Environmental Toxicology and Pharmacology 45 (2016) 20–27

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/etap

Human exposure to acrolein: Time-dependence and individual variation in eye irritation

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ARTICLE INFO

Article history:
Received 14 December 2015
Received in revised form 10 May 2016
Accepted 12 May 2016
Available online 13 May 2016

Keywords:
Human exposure
Eye irritation
Sensory irritation detection threshold
Time dependence
Acrolein
TRPA1

ABSTRACT

The aim of the study was to examine the time dependence on sensory irritation detection following exposure to threshold levels of acrolein, in humans. The exposures occurred in an exposure chamber and the subjects were breathing fresh air through a mask that covered the nose and mouth. All participants participated in four exposure conditions, of which three consisted of a mixture of acrolein and heptane and one of only heptane. Exposure to acrolein at a concentration half of the TLV-C lead to sensory irritation. The perceived sensory irritation resulted in both increased detectability and sensory irritation after about 6.8 min of exposure in 58% of the participants. The study confirm the previously suggested LOAEL of about 0.34 mg/m^3 for eye irritation due to acrolein exposure. The sensory irritation was still significant 10 min after exposure. These results have implications for risk assessment and limit setting in occupational hygiene.

1. Introduction

The detection of chemicals in the environment is mediated by two separate, but interrelated, systems in humans: the olfactory and trigeminal systems. Stimulation of the olfactory system (cranial nerve I) results in sensations of smell, while stimulation of the trigeminal system (cranial nerve V) evokes reactions such as sneezing, watering of the eyes, irritation, and pain (Doty et al., 2004). For most chemicals, both nerves are activated, although at different concentrations. At low concentrations only odor is detected; as the concentration increases, sensory irritation is perceived. The difference between estimated sensory irritation thresholds and corresponding odor thresholds are generally orders of magnitude (Cometto-Muñiz et al., 2004). The chemicals identified in indoor air are usually present at concentrations below the sensory irritation threshold (as well as below occupational threshold limit values) (Brown, 1999; Korpi et al., 2009; Sunesson et al., 2006), but problems related to sensory irritation attributed to indoor air are nevertheless reported by about 4–7% of the population (Eriksson and Stenberg, 2006). There is convincing evidence demonstrating that if the ventilation rate increases, the number of reported symptoms decreases (Sundell et al., 2011). Volatile organic compounds (VOCs) can be ventilated, and despite the fact that they are typically present at low concentrations, they are a possible contributing factor to perceived sensory irritation in indoor air. Sensory irritation is therefore an important endpoint in the development of guidelines in both occupational and environmental toxicology.

The influence of time on sensory irritation is well documented and probably dependent on both the concentration and the compound. Perceived irritation has in some studies been found to increase during the first 20–40 min of exposure with no evidence of adaptation (Hempel-Jørgensen et al., 1999; Hudnell et al., 1992; Molhave et al., 1986). In other studies increased sensitivity were reported in the beginning of the exposure but then adaptation occurred after about 30 – 60 min (Cain et al., 1986; Ernstgård et al., 2006) or after repeated exposures during consecutive days (Dalton et al., 2006). However, in these studies, VOCs at relatively high concentrations with little relevance to actual indoor air exposure levels were used. Exposure studies using lower concentrations of VOCs did not report an effect of time (Cain et al., 2007; Claeson et al., 2009; Ernstgård et al., 2013). Temporal integration is often studied by brief exposures (up to 10 s) at concentrations above threshold and sensory irritation has been shown to be dependent on the total mass delivered to the site of action. According to Haber's rule (c x t = k) used in risk assessment, time and concentration is equally important to produce sensory irritation, but for longer durations, it has been demonstrated that concentration usually have a larger influence on sensory irritation than time (Shusterman et al., 2006).

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http://dx.doi.org/10.1016/j.etap.2016.05.011
1382-6689/

Studies investigating the effect of time on exposures at or below threshold levels are rare. Wise and colleagues investigated temporal integration at the threshold level for CO_2, NH_3, and ethanol (Wise, 2004; Wise et al., 2007, 2005). The same model of imperfect integration as identified for exposures above threshold could also be applied in subthreshold exposures, but the degree of integration could not be predicted (e.g., the slope). Certain reactive compounds, such as methylisothiocyanate (MITC), with known reactive properties towards specific receptors (e.g., TRPA1) show near perfect integration, where half of the concentration required the doubling of time (Cain et al., 2010).

