



Review

Reactive indoor air chemistry and health—A workshop summary

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ABSTRACT

The chemical composition of indoor air changes due to the reactive nature of the indoor environment. Historically, only the stable parent compounds were investigated due to their ease of measurement by conventional methods. Today, however, scientists can better characterize oxidation products (gas and particulate-phase) formed by indoor chemistry. An understanding of occupant exposure can be developed through the investigation of indoor oxidants, the use of derivatization techniques, atmospheric pressure detection, the development of real-time technologies, and improved complex modeling techniques. Moreover, the connection between exposure and health effects is now receiving more attention from the research community. Nevertheless, a need still exists for improved understanding of the possible link between indoor air chemistry and observed acute or chronic health effects and long-term effects such as work-related asthma.

1. Introduction

Indoor chemicals' oxidation processes can be driven in the gas phase by oxidants like ozone (O₃), hydroxyl radicals (OH) and nitrate radicals (NO₃) and can lead to the formation of oxygenated species (e.g. formaldehyde) and secondary organic aerosols (SOA). Detection and quantification of these oxidants in conjunction with oxidant precursors, reactants, and the reaction products (such as oxygenated organics, organic nitrates, SOA) are necessary to understand the oxidation processes indoors. This capability to measure oxidized species is important for characterizing the numerous contributions (emission, outdoor input, homogeneous and heterogeneous chemistry, ...) that can lead to their formation, as well as gas- and surface-phase chemistry that can lead to their removal and the formation of new oxidation products.

Oxidative chemistry occurring indoors leads to the formation of several traditionally observed organics such as aldehydes (e.g. formaldehyde), ketones (e.g. acetone), carboxylic acids, esters, epoxides and dicarbonyls (Atkinson and Arey, 2003; Finlayson-Pitts and Pitts, 2000); if their vapor pressure is sufficiently low, SOA are formed. However, numerous other oxidized species, such as primary/secondary ozonides, peroxides, organic nitrates, and multi-functional organics (e.g. hydroxy and nitroxy alkyl radicals, peroxy-hemiacetals, and carbonyl nitrates), and polymeric species are also generated indoors and

require specialized detection methods (Atkinson and Arey, 2003; Docherty et al., 2005; Epstein et al., 2010; Li et al., 2002; Mutzel et al., 2013; Nørgaard et al., 2013; Tobias and Ziemann, 2000). Characterizing the formation (identification and yields) of these products and their respective phases (gas or particulate) in the indoor environment may help to resolve the gap between indoor occupant exposure and health effects. Understanding the physiological responses to these exposures is also a challenging endeavor. Potential avenues leading to health effects in the airways and the cardiovascular system include: sensory irritation, inflammatory reactions in the airways, sensitization, heart rate effects, delayed physiological response, and possibly dermal exposure routes (Nazaroff and Goldstein, 2015; Weschler and Nazaroff, 2012).

In an effort to highlight the recent developments toward understanding indoor air quality (IAQ), a session entitled "Reactive Indoor Air Chemistry and Health" was held at the 14th International Conference on Indoor Air Quality and Climate (Indoor Air 2016) in Ghent, Belgium, July 3–8, 2016. The workshop presentations included the following topics: The Role of Oxidants, Analytical Technologies, Modeling, and Health Effect Studies. Each of these topics will be discussed in a separate section below. While this summary is not all inclusive, it provides a current update of the topics highlighted above, recognizing that "reactive chemistry", *per se*, is a much broader field,

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see e.g. (Uhde and Salthammer, 2007).

2. Role of oxidants: sources and impact on the indoor air quality

The limited number of oxidant (O_3 , OH, and NO_3) measurements is due to both concentration and analytical challenges. There are commercially available instruments to measure the concentration of indoor O_3 which is about 10^{11} molecules cm^{-3} (a few dozen ppb). However, indoor O_3 concentration is strongly dependent on the air exchange rate (AER) and the outdoor concentration. OH and NO_3 are even more challenging to measure because their concentrations have been estimated to be 10^5 and 10^7 molecules cm^{-3} (4×10^{-3} and 0.4 ppt), respectively, and being highly reactive, they are difficult to collect and analyze (Sarwar et al., 2003). Only one article reports a measurement of the sum of N_2O_5 and NO_3 concentrations indoors in the range of 10^7 – 10^8 molecules cm^{-3} (Nøjgaard, 2010). Existing instruments, developed for atmospheric measurements could be deployed in the future (Fuchs et al., 2008) to characterize NO_3 and other species such as N_2O_5 (Goulette et al., 2016; Schuster et al., 2009; Womack et al., 2017).

