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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

shown that organic amines activate a sensory irritant receptor by an acid base reaction (Nielsen and Yamagiwa, 1989), and this is also inferred to apply for ammonia used in the examples below.

3. Concentration–response relationships in animal studies and prediction of effect in humans

3.1. Extrapolation from animals to humans

Both behavioural (e.g. Wood, 1979) and electrophysiological methods (Silver, 1990) have been used in the study of sensory irritation in animals. However, in relation to estimation of air quality standards or guidelines for exposures of humans, most studies have been conducted with the "Alarie test". This mouse bioassay takes into account that sensory irritants decrease the respiratory rate in a concentration-dependent manner due to a trigeminal reflex (Alarie, 1973). In general, sensory irritant exposures in mice cause a rapid onset of the irritation response that may be followed by a sustained response during the remaining exposure period (Nielsen, 1991) or it may decrease, i.e. showing desensitization (e.g. Kristiansen et al., 1988). Also, a response may continue to increase during the entire exposure period (e.g. Sangha and Alarie, 1979). The maximum decrease in the respiratory rate due to the trigeminal effect is used in concentration–response relationships. A comprehensive list of experimentally determined RD_{50} values has been published; the values were correlated with OELs and the relationship $OEL \sim 0.03 \times RD_{50}$ was established (Schaper, 1993). This relationship was further substantiated (Alarie et al., 2000). Furthermore, a recent study compared RD_{50} values with Polish OELs, established from 1994–2004, for 17 sensory irritants. A mean OEL/RD_{50} of 0.03 was ascertained, with OEL/RD_{50} ratios ranging from 0.01–0.09 (Kupczewska-Dobecka et al., 2006). Published RD_{50} values since Schapers' review are compiled in Table 1.

Since the slopes of the concentration–response relationships for sensory irritants are within a narrow range (Alarie, 1981), as a first approximation, the relationship has been broken down into $RD_0 \sim 0.15 \times RD_{50}$ and $OEL \sim 0.2 \times RD_0$, where the RD_0 is the threshold (~no-observed-effect level; NOEL) extrapolated from the log concentration–response relationship (Nielsen, 1991). The extrapolation factor 6.7 (1/0.15) from RD_{50} to RD_0 corresponds to a steep concentration–response relationship, as the RD_{50} level is considered extremely irritating in humans (Alarie, 1981). The RD_0 is based on a protective reflex and, thus, an uncertainty factor (UF/"safety factor"/extrapolation factor) has to be applied if RD_0 is used to estimate a no-observed-adverse-effect level (NOAEL) in humans. The derived UF is 5 (1/0.2) in the present case.

We will use ammonia for illustrating the evaluation processes, which includes integration of animal and human data. Ammonia is mainly retained in the upper airways and the critical effect is sensory irritation, as has been recently reviewed (Liesivuori, 2005). The threshold limit value (TLV) is 25 ppm (ACGIHs, 2001) and the RD_{50} is 303 ppm (Barrow et al., 1978). The estimated OEL ($0.03 \times RD_{50}$) is 9 ppm and the RD_0 42 ppm, calculated from the concentration–response relationship reported by Alarie (1981). Estimates are compared with sensory irritation effects in humans (Table 2).

3.2. Performance and interpretation of animal studies

The Alarie test has been standardized (ASTM, 1984). The standardized test distinguishes sensory irritation from effects occurring below the upper airways. However, computerization of the ASTM method (Alarie, 1998, 2000; Larsen et al., 2004) allows simultaneous determination of sensory irritation, bronchoconstriction, and reflex effects from the alveolar level. If it is possible, computer-based methods are preferred, as they are more sensitive (Alarie, 1998, 2000; Vijayaraghavan et al., 1994) and furnish more information on the different types of airway effect. Also, exposures can be followed by bronchoalveolar lavage, which adds information on airway inflammation (Larsen et al., 2004). Detailed guidelines for evaluation of the tests are available (ASTM, 1984; Alarie, 2000; Alarie et al., 2000).

Male Swiss–Webster mice were recommended to be used in the ASTM test. In a study of nine different types of mice, the RD_{50} for sulphur dioxide deviated by a factor of 10 between the most and least sensitive type of mice (Alarie et al., 1980). Additionally, differences between sexes deviated by up to a factor of 3, but in most cases much less. Swiss-Webster mice had a sensitivity, which was approximately in the middle of the range and they showed little difference between the sexes. Other stocks and strains may have a similar sensitivity, e.g. the case for CF1, OF1, B6C3F1 and BALB/c mice (e.g. Alarie et al., 1980; Schaper, 1993; Nielsen et al., 1999). As results in Swiss–Webster mice are considered the standard, they should be used where possible. If other types of mice are used, it should be demonstrated that they have the same sensitivity as Swiss-Webster mice and if this is not possible, the test results obtained in such mice should only be interpreted qualitatively.