Acrolein (2-propenal), another known TRPA1 agonist, is a highly reactive VOC present in cigarette smoke, smoke from fires, automobile exhaust, and smog. Emissions from certain building materials also contain acrolein. The compound is found in both outdoor and indoor air, but it is present at higher concentrations indoors (Seaman et al., 2009). Indoor air concentration ranges from <0.05–29 $\mu g/m^3$, although in restaurant kitchens and bakeries, higher levels have been measured (0.02–0.6 mg/m^3) (Faroon et al., 2008). Acrolein has an acrid, pungent odor, with sensory irritating effects on the mucous membranes, especially in the eyes (Beauchamp et al., 1985). It has been shown to exacerbate asthma in children and it is also suspected to contribute to other chronic airway diseases (Bein and Leikauf, 2011; Woodruff et al., 2007). Acrolein causes sensory irritation by reacting with the TRPA1 channel, a channel known to be activated by a wide variety of environmental irritants that share a special electrophilic group (Bautista et al., 2006). The reactive group forms reversible covalent bonds with cysteine residues and, therefore, activation is expected to be time dependent, as more energy is required to break the bond than to make it. Sensory irritation through such covalent bonds seems to be a unique feature of the TRPA1 channel, and this modification can lead to irritation at low levels of exposure, and possibly to time-dependent amplification of sensory irritation (Bessac and Jordt, 2008). The reaction is also likely to be highly dependent on the chemical environment surrounding the channel. Moreover, most TRPA1 agonists react with cellular and extracellular glutathione, a compound that acts to remove potentially harmful substances from the body. The concentration of glutathione is therefore crucial, since when all available glutathione is depleted, sensory irritation will likely increase, leading to a cumulative effect of the environmental irritant reacting with the TRPA1 channel (Bessac and Jordt, 2008; Ganea and Harding, 2006; Hinman et al., 2006; Macpherson et al., 2007). Knowledge about the reactivity towards such special receptors makes it plausible that acrolein and other compounds containing the same functional group (α,β-unsaturated aldehydes) would react differently when compared to other compounds (Cain et al., 2010). Therefore methods, such as continuous exposure in an exposure chamber, which takes time-dependence into account should be used when investigating sensory irritation detection thresholds to compounds like acrolein.

In addition to exposure level and duration, the intensity of the reported sensory irritation is dependent on a number of non-sensory factors (Brüning et al., 2014), such as earlier experiences and/or negative information about a compound (Andersson et al., 2013; Dalton, 1996). Self-reported stress and negative affect have been proposed to exacerbate the reports of sensory irritation from some exposures but not from others (Andersson et al., 2013; Dalton and Jaén, 2010; Mueller et al., 2013; Smeets and Dalton, 2005). Women generally report more sensory irritation than do men (Cometto-Muniz and Noriega, 1985; Olofsson and Nordin, 2004; Shusterman et al., 2003); however, the difference might not be that women are more sensitive per se (Hummel et al., 2003; Mattes and DiMeglio, 2001). Rather, women, compared to men, perceive weak concentrations as more irritating and seem to use different strategies when detecting possible health hazards (higher false-alarm rate) (Claeson and Nordin, 2011). Inter-individual differences in sensory irritation thresholds have been reported in earlier studies and are concluded to originate mainly from input from the olfactory system (Dalton et al., 2000; van Thriel et al., 2008) or from methodological differences between studies (Cain and Schmidt, 2009)

The main objective of this study was to examine the time dependence of sensory irritation detection following exposure to threshold levels of the TRPA1 agonist, acrolein, in humans. The focus of the study was on the detection of sensory irritation, and not to evoke health symptoms; therefore, only the eye – which is considered to be most sensitive towards acrolein – was investigated (Beauchamp et al., 1985; Gomes et al., 2001). The eye-only exposures were also performed to avoid any bias from olfaction. Concentrations at or below previously reported sensory irritation thresholds that were initially too low to evoke sensory irritation in the eye, but that might do so in exposures of up to 60 min, were used. Detection of sensory irritation was measured with confidence ratings which in earlier studies have shown to correlate well with actual detection (Cain et al., 2007). Data on perceived intensity was also collected using magnitude estimation during exposure. Objective measurements of eye irritation, such as blink frequency and self-reported tear-film break-up time (BUT[s]), were also used. The second objective was to study inter-individual differences in sensory irritation detection and perceived intensity during exposure to acrolein.

2. Material and methods

2.1. Subjects

Twenty-six non-smoking individuals (18 women and 8 men) were recruited by an advertisement in the local newspaper and through billboard advertisement. All participants considered themselves to be healthy and are further described in Table 1. Smoking and pregnancy constituted the exclusion criteria. Subjects normally wearing contact lenses (n = 2) were asked not to wear them during the exposures. The subjects also filled out the Chemical Sensitivity Scale (CSS) (Nordin, 2003) and the Perceived Stress Questionnaire (PSQ) (Levenstein et al., 1993). The CSS is a questionnaire that is used to assess the affective reactions and behavioral disruptions resulting from odorous/pungent substances, and the PSQ quantifies the extent to which individuals subjectively perceived stress during the previous 4 weeks. The study was conducted in accordance with the Declaration of Helsinki, and the subjects provided their informed consent. The protocol was approved by the Ethics Committee of Umeå University (Dnr: 2012-112–31 M).

2.2. Exposure chamber

Exposure occurred in an exposure chamber ($1.5 \times 0.9 \times 2.0$ m). The mean temperature during exposure was $21\,^{\circ}C \pm 1\,^{\circ}C$ and the mean relative humidity (RH) was $18\% \pm 3\%$, which was slightly higher than the outside RH at the time of exposure. There were no significant differences in either RH ($P = 0.68$) or temperature ($P = 0.24$) between the exposures. Carbon-filtered air entered the chamber through an inlet at floor level and exited in the ceiling; the air exchange rate was set to 7.5 times/hour (approximately 330 L/minute). A metered amount of stimulus material was continuously pumped (by a syringe pump) through a nebulizer (OneNeb, Agilent Technologies). The aerosol from the nebulizer was mixed with air (4 L/minute) in an evaporation chamber with a volume of ~1 L. The air mixture was then further diluted and transported to the exposure chamber. In order to perform eye-only exposure, the subjects used a fresh air mask covering the nose and mouth.