1	2 h	2	0.8	0.40
Throat	2	1 h	2	1.1	0.55

[a]Leikert scale: 0 = "no sensation"; 1 = "just perceptible"; 2 = "distinctly perceptible"; 3 = "a nuisance"; 4 = "offensive"; 5 = "unbearable."

examining physicians for "plausibility," rendering them uninterpretable (Schins et al., 2000). Finally, two studies (Anglen, 1981; Joostings & Verberk, 1975) described findings for both multiple concentrations and times, and hence presented data suitable for comparison with the predictions of Haber's law.

Anglen (1981) exposed 31 subjects (16 male; 25 nonsmokers) to chlorine concentrations ranging from 0.5 to 2.0 ppm for 4 hrs. Subjects reported subjective eye, nose, and throat irritation, as well as a variety of chest symptoms, using ordered category (Leikert) scales. Sensory data were tabulated as percent of subjects rating a given symptom at or above a criterion number on a scale of 1–5. Data for ratings ≥ 1 ("barely perceptible") are abstracted in Table 5, comparing experiments in which identical $c \times t$ products were achieved under differing experimental conditions. When rating percentages were divided by the $c \times t$ product (with the expectation of consistency), the results spanned the range of 21–42%/ppm·h, with the data showing a consistent trend toward higher ratings with higher exposure concentrations for a given $c \times t$ product. These findings suggest that a power function in the form $c^n \times t = k$ would provide a better data fit than would Haber's law per se.

Joostings and Verberk (1974) exposed 8 subjects for 2 h to 0.5, 1, 2, and 4 ppm chlorine. Symptom reporting for eye, nose, and throat irritation was obtained at 15-min intervals during the exposure. Symptom data (mean score on a Leikert scale of 0–5) was abstracted for two different c and t combinations with the same cross-product (1 ppm × 2 h [or] 2 ppm × 1 h = 2 ppm·hr; Table 6). Dividing sensory ratings by $c \times t$ yielded an index which should be constant (for a given type of irritation) were Haber's law, rather than a more generalized power-law model, to apply. In fact, higher irritation ratings were obtained (particularly for nasal irritation) when the same $c \times t$ was achieved with a higher exposure concentration, implying that a power law formulation in the form of $c^n \times t = k$ (with $n > 1$), rather than Haber's law per se, may apply. However, given the paucity of data points, no attempt was made to empirically derive the exponent "n."

Formaldehyde

We reviewed 12 controlled human exposure studies for formaldehyde (Table 7). Two of these studies examined only multiple exposure concentrations and two others employed only multiple rating times. There were an additional two studies in which both concentration and rating time varied. Both studies with multiple exposure levels only (Bender et al., 1983; Kulle et al., 1987) showed a dose-response with respect to symptom ratings. Of the two studies that included multiple times, only one (Sauder et al.,1987) presented quantitative symptom ratings for multiple time points; these data showed a trend toward increased symptom ratings as a function of time (up to 120 min for eye irritation and 60 min for nose/throat irritation), with a plateau or fall thereafter. One of the two studies that varied both concentration and rating time (Andersen, 1979) grouped all symptoms—including both upper and lower respiratory tract—into an index of "discomfort," and hence was not further considered in this analysis.

A single study involved both multiple rating times and exposure concentrations and also generated usable (modality-specific) sensory rating data (Cain et al., 1986). The latter included separate visual analog scale ratings of eye, nose, and throat irritation. The subexperiment of greatest interest here involved exposures at 0, 0.25, 0.5, 1, and 2 ppm for 30 min, although a separate 90-min experiment at 1 ppm is instructive in terms of the time course of subjective irritation. With the exception of an anomaly in which mucosal irritation at 0.5 ppm was rated as less intense than at 0.25 ppm at several points in time, both concentration and time exhibited monotonic effects up to approximately 30 min exposure duration. Beyond that time, subjective mucosal irritation tended to plateau or even decrease. Sensory rating data are presented for exposures at 0.5 and 2 ppm in Table 8; no direct comparisons were possible of ψ at identical $c \times t$ products, nor c and t at identical ψ ratings. What is apparent from the tables, however, is a consistently lower