4. Concentration–response relationships in human studies

Sensory irritation of eyes and upper airways has been studied using different methods, including electrophysiological effects from the trigeminal nerve or evoked brain potentials, reflex-induced decrease of breathing, and by means of psychophysical methods (cf. Doty et al., 2004). Depolarisation of the trigeminal nerves due to receptor-activation results in a "negative mucosal potential", which is closely related to effects determined in psychophysical tests (Cain et al., 2006). The concentration–response relationship has a steep slope both seen from the psychometric function and the negative mucosal potential. Major

Table 1
RD_{50} values in mice published since the review of Schaper (1993) and until 2006

Chemical name	CAS number	Type of mouse	RD_{50} (ppm)	References
Acetic acid	64-19-7	♂ Ssc: CF-1	308	Nielsen et al. (1996b)
		♂ OF1	227	Gagnaire et al. (2002)
		♂and ♀ C57Bl/6J	239	Morris et al. (2003)
Acrolein	107-02-8	♂and ♀ C57Bl/6J	1.6	Morris et al. (2003)
Allylamine	107-11-9	♂ OF1	9	Gagnaire et al. (1993)
Butyric acid	107-92-6	♂ Ssc: CF-1	285	Nielsen et al. (1996b)
Benzyl bromide	100-39-0	♂ Swiss-Webster	5.2	Dudek et al. (1992)
Benzyl chloride	100-44-7	♂ Swiss-Webster	27	Dudek et al. (1992)
Benzyl iodide	620-05-3	♂ Swiss-Webster	4.3	Dudek et al. (1992)
n-Butyl acetate	123-86-4	♂ BALB/c	1755	Korsak and Rydzynski (1994)
n-Butyl alcohol	71-36-3	♂ BALB/c	3010	Korsak et al. (1993)
		♂ BALB/c	4300	Korsak and Rydzynski (1994)
n-Butylamine	109-73-9	♂ OF1	84	Gagnaire et al. (1993)
d-Δ^3-Carene	13466-78-9	♂ Ico:OF1	1345	Kasanen et al. (1999)
Chlorine	7782-50-5	♂ OF1	3.5	Gagnaire et al. (1994)
		♀C57Bl/6J	2.3	Morris et al. (2005)
o-Chlorobenzyl chloride	611-19-8	♂ Swiss-Webster	4.9	Dudek et al. (1992)
m-Chlorobenzyl chloride	620-20-2	♂ Swiss-Webster	13	Dudek et al. (1992)
p-Chlorobenzyl chloride	104-83-6	♂ Swiss-Webster	14	Dudek et al. (1992)
Cyclohexylamine	108-91-8	♂ OF1	51	Gagnaire et al. (1993)
Diallylamine	124-02-7	♂ OF1	4	Gagnaire et al. (1993)
α,α-Dichlorotoluene	98-87-3	♂ Swiss-Webster	27	Dudek et al. (1992)
Di-*n*-butylamine	111-92-2	♂ OF1	173	Gagnaire et al. (1993)
Diisobutylamine	110-93-3	♂ OF1	300	Gagnaire et al. (1993)
Diisopropylamine	108-18-9	♂ OF1	161	Gagnaire et al. (1993)
Di-*n*-propylamine	142-84-7	♂ OF1	92	Gagnaire et al. (1993)
Ethyl-2-cyanoacrylate	7085-85-0	♂ OF1	0.7	Gagnaire et al. (2003)
4-Ethyltoluene	622-96-8	♂ BALB/c	884	Korsak et al. (1999)
		♂ BALB/c	858	Swiercz et al. (2000)
Farbasol[a]	–	♂ BALB/c	639	Korsak et al. (1999)
Formaldehyde	50-0-0	♂ BALB/cA	4	Nielsen et al. (1999)
Formic acid	64-18-06	♂ Ssc: CF-1	438	Nielsen et al. (1996b)
Glutaraldehyde	111-30-8	♂ Swiss OF1	2.6	Zissu et al. (1994)
		♂ ND4 Swiss Webster	13.9	Werley et al. (1995)
n-Heptylamine	111-68-2	♂ OF1	25	Gagnaire et al. (1993)
Hexafluoroisopropanol	920-66-1	♂ Ssc: CF1	165	Nielsen et al. (1996a)
n-Hexylamine	111-26-2	♂ OF1	42	Gagnaire et al. (1993)
Hydrogen peroxide	7722-84-1	♂ OF1	113	Gagnaire et al. (2002)
Isobutylamine	78-81-9	♂ OF1	91	Gagnaire et al. (1993)
Isopropylamine	75-31-0	♂ OF1	157	Gagnaire et al. (1993)
Isopropyl-2-cyanoacrylate	10586-17-1	♂ OF1	0.6	Gagnaire et al. (2003)
R-(+)-Limonene	5989-27-5	♂ BALB/cA	1076	Larsen et al. (2000)
S-(−)-Limonene	5989-54-8	♂ BALB/cA	1467	Larsen et al. (2000)
Methacrolein	78-85-3	♂ BALB/cA	10.4	Larsen and Nielsen (2000)
2-Methoxyethyl-2-cyanoacrylate	27816-23-5	♂ OF1	1.0	Gagnaire et al. (2003)
Methyl *tert*-butyl ether	1634-04-4	♂ Swiss-Webster	4604	Tepper et al. (1994)
Methyl-2-cyanoacrylate	137-05-3	♂ OF1	1.4	Gagnaire et al. (2003)
Methyl hexafluoroisopropyl ether	27215-56-1	♂ Ssc: CF1	$\geqslant$160000[b]	Nielsen et al. (1996a)
1-Methylnaphthalene	90-12-0	♂ BALB/c	22	Korsak et al. (1998a)
2-Methylnaphthalene	91-57-6	♂ BALB/c	11.5	Korsak et al. (1998a)
Nitrogen trichloride	10025-85-1	♂ OF1	2.5	Gagnaire et al. (1994)
3-Octanol	589-98-0	♂ Ico: OF1	256	Korpi et al. (1999)
3-Octanon	106-68-3	♂ Ico: OF1	3360	Korpi et al. (1999)
1-Octen-3-ol	3391-86-4	♂ Ico: OF1	35	Korpi et al. (1999)
n-Octylamine	111-86-4	♂ OF1	17	Gagnaire et al. (1993)
tert-Octylamine	107-45-9	♂ OF1	80	Gagnaire et al. (1993)
n-Pentylamine	110-58-7	♂ OF1	64	Gagnaire et al. (1993)
Peroxyacetic acid	79-21-0	♂ OF1	5.4	Gagnaire et al. (2002)
n-Propylamine	107-10-8	♂ OF1	115	Gagnaire et al. (1993)
(+)-α-Pinene	7785-70-8	♂ OF1	1053	Kasanen et al. (1998)
		♂ NIH/S	1107	Kasanen et al. (1998)
		♂ BALB/cA	2125	Nielsen et al. (2005)

