Non-cancer effects of formaldehyde and relevance for setting an indoor air guideline

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Abstract

Article history:
Received 22 February 2010
Accepted 25 May 2010
Available online 16 June 2010

Keywords:
Airways
Asthma
Children
Formaldehyde
Sensory irritation
Susceptible subgroups

There is considerable recent focus and concern about formaldehyde (FA). We have reviewed the literature on FA with focus on chemosensory perception in the airways and lung effects in indoor environments. Concentrations of FA, both personal and stationary, are on average in the order of 0.05 mg/m³ or less in Europe and North America with the exception of new housing or buildings with extensive wooden surfaces, where the concentration may exceed 0.1 mg/m³. With the eye the most sensitive organ, subjective irritation is reported at 0.3–0.5 mg/m³, which is somewhat higher than reported odour thresholds. Objective effects in the eyes and airways occur around 0.6–1 mg/m³. Dose–response relationships between FA and lung function effects have not been found in controlled human exposure studies below 1 mg/m³, and epidemiological associations between FA concentrations and exacerbation of asthma in children and adults are encumbered by complex exposures. Neither experimental nor epidemiological studies point to major differences in susceptibility to FA among children, elderly, and asthmatics. People with personal trait of negative affectivity may report more symptoms. An air quality guideline of 0.1 mg/m³ (0.08 ppm) is considered protective against both acute and chronic sensory irritation in the airways in the general population assuming a log normal distribution of nasal sensory irritation.

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Abbreviations: FEV1, forced expiratory volume in 1 s; FEV3, forced expiratory volume in 3 s; PEF, forced expiratory flow; FVC, forced expiratory vital capacity; FA, formaldehyde; IgE, immunoglobulin E; IgG, immunoglobulin G; LOEL, lowest observed effect level; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; PEF, peak expiratory flow; VOC, volatile organic compound.

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doi:10.1016/j.envint.2010.05.012
1. Introduction

Exposure to ubiquitous formaldehyde (FA) has received considerable focus among indoor air scientists during the last decade for four reasons: 1) classification of FA as a human carcinogen by (International Agency for Research on Cancer (IARC), 2006); 2) research that atmospheric reactions between ozone and monoterpenes, emitted e.g. from indoor materials, household products, and personal care products (Nazaroff and Weschler, 2004) produce FA (Carslaw, 2007; Poppen-diek et al., 2007); 3) some epidemiological studies lead to speculation that FA exposure may have caused lung effects among cleaning personnel or among children from domestic use of household products, e.g. (Sherriff et al., 2006; Medina-Ramón et al., 2006) and, 4) one epidemiological study in children (Rumchev et al., 2002) and recent rodent studies suggest that FA may exacerbate asthma symptoms, e.g. (dos Santos Franco et al., 2009).

These concerns and suggestions, of which some have been applied for national regulation, have motivated a risk assessment of the experimental and epidemiological data on non-cancer effects of FA in the airways and eyes in humans reported over the last decade and a half, i.e. since the last air quality guideline by WHO (World Health Organization, 2000) that covered the literature up to 1995; cancer effects of FA are presented elsewhere (Nielsen and Wolkoff, 2010). We focus specifically on chemosensory perception (odour and sensory irritation) and certain nasal and lung effects (asthma and allergy) in adults and children in indoor environments.

National and international regulatory agencies have established occupational exposure limit values (OELs), threshold limit values (TLVs) or air quality guidelines. For instance, an OEL value of 0.25 mg/m³ (8 h) has recently been proposed by the EU Scientific Committee on Occupational Exposure limits (SCOE, 2008), partly on the basis of a recent human exposure study about sensory irritation in the eyes and airways (Lang et al., 2008). An air quality guideline of 0.1 mg/m³ (0.08 ppm) as a 30 min average was recommended for the general population, since it was concluded that “the lowest concentration that has been associated with nose and throat irritation in humans after short-term exposure is 0.1 mg/m³” (World Health Organization, 2000). Health Canada has developed two residential guidelines for FA, a 1-hour averaged exposure value of 0.123 mg/m³1 and an 8-hour averaged exposure value of 0.050 mg/m³ considered preventive of allergic sensitization or asthma in children (Gilbert, 2005). This latter value was derived from a case–control study of small children exposed inter alia to FA. California Office of Environmental Health Hazard Assessment (OEHHAA) has recently implemented a 1 h FA acute reference exposure level of 0.055 mg/m³ (OEHHAA, 2008). This value was derived from the point of departure (lowest observed adverse effect level (LOAEL) and benchmark concentration approach) of 0.5 ppm for sensory irritation in the eyes (Kulle et al., 1987; Kulle, 1993), in agreement with the conclusion reached by (Lang et al., 2008), and the use of a selected assessment factor of 10 for protection of potential exacerbation of asthma in children. Similarly, OEHHAA has suggested both an 8-hour and a chronic reference exposure level of 0.009 mg/m³ derived from a NOAEL value of 0.09 mg/m³ obtained from an occupational chemical plant study (Wilhelmsson and Holmström, 1992).

In their extensive review, that covered the literature up to 1995, Paustenbach et al. (1997) concluded “if concentrations of formaldehyde are kept below 0.1 ppm (0.12 mg/m³) in the indoor environment (where exposure might occur 24 h/day) this should prevent irritation in virtually all persons”. In their extensive analysis for the German Federal Institute for Risk Assessment, Appel et al. (2006) concluded that “ocular and upper respiratory tract irritation is not present below 0.1 ppm”.

2. Methods

The term formaldehyde was searched from 1995 and up to the present, and in combination with: allergy, asthma(tics), airway (irritation), bronchoconstriction, children, eye (irritation), emission, inflammation, homes, IgE, (nasal) irritation, kindergartens, lung effects, lung function, offices, odour, schools, sensory irritation, sick-building syndrome, sensitization, and trigeminal stimulation. Cancer effects were excluded and eczema was not included except if retrieved in above searches. In addition to databases, such as PubMed and Google Scholar, recent comprehensive reviews were also considered (Appel et al., 2006; Arts et al., 2006; Wibowo, 2003), including Health Canada (Gilbert, 2005; Leikauf, 2009), and international reports (World Health Organization, 2002; International Agency for Research on Cancer (IARC), 2006; SCOEL, 2008). This review is a risk evaluation with emphasis on human effects at indoor concentrations.