For OH radicals indoors and more generally HO_x (OH and hydroperoxyl (HO_2) radicals), advances in optical spectroscopy and detection technologies have contributed to improved characterization of these elusive species. Instruments based on spectroscopic techniques (Fluorescence Assay by Gas Expansion, FAGE) capable of measuring real-time OH and HO_2 radicals have already been deployed by two groups: Lille (France) (Blocquet et al., 2016; Gómez Alvarez et al., 2013) and Leeds (United Kingdom) (Carslaw et al., 2017) to quantify HO_x in different buildings under different conditions.

Two major sources of HO_x radicals have been identified: the photolysis of nitrous acid (HONO) and the reaction of O_3 with alkenes (Blocquet et al., 2016; Carslaw et al., 2017; Gómez Alvarez et al., 2013; Mendez et al., 2017a; Weschler and Shields, 1996). Measurements indicate multiple sources of HO_x and the relative importance of each source will depend strongly on the ambient conditions, an association that has been implicated in recent models (Carslaw, 2016; Mendez et al., 2017a). Compared to predicted and previously measured indoors (Sarwar et al., 2003; Weschler and Shields, 1997; White et al., 2010), high concentrations (up to 10^7 molecules cm^{-3} for OH) have been measured during the use of an air cleaning device and cleaning products (Carslaw et al., 2017).

The investigation of indoor radical concentrations has highlighted the need for numerous ancillary measurement techniques such as: the sunlight transmission through windows to quantify the photolysis processes and the light distribution in the room (Gandolfo et al., 2016; Kowal et al., 2017), the radicals' precursors (HONO, O_3 , alkenes, ...), species involved in the recycling of the radicals (like NO), and a better understanding of the linkage of heterogeneous processes (especially HONO production) on indoor surfaces (Gómez Alvarez et al., 2014; Mendez et al., 2017b). These investigations have also challenged previous assumptions about indoor oxidation pathways such as photolysis indoors. Additionally, recent research using high temporal resolution instruments such as proton-transfer reaction mass spectrometry (PTR-MS) investigated the potential of occupants to contribute to indoor chemistry (Tang et al., 2016; Wisthaler and Weschler, 2010) and showed that occupants can react with ozone and emit oxidized organic compounds (Liu et al., 2016, 2017; Tang et al., 2015; Zhou et al., 2016a,b). There is continuous development of new methods for the detection of transient oxidant species, related intermediate species (like peroxy radicals RO_2) for atmospheric applications (Tan et al., 2016; Whalley et al., 2013), and parameters such as the OH reactivity (representing the sum of OH removal reactions) (Blocquet et al., 2016; Fuchs et al., 2017). There is also interest in developing the use of these instruments in indoor environments to better characterize the gas-phase chemistry. Complementary research concerning kinetic studies of interest for indoor chemistry (Borduas et al., 2016) and measurement in real conditions are needed to evaluate its impact.

3. Analytical technologies: methods/instrumentation for indoor air contaminants

3.1. Gas-phase and particulate-phase measurements

As discussed above, understanding volatile organic compounds' (VOC) oxidation indoors is important for assessing gas-phase and particulate-phase occupant exposure. Thus, collection and transport of compounds without degradation for off-line laboratory analysis becomes relevant. Several methods have been used for field measurements that maintain compound stability until analysis, such as: active and passive desorption sampling tubes, canisters, annular denuders, impingers, and solid-phase microextraction (SPME) and chemical derivatization (Forester and Wells, 2009; Ham et al., 2016, 2015; Harrison and Wells, 2013; Jackson et al., 2017; Plog, 2012; Wells and Ham, 2014).

Gas-phase oxidation products have been measured using Fourier transform infrared spectroscopy (FTIR), gas and high-performance liquid chromatography/mass spectrometry (GC/MS and HPLC/MS), but recent techniques such as PTR-MS and atmospheric-pressure ionization mass spectrometry (API-MS) provide the advantage of real-time or near real-time data of target compounds coupled with high sensitivity (Cochran et al., 2016; Nozière et al., 2015).

