
Odor-associated Health Complaints: Competing Explanatory Models

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Abstract

Physical symptoms may be reported in workplace and community settings in which odorous airborne chemicals are present. Despite the relative frequency of such reports, clinicians, public health authorities and sensory scientists often experience difficulty interpreting odor-associated symptoms. The approach to interpretation advocated in this review involves: (i) understanding the toxicology of the agent(s) involved (in particular their relative irritant and odorant potencies); (ii) assessing exposure parameters (i.e. concentration and duration). Depending upon exposure concentration, duration and relative irritant and odorant potencies, a variety of pathophysiological mechanisms may be invoked in explaining odor-associated health symptoms. Some of these imputed mechanisms fall under the traditional scope of toxicology and others involve attitudinal and/or behavioral responses to odors.

Introduction

Community residents, workers and patients not infrequently report physical symptoms in relationship to environmental odors. The question of cause and effect often follows. How can a physician, public health official or scientist evaluate such cases? This paper presents an analytical framework based upon the formal toxicological properties of the odorant(s) involved. The format for discussion will utilize three case studies in which an individual (or multiple individuals in a community) reported odor-associated physical symptoms.

In order to classify the following scenarios in a paradigmatic fashion some simplification was necessary. First, emphasis was placed on olfaction and sensory irritation, as opposed to potential toxicological effects (i.e. carcinogenesis, mutagenesis, teratogenesis or specific organ toxicity). Second, the term ‘threshold’ was employed in a simplified manner, disregarding specific methodologies and testing conditions. Finally (and related to the second point), the variable of exposure duration was disregarded when comparing odor and irritation thresholds.

The basic thesis of this discussion is that environmental odors may play either a central or ‘bystander’ role in the genesis of acute air pollution-related symptoms. The specific role depends, in large measure, upon the specific chemical agent(s) involved. For a few *potent* irritants the [population mean] irritation threshold may actually be lower than the odor [detection] threshold (i.e. irritation may precede olfaction on an ascending concentration scale; Figure 1a). This is a distinctly unusual situation, however, and for the

vast majority of industrial chemicals odor precedes irritation (Figure 1b).

Finally, for a subset of odorants (principally organic amines and reduced sulfur gases such as hydrogen sulfide and various mercaptans) irritation thresholds may be 3–5 orders of magnitude higher than odor thresholds, what would be considered by many a very wide ‘margin of safety’ (Figure 1c). Despite this wide margin, however, environmental exposures to biogenic amines and sulfur gases are frequently accompanied by complaints of symptoms, giving rise to questions regarding the role of odors *per se* in the genesis of health complaints. Because of the complexity of the subject the reader is referred to an earlier review of the various pathophysiological mechanisms which could be operative in the genesis of odor-related symptoms (Shusterman, 1992).

Three case studies follow in which the exposure agent (or agents) involved varies in its relative odorant and irritant potencies. In the course of the discussion the three dose–response models referred to above will be invoked as explanatory.

Case 1

Late in the evening of July 14, 1991 a tank car filled with 19 000 gallons of the pesticide Metam Sodium (sodium *n*-methylthiocarbamate) derailed and fell into the upper reaches of the Sacramento River near the town of Mt Shasta, CA. Because the compound is stable in concentrated solution the US Department of Transportation had not, at

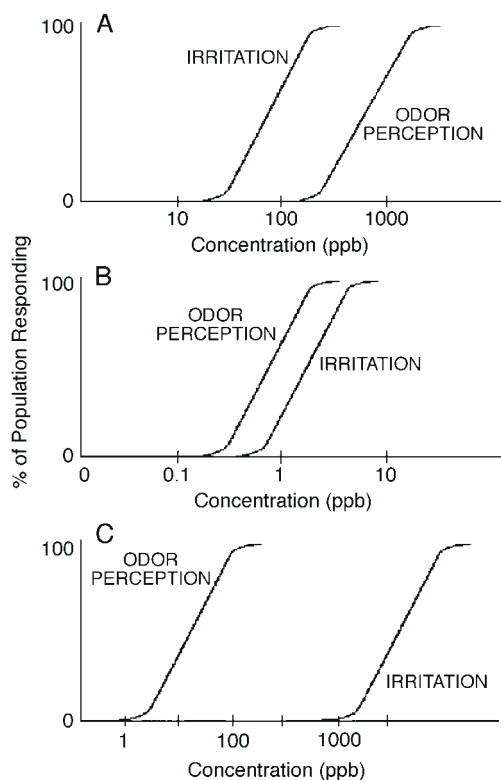


Figure 1 Cumulative population dose–response curve for olfactory and irritant effects: (a) of a potent irritant compound (for example MITC); (b) of an intermediate potency irritant compound (for example PH₃); (c) of weakly irritant/potent odorant compounds (e.g. H₂S and various mercaptans).

