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Environmental Toxicology and Pharmacology 19 (2005) 531–541
ENVIRONMENTAL TOXICOLOGY AND PHARMACOLOGY
ETAP
www.elsevier.com/locate/etap

Eye blinks as indicator for sensory irritation during constant and peak exposures to 2-ethylhexanol

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Abstract

Two experiments were performed to re-evaluate the sensory irritating properties of 2-ethylhexanol in relation to dose and time and to examine the usability of electromyographic eye blink recordings as indicator of sensory irritation. Mean exposure levels of 1.5, 10 and 20 ppm were realized in experimental models simulating either constant or variable 4 h exposure. Each study was carried out with two subject samples, healthy young men with self-reported multiple chemical sensitivity (sMCS) and age matched controls. Although 2-ethylhexanol exposure was below the occupational threshold limit value of 50 ppm, the study revealed strong dose–response relationships between airborne solvent concentrations and blink rates. During 40 ppm peak exposures the blink rate increased threefold. In the course of 4 h, exposure blink rates increased significantly showing no adaptation. Subjects with sMCS revealed, with one exception at start of exposure, no significantly higher blink rates than controls. The results indicate that the irritative potential of 2-ethylhexanol is higher than commonly expected. In both exposure scenarios with either constant or peak exposures, electromyographic eye blink recordings were an appropriate method for the examination of acute sensory irritations in time.
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Keywords: Sensory irritation; Eye blinks; 2-Ethylhexanol; Occupational exposure limit; Short-term exposure limit; Adaptation

1. Introduction

1.1. Validity of sensory irritation models for occupational settings, study aims

Organic solvents are poorly characterized with respect to their irritative properties in relation to time and pattern of acute exposures in occupational settings (e.g. Meldrum et al., 2001). It is a well known phenomenon that workers report irritative symptoms at airborne solvent concentrations which are estimated by occupational safety experts as sub-irritant. Workers might misdiagnose their individual irritative sensations biased by odors and cognitive factors (Dalton et al., 1997b; Dalton, 2001). However, the more serious problem might be that health care personal and experts misdiagnose the responses of workers because they refer to inadequate models of sensory irritation.

There are critical problems related to reliability, validity and relevance of reported irritation data in the literature.

Reliability: The irritation thresholds reported in the literature for specific solvents vary considerably in the range of one or two orders of magnitude, depending on provocation methods, threshold criteria, and subject samples (Arts et al., 2002; Harreveld et al., 1999; Ruth, 1986).

Validity: Some important irritation models are based on systematic investigations of several solvents and allow to deduce information of the relative irritation potential of specific solvents. However, although the validity of these models is limited they seem to be strained very much for the extrapolation of occupational limit values (e.g. Dalton, 2001; Feron et al., 2001; Meldrum, 2001; Paustenbach, 2001). One model focuses on the lateralization technique (Cometto-Muniz and Cain, 1998). This psychophysical approach uses short sniffs of gases and is based on the phenomenon that irritative stim-

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doi:10.1016/j.etap.2004.12.056

uli, in contrast to olfactory stimuli can be localized concerning the side of the stimulated nostril. The lateralization is a very high sensory criterion. Less differentiated sensations are presumably possible at lower concentrations and continuous whole shift exposures may reduce the irritation level additionally (e.g. Hempel-Jørgensen et al., 1999). A second model is based on signs of eye irritation in rabbits which are scored according to a scheme of Draize after instillation of chemicals into the conjunctival sac. As a result of several investigations a list of chemicals is available ranked on the basis of irritation scores (Bagley et al., 1999) showing compatibility with eye irritation thresholds in humans (Abraham et al., 2003). A further animal model uses the dose-related decrease of breathing frequency in rats (Alarie, 1973). RD_{50} is the concentration that causes a 50% decrease of respiratory rate. This concentration multiplied with .03 is used as estimate of airway irritation threshold (Schaper, 1993).