The need to characterize gas- and particle-phase species in real-time continues to grow. Current real-time instrumentation typically collects information on total organics for the gas-phase species and particle number, size, surface area and distribution over time for the particulate-phase (Stefaniak, 2016). Manufacturers and academia have worked to address this need through the development of miniature GC/MS devices and gas-specific sensors; however, chromatography limits, power requirements, sensor "fouling", and the sheer number of potential oxidized compounds continue to plague their integration into the field (Brüggemann et al., 2015; Laborie et al., 2016; Nölscher et al., 2012; Wang et al., 2015; Wolf et al., 2016; Wolf et al., 2015a,b; Zhou et al., 2015).

3.2. Reactive oxygen species (ROS)

Reactive oxygen species can occur indoors (Fan et al., 2005) and include chemical species such as peroxides ($ROOR'$), OH, superoxide (O_2^-), hydrogen peroxide (H_2O_2), HO_2 , hypochlorite ions (OCl^-) and O_3 . Exposure to these species could induce oxidative stress in the respiratory tract and other areas such as skin (Brem et al., 2017; Kehrer, 1993; Klaunig and Kamendulis, 2004; Schuch et al., 2017). Indoor ROS concentrations have been measured by derivatizing them with 2',7'-dichlorofluorescein diacetate to form the fluorescent compound, dichlorofluorescein (Hung and Wang, 2001; Venkatachari et al., 2005). Indoor air ROS is determined as a concentration, yet actual chemical structural information remains elusive (Hopke et al., 2011; Khurshid et al., 2014, 2016; Liu and Hopke, 2014; Pavlovic and Hopke, 2011).

4. Modeling to characterize personal exposure to reactive chemistry

Exposure is defined as the time integral of concentration between relevant time durations of interest. Utilizing the U.S. National Research Council 1983 Risk Assessment Paradigm, once hazard identification occurs, exposure and dose-response assessments occur in parallel and are combined to provide information on the risk characterization, for which a risk management program may be developed if warranted. One problem with using modeling within this approach is that modeling typically predicts indoor, not personal concentrations, which is the most relevant parameter for exposure assessments. However, combining computational fluid dynamics (CFD) with reactive chemistry modeling could be used to develop personal factors, PF, defined as $PF = (\text{personal exposure concentration}/\text{room concentration})$, in the future for a variety

of typical scenarios. However, modeling is beneficial within this risk assessment paradigm in that some reactive chemistry products, such as short lived intermediates (e.g. radicals) or highly oxidized compounds, cannot be measured indoors without highly sophisticated equipment as described above, so modeling can fill this informational gap.

For this discussion, reactive chemistry models are broadly classified into reduced-order, inexplicit models *versus* detailed, largely explicit manifestations. One advantage of reduced order models is that they are less computationally intensive than detailed models, so they are useful in large modeling efforts such as Monte Carlo frameworks, which use probability distributions as inputs in mechanistic models to bound uncertainty and/or understand stochastic influence (Saltelli et al., 2006).

For instance, studies have used Monte Carlo approaches with reduced-order models to explore indoor oxidation and SOA formation from VOC oxidation as described above. To parameterize formation, modelers use the aerosol mass fraction, $AMF = (\text{SOA mass formed} / \text{VOC mass reacted})$, which is an empirical parameter, not constant, and varies with the SOA concentration, compound class, and O_3 -to-VOC ratio for alkenes. The AMF frameworks lump the many semi-volatile organic compounds (SVOCs) generated by VOC/ O_3 reactions that can form SOA into groups delineated by volatility, and overall partitioning is owing to the sum of the individual group behaviors (Odum et al., 1996; Presto and Donahue, 2006). The AMF has been measured for ozonolysis of VOC under indoor relevant conditions, for instance for α -pinene (Chen and Hopke, 2009b; Youssefi and Waring, 2015), limonene (Chen and Hopke, 2010; Waring, 2016; Youssefi and Waring, 2014), α -terpineol (Yang and Waring, 2016), and linalool (Chen and Hopke, 2009a).