(*continued on next page*)

Table 1 (*continued*)

Chemical name	CAS number	Type of mouse	RD_{50} (ppm)	References
(−)-α-Pinene	7785-26-4	♂ OF1	n.o[c]	Kasanen et al. (1998)
		♂ NIH/S	n.o.	Kasanen et al. (1998)
		♂ BALB/cA	6302[d]	Nielsen et al. (2005)
(+)-ß-Pinene	19902-08-0	♂ OF1	1279	Kasanen et al. (1998)
		♂ NIH/S	1419	Kasanen et al. (1998)
(−)-ß-Pinene	18172-67-3	♂ OF1	4663[d]	Kasanen et al. (1998)
		♂ NIH/S	5881[d]	Kasanen et al. (1998)
Propionic acid	79-09-4	♂ Ssc: CF-1	386	Nielsen et al. (1996b)
1,2,4,5-Tetramethylbenzene, durene	95-93-2	♂ BALB/c	153	Korsak et al. (1998b)
1,1′-Thiobis (2-chloroethane), sulphur mustard	505-60-2	♀ Swiss	4.2	Vijayaraghavan (1997)
Toluene	108-88-3	♂ Swiss-Webster	4900	Dudek et al. (1992)
2,4,6-Trichlorotriazine, cyanuric chloride	108-77-0	♂ BALB/c	0.78	Rydzynski and Jedrychowski (1994)
Trifluoroethanol	75-89-8	♂ Ssc: CF1	11400	Nielsen et al. (1996a)
1,2,3-Trimethylbenzene, hemimellitene	562-73-8	♂ BALB/c	541	Korsak et al. (1997)
1,2,4-Trimethylbenzene, pseudocumene	95-63-6	♂ BALB/c	578	Korsak et al. (1997)
1,3,5-Trimethylbenzene, mesitylene	108-67-8	♂ BALB/c	519	Korsak et al. (1997)
Oulu A1 turpentine	–	♂ Ico:OF1	1173	Kasanen et al. (1999)
m-Xylene	108-38-3	♂ BALB/c	1360	Korsak et al. (1993)

[a] A commercial solvent, mainly composed of isomers of trimethylbenzenes (44%), ethyltoluenes (41%), *n*-propylbenzene (7.6%), and cumene (1.4%).
[b] Estimated value based on the approximated RD_0 value.
[c] Abbreviations: not obtainable (n.o.).
[d] Obtained by extrapolation above the saturated vapour pressure.

differences in slopes were not seen across compounds, provided the size of a molecule is not approaching the size close to the cut-off point (Cain et al., 2006). Over a range of hardly more than one order of magnitude of concentration, sensory irritation may increase from barely detectable to painful irritation (Cain et al., 2006).

Experimental studies of indoor and occupational-relevant VOCs as well as field studies have mainly been carried

Table 2
Sensory (eye and upper airway) irritation effects of ammonia

Type of effect	Ammonia exposures (ppm)	Effect–concentration (ppm)	Comment	Reference
Sensory irritation in mice	Ca. 100–1000		The RD_0 was estimated from Alarie (1981)	Barrow et al. (1978)
RD_{50}		303	$RD_{50}/RD_0 = 7.2$. RD_{50}s are extremely irritating concentrations	Alarie (1981)
RD_0		42		
Eye lachrymatory threshold in humans	Not given	55	Exposure was for 15 s	Douglas and Coe (1987)
Nasal lateralization threshold in humans	⩾37	37–67	Pulse duration: ∼10 s	Wise et al. (2005)
Sensory irritation in humans	50, 80, 110 and 140		Students (18–30 years) were exposed for 2 h/concentration. Steep concentration–effect relationship from 140/50 ∼ 3	Verberk (1977)
LOAEL		50		
∼Unbearable		140		
Sensory irritation in humans	5 and 25		Healthy subjects (21–28 years) were exposed for 3 h/concentration	Sundblad et al. (2004)
LOAEL		25	LOAEL/NOAEL = 5	
NOAEL		∼5		
Sensory irritation in humans	10, 20, 20 with two 30-min peaks at 40, and 50		Healthy male subjects (21–47 years) were exposed for 4 h/concentration	Ihrig et al. (2006)
LOAEL		50	LOAEL/NOAEL = 2.5	
NOAEL		20		