3. Indoor sources and concentrations

3.1. Indoor sources

The main source of FA is emission from building and furnishing materials, notably wood and wood-based products (Salthammer et al., 2010), such as medium-density fibre board, particleboard, and plywood, all of which contain phenol–formaldehyde or urea–formaldehyde resin glues, e.g. (Baumann et al., 2000; Brown, 1999); glass wool insulation with similar types of binders also emits FA. Other products that release FA include those with fungicides, e.g., waterborne lacquers, paints, consumer products, and cosmetics (Kelly et al., 1999), and some with added free FA (Fryholm, 2005).

FA can also result from gas-phase ozonolysis of indoor alkenes often monoterpenes (Atkinson and Arey, 2003), that occur in numerous consumer products, e.g. air fresheners, as solvents or fragrances. The reactions may occur at a rate that competes with the air exchange rate, thus becoming important in indoor environments and aircraft cabins (Weschler, 2000; Wisthaler et al., 2005). High local concentration of FA occurs during application of terpenoid-based products in the presence of ozone, e.g. (Destaillats et al., 2006). A number of other products for both domestic do-it-yourself and professional use emit FA, e.g. painting (Gilbert et al., 2006). Electronic equipment such as photocopiers and laser printers also emit FA (Leovic et al., 1996; Tuomi et al., 2000).

1 0.123 mg/m³ formaldehyde = 0.1 ppm at 25 °C and 1 atm.
Sidestream tobacco smoke contains notable amounts of FA, as does environmental tobacco smoke (sidestream plus exhaled smoke). The smoke plumes contain amounts of FA in the order of 0.1 mg/m³ (Ayer et al., 1978; Baker, 2006). However, elevated FA concentrations have not been associated with smoking in cases of extended sampling duration (Gilbert et al., 2006, 2005; Lovreglio et al., 2009). In non-smokers, exhalation contains FA in the order of 0.001 to 0.01 mg/m³ (Kushch et al., 2008; Moser et al., 2005; Wehinger et al., 2007).

3.2. Concentrations

Reported mean indoor concentrations of FA generally lie in the range of 0.005 to 0.1 mg/m³ with some higher concentrations in new or renovated housing, e.g. (Gilbert et al., 2006; Hodgson et al., 2002). A number of European projects reported mean exposure concentrations in homes (sampling time: 1–7 days), generally as less than 0.05 mg/m³ (Bruinen de Bruin et al., 2008; Clarisse et al., 2003; Gustafson et al., 2005; Jurvelin et al., 2001; Lovreglio et al., 2009; Marchand et al., 2008; Raw et al., 2004); slightly lower concentrations (sampling time: 2 days) were measured indoors (home, work, and transport) in Boston across seasons (Dodson et al., 2007). Further, 353 measurements in 234 homes (48 h) across the USA showed a median value of 0.020 mg/m³ (Liu et al., 2006), and similar to homes in Québec City (Gilbert et al., 2006). Higher concentrations (24 h) in older Japanese homes had a mean of 0.09–0.1 mg/m³ and slightly higher concentrations between 0.09 and 0.13 mg/m³ in new homes, highest the first year (Park and Ikeda, 2006). Generally, higher temperature, relative humidity, and larger wood-based surfaces in comparison with Swedish homes explain the difference (Sakai et al., 2004). Yet, substantially higher concentration concentrations are measured in Chinese homes (Tang et al., 2009), probably due to the use of high FA emitting construction materials.

The emission of FA from wood-based products with urea-formaldehyde glue is proportional to the relative humidity at a given temperature (Myers, 1985; Van Netten et al., 1989), while temperature dependence is more complex (Zhang et al., 2007). It should be noted that FA concentrations depend on averaging times of sampling, for example, the temporary use of FA combustion sources may result in brief exposure peaks, that are not seen at 24-h average sampling times (Lovreglio et al., 2009).

Concentrations of FA measured in public buildings in Europe generally lie below those measured in homes (Bruinen de Bruin et al., 2008). In some offices, mean concentration has fallen below 0.025 mg/m³ (Bruinen de Bruin et al., 2008; Reynolds et al., 2001; Salonen et al., 2009) with personal exposures of the same order or less (Kotzias et al., 2009). Concentrations may be two- to ten-fold higher in Chinese public buildings, including offices (Tang et al., 2009).

Control of FA concentration depends primarily on air exchange rate (Gilbert et al., 2006; Salthammer et al., 1995). It was estimated that an exchange rate of 0.26 h⁻¹ would ensure a FA concentration <0.05 mg/m³ in 95% of Canadian homes, though 0.37 h⁻¹ was necessary in homes with new FA sources (Gilbert et al., 2008). Half an air exchange rate was required to obtain a concentration <0.06 mg/m³ FA in 90% of new Californian homes (Sherman and Hodgson, 2004). Other continuous factors influencing the FA concentration include age of housing and wood-based floor coverings (Clarisse et al., 2003; Gilbert et al., 2005; Raw et al., 2004); thus, selection of FA low emitting materials, products, and furnishings decreases FA exposure. Seasonal dependence with higher concentrations during summer and fall has also been seen (Dassonville et al., 2009; Kotzias et al., 2009; Raw et al., 2004; Wolkoff et al., 1991a). Short-term contributions include combustion processes, e.g. smoking, and the use of terpenoid-based consumer products, e.g. air fresheners and cleaning products that undergo ozone-initiated oxidation, e.g. (Destaillets et al., 2006). If ozone–terpenes initiated reactions cause upper airway and eye symptoms as suggested in the US BASE study (Apte et al., 2008), FA formation from limonene, which is among one of the most abundant VOCs indoors, could be salient (Wolkoff et al., 2008).

In summary, mean FA concentrations generally lie below 0.05 mg/m³ in homes, and below 0.025 mg/m³ in public buildings in Europe and the US. Outdoor concentrations fall below 0.01 mg/m³ in European cities (Bruinen de Bruin et al., 2008), but concentrations about twice of that have been found in some major capitals (Wang et al., 2007).

4. Metabolism and retention

4.1. Metabolism and distribution in the body

In unexposed humans, FA is a normal component of blood and an essential intermediate in all cells at concentrations about 2.0–2.6 µg/g of blood (Franks, 2005; Heck et al., 1985): it is formed endogenously from amino-acids and choline, and by demethylation of N-, O-, and S-methyl compounds, and hydroxymethylglutathione (International Agency for Research on Cancer (IARC), 2006). Its interaction with macromolecules is reversible formation of e.g. Schiff bases. Extensive inhalation exposure studies of humans, monkeys, and rats to FA, even up to 2.5 mg/m³ for humans, do not result in a significant increase of the FA blood concentration, owing to its rapid absorption, reaction and metabolism at the site of contact, e.g. (Bosetti et al., 2008; Franks, 2005; Casanova et al., 1988; Heck et al., 1985). For example, the metabolism of FA is so fast that 0.5 mg/m³ exposure does not increase urinary formate excretion; further, FA does not accumulate in the blood after intravenous administration to animals (cats, dogs, and monkeys) (Heck and Casanova, 2004), due to its short life-time of <1 1/2 min (Heck et al., 1983). In summary, it appears unlikely that inhaled FA reaches internal organs after portal of entry (Lu et al., in press).