Waring (2014) used a variant of the modeling framework first set forth in Youssefi and Waring (2012) in a Monte Carlo framework to predict the fraction of fine particle mass of SOA and determinants of SOA formation strength in residences. This application was insightful since SOA formation had been anecdotally observed, but actual bounds of its strength in buildings were little studied. Distribution data were derived using the Relationship of Indoor, Outdoor, and Personal Air Study (RIOPA) (Weisel et al., 2005), which measured AERs, aerosol deposition rates, outdoor and indoor VOCs, and organic and inorganic aerosol in 300 U.S. homes. Waring (2014) predicted that the median SOA concentration was $1.0 \mu\text{g}/\text{m}^3$, much less than median total organic and fine aerosol concentrations of 8.7 and $17 \mu\text{g}/\text{m}^3$, respectively (Waring, 2014). However, the Monte Carlo approach demonstrated that for certain combinations of parameters realized in the RIOPA dataset (low AER, high O_3 , and high terpenes), SOA formation was greater than ~50% of indoor organic and ~30% of fine aerosol for ~10% of homes. Relatedly, other Monte Carlo efforts have examined indoor O_3 alone, since it is a driver of indoor chemistry with pulmonary effect (World Health Organization, 2006). Morrison et al., (2011) explored setting maximum O_3 emission rates from consumer appliances, Rackes and Waring (2013) investigated the impact of demand controlled ventilation (DCV) on O_3 in U.S. offices, and Waring and Wells (2015) explored sources and sinks of oxidants in U.S. residences.

Detailed chemical models for indoor air have strengths that differentiate them from reduced order inexplicit models. There is a wealth of chemical detail inherent within their design, which permits the user to investigate reaction pathways and products. For instance, the Indoor air Detailed Chemical box Model (INDCM) (Carslaw, 2007; Carslaw et al., 2015) contains around 5000 species and 20,000 reactions and is based on a detailed chemical mechanism called the Master Chemical Mechanism (MCM) (<http://mcm.leeds.ac.uk/MCM/>; Jenkin et al., 1997). Given that measurements are only available for a small sub-set of these 5000 species, model predictions provide insight that is not possible by current measurement techniques.

Results from detailed chemical models have provided some useful insights with regards to how people are exposed to reactive chemicals indoors. One interesting revelation has been the importance of radical

species indoors, particularly the OH radical. Carslaw (2007) demonstrated with the INDCM that many reaction fluxes involving radical species were of similar magnitude indoors to outdoors. Although photolysis processes involving ultraviolet (UV) light were significantly diminished indoors compared to outdoors (factor of ~100), those involving longer wavelengths of light such as carbonyl photolysis were only 2–3 times lower than outdoors. Oxidation of VOCs by OH can also proceed at a similar rate indoors and outdoors: although OH concentrations are typically lower indoors than outdoors by a factor of 5–10 (Carslaw, 2007; Sarwar et al., 2003), VOC concentrations show the reverse trend.

Another insight provided through detailed chemical modeling is the range of secondary species in indoor air. Using the INDCM highlighted the important secondary species that follow cleaning activities (Carslaw, 2013). For limonene the preliminary reactions have been studied in a kinetics laboratory, but then much of the mechanism is assembled via the MCM protocol (through analogy and structure activity relationships). Note that for 3-isopropenyl-6-oxo-heptanal (IPOH) and 4-acetyl-1-methylcyclohexene (4-AMCH), the human reference values have been derived for airway effects (Wolkoff et al., 2013). The modeling study suggests they do not reach high enough values during typical cleaning activities to cause health effects, but there is little information about most of the other species (see Health effects section). Many research groups have confirmed the presence of IPOH from limonene oxidation, although the experimental existence of 3-acetyl-6-oxoheptanal (3-AOH) in the same system depended on the co-concentrations of OH or O_3 (Grosjean et al., 1992; Wells and Ham, 2014; Weschler and Shields, 1999).

The INDCM has also been used to investigate the surface composition of SOA following cleaning with a limonene-containing cleaner (Carslaw et al., 2012). A key finding is the importance of nitrated and peroxide material at the surface of the particles. There has been little focus on nitrated material in indoor SOA to date, despite Weschler suggesting such species could be important indoors more than 15 years ago (Weschler, 2001). This could be because many of the laboratory studies investigating particle formation following limonene oxidation have been carried out under low NO_x conditions (~30 ppb; 7×10^{11} molecules cm^{-3}) (Carslaw et al., 2012). However, such conditions are not always relevant for indoors. Outdoors, organic nitrates are common components of ambient sub-micron particles: a study of high- NO_x (500 ppb; 1.2×10^{13} molecules cm^{-3}) photo-oxidation of limonene found that organic nitrates comprised ~36% of SOA mass (Rollins et al., 2010) further suggesting the potential for organic nitrates to be important components of indoor SOA. Also, recent work by the National Institute for Occupational Safety and Health (NIOSH) on terpene oxidation in the presence of varying NO concentrations suggested that nitrate formation occurred (Ham et al., 2016).