out using psychophysical methods (e.g. Cometto-Muñiz and Cain, 1995; Cometto-Muñiz et al., 1998; Hempel-Jørgensen et al., 1999a; Frasnelli and Hummel, 2005; Verberk, 1977; Ihrig et al., 2006; Sundblad et al., 2004).

4.1. Short-term exposures

The psychophysical methods can broadly be divided into methods with brief exposures, typically with duration of exposures of a few seconds (e.g. Cometto-Muñiz and Cain, 1995; Cometto-Muñiz et al., 1998) to minutes, and longer exposure durations, typically lasting several hours (Verberk, 1977; Ihrig et al., 2006; Sundblad et al., 2004). The short-exposure studies are, for example, used for establishing objective sensory irritation thresholds. Thus, irritation thresholds can be determined by comparison of effects of clean air and air with different concentrations of the test compound in subjects, which cannot detect odours (anosmics), or from eye irritation as exposures of the eyes can be performed without exposure of the olfactory nerve in the nose (e.g. Cometto-Muñiz and Cain, 1995; Cometto-Muñiz et al., 1998; Hempel-Jørgensen et al., 1999a). The nostril through which a sensory irritant is presented can be identified, which is not the case with an odour cue. This allows detection of lateralization-based sensory irritation thresholds, which is unconfounded by odour (Frasnelli and Hummel, 2005); this method has recently been reviewed (Smeets et al., 2006). Lateralization-based thresholds were higher than concentrations causing pungency and other trigeminal sensations (van Thriel et al., 2006).

Studies with short exposures showed that the eye irritation thresholds and the corresponding nasal pungency thresholds were virtually the same for a number of different compounds (e.g. Cometto-Muñiz and Cain, 1995). However, the eyes were slightly more sensitive to 2-heptanone (Cometto-Muñiz et al., 1999) and ethyl heptanoate (Cometto-Muñiz et al., 2004). In these cases, the eye irritation thresholds were about half of the nasal irritation thresholds. The irritation threshold in eyes was equal in individuals with normal olfaction (normosmics) and anosmics (Cometto-Muñiz et al., 1999). However, it is tempting to speculate that differences in the mucus layer in the nose and in the precorneal tear film may influence the access of airborne chemicals to the trigeminal nerve endings. The role of precorneal tear film properties regarding causes of eye irritation from VOC exposures has been discussed recently (Wolkoff et al., 2005, 2006a).

The short-term thresholds allow ranking of VOCs according to their potency as sensory irritants and they can be used for study of sensory irritation mechanisms (e.g. Cometto-Muñiz et al., 1998). However, short-term thresholds may be influenced by the method used, exemplified by the differences in lateralization thresholds compared with pungency thresholds. Often, the stimulus is presented in one nostril or eye. If both nostrils are exposed, the threshold may be lower due to "spatial summation" (cf. Smeets et al., 2006). It may be even more important that sensory irritation effects may continue to increase over time, e.g. for formaldehyde (Cometto-Muñiz et al., 1989; Wolkoff et al., 1991). For some compounds a steady state level of sensory irritation may first be reached after half an hour (Hempel-Jørgensen et al., 1999a). Thus, thresholds obtained from short-term exposures may not be applied to longer exposure periods (van Thriel et al., 2006; Wise et al., 2005). Nevertheless, in spite of the different duration of the exposures, overall there is a high correlation between the short-term sensory irritation values and the results from the Alarie test (e.g. Cometto-Muñiz and Cain, 1995).

For exposures lasting up to a few seconds, the irritation intensity increases with the duration of the length of the exposure period and thus expresses a lack of steady state or equilibrium. Empirically, the concentration–time relationship follows a power law model, i.e. the extended Harber's law model (Wise et al., 2005; Shusterman et al., 2006). Thus, it may be possible to estimate very short-term thresholds with other exposure times, and thus normalizing different results to a common short-term period. For formaldehyde (Wolkoff et al., 1991), a latency period was observed before an irritation response appeared. It is tempting to speculate that proteins and other physiological compounds in the mucosa may react with formaldehyde and initially prevent its access to the receptors. Thus, the irritation "breakthrough" appears after the saturation of these protective binding sites has occurred. Also, there is no mechanistic support for calculating long-term effects from short-term exposures. In these cases, the extrapolations based on Harber's law are dubious.

RD_0 for ammonia is close to the lachrymatory threshold (55 ppm) in humans (Douglas and Coe, 1987). Short-term studies also showed that reliable lateralization required concentrations from 37 to 67 ppm, depending on the individual, even for pulses greater than about 10 s (Wise et al., 2005). Thus, the short-term detection occurs at concentrations above the NOEL for the reflex effect (RD_0) in the Alarie test and above the NOAEL in the chamber studies discussed below.