4.2. Retention of formaldehyde in the nasal cavity

Retention of FA in the moist layers covering the nasal mucosa, i.e. regions of the upper respiratory tract, exceeds 90–95% in rodents and primates owing to its high solubility in water and reactivity, e.g. (Heck et al., 1983; International Agency for Research on Cancer (IARC), 2006). For example, a maximum of 5% FA reaches the lower airways in dogs (Egle, 1972) and high retention is also inferred from a mouse bioassay, because only sensory irritation of the upper airways has been observed below 4 ppm FA (Nielsen et al., 1999). Computational fluid dynamic (CFD) calculations at boundary conditions of maximum and fast uptake of FA showed similar total nasal extraction in adults and children (age 7–8 years), on average 90%, indicating that maximum 10% of inhaled FA may pass the nasal cavity and reach the larynx and possibly the lower airways at resting conditions in humans (Garcia et al., 2009).

5. Chemosensory perception — effects on the airways after acute and short-term exposure

5.1. Odour

In general, odour perception is at its maximum intensity at the initiation of the response due to receptor mediated decrease (adaptation) at extended exposure. A large variety of odour thresholds has been reported for FA from 0.05 to 0.5 mg/m³ (van Gemert, 2003); some are listed in Table 1 on the basis of quality, control of dosage, and data treatment. Detection of the odour of FA occurs at concentrations of approximately 0.12 mg/m³ according to credible experiments performed at the University of Stockholm. The experiments entailed careful generation of FA and close monitoring of concentration (Berglund and Nordin, 1992). Exposures took place against a background of carbon-filtered air, presumably with approximately zero FA concentration. The authors found 25% detection,
corrected for chance, at concentrations of 0.030 and 0.053 mg/m³ in non-smoking (n = 22) and smoking (n = 22) females, respectively, 50% detection at 0.063 and 0.112 mg/m³, respectively, and 75% detection at 0.132 and 0.239 mg/m³, respectively. At concentrations just above those for 50% detection, subjects could judge perceived magnitude reliably and monotonically up to 1.2 mg/m³, an endorsement of the results for detection.

In some experiments that included males, concentrations of 50% detection as high as 0.220 mg/m³ were found (Berglund et al., 1987). That kind of variation, some of it possibly systematic (e.g., a sex difference) and some of it possibly random (e.g., individual sensitivity of participants), poses no essential issue regarding the finding that human beings evince quite high sensitivity to the odour of FA. As the findings for 25 through 75% detectability showed, the “threshold” summarizes a distribution.

Some methodologies sample the higher end of the distribution and some the lower end. Generally, the personal exposure is a median of around 0.025 mg/m³ in daily life (Gustafson et al., 2005; Kotzias et al., 2009). A background such as that, which actually represented an average of outdoor and indoor concentrations, might elevate the point of detectability. This would depend upon the criterion concentration of detectability explored. A methodology employed in Japan, for instance, gathered the points of 100% detection for a small number of trained individual subjects and accordingly obtained higher “thresholds” than Berglund and colleagues (0.2–0.3 mg/m³) (Nagata, 2003), in agreement with a recent German study measured after 195 min of exposure (0.2–0.4 mg/m³) (Lang et al., 2008); probably, this value is more at the high end due to expected adaptation over time, e.g. (Cain et al., 1986). It is considered, in view of the above reported odour thresholds, that a significant fraction of the population perceives FA at or below 0.1 mg/m³ without interfering background.

5.2. Chemesthetic sense

5.2.1. Sensory irritation

Formaldehyde stimulates not only to the sense of smell, but also the chemesthetic sense, i.e., the capacity to feel chemicals (Doty et al., 2004). Thus, a trial to detect odour may need to last only a second or so, and the chemesthetic sense may respond most vigorously after an indeterminate length of time. Humans exposed to the vapour have long noted oral and nasal irritation. Such responses occur principally via stimulation of the trigeminal nerve (Doty et al., 2004; Kulle and Cooper, 1975). Recent research has elucidated cation channels, part of the transient receptor potential (TRP) gene superfamily that mediate such responses. At first, it appeared that FA might activate only members of the TRP family, as do many other chemically reactive chemicals, and notably electrophilic agents (e.g., acrolein, acetaldehyde) (Bessac and Jordt, 2008). In such cases, reversible covalent binding to cysteine residues of the channels provides the means of activation (McNamara et al., 2007). It now appears that members of the TRPV1 family, best known for their activation by capsaicin and a variety of chili pepper spices, also respond to FA (Tian et al., 2009). In that case, chemical reactivity seems unlikely to cause the effect. Both TRPA1 and TRPV1 channels occur in the same nociceptive fibers (c-fibers) of the trigeminal nerve and ganglion. In Tian et al.’s electrophysiological assay, the latency of response could exceed minutes (Tian et al., 2009). This complicates the determination of a chemesthetic threshold for FA.

A trial to detect the feel of a chemical may need to last tens of minutes. In general, the lower the concentration, the longer will be the latency (Wise et al., 2009). In a study of the TRPA1 agonist methyl isothiocyanate flowed into goggles, subjects reported that they could feel the chemical at about a minute at a concentration of 3 ppm and at an hour at a concentration of 0.8 ppm (Cain et al., submitted for publication). In a study of chloropicrin, another TRPA1 agonist, subjects could detect the vapour in the eye at 0.8 ppm in exposures that lasted half a minute and at 0.1 ppm in exposures that lasted 20 min (Cain, personal communication, 2010). Ratings of the perceived feel of FA in exposures from 0.25 to 2.4 mg/m³ indicated concentration-related time-dependence as well (Cain et al., 1986). Also, latency was observed among subjects exposed to about 0.8 mg/m³ FA before an irritative response appeared (Wolkoff et al., 1991b). It is tempting to speculate that the irritative effect of FA is retarded by reaction with the macromolecules and other physiological compounds in the mucosa before access to the receptor cites. Thus, the irritation “breakthrough” may appear after the saturation of these “protective” binding sites. Formaldehyde, unlike methyl isothiocyanate and chloropicrin, has a detectable odour at all the concentrations of interest for chemesthesia. Thus, the odour interferes with judgment of those concentrations, i.e. difficulty of separating the integrated input of the odour and sensory irritation (Dalton and Jaén, 2010; Doty et al., 2004; Shusterman, 2007). This and odour adaptation are important to consider when deriving guidelines that are based solely on subjective reporting of symptoms, as discussed for FA by (Arts et al., 2006).