The potential importance of peroxides in the aerosol phase following limonene oxidation has been suggested previously (Fan et al., 2005; Nazaroff and Weschler, 2004). Like organic nitrates, peroxides are challenging to measure. Peroxides formed from terpene oxidation have been shown to contribute significantly (47 and 85% for α - and β -pinene, respectively) to the total SOA mass in NO_x -free chamber experiments (Docherty et al., 2005). Peroxides and nitrated species may be more important for exposure indoors than outdoors, owing to their much lower photolysis rates and hence longer lifetimes indoors (Chen and Hopke, 2009b; Fan et al., 2005).

A more direct link to exposure was described by Terry et al., (2014), who used a reduced version of the INDCM (19 species, 44 reactions) and combined it with the INDAIR/EXPAIR modeling framework that aimed to simulate frequency distributions of indoor concentrations (INDAIR) and personal exposures to air pollutants (EXPAIR) within urban populations (Dimitroulopoulou et al., 2006). The reduced model was used to show that IAQ deteriorated during heatwave conditions, when high outdoor temperatures were accompanied by high outdoor and hence indoor O_3 and PM. There was a particularly important

impact on the time of day of cleaning. If cleaning was carried out at the start of the day (with a limonene-containing cleaner), outdoor and hence indoor concentrations of O_3 and those of reaction products indoors formed through chemistry were relatively low. However, office workers would then begin work while reaction product concentrations remained elevated for several hours (e.g. at an AER of 1.5 h^{-1} , formaldehyde concentrations were 6.7 ppb compared to 5.7 ppb with no cleaning). Cleaning at the end of the working day led to higher reaction product concentrations as indoor O_3 concentrations were higher relative to the morning (for the same AER, formaldehyde concentrations were 14.8 ppb compared to 8.9 ppb with no cleaning). Although office workers had gone home, the cleaners were subjected to higher concentrations than if they carried out their tasks in the morning.

5. Health effect studies

5.1. *In vitro* technologies to assess health effects

In vitro testing approaches have been applied in the last decade to assess acute airway effects from chemical species in indoor air (Rohr, 2013).

For *in vitro* health effect studies of indoor air compounds, so far mostly single-cell models consisting of lung epithelial cell types have been used for air-liquid-interface (ALI) exposures (Anderson et al., 2010; Bardet et al., 2014; Doyle et al., 2004).

Different *in vitro* studies have indicated that the exposure of lung epithelial cells to reaction products from major indoor air compounds and O_3 may produce more severe effects compared to the parent compounds (Anderson et al., 2013; Doyle et al., 2004; Gaschen et al., 2010; Pariselli et al., 2009; Sexton et al., 2004; Zavala et al., 2016). The measured toxicity outcome seems, however, to vary depending on the physiology and sensitivity of the applied cell/tissue model (Anderson et al., 2013; Doyle et al., 2004; Lipsa et al., 2016; Persoz et al., 2012), as well as the specific aerosol exposure set-up. Related to the latter, the main parameters introducing variability among different studies include: the applied methods for atmosphere generation, premixing of atmospheres in environmental chambers of different dimensions showing variable AERs and reaction times, the *in vitro* aerosol exposure technique such as placement of cell cultures directly in the test (Ayyagari et al., 2004; Doyle et al., 2004; Liu et al., 2013), in-line coupling of the exposure atmosphere to a CULTEX® or VITROCELL® device containing cells (Gminski et al., 2010; Pariselli et al., 2009; Persoz et al., 2010), or magnetic nanoparticle-mediated SOA deposition onto the cells (Jang et al., 2006), *in vitro* aerosol exposure flow rate and humidification, and lastly the chemical doses and exposure duration (Anderson et al., 2013). The classical toxicity endpoints studied so far include cell proliferation, cell membrane integrity, oxidative stress, pro- and/or anti-inflammatory response, and DNA damage. Among these upregulated mRNA expression and/or secretion of inflammatory cytokines, such as interleukin (IL)-8, seems to be most sensitive and consistent indicators of cell homeostatic interruption at chemical concentrations that do not affect cell viability (Bardet et al., 2014; Gaschen et al., 2010; Kastner et al., 2013; Lipsa et al., 2016; Rohr, 2013).

