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Sensory irritation: Risk assessment approaches

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Abstract

Irritation of eyes and upper airways—sensory irritation—is commonly used as a parameter for setting occupational exposure limits and is a common complaint in occupants of non-industrial buildings. Sensory irritation occurs from stimulation of receptors on trigeminal nerves. In general, chemically reactive compounds are more potent than non-reactive congeners. Animal studies allow prediction of sensory irritation effects in humans; the concentration–effect relationships are often steep. In humans, thresholds and suprathreshold effects can be obtained from short-term (~seconds) exposures and from longer exposures (~hours). Sensory irritation may develop over time and odour cues may influence reported sensory irritation symptoms; generally, the slope of the irritant effect is steeper than the slope of odour cues. A best available no-observed-adverse-effect level (NOAEL) should be based on a combined estimate from the three types of study. The NOAEL/5 is considered sufficient to protect individuals not especially sensitive. The present knowledge suggests that especially sensitive individuals may be protected by an additional uncertainty factor (UF) of 2, suggesting a combined UF of 10. In published studies, the combined UF is up to 300, highlighting the need of evidence-based UFs. Combined effects of sensory irritants can be considered additive as a first approximation.

Keywords: Eye irritation; Nasal pungency; Sensory irritation; Mice; Mechanisms; Mixtures; Uncertainty factors; Risk assessment

1. Introduction

Perceived irritation in the nose (nasal pungency) and eyes is a critical effect of many airborne exposures and the endpoint is important in setting occupational exposure limits (OELs)[1] (Paustenbach and Gaffney, 2006; Smeets et al., 2006). For example, it was the critical effect in 40% of 141 OELs set from 1988–1998 in Sweden (Edling and Lundberg, 2000). Also, occupants in buildings commonly report upper airway and eye complaints. In a European study in 56 office buildings in nine countries, a questionnaire was used to evaluate symptoms "here and now" in 6537 occupants with an average responder fraction of 79% (Bluyssen et al., 1996). On average, 27% of the occupants deemed the indoor air quality as not acceptable. The top-five symptoms were dry skin (32%), stuffy nose (31%), lethargy (31%), irritated throat (29%) and dry eyes (26%). Tobacco smoke is, for example, a commonly encountered indoor irritant (Cain et al., 1987; Urch et al., 1991).

The reported eye and airway symptoms may be due to airborne compounds stimulating the sensory nerve endings of the trigeminal nerves (Alarie, 1973; Nielsen, 1991; Doty et al., 2004). However, odours may also increase reports of symptoms (cf. Wolkoff et al., 2006b). Thus, odour may serve as a sensory cue for a "stress-related illness" or it may heighten awareness of underlying symptoms, which

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[1] *Abbreviations:* ASIC, acid-sensing ionic channel; LFER, linear free energy relationship; LOAEL, lowest-observed-effect level; NOAEL, no-observed-adverse-effect level; NOEL, no-observed-effect level; OEL, occupational exposure limit; QSAR, quantitative structure–activity relationship; RD_{50}, the concentration depressing the respiratory rate by 50% due to stimulation of the trigeminal nociceptors; RD_0, the threshold (~NOAEL) for the decrease in respiratory rate due to stimulation of the trigeminal nociceptors; TLV, threshold limit value (OEL established by the American Conference of Governmental Industrial Hygienists); UF, uncertainty factor or extrapolation factor; VOC, volatile organic compound; VR1, vanilloid receptor 1, previously termed the "capsaicin receptor"—recently it has been named TRPV1 as it belongs to the "transient receptor potential family".

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may increase reports of, for example, headache, nausea, eye and throat irritation (Shusterman et al., 1991). Other mechanisms are hyperventilation or conditioned responses triggered by odours (Shusterman, 2002a). This indicates that different tools have to be used for evidence-based prevention of eye and upper airway symptoms reported from occupational as well as indoor environments.

This review focuses on sensory irritation, which is the unpleasant sensation from the eyes and upper airways due to stimulation of the trigeminal nerve endings by airborne exposures (Alarie, 1973; Nielsen, 1991; Doty et al., 2004). However, at a low degree of stimulation of sensory nerves a non-painful sensation may appear that is not considered unpleasant or adverse (Smeets et al., 2006), whereas at high stimulation unpleasant sensations appear, which include stinging, piquancy and burning sensations (Alarie, 1973; Nielsen, 1991; Doty et al., 2004).