the time, required placarding as a hazardous substance nor use of a double-walled tank car to prevent spillage in the event of an accident. As the ruptured tank car released its contents into the river over the following hours the parent pesticide hydrolyzed into a mixture of hydrogen sulfide (H₂S) and methyl isothiocyanate (MITC, the sulfur analog of methyl isocyanate or MIC, the compound catastrophically released in Bhopal, India). MITC and MIC share the properties of being vesicants (potent mucous membrane irritants).

The Sacramento River courses southward through a canyon, portions of which are relatively densely inhabited. Soon after the spill public health officials were informed that many residents of the towns of Dunsmuir and Mt Shasta were complaining of unusual odors emanating from the river, as well as reporting various symptoms, including headaches, nausea, eye, nose and throat irritation, cough and wheezing. Three nearby emergency rooms (ERs) quickly filled with patients seeking treatment for spill-related complaints. A team of medical epidemiologists and toxicologists from the state government was dispatched to the area and local hospitals and physicians' offices were surveyed.

Over 240 spill-related visits were documented in a single hospital ER during the 2 weeks following the event and more than 700 symptomatic individuals (nearly one-third of

the local population) were eventually identified at hospitals, doctors' offices and the local evacuation center (Alexeeff *et al.*, 1994; Kreutzer *et al.*, 1996). The majority of cases involved minor complaints with minimal physical findings (e.g. reddened ocular conjunctivae). However, among 197 individuals complaining of persistent health effects following the spill, 10 were documented to have sub-acute or chronic exacerbations of pre-existing asthma and another 20 were found to have developed asthmatic conditions *de novo* (so-called 'irritant-induced asthma') (Cone *et al.*, 1994).

Public health officials were originally puzzled by the protracted period during which new symptoms were reported, until the local topography and meteorology were considered. It was discovered that the wind direction through the populated canyon reversed on a diurnal basis and that as the pesticide traveled some 40 miles downstream to Shasta Lake over a 3 day period it continued to hydrolyze and off-gas along the way. Community residents thus continued to be exposed during the night-time hours, even after the spill had passed their community.

After reviewing the toxicology literature and the available environmental monitoring data, public health officials concluded that the reports of a 'rotten egg' odor by local residents was largely a sentinel phenomenon related to the presence of H₂S as one of the two main Metam Sodium breakdown products. The agent thought responsible for the majority of the mucous membrane/irritant health complaints, on the other hand, was MITC. Airborne concentrations of the latter compound were documented beginning the third day after the spill, at which time measurements ranged as high as 37 p.p.b. Exposure concentrations for earlier periods were back-extrapolated using water concentration data and were estimated to have peaked in the 140–1600 p.p.b. range. (Alexeeff *et al.*, 1994). MITC is one of a small group of compounds whose threshold for mucous membrane irritation is actually lower than its odor threshold. Nesterova and Verschueren reported a human olfactory threshold for MITC of at least 700 p.p.b. and an animal irritant threshold (ocular irritation in cats) of one-tenth that concentration (i.e. 70 p.p.b.) (Nesterova, 1969; Verschueren, 1963). Among residents interviewed, the characteristic 'horseradish-like' odor of MITC appears to have been largely overshadowed by the accompanying smell of H₂S (author, unpublished data).

From a sensory science perspective the exposure was compound in nature, with a potent odorant/weak irritant (H₂S) heralding the presence of a potent irritant/weak odorant (MITC). Although symptoms were often experienced in the presence of perceived odors, the symptoms could not be said to be 'odor induced'. Graphically, the compound exposure is represented by a combination of Figure 1a,c.

The situation in which a potent odorant serves as warning of a more serious exposure (i.e. acts as a sentinel or

co-pollutant) is of more general relevance. One contemporary example may occur when rural and suburban dwellers are exposed to the complex airborne effluent emanating from animal confinement facilities (see the accompanying paper by R.W. Bottcher). Biogenic amines and sulfurous gases (potent odorants) often accompany ammonia (moderate potency irritant and odorant) as well as pro-inflammatory endotoxins in particulate form in such situations (Schiffman, 1998). In such cases there may be a need to combine toxicological and non-toxicological (odor-related) paradigms in order to explain the genesis of community symptom reports.