TABLE 7
Controlled human exposure studies of formaldehyde

First author (Year)	Study type	Level(s) (ppm)	Duration (s)	Endpoints (lower respiratory tract)	Endpoints (upper respiratory tract)	Conclusions with regard to Haber's law
Andersen (1978)	Controlled exposure	0, 0.3, 0.5, 1.0, 2.0 mg/m^3	5 h (symptoms rated at 1–3 and 3–5 h)	Spirometry	Nasal mucociliary clearance; Nasal airway resistance	Symptom data on overall "discomfort" increased by exposure level and time (except after 2 h at highest exposure). Dose and time response *not* apparent for NAR or mucociliary clearance. Limited value with regard to Haber's law.
Bender (1983)	Controlled exposure	0, 0.35, 0.56, 0.7, 0.9, 1.0	6 min (with initial response time noted)	None	Eye irritation (subjective)	Dose-response for both severity of eye irritation and time to first sensation with increasing concentration. Rating at end of 6-min test lower than when first noticed (i.e., accommodation), inconsistent with Haber's law.
Cain (1986)	Controlled exposure	0, 0.27, 0.46, 1.10, 2.05	30 min × 2, with/15-min break; symptom rating every 2 min	None	Eye, nose, throat irritation (subjective)	Dose responses for concentration and time (throat > eye > nasal). Continuous exposure for 90 min at 1.0 ppm resulted in plateau and decrease in sensory irritation. May be consistent with power law.
Green (1987)	Controlled exposure	0, 3.0	1 h	Spirometry	Eye, nose, throat irritation (subjective)	Peak ratings occurred at 15 min, with plateau or drop thereafter. Implies no temporal integration—or frank accommodation—after 15 min.
Green (1989)	Controlled exposure	0, 3.0	2 h (with symptom rating at 20, 50, 80, and 110 min)	Spirometry	Eye, nose, throat irritation (subjective)	Quantitative ratings presented only for 80 min; other times reportedly "similar." Not interpretable with regard to Haber's law.

Krakowiak (1998)	Controlled exposure	0.5 mg/m^3	2 h	Spirometry, histamine challenge	Sneezing, rhinorrhea, eye itching. Nasal lavage (tryptase, ECP)	Symptom reporting sketchy and limited to end of exposure and recovery period. Not interpretable with regard to Haber's law.
Kulle (1987)	Controlled exposure	0, 0.5, 1.0, 2.0, 3.0	3 h (symptom rating at end of exposure only)	Spirometry	Eye, nose irritation (subjective); nasal airway resistance	Concentration-response relationship for eye—but not nasal—irritation. Threshold for increased nasal airway resistance 2.0–3.0 ppm. Limited utility with regard to Haber's law.
Sauder (1986)	Controlled exposure	3.0	3 h	Spirometry	Eye, nose, throat irritation (subjective)	Single exposure level and rating time; significant increases in eye, nose, throat irritation with exposure. Not interpretable with regard to Haber's law.
Sauder (1987)	Controlled exposure	3.0	3 h (symptoms rated at 0, 2, 15, 30, 60, 120, and 180 min)	Spirometry	Eye, nose, throat irritation (subjective)	Trend toward increasing ratings of eye irritation over 120 min; "nose or throat" irritation over 60 min; plateau or fall thereafter. Limited utility with regard to Haber's law.
Schachter (1987)	Controlled exposure	2.0	40 min	Spirometry	Eye, nose, throat irritation (subjective)	Single symptom rating at 30 min showed increase principally in eye irritation ratings (not quantified). No evidence of tolerance in occupationally exposed subgroup. Not interpretable with regard to Haber's law.
Sim (1957)	Controlled exposure	13.8	30 min	None	Eye, nose irritation (subjective)	Qualitative report of "considerable nasal and eye irritation " which "wore off after 10 min in chamber." Not interpretable with regard to Haber's law.
Witek (1987)	Controlled exposure	2.0	40 min	Spirometry	Eye, nose, throat irritation (subjective)	Single symptom rating at 30 min showed increase principally in eye irritation ratings (not quantified). Not interpretable with regard to Haber's law.