4.2. Chamber studies

Controlled chamber studies can be used to obtain estimates of suprathreshold effects in humans. Most often, the effects are based on subjective evaluations using rating scales. Often, such scales have "none", "very weak" or "barely detectable" at one end and "very strong" or "strongest imaginable" at the other end (Doty et al., 2004). For comparison with effects in the Alarie test and the short-term thresholds in humans, three chamber studies with exposures to ammonia are discussed below.

In a 2-hour chamber study (Verberk, 1977), the ratings of sensations were: "no sensation" (0), "just perceptible" (1), "distinctly perceptible" (2), "nuisance" (3), "offensive" (4) and "unbearable" (5). Eight students with no experience in the toxicity of ammonia were exposed. The eye and throat irritation effects increased to about 1.5 at

50 ppm during the exposure period. At 140 ppm, all students scored "unbearable" (5) for at least one symptom and left the exposure chamber before the end of the 2-hour exposure period. Cough was reported at $\geqslant$80 ppm. In similar exposure conditions, eight toxicologists completed the 2-hour exposure period. They reported no cough and they seldom rated the exposure as "offensive" (4). Exposures did not change lung function parameters in the two groups. The concentration–response relationships for the irritation effects were steep; the low irritation level increased to high irritation levels with a concentration increasing by a factor of 3. From this study the lowest-observed-adverse-effect level (LOAEL) is 50 ppm.

In a 3-hour chamber study with 12 subjects (Sundblad et al., 2004), the visual analogue scale was labelled "not at all", "hardly at all", "somewhat", "rather", "quite", "very" and "almost unbearable". Eye irritation at 5 ppm was close to "hardly at all" and at 25 ppm close to "somewhat". At 5 ppm, discomfort in the eyes, solvent smell, headache, dizziness and feeling of being intoxicated were significantly increased. The exposures did not influence lung function, bronchial responsiveness to methacholine, exhaled NO, inflammatory markers in nasal lavage fluid, leucocytes in blood and complement factor C3b in plasma. In this case the LOAEL for sensory irritation is the 25 ppm level. The 5 ppm level is close to the NOAEL, i.e. in this case the ratio between the LOAEL and the NOAEL is 5.

In a 4-hour chamber study with 33 subjects not normally exposed to ammonia (Ihrig et al., 2006), the rating scale was labelled "not at all" (0), "hardly at all" (1), "somewhat" (2), "rather much" (3), "considerably" (4) and "very much" (5). The median exposure effects at 0, 10, 20 and 50 ppm were 0.16, 0.28, 0.34 and 0.82, respectively, for irritative symptoms in eyes, nose, throat and skin. Irritation levels were close to "not at all" at exposures up to 20 ppm. Slight conjunctival hyperaemia was observed at 50 ppm in few individuals (3/33). No hyperaemia was observed at lower concentrations or in the nose and throat (Hoffmann et al., 2004; Ihrig et al., 2006). A concentration-dependent trend was neither observed for lacrimation, nasal resistance, nasal inflammatory and lung function parameters, nor for cognitive functions (concentration, attention and reaction time). Bronchial reactivity to acetylcholine did not increase in six individuals with pre-existing hyper-reactivity (Hoffmann et al., 2004). From this study the LOAEL is 50 ppm and the 20 ppm level is close to the NOAEL. An extrapolation factor of 2.5 can be obtained from the LOAEL/NOAEL ratio. The irritation effect at the 50 ppm agrees with that of Verberk (1977).

The dominating cue in the Ihrig et al. (2006) and the Sundblad et al. (2004) studies was the odour that may have influenced the subjective ratings. The odour cue was less dominating at the higher concentrations used by Verberk (1977), which suggests that a more prominent sensory irritating response may be less biased by odour cues. The extrapolation factors are probably influenced both by varying degrees of odour cues and the differences between spacing of concentrations. Most likely, the extrapolation from LOAEL to NOAEL for ammonia would be reasonably obtained using a factor of 2 (for influence from odour and spacing, cf. section 8). For ammonia, the RD_0 in mice is close to the LOAEL in humans (Table 2).

4.3. Occupational exposure

For sensory irritants, the first threshold limit values (TLVs) were primarily based on the results of workplace investigations. Thus, industrial hygienists measured airborne concentrations and collected information on sensory irritation responses. Irritating and non-irritating exposure levels were identified and used to construct exposure–response relationships, which were used in TLV settings (Paustenbach, 2000). These studies have furnished much information on sensory irritation at use conditions (Paustenbach, 2000) and where available, such data should always be part of the evaluation of exposure–effect relationships for sensory irritants. However, industrial exposures are often to mixtures, which may hamper assessment of responses from single compounds.

Although the toxicological database on ammonia is considerable (Liesivuori, 2005), we are not aware of relevant, published data on sensory irritation from occupational settings.