Case 2

A 43-year-old female electronics worker experienced a one-time overexposure to phosphine (PH_3) gas when a semiconductor processing machine malfunctioned. She experienced immediate eye, nose and throat irritation and cough and was transported to a nearby ER. There she was noted to be anxious and to have reddened ocular conjunctivae; her physical examination was otherwise unremarkable. She was evaluated with a chest radiograph, electrocardiogram, cardiac enzymes, complete blood count and arterial blood gases. Of the various laboratory tests the only abnormality was that of an acute respiratory alkalosis on blood gas analysis, consistent with acute hyperventilation. After overnight observation she was released from the hospital and she returned to the workplace within a few days.

Upon return to work the patient reported that transient exposures to the garlic-like odor of phosphine gas, which she tolerated prior to the overexposure, had begun to trigger new symptoms. Specifically, she complained of episodic shortness of breath ('air hunger'), dizziness and acrodigital paresthesias (tingling of the hands and around the mouth). She was evaluated by a pulmonologist, who noted minimal (non-reversible) obstructive changes on pulmonary function testing (she was a former smoker) and diagnosed 'persistent tracheobronchitis secondary to irritant exposure'. The pulmonologist prescribed an asthma medication (an inhaled β -adrenergic agonist), but the patient failed to improve, continuing to have episodic respiratory and central nervous system symptoms, as described above, when she smelled phosphine at work. Eventually she left her job and obtained employment as a counter person at a dry-cleaning establishment. Her symptoms then abated (Shusterman *et al.*, 1988).

The finding of episodic dyspnea (shortness of breath) in response to odorant exposures is not uncommon in the workplace and may occur via multiple mechanisms. Asthmatics frequently point to odors as a factor in asthma exacerbations (Stein and Ottenberg, 1958; Herbert *et al.*, 1967; Shim and Williams, 1986; Eriksson *et al.*, 1987; Kumar *et al.*, 1995). However, not all episodic dyspnea is due to

asthma. Other possibilities include: (i) vocal cord dysfunction (VCD); (ii) hyperventilation/panic attacks.

VCD is a condition in which the cords inappropriately adduct (come together) during inspiration, resulting in the sensations of dyspnea, hoarseness, globus (pressure sensation in the throat) and abnormal breath sounds (stridor, an inspiratory sound, or laryngeal 'wheezing', an expiratory sound). VCD is frequently mistaken for asthma, at times leading to inappropriate therapeutic interventions (Newman *et al.*, 1995). Of interest, a variant of this condition has recently been described in which the onset and/or triggering of symptoms is temporally related to an inhalation exposure ['irritant-associated VCD' (Perkner, 1998)]. The patient described above did not, however, report any symptoms referable to the larynx that would suggest this diagnosis.

The remaining possibility, after eliminating asthma and VCD, is that the patient was hyperventilating intermittently in response to odors. Favoring this explanation were the factors of air hunger, lightheadedness and paresthesias (which result from the acute acid-base changes of hyperventilation), as well as the lack of response to asthma medications. Although the patient reported some stimulus generalization within the workplace, she was subsequently unaffected by odors associated with the dry-cleaning process, indicating that any stimulus generalization was context sensitive. A further hypothesis is that this hyperventilation was related to the odor of phosphine by a process of respondent conditioning (Figure 2).

In this model a high [irritant] concentration of a gas (such as PH_3) serves as an unconditioned stimulus (US) for a fight-or-flight/panic response and a low [odorant] concentration serves as a conditioned stimulus (CS). Since the case in question was first published the author has seen numerous similar cases involving a wide variety of index exposures, with and without stimulus generalization. It should be emphasized that the index odor is generally well-tolerated without associated symptoms prior to the accidental overexposure. Agents involved in this type of reaction are typically described by Figure 1b, in which the irritation threshold is roughly 3- to 10-fold higher than the odor threshold. Unlike in most conditioning paradigms, the same agent, but at different concentrations, acts as both UCS and CS.

Experimental support for this model has recently been

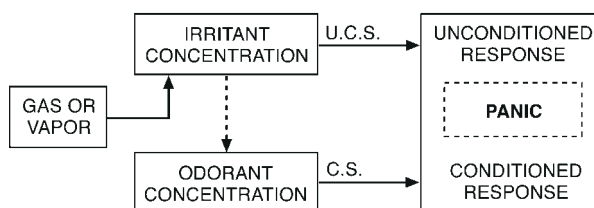


Figure 2 Respondent conditioning model for odor-triggered symptoms (UCS, unconditioned stimulus; CS, conditioned stimulus). (Shusterman and Dager, 1991) ©1991, Hanley & Belfus Inc.

generated in several conditioning experiments on human subjects. These utilized carbon dioxide at sub-irritation levels as a US for hyperventilation and various positive and negative valency odorants as the CS. (Inspired CO₂ in the 5–8% concentration range increases respiratory rate, via stimulation of the carotid chemoreceptor body, without producing mucous membrane irritation.) In general, both symptoms (dyspnea) and respiratory behavior (increased respiratory frequency) can be conditioned to an odorant exposure after a relatively small number of acquisition trials. Although pre-trial (unconditioned) odor responses appear to have little role in the above outcomes, negative valency odors are much more efficient CSs than positive valency odors. (Van den Bergh *et al.*, 1995, 1997, 1999).