TABLE 8
Sensory irritation data: Formaldehyde exposure (Cain et al., 1986)

Type of irritation	Concentration (ppm)	Duration (min)	$c \times t$ (ppm-min)	Sensory rating[a] (0–5)	Sensory rating/ $(c \times t)$
Eyes	0.5	10	5	1.6	0.32
		20	10	1.9	0.19
	2.0	10	20	3.3	0.17
		20	40	3.8	0.09
Nose	0.5	10	5	1.8	0.36
		20	10	2.0	0.20
	2.0	10	20	4.4	0.22
		20	40	4.3	0.11

[a]Visual analog scale: 0 = "none"; 1 = "slight"; 2 = "moderate"; 3 = "strong"; 4 = "very strong"; 5 = "overpowering".

TABLE 9
Eye irritation data: 1-octene exposure (Hempel-Jorgensen et al., 1999)

Concentration	Duration (min)	$c \times t$ (mg/m^3 min)	Sensory rating[a] (0–100)	Sensory rating/ $(c \times t)$ $(\times 10^3)$
6000 mg/m^3	60	360,000	10	0.028
10,400 mg/m^3	20	208,000	64	0.308
	40	416,000	82	0.197
	60	624,000	85	0.136
18,000 mg/m^3	10	180,000	37	0.206
	20	360,000	54	0.150
	40	720,000	56	0.078
	60	1,080,000	56	0.052

[a]Visual analog scale: 0 = "no irritation"; 100 = "unbearable irritation."

quotient of $\psi/c \times t$ with lengthening exposure duration, indicative of a strong dose-rate effect. Because of potential imprecision on our part in abstracting data from the graphs, no attempt was made at estimating "n" values for a power law model. However, the authors concluded that simultaneous processes of "potentiation" and "adaptation" appeared to be at work, and suggested the general form of a mathematical model to describe this phenomenon.

Miscellaneous Agent(s)

A single study contained sufficient data to compare with the predictions of Haber's law for the endpoint of eye irritation from a volatile organic compound (VOC). Hempel-Jorgensen et al. (1999) described findings for both multiple exposure levels and times for the VOCs n-butanol and 1-octene, although only the latter compound produced significant subjective irritation. Sixteen subjects (7 males, 9 females) rated eye irritation on a visual analog scale at 2.5-min intervals during 1-h exposures to 0, 6000, 10,400 and 18,000 ppm of 1-octene. In general, mean sensory ratings tended to plateau with time, reaching near-maxima after 20 to 40 min. The concentration dose-response for peak irritation values showed a monotonic trend from 0 to 10,400 ppm, then a paradoxical drop at 18,000 ppm. Representative sensory rating data abstracted from the authors' graphs appear in Table 9, and within each concentration stratum show a monotonic decrease in $(\psi/c \times t)$ with increasing exposure time, consistent with a dose-rate effect. Visual examination of the ψ–time curves likewise shows progressive flattening. In light of the [concentration] dose-response anomaly, data from this study would provide only limited ability to derive an exponent for a power law model.