2. Physiological mechanisms

Sensation of pain alerts us to injury and triggers protective responses (Julius and Basbaum, 2001). A pain sensation involves both transduction of noxious environmental stimuli as well as cognitive and emotional processing by the brain (Julius and Basbaum, 2001). Thus, sensory irritation is mediated by the general nociceptive system of the body (Nielsen, 1991; Julius and Basbaum, 2001). The "pain pathway" uses activation of two types of nerve fibres: fine unmyelinated C-fibres and small myelinated Aδ-fibres, which are often polymodal nociceptors (Julius and Basbaum, 2001; Doty et al., 2004; Belmonte et al., 2004) and thus may be stimulated by noxious heat, mechanical and chemical stimuli. However, some fibres may exclusively respond to noxious mechanical forces (Belmonte et al., 2004). The chemosensory system is referred to as "the common chemical sense" (Nielsen, 1991). Airborne chemicals activate the common chemical sense mainly via mucous membranes in the eyes and the airways, where the compounds have easy access to the sensory nerves (Nielsen, 1991).

C-fibres and Aδ-fibres, including those of the trigeminal nerves (Caterina et al., 1997; Taylor-Clark et al., 2005; Nakagawa and Hiura, 2006), contain the vanilloid receptor 1 (VR1) for capsaicin (Caterina et al., 1997; Julius and Basbaum, 2001; Taylor-Clark et al., 2005; Nakagawa and Hiura, 2006), which if activated causes a burning sensation (Caterina et al., 1997). The sensitivity of nociceptors may be up-regulated (Julius and Basbaum, 2001; Belmonte et al., 2004), i.e. lowering of the activation threshold. In this case, pain may be produced by innocuous stimuli (allodynia). Both the receptors for nerve growth factor and bradykinin can up-regulate the sensitivity of VR1 (Julius and Basbaum, 2001). Also, protons may activate VR1 as well as other H^+ sensitive (ASIC) ionic channel receptors (Julius and Basbaum, 2001). Sensory irritation by ethanol may be caused by activation of VR1 (Trevisani et al., 2002). Nociceptors contain receptors for ATP, and prostaglandins (Julius and Basbaum, 2001), as well as nicotinic acetylcholine receptors (Walker et al., 1996; Alimohammadi and Silver, 2000). Thus, the trigeminal nerves can be stimulated by nicotine and the response reduced by addition of a receptor antagonist. However, the receptor antagonist had no effect on the cyclohexanone-induced trigeminal stimulation (Alimohammadi and Silver, 2000), which suggests that the nicotinic receptor does not mediate the ketone response. Furthermore, the nasal trigeminal nerves contain histamine H_1 receptors activation of which evokes sneezing (e.g. Taylor-Clark et al., 2005).

Several findings support the hypothesis that sensory irritation due to volatile organic compounds (VOCs) is caused by a receptor-mediated process. Thus, small changes in molecular structure, which have little effect on partition coefficients or physical adsorption properties, may result in huge differences in the potency as sensory irritants (Alarie et al., 1998a; Nielsen, 1991). Also, sensory irritation effects of VOCs may show stereo-specific effects, e.g. for terpenes (Kasanen et al., 1998; Larsen et al., 2000; Nielsen et al., 2005). Additionally, it was possible to describe results from interaction experiments by use of dynamic constants derived from experiments with single compounds (Kane and Alarie, 1978; Nielsen et al., 1988; Cassee et al., 1996). Although different receptors exist for VOC-induced sensor irritation (Nielsen, 1991), the lipophilicity of the receptor compartment(s) is comparable for alkylbenzenes, alcohols, ketones and organic amines (cf. Nielsen et al., 1990; Hansen and Nielsen, 1994; Nielsen and Yamagiwa, 1989), and this provided a sound basis for the later established quantitative structure–activity relationships (QSARs) across different chemical groups of sensory irritants. QSARs have shown that the receptor or receptor phase is moderately dipolar, a quite strong hydrogen-bond base, and highly lipophilic (e.g. Abraham et al., 1990; Alarie et al., 2000).

Recently, an attempt has been made to study the size of the "receptor pocket" based on the cutoff point, i.e. the size of compounds in homologous series where the smaller molecules cause sensory irritation but larger molecules show no sensory irritating effect (Cain et al., 2006; Cometto-Muñiz et al., 2006). Whatever the reason for the cutoff point, the study addressed a relevant property for risk assessment.

For compounds with closely related structures, it appears that those, which react chemically with a receptor, are more irritating than congeners, which are only adsorbed physically to a receptor (Alarie et al., 1998a,b). This can be illustrated using the equipotent sensory irritation effects of formaldehyde and methanol. The concentration that depresses the respiratory rate by 50% (RD_{50}) in mice due to sensory irritation mediated by the trigeminal nerves is 3.2 and 41514 ppm, respectively, which indicates that formaldehyde is approximately 10,000 times more potent than methanol. This and similar examples are found in Nielsen (1991) together with a discussion of the binding mechanisms to the receptors. The potency of reactive compounds as sensory irritants has been analysed (Nielsen, 1991; Alarie et al., 1998a,b). For example, it has been