5. Quantitative structure–activity relationships for sensory irritants

Several QSARs have been developed for the sensory irritation effect of VOCs in mice, which causes irritation by physical mechanisms, i.e. receptor-activation by electrostatic, hydrogen bonds, van der Waals attractions and hydrophobic forces (Abraham et al., 1990; Alarie et al., 1995, 1998b, 2000; Luan et al., 2006). The general linear free energy relationship (LFER) has been used for mechanistic studies (Abraham et al., 1990; Alarie et al., 1995, 1998b, 2000), which described the irritant processes from solute dipolarity/polarisability, hydrogen-bonding activities, and from the Ostwald partition coefficient on hexadecane (Abraham et al., 1990). RD_{50} estimates from LFERs and the experimentally determined values showed a high correlation ($r^2 \geqslant 0.88$). This suggests that the LFER-based QSARs may be used to estimate RD_{50} values of non-reactive VOCs, which have not been investigated experimentally (Alarie et al., 1995). Also, LFER may facilitate experimental determination of RD_{50} values from fewer, preselected concentrations (Alarie et al., 1995). However, RD_{50} estimates may also be obtained simply from the saturated vapour pressure of VOCs, which are not reacting chemically with receptors, as the correlation coefficient between test results and estimated values was high ($r^2 \geqslant 0.83$) (Alarie et al., 1995, 1998b, 2000).

Several QSARs have been attempted to predict RD_{50}s for chemically reactive VOCs (Alarie et al., 1998b, 2000;

Luan et al., 2006), i.e. compounds which form covalent or ionic bonding with the receptor. These attempts have been met with limited success due to the complexity in predicting organic chemical reactions in biological compartments (Alarie et al., 1998a,b).

In humans, mechanistically based QSARs have been established for prediction of short-term nasal pungency thresholds (e.g. Abraham et al., 1998; Hau et al., 1999) and efficient LFER-based QSARs have been established for prediction of both nose and eye irritation thresholds, as recently reviewed (Doty et al., 2004).

6. Mixtures

Based on the interaction mechanisms, extrapolation of effects to occupational exposure levels and thus also to the lower indoor air levels should be purely additive (Nielsen et al., 1988). It was possible to predict the sensory irritation effect in humans of a 22-compound mixture by use of the mice results from the single compound studies (Alarie et al., 1996). In humans, perceived sensory irritation may not fully obey a purely additive function, if olfaction contributes to the perithreshold and suprathreshold estimates. An interaction is especially important at low sensory irritation effects (Shusterman, 2002b).

Several studies have used short-term exposures (seconds) and methods, which were unbiased by odour perception, to determine sensory irritation thresholds of mixtures. Thus, 1-butanol and 2-heptanone mixtures showed additive nasal pungency as well as eye irritation effects from the compounds at the perithreshold levels (Cometto-Muñiz et al., 1999). Both eye-irritation and nasal-pungency effects from mixtures of butyl acetate and toluene followed the additivity principle at stimuli of low detectability, whereas stimuli of high detectability were hypoadditive (Cometto-Muñiz et al., 2001). Also, eye and nose irritation thresholds were determined for mixtures of ethyl propanoate and ethyl heptanoate. The nasal irritation effects showed complete additivity of effects of the compounds. Although less than complete additivity was observed for eye irritation effects, the results overall consolidated a picture of a high degree of additivity at the perithreshold levels of sensory irritation effects (Cometto-Muñiz et al., 2004). A previous study on nose and eye irritation thresholds for mixtures of up to nine VOCs had been conducted (Cometto-Muñiz et al., 1997). The type of agonism varied from less than additivity of the single compound effects to synergistic interaction that was associated with high lipophilicity of the compounds. Combining the 5 eye and 5 nasal tests, 7 of the 10 tests deviated by less than a factor of 2 from complete (simple) additivity. Partial agonism (less than additivity/hypoadditivity) was observed for 5, complete additivity for 3 and synergistic interaction for 2 of the mixtures.

Short-term (few seconds) suprathreshold exposures to ammonia and formaldehyde showed hypoadditivity of the total nasal perceived intensity in the low concentration range, additivity in a broad range of middle concentrations and hyperadditivity at high exposure levels (Cometto-Muñiz et al., 1989; Cometto-Muñiz and Hernãndez, 1990). The hypoadditivity was due to odour cue that dominated the low-concentration intensity; combined effects of odours being hypoadditive (Cometto-Muñiz and Hernãndez, 1990). Overall, the study suggests that sensory irritation is mainly additive (Cometto-Muñiz and Hernãndez, 1990). Short-term eye irritation studies (~1.5 min) were performed using different levels of an 8-compound mixture and two 4-compound mixtures, each containing four of the compounds in the 8-compound mixture (Hempel-Jørgensen et al., 1999b). The eye irritation effect of the 8-compound mixture could be predicted correctly from the irritation effects of the two 4-compound mixtures by assuming complete additivity.

Based on animal and human studies, additive interaction, although not perfect, can be assumed as a first approximation for effects of sensory irritants.

7. Groups at extra risk

The sensory irritation sensitivity of several groups has recently been reviewed (Shusterman, 2002b; Doty et al., 2004). Thus, the sensitivity depends on physiological parameters (age and gender), the lifestyle factor smoking, and diseases. Overall, the known differences in sensitivity can be accounted for by a UF of about 2.

