Indoor chemistry and health: where are we going?

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ABSTRACT
Indoor chemistry is receiving attention due to the possible health effects of products of reactions between indoor pollutants, and the potential for such products to contribute to indoor particulate matter (PM). Much of the focus with respect to indoor chemistry has been on terpene/ozone reaction products, since terpenes are ubiquitous indoors, ozone readily infiltrates from outdoors, and the reaction rates are comparable to typical air exchange rates in many indoor settings. Several studies have documented particle formation from reactions between ozone and α-pinene or *d*-limonene. In addition, respiratory effects in mice have been noted with these reaction products, and those of isoprene and ozone and isoprene and nitrogen dioxide. Sensory irritation and airflow limitation have been observed during exposure to terpene oxidation products (TOP), and enhanced effects were observed with repeated exposures, suggesting a cumulative effect. These findings have important implications for indoor settings where occupants may be chronically exposed to TOP. However, although terpenes are important indoor pollutants, other unsaturated hydrocarbons and oxidants warrant study. This paper reviews the accumulating literature regarding possible health impacts from products formed through indoor air chemistry, and suggests additional research directions.

INDEX TERMS
Indoor chemistry; Terpenes; Ozone; Building-related symptoms; Particulate matter

INTRODUCTION

A body of literature is accumulating implicating reactions among indoor air pollutants as potential generators of irritating compounds that may contribute to building-related symptoms. Recent work has shown that strong airway irritants are formed from reactions between terpenes and ozone (e.g. Rohr *et al.*, 2002, 2003b; Wilkins *et al.*, 2003). Ozone can react with unsaturated hydrocarbons in a multistep process to produce hydroxyl radicals and a variety of carbonyl products and alkyl radicals (Weschler and Shields, 1997).

A number of investigators have demonstrated the importance of indoor oxidation reactions; excellent reviews of this subject are provided by Weschler and Shields (1997) and Wolkoff *et al.* (1997). Aldehyde formation from exposure of carpet (Weschler *et al.*, 1992) and latex paint (Reiss *et al.*, 1995) to ozone has been documented. Formaldehyde increased in a simulated office environment including photocopying and laser printing (Wolkoff *et al.*, 1992). Sundell *et al.* (1993) reported an increased risk of symptoms in rooms with lower TVOC levels in room air than in supply or intake air, and hypothesized that irritants were forming en route from intake to room. In a study of five assumed ozone risk groups (Hoppe *et al.*, 1995), lung function decrements were noted in the two lowest-exposed groups; the authors suggested that other substances besides ozone were contributing to the this effect.

This paper reviews recent findings regarding indoor chemistry and health, including (1) sources and reactants; (2) reaction products; (3) particle formation; and (4) health effects. Future research directions are discussed.

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REACTANTS AND SOURCES

Of the unsaturated hydrocarbons, the gas-phase reactions of terpenes in particular have received a great deal of attention due to their important role in tropospheric chemistry. Terpenes react readily with ozone, the nitrate radical, and $OH^{\cdot}$ (Calogirou *et al.*, 1999), and have been implicated in photochemical ozone formation and secondary organic aerosol production. The monoterpenes ($C_{10}H_{16}$) and sesquiterpenes ($C_{15}H_{24}$) are volatile and are emitted from vegetation in large quantities. Monoterpenes such as α-pinene and *d*-limonene are commonly found in room fresheners and pine cleaners, wood products, and wood-based furniture coatings. Peak concentrations can exceed 500 ppb though cleaning or other activities. Isoprene (C_5H_8; a hemiterpene) is emitted from vegetation and is also a mammalian bioeffluent; it is present in human exhaled breath at 12–580 ppb (Fenske and Paulson, 1999).

Other unsaturated hydrocarbons in indoor air that may be important in terms of indoor chemistry include linolenic, linoleic, and oleic acid from linoleum and paints containing linseed oil; 4-phenyl cyclohexene, 4-vinyl cyclohexene, and styrene from carpets; neoprene and styrene from HVAC components; and other terpenes, e.g. 3-carene, α-terpinene, from cleaners and waxes (Weschler and Shields, 1997 and references therein).