Additionally, the use of advanced *in vitro* cell models, e.g. co-cultures consisting of different cell types (Klein et al., 2013; Rothen-Rutishauser et al., 2005), tissue slices (Switalla et al., 2010), or 3D reconstructed lung tissue models (Anderson et al., 2013; Zavala et al., 2016), that capture in a realistic way the lower airway physiology in healthy or diseased conditions, and allow for chronic or repeated, low-dose exposure (Anderson et al., 2010, 2013; Bardet et al., 2014; Kastner et al., 2013) may further improve the predictive capacity for humans. Finally, to be able to use *in vitro* ALI exposure methods as a valuable proxy for real-life exposure situations and supplement to animal studies, further integration of cell biological and aerosol characterization disciplines, and in-depth validation with inhalative *in vivo* studies and standardization of the various aspects related to such methods is needed

(Paur et al., 2011).

5.2. Animal studies for health effect assessment

A number of acute airway effects studies of ozone-terpenes reaction mixtures in rodents have been reviewed by Rohr (2013). The major effects were sensory irritation in the upper airways with some minor effects observed in the conducting airways, while inflammation was not observed. For instance, bronchoalveolar lavage (BAL) in mice exposed repeatedly to O_3 -initiated limonene oxidation products for 10 days showed no signs of inflammation and did not cause elevated development of airflow limitation or inflammation in the airways; sensory irritation was the major effect observed (Wolkoff et al., 2012). Based on the study, it was concluded that $O_3 < 200\text{ }\mu\text{g}/\text{m}^3$ (0.1 ppm; $2.5 \times 10^{12}\text{ molecules cm}^{-3}$) would be safe, even at high levels of limonene. About 75% of the sensory response could be assigned to formaldehyde and residual limonene (Wolkoff et al., 2008); however, moderate airflow limitation (bronchoconstriction) was also observed (Rohr et al., 2002; Wolkoff et al., 2008). The O_3 -initiated limonene products in a reaction mixture showed no biological response from denuded SOA regarding sensory effects or airflow limitation (Wolkoff et al., 2008).

In one study, F344 rats and ApoE $^{-/-}$ mice were exposed for seven days to denuded α -pinene SOA ($200\text{ }\mu\text{g}/\text{m}^3$), derived from UV radiation of a mixture of NO_2 (+/- SO_2) and α -pinene (McDonald et al., 2010). Pulmonary inflammation was not observed in either mice or rats. The authors suggested the gaseous products to be of concern rather than SOA. Furthermore, the biological response was mild, also for cardiovascular effects. Further, denuded SOA generated from $1670\text{ }\mu\text{g}/\text{m}^3$ (300ppb; $7.4 \times 10^{12}\text{ molecules cm}^{-3}$) α -pinene and $975\text{ }\mu\text{g}/\text{m}^3$ (500ppb; $1.2 \times 10^{13}\text{ molecules cm}^{-3}$) O_3 did not show clear pulmonary or systemic responses in rats, cf. (Rohr, 2013).

Interestingly, limonene may act as a scavenger for O_3 and ROS (inflammatory mediators); for instance, as a local scavenger in the airways. Thus, an anti-inflammatory prophylactic effect of limonene alone has been shown in rodent inhalation models of allergic inflammation (Bibi et al., 2015; Hirota et al., 2012; Keinan et al., 2005) and also in a mice inhalation model for the O_3 /limonene system (Hansen et al., 2013, 2016). Anti-inflammatory effects in lungs have also been suggested for linalool (Huo et al., 2013).