5.2.2. Threshold for sensory irritation

Selected key studies about human exposure–response relationships on FA are listed in Table 2; some key studies prior to 1995 are also added. About half of the studies represent controlled human exposure studies of which some are double-blind, including both gender, and tested with questionnaires and/or objective methods, while the other half are epidemiological studies carried out in the field, e.g. anatomy laboratories.

A number of reviews have assessed the threshold for self-reported sensory irritation. In general, the eyes are considered to be more sensitive to chemestheses than the upper airways, cf. (Doty et al., 2004). Threshold values for sensory irritation have been suggested from 0.25–0.35 mg/m³ to 1.2 mg/m³ (Appel et al., 2006; Arts et al., 2006; Paustenbach et al., 1997). Raw data of exposure–response relationships obtained from reported human exposure studies on irritating effects were used in a regression model. Based on identified dose–response relationships, a value below 0.9 mg/m³ FA was considered safe against sensory irritation in the eyes for all workers (i.e. 8 h), while about 6% of the workers may experience moderate irritation between 0.9 mg/m³ and 1.2 mg/m³, though none would experience severe irritation (Nøisel et al., 2007).

One key experimental study involved 21 healthy subjects that were exposed double-blind and randomly to 10 different FA concentrations for 4 h (Lang et al., 2008). These included FA concentrations of 0, 0.18, 0.36, and 0.6 mg/m³; further conditions had concentrations at 0.36 and 0.6 mg/m³ FA that included peak concentrations of 0.7 and 1.2 mg/m³, respectively, and the presence of 36 mg/m³ ethyl acetate at 0, 0.18, 0.36, and 0.6, and 0.6 and 1.2 mg/m³ FA peaks. Questionnaires and objective methods were used to evaluate eye and airway irritation and lung functions. Eye irritation was found to be the most significant effect. Subjective sensory

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Selected odour threshold determinations for formaldehyde.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odour detection threshold (mg/m³)</td>
<td>Subjects</td>
</tr>
<tr>
<td>0.068a</td>
<td>22 non-smoking women (age-matched)</td>
</tr>
<tr>
<td>0.116b</td>
<td>22 smoking women (age-matched)</td>
</tr>
<tr>
<td>0.19–0.36b</td>
<td>21 healthy (11 men and 10 women)</td>
</tr>
<tr>
<td>0.2–0.3c</td>
<td>6 adults (2 men and 4 women)</td>
</tr>
</tbody>
</table>

a Forced choice method, P50 threshold.
b Olfactory perception differed significantly from background air after 195 min of exposure in a climate chamber.
c Trained panellists, triangle method and 100% detection.
irritation was perceived as low as 0.36 mg/m³ for the eyes and 0.6 mg/m³ with peaks up to 1.2 mg/m³ for the nose with the personal trait as a covariate. Adjustment for the personal trait of negative affectivity (anxiety), however, lead to a value of 0.6 mg/m³ for the eyes at constant variable. Adjustment for the personal trait of negative affectivity exposure and 0.3 mg/m³ plus peak exposure up to 0.6 mg/m³. A 0.6 mg/m³ FA exposure with four 1.2 mg/m³ peaks, but not without the signifi
cant increase of the eye blink frequency, which re
mained unaffected. Although eye and nasal irritation did not occur concerted, and to some extent depended on personal factors (e.g. personal trait and odour), the authors concluded that a corrected LOEL is 0.6 mg/m³ (0.5 ppm) at constant exposure without peak exposure, as previously observed (Kulè et al., 1987; Kulè, 1993). However, the LOEL may be higher at constant levels, since no significance occurred without FA peaks of 1.2 mg/m³. This is further supported by prediction of LOAEL for the general population according to (Kuwabara et al., 2007) to lie between 0.75 and 0.77 mg/m³ on the basis of the mean value of reported RD₅₀ values and a log normal distribution of nasal sensory irritation. RD₅₀ is the exposure concentration that produces a 50% respiratory rate decrease in a mouse bioassay. (Lang et al., 2008) also concluded that the NOAEL (no observed adverse effect level) value for both subjective and objective eye irritation is close to the LOEL value, i.e. 0.6 mg/m³ at constant exposure concentration; the observed effects were only considered weak, because “less” and “somewhat” were ranked almost equal. In addition, a slightly lower NOAEL was considered 0.36 mg/m³ at peaks of 0.7 mg/m³ FA. This agrees with a directly determined NOAEL value for upper airway irritation in mice that was 0.35 mg/m³, obtained from the mouse bioassay (Nielsen et al., 1999).

The sensory effect of FA together with other sensory airway irritants is generally considered additive (Nielsen et al., 2007a). In a controlled human exposure study with 130 women (mean age 27) exposed to human exposure study with 130 women (mean age 27) exposed to

### Table 2

Effects of the airways in humans after acute and short-term exposure to formaldehyde (FA): Controlled human exposure and epidemiological studies.