Ozone is present in indoor air through infiltration from outdoors and through point sources such as photocopiers and laser printers; the reader is referred to Weschler (2000) for a thorough review of this subject. Indoor ozone concentrations vary widely depending on ventilation and other factors; however, average concentrations of 28–60 ppb and a peak concentration of 247 ppb have been reported (Weschler, 2000 and references therein).

Other oxidants are also present indoors. In particular, nitrogen oxides (NO_x) can come from outdoor-to-indoor transport or indoor combustion processes. Indoor nitric oxide (NO) concentrations can range from less than 1 ppb to several hundred ppb, while nitrogen dioxide (NO_2) is normally present indoors at 20–50 ppb (Weschler *et al.*, 1994; Spengler *et al.*, 1996).

REACTION PRODUCTS

Alkene ozonolysis involves electrophilic attack of the C=C double bond by O_3 to form a highly unstable primary ozonide, which decomposes to produce two combinations of an energy-rich biradical (Criegee intermediate) and a carbonyl. The Criegee biradical rearranges or reacts via several mechanisms, including collision stabilization and decomposition (Weschler and Shields, 1997). Stabilized Criegee intermediates can react further, while other excited species decompose to form a number of radical species, including the hydroxyl radical. Stabilized Criegee intermediates can also react with water to form organic acids.

In α-pinene/ozone systems, the main identified reaction products are formaldehyde, acetone, pinonaldehyde, norpinonaldehyde, norpinone, pinonic acid, norpinonic acid, and pinic acid (Grosjean *et al.*, 1992; Jang and Kamens, 1999). The reaction between *d*-limonene and ozone produces primarily formaldehyde, 4-acetyl-1-methylcyclohexene, limona ketone, and limonaldehyde (Grosjean *et al.*, 1992; Hakola *et al.*, 1994), while the products of the isoprene/ozone reaction are primarily formaldehyde, hydroxy hydroperoxides, the two isomeric monoexpoxides, propene, hydrogen peroxide, methacrolein, methylvinyl ketone, methacrylic acid, and 3-methylfuran (Paulson *et al.*, 1992; Hakola *et al.*, 1994).

NO_2 reacts with unsaturated hydrocarbons by addition to the C=C double bond, and formation of a peroxy radical that can then react with NO or NO_2. NO_2 reacts with alkenes in the presence of UV light to form mixtures similar to formaldehyde with respect to irritant potency (Kane and Alarie, 1978). NO and limonene react to form glyoxal and several carbonyl compounds (Grosjean *et al.*, 1992). NO_2 reacts with isoprene to produce nitro or hydroxyaldehydes (Skov *et al.*, 1992).

Possible products from reactions of ozone with other unsaturated hydrocarbons found indoors include a variety of aldehydes, e.g. hexanal, nonanal, decanal, benzaldehyde, tolualdehyde; ketones, e.g. acetone, butanone; and carboxylic acids, e.g. formic, acetic, propionic, butyric, hexanoic, nonanoic, and benzoic acids (Weschler and Shields, 1997 and references therein). Organic nitrates and peroxyacyl nitrates can also be formed through free radical chemistry.

PARTICLE FORMATION

Because many of the products formed in alkene/ozone reactions have low vapour pressures, they can self-nucleate or condensate onto existing particulate matter (PM) to form secondary organic aerosol. In many terpene/ozone systems, in particular, ultrafine particle ($d < 0.1\mu m$) formation occurs readily, and aerosol yield can be significant. Griffin *et al.* (1999) reported yields of about 7–11 and 25–40% for aerosol mass concentrations of approximately 40–100 $\mu g/m^3$ in the α-pinene/ozone and *d*-limonene/ozone systems, respectively. Aerosol forms much less readily in the isoprene/ozone system, with an observed yield of about 1% of homogeneously nucleated aerosol under conditions of 4 ppm isoprene (Kamens *et al.*, 1982).