The nasal irritation threshold of *n*-propanol and CO_2 increased with age and emerged as the strongest predictor of nasal irritation sensitivity (Shusterman et al., 2003). Similarly in the eyes, the CO_2 irritation threshold concentration was increased by 65% in the elderly compared to younger adults (Kjaergaard et al., 1992). However, in a study of 15 compounds (13 organic and 2 inorganic), the lateralization thresholds from 13 compounds were not affected by age whereas two compounds had increases in thresholds of 28–41% in the age group $\geqslant$45 years compared with thresholds in adults aged 18–35 years (van Thriel et al., 2006).

Females may be 14–30% more sensitive than males to nasal irritant exposures (Doty et al., 2004). Thus, females had a significantly lower CO_2 threshold, but the *n*-propanol threshold was not significantly different from males (Shusterman et al., 2003). Also, the suprathreshold intensity was increased in females, as the concentration–effect relationship was displaced leftwards with a steeper slope (Cometto-Muñiz and Noriega, 1985). However, no clear gender difference appeared from perceived nasal irritation with pyridine (Olofsson and Nordin, 2004). Gender neither influenced the lateralization thresholds nor the suprathreshold irritation intensity for 15 compounds (van Thriel et al., 2006).

Smoking may increase the nasal irritation threshold (cf. Shusterman, 2002b; Doty et al., 2004). In one study, it was increased by 44% (Shusterman and Balmes, 1997).

Short-term eye irritation threshold for CO_2 was studied in subjects without indoor-air-related symptoms and

subjects who had sought medical assistance for the complaints. The eye irritation threshold was 48% lower in the symptomatic subjects (Kjaergaard et al., 1992). The equipotent sensory irritation concentration decreased by approximately 23% in individuals with self-reported chemical sensitivity compared with individuals with normal sensitivity. Nevertheless, the chemosensory event-related potentials were similar in such groups (Nordin et al., 2005).

The nasal sensitivity in patients with allergic rhinitis is less clear (Doty et al., 2004). The threshold of *n*-propanol was less, but not the threshold to CO_2 (Shusterman et al., 2003). Additionally, nasal allergy was a weak predictor of nasal irritant sensitivity (Shusterman et al., 2003). The summated and averaged electroencephalographic potentials ("chemosensory evoked potentials" or CSERP) caused by nasally applied chemical stimuli have been used to study nasal irritation. Trigeminal CO_2-evoked responses were normal in patients with Parkinson's disease, but influenced by temporal lobe epilepsy and idiopathic environmental intolerance (cf. Shusterman, 2002b). The nasal pungency thresholds varied little among anosmics (e.g. Cometto-Muñiz and Cain, 1990).

8. Evaluation of sensory irritation effects of airborne compounds

For non-carcinogenic compounds, standards or guideline values are derived from the same principle (Dourson et al., 1996; IGHRC, 2003). The NOAEL is divided by one or more UFs (Π UF_i); for simplicity, factors used for extrapolation from higher to lower exposure-effects are also termed UFs. In contrast to the NOAEL, the Π UF_i value depends on the population intended to be protected (e.g. IGHRC, 2003). UFs should be evidence-based rather than default values where ever possible (Dourson et al., 1996).

For sensory irritation in general, it is suggested that a small UF is needed for extrapolation from LOAEL to NOAEL. For ammonia, a UF of about 2 is obtained from one study (Ihrig et al., 2006), which is supported by the steep concentration–effect relationship in a mouse study (Alarie, 1981) and by another of the chamber studies (Verberk, 1977). However, a UF of 5 was derived from the third chamber study (Sundblad et al., 2004). This UF may have been influenced by the wide spacing of the test concentrations. Odour may also have confounded the results as the odour cue was the most conspicuous sensory effect and the reported symptoms at the 5 ppm level (discomfort in the eyes, solvent smell, headache, dizziness and feeling of being intoxicated) resemble reported odour-driven symptoms (e.g. Shusterman et al., 1991). Additional support for a small UF comes from the distribution of UFs from different types of mild acute inhalation effects (Alexeeff et al., 2002). The median value corresponded to a UF of 2 and the 95th percentile to an UF of 6.3. Overall, extrapolation from the LOAEL to the NOAEL for sensory irritation may be performed by means of an UF of 2.

Sometimes the sensitivity of the eye exceeds the sensitivity of the upper airways by a factor of 2, which should be considered in setting an overall NOAEL for sensory irritation. As this is the exception rather than the rule, a UF of 2 may be used in a case-by-case manner, but is not needed in general. In particular, if experimental values are available both from the eyes and the upper airways, the lowest NOAEL is used, and if the NOAEL is based on eye irritation, no UF may be needed.