<table>
<thead>
<tr>
<th>Concentration mg/m³</th>
<th>Subjects age, mean (range)</th>
<th>Exposure time, min</th>
<th>Health effects</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.13</td>
<td>8 with nasal congestion † 8 without nasal congestion (7 men, 8 women)</td>
<td>21 (14–44)</td>
<td>120 Swelling of nasal mucosa among those suffering from nasal congestion</td>
<td>Falk et al. (1994)</td>
</tr>
<tr>
<td>0.3–0.5</td>
<td>21 healthy† (11 men, 10 women)</td>
<td>19 (13–36)</td>
<td>0.6 Subjective sensory irritation in eyes</td>
<td>Lang et al. (2008)</td>
</tr>
<tr>
<td>0.6</td>
<td>26 (19–39)</td>
<td>240</td>
<td>Increased eye blink frequency and conjunctival redness</td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td></td>
<td></td>
<td>No effects on nasal flow and resistance, and peak flow</td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td>19 dust mite asthmatics† (7 men, 12 women)</td>
<td>(19–35) 30</td>
<td>No effects on lung functions (PEF, FEV1, FMF)</td>
<td>Casset et al. (2006)</td>
</tr>
<tr>
<td>0.1</td>
<td></td>
<td></td>
<td>No effects on lung functions (PEF, FEV1) after mouth pre-exposure of FA</td>
<td></td>
</tr>
<tr>
<td>0.13–0.41</td>
<td>27 medical students‡ (15 men, 12 women)</td>
<td>21 70 days</td>
<td>No significant decrease in PEF 4 students (one smoker) possibly IgE sensitized</td>
<td>Wantke et al. (2000)</td>
</tr>
<tr>
<td>0.27 (mean)</td>
<td></td>
<td></td>
<td>No specific FA IgE antibodies of significance, i.e. sensitization</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>12 grass pollen asthmatics† (7 men, 5 women)</td>
<td>25 (18–44) 60</td>
<td>No effects on lung functions (PFV and FEV1)</td>
<td>Ezratty et al. (2007)</td>
</tr>
<tr>
<td>0.5</td>
<td>10 healthy (men) 10 asthmatics† (7 men, 3 women)</td>
<td>(19–49) (23–52) 120</td>
<td>No effects after post inhalation of grass pollen</td>
<td>Krakowiak et al. (1998)</td>
</tr>
<tr>
<td>0.85</td>
<td>15 asthmatics (7 men, 8 women)</td>
<td>25 (15–36) 90</td>
<td>No effects on airway resistance, lung functions (FEV1 and bronchial activity). No delayed reactions</td>
<td>Harving et al. (1990)</td>
</tr>
<tr>
<td>0; 0.6; 1.2; 2.4; 3.7</td>
<td>19 non-smoking (10 men, 9 women) 9 (out of 19)</td>
<td>26 (21–31) 180</td>
<td>No effects on airway resistance, lung functions (FEV1) and bronchial activity. No delayed reactions</td>
<td>(Kulè et al., 1987; Kulle, 1993)</td>
</tr>
<tr>
<td>1.4 (mean) ≥ 0.7</td>
<td>38 phys. therapy students‡ (9 men, 29 women)</td>
<td>25 (14/14 weeks) 150</td>
<td>1–1.5% decrease of lung function (FEV1); the effect diminished after 4 weeks</td>
<td>Kriebel et al. (2001)</td>
</tr>
<tr>
<td>0.08–1.4</td>
<td>95 patients ‡</td>
<td>44 (18–65) 30</td>
<td>No or few effects on lung functions Few cases of rhinitis</td>
<td>Airaksinen et al. (2008)</td>
</tr>
<tr>
<td>0.9/0.6 (personal/mean)</td>
<td>150 medical students, 1st year§ (189 medical students, 3rd–4th year)</td>
<td>60–180</td>
<td>No differences in FEV1 and FVC among 22 randomly selected male and female subjects after first day and after end of dissection period</td>
<td></td>
</tr>
<tr>
<td>1.6–3.1 (breathing zone)</td>
<td>50 medical students‡ (men/women 1:1) 36 phys. therapy students§ (8 men, 28 women)</td>
<td>24</td>
<td>No dose–response relationship between increase of lung functions (FVC, FEV1, FEV3, FEF) and FA</td>
<td>(Akbar-Khanzadeh and Mlynek, 1997)</td>
</tr>
<tr>
<td>0.2–11.2 (mean)</td>
<td>167 medical students‡ 67 premedical#</td>
<td>24 20</td>
<td>IgE was not associated with FA exposure</td>
<td>(Kim et al., 1999)</td>
</tr>
</tbody>
</table>

† Double-blind controlled exposure study. † Control group. ‡ Field/epidemiological study. § If not otherwise stated.
concentration of typical indoor VOCs does not result in sensory irritation over 3 h of exposure. Reported complaints of sensory irritation in eyes and upper airways have been associated with concentrations about 0.4 mg/m³ FA and other exposures in recently renovated offices (Proietti et al., 2004) and at about 0.9 mg/m³ FA among anatomy students during a dissection course (Wei et al., 2007).

6. Nasal histopathological changes

OEHHAn has suggested 8-hour and chronic reference exposure levels of 0.009 mg/m³ for protection of adverse non-cancer health effects, i.e. histopathological changes in the nasal cavity, on the basis of an occupational study of chemical plant workers (Wilhelmsson and Holmström, 1992). The reference exposure levels were derived by use of a NOAEL value of 0.09 mg/m³, i.e. mean FA concentration of the control group, and an assessment factor of 10 for protection of potential asthma exacerbation in children. The original data of this study, however, was published earlier to be discussed below (Holmström et al., 1989).

The study included 70 chemical plant workers, where FA and FA-based resins were produced, 100 furniture workers in five different plants, and 36 controls, mainly office workers. The mean FA concentration was 0.3 mg/m³ (range: 0.05–0.5 mg/m³) with frequent FA peaks above 1 mg/m³ in the chemical plant. The mean exposure duration was 10.4 years. The furniture workers were exposed to 0.2–0.3 mg/m³ FA that seldom exceeded 0.5 mg/m³. The mean wood dust concentration was 1–2 mg/m³ and the mean exposure duration was 9 years. The mean FA concentration was 0.09 mg/m³ for the controls.

Nasal biopsies were evaluated by means of a nine point scale (score: 0–8), where category 1 was “stratified cuboid epithelium with loss of ciliated epithelium” and category 2 “mixed stratified cuboid/cuboidal squamous epithelium”. The mean nasal biopsy score was 1.56 (range: 0–4) in the controls, 2.07 (range: 0–6) in the furniture workers that was statistically insignificant, and a statistically significant 2.16 (range: 0–4) score in the chemical plant. The histopathological scores were not exposure dependent within the FA exposure groups themselves; the exposure metrics that were used were: current FA concentrations (both FA groups were divided into exposure groups 0.1–0.24, 0.25–0.49 and ≥0.5 mg/m³ FA), current wood dust concentrations (furniture workers were divided into exposure groups 0.1–1, 1.1–2, and 2.1–4.9 mg/m³), cumulative FA exposures (both FA groups divided into <1.5, 1.5–4.9, and ≥5 mg/m³×years), and exposure duration (≤5, 5–14, 15–24, and ≥25 years). Although the study showed histopathological changes in the FA group, the absence of an exposure-dependent effect encumbers creation of a threshold value.

7. Lung function effects and airway allergy

7.1. Sensitization hypotheses

Formaldehyde alone induces no IgE sensitization either in rodents, e.g. (Gu et al., 2008), or in humans, e.g. (Hilton et al., 1996; Wantke et al., 2000), see Table 2. The cytokine production in local lymph nodes remained unaltered in FA exposed mice indicative of no respiratory sensitization (de Jong et al., 2009). Epidemiological studies of the occupational environment have not indicated an increase of sensitization to FA exposure in agreement with (Paustenbach et al., 1997), see also Table 2.