Several studies have investigated particle formation from terpene/ozone reactions, either in experimental chambers or in simulated or actual indoor environments. Weschler and Shields (1999) demonstrated fine particle formation in an office setting from reactions between ozone and either *d*-limonene or a pine-based cleaner comprised primarily of α-pinene. Long *et al.* (2000) showed formation of ultrafine particles during mopping events using pine oil-based cleaners in residential environments. Wainman *et al.* (2000) carried out a series of ozone injections into a nested chamber into which limonene had been introduced; measurable particle formation and growth occurred in all experiments. Rohr *et al.* (2003a) investigated ultrafine particle formation in a chamber designed for toxicological assessment of terpene oxidation products (TOP). Particles formed rapidly in the α-pinene and *d*-limonene systems, while particles formed more slowly and to a lesser extent in the isoprene/ozone system. Progressive particle growth occurred, indicating condensation and coagulation processes. Fan *et al.* (2003) reported submicron particle formation from reaction of a 23-VOC mixture with ozone. Most of the PM formed was attributed to the α-pinene and *d*-limonene in the mixture, since when these terpenes were removed, PM was at background levels.

HEALTH EFFECTS

Both the gas- and particle-phase products of alkene/ozone reactions may be capable of inducing adverse health effects. Many of the gaseous products of these reactions are aldehydic or acidic; both of these classes of chemicals are known to be airway irritants due to their water solubility and chemical reactivity. Particulate matter is widely associated with both respiratory and cardiovascular health effects, including mortality and morbidity.

Some epidemiological evidence suggests that TOP may have respiratory tract effects (Soutar *et al.*, 1993; Hoppe *et al.*, 1995; Buchdahl *et al.*, 2000). Terpenes themselves have been found to be associated with adverse respiratory symptoms and/or function, although the possibility exists for these compounds to serve as proxies for the oxidation products. *d*-Limonene also forms potent allergens, namely carvone and *cis*- and *trans*- (+)-limonene oxide, upon auto-oxidation in air (Karlberg *et al.*, 1992). These allergens have been identified in *d*-limonene/ozone mixtures (Clausen *et al.*, 2001).Toxicological evidence for health effects from TOP is accumulating. Several investigators have reported airway irritation in BALB/c mice during 30-min acute exposures to mixtures of ozone and α-pinene (Wolkoff *et al.*, 2000), *d*-limonene (Clausen *et al.*, 2001) or isoprene (Wilkins *et al.*, 2001). With NO_2 introduced into the ozone/isoprene mixture, a slightly larger irritant effect was observed (Wilkins *et al.*, 2001). Identified reaction products and residual reactants could not account for

the irritation observed, suggesting that irritants were formed that were not identified or measured. No evidence of pulmonary irritation or airflow limitation was observed during these acute 30-min exposures.

Rohr *et al.* (2002) investigated airway and pulmonary effects over a longer 60-min exposure, with pre-reaction concentrations of 3.4 ppm (ozone), 47 ppm (pinene), 51 ppm (limonene) and 465 ppm (isoprene). Airway irritation was a prominent effect; however, airflow limitation also developed. The airflow limitation effect persisted for at least 45 min post-exposure, suggesting that TOP may have moderate to lasting adverse effects on the upper airways and pulmonary regions.

Wilkins *et al.* (2003) recently investigated the effect of humidity and age of reaction mixture. Results showed that the maximum irritation effect occurred at low humidity (<2% RH) and a short reaction time (16–30 s). Significantly lower irritation occurred at moderate humidity (32%) and a longer reaction time (60–90 s), suggesting that reaction products react with water vapour to produce less irritating products.

Rohr *et al.* (2003b) carried out repeated exposures (3 h/day for 4 days) to isoprene/ozone reaction products in BALB/c mice. Marked enhancement of the irritation and airflow limitation effects was observed, suggesting a cumulative effect. In addition, a significant reduction in airway responsiveness was observed, suggesting possible mucous accumulation in the airways.

A pilot study to evaluate the potential for inflammation from exposure to TOP (Rohr, 2001) showed no evidence of elevated interleukin-6 (IL-6) in either bronchoalveloar or nasal lavage fluid in mice exposed to TOP for 4 h, with the exception of a significant elevation in IL-6 in nasal lavage fluid 4 h post-exposure. It should be noted that the sample size for this study was small, and thus further study is warranted.