Case 3

In the early to mid 1980s several communities in Southern California near industrial and/or hazardous waste sites became subjects of epidemiological studies by the California Department of Health Services. In each case community members complained of offensive odors; a common denominator, exposure-wise, was the presence of sulfur-containing petroleum products. Similar questionnaires were employed in each study. Attention was directed not only to 'unusual environmental odors', but also to a variety of somatic symptoms, as well as to the cognitive variable of 'environmental worry' (typical question: 'How worried are you about the quality of your neighborhood environment?').

Similar patterns of symptom reporting emerged from each study, with a positive relationship between frequency of perceived odors and onset (or worsening) of a number of symptoms (Satin *et al.*, 1983, 1986, 1987). Much variance remained unexplained, however, and a sub-study suggested that environmental worry predicted symptoms even in unexposed ('control') communities (Lipscomb, 1989). Consequently, a meta-analysis was conducted to examine the separate and combined effects of the exposure variable, *odor*, and the attitudinal variable, *environmental worry*.

Data from a total of 2040 adult respondents (restricted to one per household) were analyzed. Odds ratios (with confidence intervals) were generated for symptom prevalence rates comparing the upper and lower extremes of both odor perception frequency and environmental worry. For each of the four symptoms studied (headache, nausea and eye and throat irritation) both explanatory variables (odor and worry) produced odds ratios which were significantly elevated. Of at least equal interest, the two explanatory variables together predicted supra-additive increases in symptom prevalence rates (i.e. odor and worry appear to be synergistic determinants of symptom reporting). This finding gave rise to the explanatory model illustrated in Figure 3, in which odors may: (i) act as markers for toxicologically significant exposures; (ii) precipitate symptoms in their own right; (iii) serve as a cue for stress-related

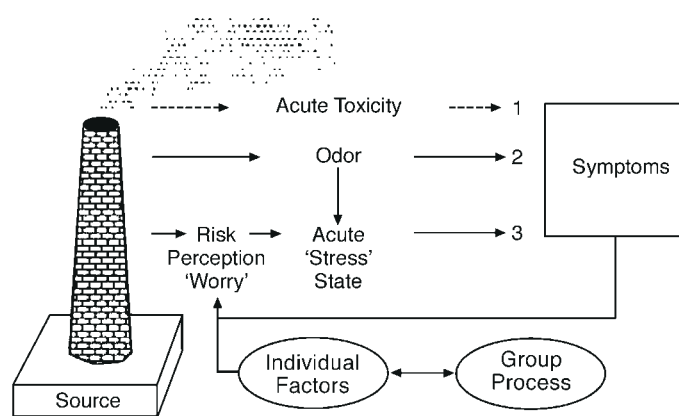


Figure 3 Potential mechanisms in the genesis of odor-related symptoms near industrial facilities (see text for further details) (Shusterman *et al.*, 1991).

symptoms among individuals who perceive the odor source as posing a toxicological risk (Shusterman *et al.*, 1991).

The possibility that cognition modulates the impact of olfactory stimuli has subsequently received experimental validation. Dalton showed that a primary perceptual measure, intensity (as well as time-related adaptation of the suprathreshold intensity rating), can be affected by a cognitive variable (specifically, risk-oriented information provided to subjects before controlled exposures) (Dalton, 1996). The same group showed that symptom reporting could also be affected experimentally by varying the toxicological characterization of an odor source in the instructions given prior to exposure (Dalton *et al.*, 1997).

Conclusion

The relationship between environmental, household and workplace odors, on the one hand, and somatic symptom reporting, on the other, is of more than passing interest to physicians, public health professionals and sensory scientists. An important first step in analyzing such situations is to catalog the chemical agent(s) involved and to consider its relative odorant and irritant/[other toxic] potencies. When potent odorants alone are involved in the exposure (or when the toxicology of co-pollutants is insufficient to explain observed symptoms) it may be necessary to invoke non-toxicological explanations for odor-related symptoms.

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