What is the variation in thresholds of sensory irritation within the human population? As younger adults may be more sensitive than elder adults and the young adults are often used in establishing NOAEL, the estimates should be from the more sensitive part of the population. Two UFs have to be used for protection of the more sensitive part of the general population, i.e. the part below the median sensitivity, as well as for protection of especially sensitive groups. A UF of 4 has been proposed for extrapolation from the NOAEL to levels, which are far below the irritation threshold based on the steep concentration–effect relationships, but disregarding especially sensitive groups (Nielsen et al., 1997). An approximately similar UF is obtained from the standard deviation of nasal pungency thresholds by assuming a log normal distribution of the thresholds in the general population (Hau et al., 2000). From these assumptions it was derived that the majority (97.5%) of the normal population should be protected by a level of 1/5 of the average nasal pungency threshold (Hau et al., 2000). Thus, an approximate UF of 5 may be used for protection of the general population. The UF for protection of especially sensitive groups can be set to 2, based on the present knowledge. Although the derivation of the NOAEL may be uncertain and thus biased, the appropriately set NOAELs are expected rather to be too low due to potential confounding by odour cues in chamber studies. Overall, this results in a combined Π UF_i of about 10 if starting from the NOAEL.

8.1. Uncertainty factors for setting occupational exposure limits

Only a small UF (perhaps a UF of 1) is used when the critical effect is sensory irritation, which is rapidly and clearly apparent, and readily and completely reversible on removal from exposure (Fairhurst, 1995). This can be illustrated from ammonia. In this case the TLV (25 ppm) is about the same as the NOAEL (~25 ppm). So, in this case Π $UF_i = 1$, which indicates that no UF has been applied. In general, there is a lack of established standards except for OELs. Therefore, it has been proposed to use OELs as substitutes for NOAELs where the OELs are set due to sensory irritation, i.e. it is accepted that the OELs are close to the NOAEL (Nielsen et al., 1997) as illustrated for ammonia.

8.2. Uncertainty factors for setting indoor air guideline values

For protection of the general population against sensory irritation in the non-industrial indoor environments, it has been proposed to divide the NOAEL by a UF of 4 based on the steep concentration–effect relationship of ammonia (Nielsen et al., 1997). However, it was also proposed to use a default value of 10 for protection of potentially sensitive groups (Nielsen et al., 1997) that results in a combined UF of 40. The combined UF results in a guideline value (NOAEL/40), which is below levels that are expected to cause sensory irritation in the general population and in sensitive groups. Using 40 as the UF and assuming the NOAEL of 25 ppm for ammonia, this results in a guideline value of 0.6 ppm. This value is in the range of the odour threshold (about 0.05 ppm (van Thriel et al., 2006) to 5 ppm (Devos et al., 1990) and it is 10-times or more less than levels causing sensory irritation in the chamber studies.

Recently, an even more conservative approach has been proposed for setting indoor air guideline values (The INDEX project, 2005). Sensory irritation and cough were accepted as being the critical effects with a LOAEL of 35 mg/m^3 (50 ppm) for ammonia. A UF of 10 was accepted for extrapolation to the NOAEL, a UF of 10 for intraspecies variability and a factor 3 for susceptible populations, which results in a combined UF of 300. The proposed indoor air guideline value for ammonia is therefore 0.1 mg/m^3 (0.14 ppm).

If the conservative guideline values are used together with the measured indoor air concentrations, and additive effect is assumed, the sum of the ratios between each exposure concentration and its guideline value can be calculated. The sum is expected to express the combined sensory irritation effect of the measured compounds. There is no scientific support that measured concentrations cause sensory irritation in non-industrial indoor environments if the sum is less than 1. However, a value of just above 1 cannot be used to demonstrate an adverse exposure–effect of the measured compounds, as the sum is a conservative estimate. In this case an in-depth evaluation is necessary.

8.3. Recommendation for setting NOAELs for sensory irritants

The NOAELs for sensory irritating effects should be based on the best available practice as they are a prerequisite for reliable OELs and guideline values. We propose that the following procedure should be used systematically for the establishment of robust NOAELs for risk assessment of sensory irritating effects:

- A NOAEL should be estimated from the Alarie test. Both the RD_{50} and the RD_0 values should be used in the estimation and for the comparison with results obtained from human studies. The slope of the concentration–effect relationship should also be available for comparison with the slopes of other tested compounds. This may indicate whether a given compound behaves as most compounds and thus follows the general relationships.
- The unbiased threshold from brief exposure studies should be used for the estimation of the human NOAEL. When available, the slope of the psychometric function (concentration–response relationship) should be reported to evaluate whether a given compound behaves as most other compounds.
- Chamber studies should also be used for deriving sensory irritation NOAELs. This type of study is closer to most of the human exposure conditions and thus should be optimal for establishing NOAELs. However, in chamber studies the irritation effect may be biased by odour cues. Therefore, the effect of odour should always be evaluated in these studies. Part of the evaluation includes considering the slope of the exposure–effect relationship; in general, the sensory irritation effects have steeper slopes, while odour effects have shallower slopes (Dalton, 2003; Cain et al., 2006).
- Where sensory irritation data are available from occupational settings, they should be used in constructing exposure–response relationships. Evaluation of possible interference from effects of other simultaneously occurring compounds and from odour cues should be part of the quality assurance of data.
- Also, it should be considered whether the NOAEL will increase, stay constant or decrease over time.
- For non-reactive VOCs, QSARs, which give reasonable valid sensory irritation estimates, are available both from animal studies and from human short-term studies.

An overall expert evaluation should take these points into account in an estimation of a best available NOAEL. The example with ammonia illustrates the proposed procedure, which can easily be used for other compounds if data are available.

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