FUTURE RESEARCH AND KNOWLEDGE GAPS

Given the above review, the role of indoor air chemistry in adverse health effects clearly warrants further research. Two primary areas can be identified: (1) unsaturated hydrocarbons other than terpenes and oxidants other than ozone; and (2) continued investigation of TOP, in terms of chemistry, toxicology (dose considerations), and toxicology (response considerations). Each of these areas is discussed below.

Other Hydrocarbon/Oxidant Mixtures

Other unsaturated hydrocarbons common in indoor environments should be studied in the same manner as the α-pinene, *d*-limonene, and isoprene. As mentioned, other alkenes, e.g. linoleic acid and styrene, are common in indoor environments. Other terpenes are also common, e.g. Δ-3-carene, α-terpinene. Additional assessment of NO_2 as an oxidant is highly relevant to indoor settings where combustion processes produce NO_x.

Terpene Oxidation Products (TOP)

Chemistry

As discussed, terpene/ozone chemistry is very complex, with gas- and condensed-phase products formed from primary, secondary and tertiary reactions involving multiple reaction intermediates and short-lived species. As a result, the nature of ‘fresh’ and ‘aged’ reaction mixtures may be markedly different. In addition, very little of the irritation response to the reaction products could be explained by the known reaction products, suggesting that unknown or unidentified products are being formed. More extensive characterization of the reaction mixtures should be carried out to identify some of these ‘missing’ chemicals as well as to assess the effect of age on mixture composition.

Exposure assessment of the reaction products is a necessary step in determining the significance of these products in the indoor environment and ultimately in carrying out risk assessment. Again, while in theory exposure assessment is a logical approach, the complex chemistry involved will complicate attempts to determine population exposures.

Toxicology—dose considerations

Because of the complicated chemistry, determining the appropriate proxy(s) for dose is challenging. First, it is unclear to what extent the aerosol-phase reaction products contribute to the observed effects. This question could be addressed through the use of a filter and/or a denuder, though removal of reactive gaseous products by filtration may be a problem. Second, other than a small number of gas-phase products evaluated, the relevant gaseous products in the reaction mixture are unknown, and their temporal modification has not been assessed.

TOP at high concentrations causes marked respiratory effects. In the risk assessment paradigm, this is considered hazard identification. However, to assess the likelihood of health effects at typical indoor concentrations, dose-response relationships need to be established for the reaction products. This is a nontrivial task, as the appropriate dose proxies are not known. Additional chemical characterization followed by basic single-component toxicological exposures will help determine the significance of TOP in indoor settings.

If dose–response analysis indicates that reaction products may be problematic, a method of 'working backwards' to the reactants must be developed; however, measuring indoor terpene and ozone concentrations will not provide information about concentrations of reaction products, since both reactants are *consumed* during the reaction. Emission-based guidelines may be more useful.

Toxicology—response considerations

The toxicological responses TOP evaluated to date include sensory and pulmonary irritation, airflow limitation, and airway hyper-responsiveness. Although these have been thoroughly characterized, there are definite opportunities for further investigation of TOP-induced responses.

The findings of the pilot inflammation evaluation would be more compelling with a larger sample size and thus increased statistical power. Such an evaluation could also include other mediators, such as TNF-α, IL-1, and MIP-2. Histopathological evaluation of nasal passages and lung tissue would enable the assessment of frank injury.

The issue of repeated exposures is particularly important in the context of indoor chemistry because of the chronic nature of exposure of workers. Although 4-day repeated exposures clearly caused an enhancement of effects, longer-term exposures at lower concentrations would more accurately reflect human exposures.

Additional investigation into the mechanism(s) of TOP effects could be conducted, e.g. since neurogenic inflammation is a hypothesized mechanism of sensory irritation, Substance P, neurokinin A, or other neuropeptides could be analyzed in lavage fluids.

The use of alternate animal models may provide insight into respiratory effects. For example, ovalbumin-sensitized mice, which approximate a murine model of asthma, may be a useful model in which to study the effects of TOP in a 'susceptible' subgroup.

The investigation of non-respiratory endpoints would be of interest. In light of the cardiopulmonary effects of exposure to particulate matter, monitoring of cardiac responses during TOP exposure would provide information related both to the specific response to the reaction products as well as the effects of PM.

Finally, controlled human exposures to TOP should be conducted, with monitoring of respiratory and other endpoints.

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