Formaldehyde induced sensitization has been hypothesized and two main causes have been suggested, inflammation and FA acting as an adjuvant for allergens. These are not supported at normal indoor air concentrations, since inflammatory mediator response was absent at the exposure of human lung epithelial cells at 0.25 and 0.05 mg/m³ FA, respectively (Pariselli et al., 2009; Persoz et al., in press), compared to clean air; even, the FA concentration was about 10–50 times higher than would be expected to reach the human lung at a 0.1 mg/m³ indoor air FA concentration, see also (Gerde, 2008). Further, inflammation was unobservable in life-long exposure of rats to 1.2 mg/m³ FA (Woutersen et al., 1989).

Rodents immunized by intraperitoneal administration to the allergen ovalbumin and followed by different airborne FA exposures after sensitization have been reported to increase lung inflammation,
decrease lung function, and increase allergen specific IgE antibody levels, e.g. (dos Santos Franco et al., 2009; Qiao et al., 2009; Gu et al., 2008). The interpretation of these studies with intraperitoneal administration, however, is not clear for risk assessment of indoor FA. Recently, TNFα pre-sensitized human lung cells exposed to 0.05 mg/m³ FA showed a significant increase of IL-8, an inflammatory marker (Persoz et al., in press); however, the FA concentration is about five times higher than would be expected to reach the lungs at a 0.1 mg/m³ indoor air FA concentration. It is thus not clear how the result as a whole can be used for risk assessment of FA.

Formaldehyde has demonstrated altered thiol biology from accelerated enzymatic reduction of endogenous bronchodilator S-nitrosoglutathione suggesting a mechanistic link between FA and lung effects (Thompson et al., 2008). The FA concentrations, however, used in the cited rodent studies in the Thompson et al. paper are high (6 mg/m³) and far above indoor air exposures to be considered relevant for risk assessment. Thus, evidence of lung effects must depend on human data.

7.2. Human exposure studies

Human exposure studies have generally found that both healthy and asthmatic subjects exposed to FA below 1 mg/m³ up to 4 h had uncompromised lung function, e.g. (Ezratty et al., 2007; Harving et al., 1990; Krakowiak et al., 1998; Sauder et al., 1987), see Table 2.

Studies about the possible exacerbation of the lung function of asthmatics, sensitive to grass pollen and dust mites, by combined exposure to an allergen and FA has been reported. The studies entailed FA exposure followed by inhalation of the allergens (outside of the season for pollens). In one cross-over study, increasing doses of inhaled grass pollen post-0.5 mg/m³ FA exposure for 1 h to 12 subjects with grass pollen allergy did not affect the lung function over an 8-hour period (Ezratty et al., 2007). The particle size distribution of the grass pollen equalled 20–40 μm (Ezratty, 2008, private communication). FA did not significantly increase the bronchial responsiveness to the allergen and the allergen-induced increase in methacholine responsiveness was unchanged. Inflammatory mediators (cytokines, eosinophils, and neutrophils) in sputum were unaffected; even, a non-significant protective lung effect of FA was observed, as in two field studies (Kriebel et al., 2001; Wantke et al., 2000).

In another study, the bronchial response increased in 19 house-dust sensitive asthmatics exposed to dust mite allergen (Der p1; mean particle size 11 μm) by prior oral breathing to 0.1 mg/m³ FA for 30 min. FEV1 decreased 20% (PD20) by an allergen dose of 34 ng after the FA exposure, but borderline significance at 45 ng (Casset et al., 2006). At this FA concentration, the lung function tests (PEF1, FVC, and FEF25% and 75% of FVC) did not differ between the two conditions of exposure. A 6-hour follow-up showed that maximum FEV1 reduction was significantly higher (mean±SEM: 15±1.6%) at the high FA concentration than at the background concentration (11±1.6%) (p<0.05). We recalculated the difference between the dust mite PD20 dose and the air and FA exposures, respectively, immediately post exposure for each subject from the reported data (Table 2 in Casset et al. (2006)). We obtained the estimated median difference and 95% confidence interval by use of Wilcoxon Signed Rank test (Minitab 15). The estimate was 6.3 (−4.6 to 31.7) that is statistically insignificant. This infers that the statistical outcome depended on the statistical method. Further, we consider the potential effect to have no clinical relevance, because an estimated inhaled allergen dose during 8-hour resting would be less than 1 ng as compared to 34–45 ng in the experiment. The amount is based on standard respiratory rates for resting males, sampled dust mite concentrations, e.g. in mattresses (Hirsh et al., 2006), and assuming a room particle concentration of 100 μg/m³. The estimate agrees with measured airborne concentrations of dust mites (Der f 1) in bedrooms (Park et al., 2002) and living rooms (Raja et al., 2010).

In summary, the exposure of asthmatics to FA and grass pollen or dust mites at indoor air concentrations does not indicate exacerbation of the lung function.

7.3. Epidemiological studies in children

Some case–control and cross-sectional studies have suggested a possible association between low FA exposure and asthma exacerbation. These studies, however, have explored complex co-exposures, which encumber the establishment of cause–effect and dose–response relationships for FA, and the evaluation of confounding effects, cf. (Gilbert, 2005). A number of studies have been unable to find association with FA and lung effects.

FA concentrations (~0.06 mg/m³) measured in bedrooms of 224 healthy children (age 6–13) were not associated with effects on the lung function (FVC and FEV1) (Franklin et al., 2000). Another study was carried out in 80 homes and 148 children (age 7–14) of which 53 were asthmatics. An association (OR=1.40, 0.98–2.00, 95% CI) between FA concentrations and atopy was found with 0.01 mg/m³ increase of FA in the bedrooms. It should be noted that no association was identified between FA concentrations in the bedrooms and asthma incidents and lung effects (Garrett et al., 1999). Between one third and one half of the children were also exposed to environmental tobacco smoke and pets, and possibly pollutants from nearby coalmines and power stations, cf. (Kränke and Aberer, 2000).

Formaldehyde was measured twice in homes (bedroom and living room) of 88 asthmatic children (age <3) and a non-asthmatic control group of 104 children (Rumchev et al., 2002). A FA concentration >0.06 mg/m³ in the bedroom was associated with 30% increase of risk of asthma compared with FA concentrations <0.01 mg/m³. Potential bias as pointed out by the authors was gas heating and new materials in the homes, low air exchange rate, and smoking; other confounding factors, e.g. hospitalization for asthma or “having” asthma, are discussed by Gilbert (2005). Although adjustment of a number of indoor effects was carried out, the result is hampered by difficulty of diagnosing asthma in small children. Perhaps, the most important confounding factor was the presence of elevated concentrations in the homes of benzene, toluene, and xylene), NO2, and SO2 (Rumchev et al., 2004), which are proxies of combustion (traffic). Traffic pollutants are known to be associated with asthma in children, e.g. (Bräbäck and Forsberg, 2003; Delfino et al., 2003); Further, dust mites and TVOC correlated significantly; i.e., the cases may be different apart from asthma and FA exposure, cf. (Dales and Raizenne, 2004). Thus, a direct cause–effect relationship with FA has not been established from this study.