Another study dealt with ocular and upper airway irritation from exposure to basic inorganic dusts, specifically calcium oxide, calcium sulfate, and sodium borate (Cain et al., 2004). Subjects exercised on a stationary bicycle while being exposed (head only) to varying concentrations of the compounds within a dome apparatus. During this protocol (which lasted 20 min), eye, nose, and throat irritation were rated periodically using the method of "intensity matching" (in which a second chemical irritant, carbon dioxide, was used as a reference standard). Representative data (for calcium oxide) are abstracted in Table 10, representing various combinations of c and t at preselected intensity ratings for nasal irritation (equivalent to 10% and 15% CO_2). These data are unique among those reviewed here, in that the $c \times t$ product is actually lower with lower exposure concentrations, rather than higher (corresponding to a power-law c exponent of <1 or a t exponent of >1). In this particular data set, then, time has a proportionally greater effect on sensory irritation than does concentration. The authors theorized that the mass transfer of solute into mucous membrane water, a process that is driven by both concentration gradient and kinetic constraints, is important in understanding the concentration and time dynamics in this system.

TABLE 10
Nasal irritation data: Calcium oxide exposure (Cain et al., 2004)

Concentration (ppm)	Duration (min)	$c \times t$ (ppm-min)	Sensory rating[a] (% CO_2 equiv.)	Sensory rating / $(c \times t)$
1	6.25	6.25	10	1.5
5	4	20	10	0.5
1	20	20	15	0.75
5	10	50	15	0.3

[a]Method of intensity matching.

TABLE 11
Summary of human sensory irritation studies relevant to Haber's Law

Compound	First author (year)	Structure	Subjective	Objective	Conclusions with regard to Haber's law[a]
Ammonia	Cometto-Muniz (1984)	Multiple c Multiple t	Nasal irritation	N/A	Consistent with Haber's law over 0–4 s.
Ammonia	Wise (2005)	Multiple c Multiple t	Nasal irritation	N/A	Consistent with power law ($c^n \times t = k$) over 0–4 s with empirically derived exponent "n" (1.30 for detection and 1.64 for intensity).
Chlorine	Joosting (1974)	Multiple c Multiple t	Eye, nose and throat irritation	N/A	Possibly consistent with power law with empirically derived exponent "n" over 0–2 h.
Chlorine	Anglen (1981)	Multiple c Multiple t	Eye, nose and throat irritation	N/A	Possibly consistent with power law with empirically derived exponent "n" over 0–2 h.
Formaldehyde	Cain (1986)	Multiple c Multiple t	Eye and nose irritation	N/A	Possibly consistent with power law with empirically derived exponent "n" over 0–30 min; dose-response anomaly observed for concentration.
1-Octene	Hempel-Jorgensen (1999)	Multiple c Multiple t	Eye irritation	N/A	Possibly consistent with power law with empirically derived exponent "n" over 0–30 min; dose-response anomaly observed for concentration.
Calcium oxide	Cain (2005)	Multiple c Multiple t	Nasal irritation	N/A	Time effect > concentration; possibly consistent with power law ($c^n \times t = k$) with empirically derived exponent "n" over 0–20 min.

[a] Validity over delimited time intervals, which varied among studies.

DISCUSSION AND CONCLUSIONS

After reviewing the controlled human exposure literature, we found a total of seven studies documenting sensory irritation in which both exposure concentration and time varied (Table 11). The agents employed in these studies included ammonia (2 studies), chlorine (2 studies), formaldehyde (1 study), 1-octene (1 study), and alkali dusts (1 study). Identified target sites included the nose (5 studies), eyes (4 studies), and throat (3 studies).

In addition to these reports, we found a number of studies that documented sensory irritation with either varying exposure levels or exposure/rating times. These studies could, at best, only provide ancillary data, since dose-response relationships for both time and concentration are necessary, but not sufficient, conditions for Haber's law to apply. The studies reviewed, with few exceptions, showed monotonic dose-response relationships for concentration, but time-response relationships showed either asymptotic (plateauing) or frank biphasic (drop-off) behavior.