5.3. Human health effect studies

Three human exposure studies have been carried out under controlled conditions in climate chambers. The studies aimed to explore both acute symptoms (sensory reactions) and inflammatory reactions in the airways. In the first one, young women ($n = 130$) were exposed to a typical indoor mixture with 23 VOCs (TVOC = $26\text{ mg}/\text{m}^3$), including α -pinene (162 ppb, $0.9\text{ mg}/\text{m}^3$, $4 \times 10^{12}\text{ molecules cm}^{-3}$) and limonene (126 ppb, $0.7\text{ mg}/\text{m}^3$, $3 \times 10^{12}\text{ molecules cm}^{-3}$), for 140 min in a controlled climate chamber (25 m^3 , 1.8 h^{-1}). The subjects' perception was masked by butyl acetate prior to the exposure. The mixture was used as such or mixed with O_3 resulting in a residual concentration of $0.08\text{ mg}/\text{m}^3$. No sign of inflammatory effects in nasal lavage was seen (Laumbach et al., 2005). The symptom rating was marginal and not statistically significant with or without O_3 (Fiedler et al., 2005). The excess of VOCs may have scavenged the effects of the reaction mixture. In the second study, young non-asthmatic subjects ($n = 33$) and mild asthmatics ($n = 38$) were blindly exposed to a steady-state reaction mixture of maximum $74\text{ }\mu\text{g}/\text{m}^3$ (36 ppb; $9 \times 10^{11}\text{ molecules cm}^{-3}$) O_3 and $200\text{ }\mu\text{g}/\text{m}^3$ (37 ppb; $9 \times 10^{11}\text{ molecules cm}^{-3}$) limonene for 3 h in a climate chamber (240 m^3 ; 1 h^{-1} , recirculation 7 h^{-1}) (Fadedy et al., 2015). The asthmatic subjects perceived significantly less nose and throat sensory irritation than the non-asthmatic subjects. The rating was less than 15 on a continuous intensity scale from 0 to 100 with 20 = slight irritation. The difference between the non-asthmatic and

asthmatic subjects is compatible with recent studies with naïve and sensitized mice exposed to formaldehyde (strong sensory irritant) or a reaction mixture of O₃ and limonene indicating that “asthmatics” are less sensitive regarding sensory irritation in the airways (Hansen et al., 2016; Larsen et al., 2013). The differences in sensory eye irritation were insignificant; the difference was less than 13 on the intensity scale which is compatible with an expected formaldehyde concentration less than 50 µg/m³ (40 ppb; 1×10^{12} molecules cm⁻³) (anticipated 20% reaction (Atkinson and Arey, 2003)), significantly lower than the threshold for sensory irritation in the eyes (Wolkoff and Nielsen, 2010). Furthermore, a stress marker (α-amylase) in saliva increased significantly in both the normal and asthmatic subjects after the exposure, but significantly more among the asthmatics. The limonene concentration was about a factor of four higher than its odor threshold (Cain et al., 2007), which may have caused concern (arousal) and provoke a slightly higher stress level among the asthmatics (non-statistical) than in the non-asthmatics (cf. (Wolkoff and Nielsen, 2017)); another possibility could be the reaction products or their added contribution to the combined odor perception. Furthermore, the higher stress level, possible caused by the odor, is compatible with the reported symptoms (e.g. chest tightness and headache), cf. Wolkoff and Nielsen (2017). In the third study, high frequency heart-rate variability (index of parasympathetic activity) was decreased about 4% in healthy women (n = 22) exposed (double-blind) to a reaction mixture of limonene and O₃ for three hours in a controlled climate chamber (22 m³). The initial/residual mean concentrations of limonene and O₃ were 900/80 µg/m³ (162/41 ppb; $4/1 \times 10^{12}$ molecules cm⁻³) and 80/10 µg/m³ (14/5 ppb; $3/0.1 \times 10^{11}$ molecules cm⁻³), respectively. The mixture was composed of gaseous products and SOA (mean 80 µg/m³) (Hagerman et al., 2014). The initial and residual concentrations of limonene and O₃ were substantially higher than commonly found in indoor air, but far below those which cause sensory or lung reactions (Wolkoff et al., 2012). However, the residual limonene concentration was twice its P₅₀ odor threshold (Cain et al., 2007); thus, the odor perception of limonene and its reaction products was intense and possibly unpleasant to some of the subjects. This may have influenced the parasympathetic tone, in agreement with Glass et al. (2014); however, the SOA could also have been causative.

All in all, apart from sensory reactions in the upper airways or eyes, neither animal nor human studies have indicated inflammatory reactions in the upper and lower airways, and similarly so for cardiovascular effects.