In an analysis of 90 matched pairs of young asthmatic and non-asthmatic children (age 4–17), measured FA in the living rooms and the bedrooms did not differ between the homes of asthmatics and non-asthmatics (Tavernier et al., 2006).

A population based case–control study of asthmatic patients (n = 84) from a paediatrics outpatient department and non-asthmatic children (N = 88) (age 0.5–3) showed that measured FA, VOCs, and dust mites in their homes were all associated with increased risk of having asthma (Pati and Parida, 2005). Diagnostic difficulty and the co-exposures encumber a direct relationship with FA.

Specific FA IgE level decreased in children (age 8), when they moved to a new school with a lower FA concentration (Wantke et al., 1996). The interpretation is unclear, because FA and reported symptoms were not associated. One school study indicated positive association between low FA values and airway effects (Smedje and Norbäck, 2001), while another failed (Zhao et al., 2008). In general, the co-exposures of animal allergens, moisture damage (fungi), outdoor air pollutants, and socioeconomic factors encumber interpretation of the association with FA.

FA specific IgE was measured in 155 Japanese children randomly recruited from outpatient clinics, 122 asthmatics (mean age 9.5) and
33 (mean age 8.8) without allergy (Doi et al., 2003). No correlation was found between severity of asthma and IgE levels and FA concentrations, in agreement with Kim et al. (2001). Formaldehyde specific IgE at low concentrations was detected only in two asthmatic children; one child suffered from severe asthma, while the other suffered from just mild asthma.

In a cross-sectional-based case–control study, comparison of FA, TVOC (total volatile organic compounds) and dampness in homes of 193 children (age 9–11) with persistent wheezing and 223 controls showed that low FA concentration was associated with an increase of wheezing, but this may be interfered with or dominated by the effects of dampness as suggested by the authors (Venn et al., 2003).

In a not yet published paper similar cross-sectional-based case–control study of children (age 9–11) with 245 cases of asthma symptoms within the last 12 months and 329 controls was carried out. It showed no association between FA exposure (median concentration 0.037 mg/m³) in the homes and reported asthma, allergy, adverse lung functions, bronchial hyper-reactivity or sensitization in the children (Genuneit et al., 2007).

In a birth cohort of 378 infants (age 0–1 1/2) mean FA sampled over 10 weeks in child bedrooms was not found to be associated with risk for wheezing symptoms on the basis of diaries reported symptoms (Raaschou-Nielsen et al., 2010).

7.4. Epidemiological studies in adults

Exposures above 1 mg/m³ caused a minor decrease in the lung function among students dissecting cadavers in an anatomy laboratory (Kriebel et al., 2001), an effect that diminished over exposure weeks, cf. (Wantke et al., 2000). Three other studies with exposed students and controls failed to find dose–response relationships (Chia et al., 1992; Akbar-Khanzadeh and Mlynek, 1997; Kim et al., 1999). A limited effect on lung function and rhinitis is in accord with a study of 95 patients with both upper and lower airway symptoms related to work that were challenged with inhaled FA (Airaksinen et al., 2008). FA had no effect, when adjusted for placebo effects, and the authors concluded that IgE-mediated FA allergy was non-existent.

In a prospective study of 998 Japanese pregnant women an association was found between FA concentrations (median/max 0.03/0.16 mg/m³) and atopic eczema, but not with asthma, allergy, and rhinitis (Matsunaga et al., 2008); however, the interpretation of this study is unclear. Another prospective study involved 143 Japanese medical students exposed to a mean personal FA concentration of 3.0 mg/m³. They responded to a questionnaire before and after a course in anatomy, two students, of which one was atopic, showed skin reaction to 1% formalin solution (Takahashi et al., 2007). No association was found between reported asthma in 182 inhabitants from 59 homes and FA concentrations measured in their kitchens (Lovreglio et al., 2009). Only eczema, but not allergic respiratory effects were reported in a study among Finish metal workers exposed to inter alia FA and metalworking fluids (Suuronen et al., 2007).

In a cross-sectional study, VOCs and FA emitted from newly painted surfaces were found to be associated with exacerbated asthma in a study of 252 asthmatics that were compared with 310 non-asthmatics (Wieslander et al., 1997). A low number of affected people, co-exposure to other compounds (e.g. wood smoke, pets, and socioeconomic status), and the possibility of chance effects have been suggested as potential bias, cf. (Dales and Raizenne, 2004; Nielsen et al., 2007b).

The FA concentration did not differ significantly in homes of asthmatics that were recruited from an outpatient clinic in South Korea (n = 36) (mean = 0.054 mg/m³) and non-patient controls (n = 28) without atopy also recruited via the same hospital (mean = 0.043 mg/m³) (Choi et al., 2009).

In summary, below 1 mg/m³ FA consistent cause–effect and dose–response relationships between FA concentrations and lung function effects have not been substantiated in human exposure studies with healthy and asthmatic subjects. Associations between FA and asthma exacerbation or sensitization in children and adults in homes and schools have generally not been convincing, mainly due to confounding factors and susceptibility to chance effects, in agreement with other studies (Paustenbach et al., 1997; World Health Organization, 2002; Dales and Raizenne, 2004).

8. Releasable formaldehyde from particles

Particles, e.g. allergens, have been proposed to carry FA down to the lower airways (Dales and Raizenne, 2004; Overton et al., 2001). However, the amount of released FA into the respiratory tract from 5 mg/m³ of wood particles (>6 μm), that have been exposed to 0.4 mg/m³ FA, is negligible (Gosselin et al., 2003). Formaldehyde release from medium-density fibre board lies between 100–1000 μg/g dust during 6 h in water at 35–37 °C (Priha et al., 2004; Elia and Messmer, 1996). This implies that the maximum amount of releasable FA from inhaled dust particles is only a few μg/day assuming a respirable particle room concentration of 100 μg/m³, a daily respiratory volume of 20 m³, and complete inhalation and deposition. Thus, estimated FA release is insignificant compared to the inhaled amount of gaseous FA per day (1 mg) at a concentration of 0.05 mg/m³, cf. (Risby, 1990), and in agreement with known from FA on ambient particles (Odabasi and Seyfioglu, 2005).