Among the six studies in which both exposure parameters varied, only two were designed in such a manner that identical $c \times t$ products were achieved with different c and t parameters. In order to avoid limiting the analysis to these two studies, we therefore constructed an index consisting of sensory rating intensity (ψ) divided by the ($c \times t$) product, with the expectation that this index should stay relatively constant within a given experiment if Haber's law applied in its "pure" form (i.e., $c \times t = k$). Depending upon the structure and presentation of the data, we compared $\psi/(c \times t)$ preferentially in the following order: (1) for identical ($c \times t$) products; (2) for identical ψ values; and (3) for observations in which both ($c \times t$) and ψ differed.

Referring to this scheme, "type 1" comparisons (identical $c \times t$ products) were possible for only the two chlorine studies. In both studies, there was a systematic trend toward higher sensory ratings when a given ($c \times t$) product was achieved with a higher exposure concentration (i.e., showing evidence of a dose-rate effect: Anglen, 1981; Joosting & Verberk, 1975).

"Type 2" comparisons (identical ψ ratings) were possible for one of the ammonia studies, (Wise et al., 2005) and the inorganic dust study (Cain et al., 2004). Similar to the chlorine studies, the ammonia study showed a stronger concentration than time effect (in this case a lower ($c \times t$) product when a given ψ was achieved with a higher exposure concentration). However, within relatively short time parameters (<4 s.) this effect could be well modeled by raising the exposure concentration to the 1.64 power (for suprathreshold rating) or the 1.30 power (for detection). The inorganic dust study, on the other hand, showed the obverse finding of a higher ($c \times t$) product when a given ψ was achieved with a higher exposure concentration (i.e., a reverse dose-rate effect; Cain et al., 2004). This apparently anomalous finding may have had to do with the kinetics of solute deposition and dissolution in mucous membrane water, which in turn is highly time dependent.

"Type 3" comparisons (i.e., studies in which it was impossible to hold either [$c \times t$] or ψ constant) included one ammonia study (Cometto-Muniz & Cain, 1984), a formaldehyde study (Cain et al., 1986), and an eye irritation study involving 1-octene (Hempel-Jorgensen et al., 1999). For all three studies, the index $\psi/(c \times t)$ decreased with increasing exposure duration at a given exposure concentration, suggesting that concentration was a more potent determinant of response than was time.

In two studies, anomalies appeared in the concentration-response curve, further complicating the analysis (Cain et al., 1986; Hempel-Jorgensen et al., 1999). Nevertheless, in most cases c–t relationships could be modeled over relatively narrow time parameters using a more generalized power law model ($c^n \times t = k$) rather than Haber's law per se ($c \times t = k$).

Limitations of this review derive from the wide variety of study designs and psychophysical methods utilized, as well as our variable ability to abstract a sufficient number of data points to conduct goodness-of-fit analyses. At the extreme positive for usability, we were provided not only with data for equipotent psychophysical outcomes, but also with regression formulas for psychophysical power curves that translated directly into power law exponents (Wise et al., 2005).

Methodologically, several issues present themselves in evaluating the predictions of Haber's law (or more general power law models) for sensory irritation. For suprathreshold psychophysical measures, for example, the psychophysical index used should be unbounded; if not, the scale will saturate and time will inevitably lose its effect. Alternatively, one can assess "fixed endpoints," such as threshold measures. Empirically, three basic issues arise with respect to the role of time in sensory irritation: (1) the relative strength of effect of varying concentration and time on ψ (within the range of durations within which time alone has a measurable effect on ψ), (2) the extent to which there is time versus concentration trade-off within this range to achieve a given toxicologic effect (i.e., per the predictions of Haber's law), and (3) nonlinearities (and other anomalies) in the time effect.

With regard to (1) relative potency and (2) concentration–time trade-off, in all of the studies reviewed here, changing exposure concentration and duration had unequal effects on perceived stimulus magnitude. In all but one of the studies, changing concentration had a stronger effect than did changing exposure time. Although the widely varying methodologies employed in these studies precluded our performing a true meta-analysis, it appears that a more generalized power law model ($c^n \times t = k$), rather than Haber's law per se ($c \times t = k$), may fit a subset of the data from each study, but only for relatively narrow time windows.