Several extrapolation issues must be addressed before any model can be used to determine critical concentrations under working conditions. Areas of uncertainty are species differences, differences in organs (throat, nose, eye) and mechanisms (e.g. different receptors, immune defense, inflammation processes), and differences in temporal aspects (duration of exposure). It can be argued that these models are presumably not valid to judge irritative sensations in ‘real life’ conditions with respect to time and pattern of exposure. Consequently, the critical and weak point of several occupational threshold limit settings for potential irritative solvents is that they were derived from animal models or studies of humans with artificial short or constant exposures (Feron et al., 2001; Meldrum, 2001). The reduction of sensory irritation on a threshold phenomenon is a very simple modelling. Relevant models simulating different exposure patterns and investigating the development of irritations in time are missing.

The objective of the present study was to test a model valid for the evaluation of irritation processes in ‘real life’-working conditions. It was started from the issue that the assessment of irritative health risks should ideally be based on an objective measures. Subordinated to this major aspect, the present study had the following aims: (1) to test the usability of an electro-physiological method as indicator of irritation processes, (2) to study irritation processes over time, (3) to study individual sensitivity, and (4) to re-evaluate the irritative potential of a relevant organic solvent.

1.2. Eye blinks as endpoints for studying the temporal course of sensory irritation (mechanisms)

As the present study aimed at portraying the temporal course of sensory irritation in varying exposure scenarios it was decided to study continuous eye blink recordings. Several endpoints were used and discussed as objective markers of irritations in human studies: breathing rate (Haumann et al., 2002, 2003; Walker et al., 2001), videotape eye blink recordings (Emmen et al., 2003; Nihlen et al., 1998; Walker et al., 2001), pressure and volume changes in the nasal passages (Wiesmüller et al., 2002), eye redness, tear film stability, conjunctival epithel damage (Emmen et al., 2003), cells and mediators of inflammatory changes in nasal and conjunctival fluid (Klimek et al., 2002; Norbäck and Wieslander, 2002; Kjaergaard et al., 1989, 1991; Koren et al., 1992; Muttray et al., 2002; Podlekareva et al., 2002; van Thriel et al., 2003). These endpoints represent different models of irritative responses indicating different states and functions and cannot replace one another. Some of these methods are invasive, suffer from significant methodological difficulties referred to standardization of sampling procedure, and can only be used in pre-post designs (e.g. Hempel-Jørgensen et al., 1998; Koren et al., 1992; Nihlen et al., 1998; Podlekareva et al., 2002; van Thriel et al., 2003; Wiesmüller et al., 2002) giving only few insights in temporal courses of irritation.

Eye blinks are a readily observable behavioural phenomenon suitable for continuous measurements. Three mechanisms might be of relevance in connection with responses of eye blinks to airborne irritants. First, the cornea contains trigeminal sensory fibres, polymodal nociceptors, responding to exogenous chemical irritants with nerve impulses that persist as long as the stimulus is maintained. The firing frequency is roughly proportional to the intensity of the stimulating force. Polymodal nociceptors possibly contribute to the pain that arises when the cornea is acutely exposed to chemical irritants (Belmonte et al., 2004). Second, eye blinks serve the necessary lubrication of the exposed eyeball. Dry eyes and irritations are often accompanied by an increasing blink rate in response to desiccation of the ocular surface (Tsubota et al., 1996). In theory, airborne substances might influence the surface tension of the tear film and increase the evaporation from the surface of the eye. The increased vaporization implies increased blinking frequency and irritation in the eyes. Third, inflammatory responses may accompany sensory irritations, indicated by the increase of specific cells and mediator substances in the tear fluid. However, in accordance with a biological model of inflammatory responses, the latter changes may occur with a delay of some hours after stimulation by an irritant (Kjaergaard et al., 1989; Koren et al., 1992; Podlekareva et al., 2002).

Studies on the dose–response relationship between irritative exposures and eye blinks have to consider potential confounding factors. Eye blinks may be influenced by attention and arousal processes (Stern et al., 1984), visual processes (Jaschinski et al., 1996), and climatic conditions.

1.3. Temporal trends of irritative responses

The understanding of time course effects is the precondition to interpret complaints in solvent polluted work environments. During continuous exposure different forms of responses are possible even in the simplest case when exposure is constant. Besides a constant response also response enhancement or response decrease are conceivable. It is well established that olfactory responses to smells show

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