5.4. Human reference values

Human reference values for life-long exposure have been derived from a mouse inhalation model for key oxygenated species such as 4-AMCH, IPOH, 6-methyl-5-heptene-2-one (6-MHO), dihydrocarvone (DHC), and 4-oxo-pentanal (4-OPA). Pulmonary irritation was not observed as a critical effect for these oxidation products; relatively low reference values were derived for airflow limitation for 4-OPA (123 µg/m³, 30 ppb; 7.4×10^{11} molecules cm⁻³) and sensory irritation for IPOH (1100 µg/m³, 160 ppb) (Wolkoff et al., 2013, 2014). Although the number of reference values is limited to a few oxidation products, it is important to note that the major effect from α-pinene or limonene reaction mixtures is sensory irritation in the upper airways and without sign of an increase upon repeated exposure or effects in the lower airways; furthermore, BAL has not indicated inflammation.

6. Conclusions

Describing IAQ based on health effect outcomes continues to be a challenge. However, as can be seen from the preceding summary, there have been many advances in the areas of transient radical detection and concentration measurement, indoor air chemistry modeling, gas- and particulate-phase characterization, and physiological responses to

reactive indoor air. There are several potential areas of improvement in these research areas that, if successfully achieved, could facilitate practical ways to carry out risk assessments, improve IAQ and reduce occupant exposure. Current challenges for improved screening of potential airway effects from indoor air reactants should include quantification of aerosol particles and radicals that impact the function of airway cells, besides methods that allow for real-time quantification of chemical reactants present at low levels.

Due to large surface to volume ratios in many indoor environments, a growing need to understand the impact of surfaces on indoor occupant exposure has evolved. Topics such as O₃ removal, terpene-bound surface chemistry and formed products, surface pH, and surface-bound water need improved understanding (Gall et al., 2015; Wang and Waring, 2014; Waring and Siegel, 2013). Another type of surface chemistry, though on a much smaller scale, is on and within particulate matter such as SOA (Borrowman et al., 2016; Dilbeck and Finlayson-Pitts, 2013; George and Abbatt, 2010; Kolb et al., 2010; Shiraiwa et al., 2011). Experimental challenges include: development of methods to coat surfaces with chemicals/formulations of interest, oxidant introduction to surfaces, and surface emission collection with reaction yield determination, characterization of the oxidized surface to identify reaction products remaining on surface, SOA generation, SOA collection, and characterization of SOA components. The reactions within and on particulate matter is only now being explored through the use of API mass spectrometers using different ionization techniques (Brüggemann et al., 2015; Zhou et al., 2015).

Future indoor field campaigns regarding indoor oxidant chemistry should have goals of:

- continued characterization of oxidant sources and sinks,
- measurements to confirm the existence of species that models predict to reach concentrations relevant for occupant exposure and to reduce uncertainties in photolysis,
- deposition and surface production rates.

Future laboratory experiments could have the goals of:

- developing analytical techniques, in both time-integrated and real-time, to confirm key intermediates in chemical oxidation mechanisms,
- investigating adverse airway effects from exposure to single/mixtures of oxidized species in both gas- and particle-phases,
- exploring the potential anti-inflammatory effects of terpenes and their O₃-initiated terpene reaction mixtures, characterizing indoor generated particulate matter,
- developing biological cell-based models that mimic realistic exposure scenarios in parallel with and validated against *in vivo* inhalation models, and investigating ways for parameterizing indoor surface reactions.

In order to improve models for indoor air chemistry and to understand the impacts on health of reactive chemicals, greater collaboration is needed between different modelers, experimentalists and those with health and toxicological expertise. In particular, the indoor modeling community needs:

- more population- and probability-based studies of exposure,
- more indoor measurements to confirm presence of species that models predict to attain high concentrations indoors,
- more laboratory experiments to confirm key intermediates for chemistry,
- model studies to determine deposition rates of key intermediates in the airways.

Future health effect studies to improve our understanding of the mechanisms of physiological response to indoor air chemistry would be

essential as an alternative to controlled human exposure studies. The development of a universal response model that could be used in many different indoor air scenarios and would be used by the health effects research community would be advantageous for identifying strategies to improve indoor air.

While several of these needs are similar to ones noted previously (Nazaroff and Goldstein, 2015; Weschler, 2011; Weschler et al., 2006), new needs to improve the indoor environment were identified in this workshop.

Competing financial interests

The authors declare no competing financial interests.

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry. Mention of any commercial product or trade name does not constitute endorsement by the Centers for Disease Control and Prevention/NIOSH.

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