With regard to nonlinearities in the time effect, the studies reviewed here all showed either a plateauing or a frank reversal of the time effect when observations were carried out sufficiently long. For ammonia, diminution of the time effect was apparent within the first 10 s of exposure. For chlorine, flattening of the time–intensity curve occurred within 10 min. of initial exposure (and might have been apparent sooner had finer time resolution been employed in the sensory rating procedure). For formaldehyde, sensory irritation ratings peaked by 90 min and began to drop off thereafter in both of the studies reviewed. Thus, even

concentration-weighted power-law models can only predict sensory irritation over limited periods, and prediction of the sensory impact of exposures lasting in the order of hours (or more) would require additional modeling tools that could predict sensory accommodation and/or other countervening processes (Rozman, 2000).

The implications for risk assessment vary by compound studied. The studies reviewed here for ammonia, chlorine, formaldehyde, and 1-octene all suggest that extrapolation of effects utilizing the formulation $c \times t = k$ ("Haber's law") may overestimate risk of sensory irritation (if extrapolating from short to long durations) or underestimate risk (if extrapolating from long to short durations). For calcium oxide-induced sensory irritation, the errors would likely be in the obverse direction. Utilization of more generalized power-law formulations, on the other hand, may circumvent some of these modeling pitfalls, although the data to test these models are currently sparse.

The past few decades have seen an increasing move toward physiologically based pharmacokinetic (PBPK) models in risk assessment, including for emergency planning purposes (Bruckner et al., 2004). In the context of the current discussion, factors to be accounted for in more pharmacokinetically based models would include toxicant deposition, activation, buffering/deactivation/clearance, and mechanisms of sensory transduction, central sensory integration/adaptation, and (potential) tissue disruption and repair. There is no reason to expect, for example, that the time kinetics of sensory irritation will be the same for an alkaline dust (requiring considerable time to dissolve in mucous membrane water and being subject to clearance by the mucociliary apparatus) as for a water-soluble gas or vapor (with rapid transfer and equilibration into airway lining fluid). Heuristically, the most detailed understanding of stimulus dynamics for a sensory irritant exists for a model agent: carbon dioxide. CO_2 produces mucous membrane irritation via its [enzyme-facilitated] dissolution in mucous membrane water and formation of carbonic acid/hydrogen ion. For this agent, investigators have studied not only empirical concentration-time tradeoffs, but also mucosal acidification and enzymology, as well as central electrophysiologic (EEG) responses to varying exposure concentrations and times (Frasnelli et al., 2003; Shusterman & Avila, 2003; Tarun et al., 2003; Wise et al., 2004). Based on this example, physiologic compartmentalization of sensory irritation appears practical, and may, in fact, be necessary to provide the basis for more sophisticated predictive models.

In future studies, the choice of psychophysical measures should be carefully considered. Although a fixed endpoint can be achieved using threshold measures, suprathreshold scaling may also be valid as long as either open-ended scales (e.g., method of magnitude estimation) or scales with true ratio properties (e.g., labeled magnitude scale) are utilized to minimize bias against finding "late" time effects. Use of study designs incorporating reciprocally varying (concentration–time) combinations would facilitate hypothesis-testing that equal products $c \times t$ (or $c^n \times t$) are toxicologically equivalent. Actual concentrations and times employed should, to the extent possible, span ranges of regulatory interest. The agents tested should have value not only as model irritants but also by virtue of their occupational and/or environmental relevance. If possible, investigators should consider combining both subjective (psychophysical) and objective (physiologic) measures of sensory irritation in order to obtain further insight into tissue reactions. In sum, broadening of models to take into account the full range of information available regarding the physical chemistry, dosimetry, and biological impact of specific airborne toxicants will likely produce more robust successors to Haber's law for the explanation of concentration–time relationships in sensory irritation.

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