Subjects exposed to 0.5 mg/m³ particles of active charcoal (diam.: 1.4 μm) and 3.5 mg/m³ FA for 2 h reported more coughing and small, but significant decrease of FVC and FEV3 than exposed to FA alone (Green et al., 1989). Similar combined effects have been shown with mice and guinea pigs (Amdur, 1960; Riedel et al., 1996; Tarkowski and Gorski, 1995). However, the FA concentrations are orders of magnitude higher than normally found indoors that encumbers a risk assessment of the clinical importance.

In summary, the reported studies about FA in the wood industry indicate that release of FA into the airways from inhaled particles in indoor environments is negligible in comparison with inhaled gaseous FA.

9. Susceptible subgroups

9.1. Single exposure

Generally, susceptible (or vulnerable) subgroups are represented by children, pregnant women, elderly people (>65 years), and persons suffering from asthma and other respiratory diseases and cardiovascular diseases. It is assumed that different susceptibility is based on age-dependent differences in physiology and toxicokinetics, and responses of existing diseases and genetic factors (Scientific Committee on Health and Environmental Risks (SCHER), 2007).

Susceptibility has seldom been addressed in context of exposure to indoor pollutants. However, a number of human exposure studies do not indicate increased sensitivity among asthmatics exposed to FA (Eratty et al., 2007; Harving et al., 1990; Krakowiak et al., 1998; Sauder et al., 1987).

Higher susceptibility in children has been reported for environmental tobacco smoke and lead (Scientific Committee on Health and Environmental Risks (SCHER), 2007), but no studies have unequivocally indicated a higher susceptibility for FA in children. FA induced DNA-protein cross-linking has been shown in a CFD nasal model to be about 1.5 higher in adults than in children (Firestone et al., 2008), indicative of about 50% lower maximum effective dose in children; thus suggesting they are not more susceptible than adults. This agrees with the predicted FA adsorption rates per unit surface area of the nasal cavity that equals in children and adults (Garcia et al., 2009). The amount of nasal breathing at rest and during exercise appears to be less for children, but the difference from adults is insignificant (Bennett et al., 2008). Thus, the
use of an assessment factor of 10 for children (OEHHA, 2008) is not supported for FA, cf. (Dourson et al., in press).

It has been hypothesized that repeated low concentration exposure to sensory irritants increases the sensitivity to irritants. This hypothesis is counterintuitive, because older persons appear to be less sensitive than younger persons (Doty et al., 2004), and the sensitivity might decrease at age >60 years (Hummel et al., 2003; Wysocki et al., 2003). No new studies have appeared since the (Paustenbach et al., 1997) review that indicates elderly and asthmatics are more susceptible to FA exposure (Arts et al., 2006). Further, sensitization of the airways by exposure of humans to FA has not been found, in agreement with (Appel et al., 2006; Dales and Raizenne, 2004).

9.2. Combined exposure

One study shows that grass pollen sensitive asthmatics are insensitive to FA pre-exposure and subsequent nasal inhalation of grass pollen (Ezraty et al., 2007). Another study indicates that dust mite sensitive asthmatics may be more sensitive to a relatively high dust mite dose after FA exposure during mouth breathing (Casset et al., 2004), and the effect, however, if real, is not considered clinically relevant due to the excessive high mite dose required for demonstration of the effect. Mucosa swelling at 0.13 mg/m³ FA exposure for 2 h in a climate chamber was observed in healthy people suffering from nasal congestion in their homes compared with a control group without nasal congestion (Falk et al., 1994). These results indicate an exacerbating effect over 2 h (p < 0.05). A number of recent studies with rodents sensitized by intraperitoneal administration of ovalbumin and exposed to FA have demonstrated exacerbation of immunized effects; however, a risk assessment of combined airborne exposure of FA with an allergen in humans is not possible from these studies due to dissimilar exposures. A number of epidemiological studies have attempted to associate FA with asthma exacerbation in children, but analysis thereof shows that the studies are biased by inter alia co-exposures with other compounds. No identified association was found in four studies (Doi et al., 2003; Genuneit et al., 2007; Raaschou-Nielsen et al., 2010; Tavernier et al., 2006), while the Rumchev et al. study (Rumchev et al., 2002) in children is hampered inter alia by co-exposures of FA with combustion products known to be associated with asthma in children, and thus, this study is invalid for derivation of a guideline.

10. Conclusion

The FA average concentration in homes is generally below 0.05 mg/m³ and below half of that in offices in the Western world, except in cases of new and renovated housing, or with the presence of sources such as new furnishing. The primary ways to control FA exposure are through reduction of FA sources in new housing and furnishings and increase of the air exchange rate. Additional precautions are elevated temperature and relative humidity that increase the emission rate of FA from wood-based materials and ozone-initiated production of FA from products that emit unsaturated VOCs, e.g. fragrances.

The odor of FA is considered perceivable by a major fraction of the population below 0.1 mg/m³ without an interfering background. This is important to consider, because reported sensory irritation may be induced by its odor. Thus, guidelines for sensory irritation that solely rely on reporting of sensations may be biased towards a value lower than measured sensory irritation. This may also be the case for FA, because the odor threshold for FA appears to be about fivefold lower than the threshold of 0.36 mg/m³ for reported eye irritation. An increase of eye redness and blink frequency at 0.6 mg/m³ may not necessarily result in chemosensory perception.

Neither experimental nor epidemiological studies of adults and children have identified lung effects at FA exposure below 1 mg/m³; this agrees with the high retention of FA in the nasal cavity. No evidence points to a major increase of FA induced airway susceptibility among children, elderly, and asthmatics. However, people with a personal trait of negative affectivity may report more eye and airway symptoms. Epidemiological studies with minimum of chance effects and confounding are lacking; in particular, exposure effects of FA on children and adults suffering from nasal congestion should be reinvestigated. The effect of combined exposures of FA with common allergens of different particle sizes needs to be reinvestigated in human exposure studies.

An indoor air guideline of maximum 0.100 mg/m³ (0.08 ppm), protective of the general population against acute and chronic sensory irritation, agrees with both a recent and old human exposure study by applying an assessment factor of 5 assuming log normal distribution.

Acknowledgements

The work was partially carried out in the framework of WHO Indoor Air Quality Guideline development (2006–2010). Partial support was also obtained from the Centre for Indoor Climate and Diseases in Dwellings supported financially by Real Dania. We are grateful to Dr. W.S. Cain for helpful comments and suggestions. The authors declare no conflict of interests.

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