



Opinion: The Germicidal Effect of Ambient Air (Open Air Factor) Revisited

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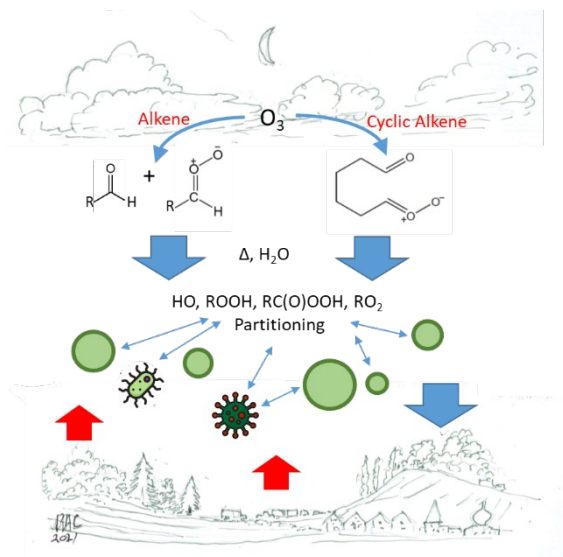
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Abstract. The term Open-Air Factor (OAF) was coined following microbiological research in the 1960s and 1970s which
20 established that rural air had powerful germicidal properties and attributed this to Criegee intermediates formed in the reaction
of ozone with alkenes. We have re-evaluated those early experiments applying the current state of knowledge of ozone-alkene
reactions. Contrary to previous speculation, neither Criegee intermediates, nor the HO radicals formed in their decomposition,
are directly responsible for the germicidal activity attributed to the OAF. We identify other potential candidates, which are
25 formed in ozone-alkene reactions and have known (and likely) germicidal properties, but the compounds responsible for the
OAF remain a mystery. There has been very little research into the OAF since the 1970s and this effect seems to have been
largely forgotten. In this opinion piece we remind the community of the germicidal open-air factor. Given the current global
pandemic spread by an airborne pathogen, understanding the natural germicidal effects of ambient air, solving the mystery of
the open-air factor, and determining how this effect can be used to improve human welfare should be a high priority for the
atmospheric science community.

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TOC Graphic



1 The history of the Open Air Factor

The public health benefits of fresh air have been recognized since ancient times (Brimblecombe, 1995; Hobday, 2019) and polluted air has been found to contain phytotoxins and to have germicidal effects (Arnold, 1959; Druett and Packman, 1968). Druett and May (1968) reported detection of a reactive airborne species in rural air, which possessed powerful germicidal properties and called this the Open Air Factor (OAF). Flowing ambient air over microorganisms supported on spiders-web filaments resulted in a loss of viability, which was reduced to zero after ~3 hours of exposure unless the air was first passed through a brass tube, which removed the germicidal agent (hence the term Open Air). Laboratory experiments exposing *Escherichia coli* to ozone, sulphur dioxide (SO₂), nitrogen oxides (NO_x), formaldehyde (HCHO), and ionised air at ambient levels showed that none of these were the responsible agent, and fluctuations of temperature and RH were also ruled out. Exposure to direct sunlight did however kill the microorganisms, so the experiments were carried out at night-time. Druett and May (1968) postulated that the OAF was identical, or closely related, to the “ozone-olefin complex” identified earlier in phytotoxic air pollution. This postulate was supported by additional laboratory work at the Microbiological Research Establishment at Porton Down (MREPD) by Dark and Nash (1970) who showed that the ozonolysis of a series of alkenes resulted in significant, but variable, inactivation of *E. coli* and *Micrococcus albus*. It was not the first time that alkene ozonolysis was related to germicidal effects, as ozonated unsaturated oils have long been known as simple disinfectants (H., 1934; Travagli et al., 2010; Ugazio et al., 2020). Dark and Nash suggested that peroxide zwitterions (now known as Criegee intermediates) formed in the reaction of ozone with alkenes were the active agent of the OAF. Later work at MREPD by Hood (1974) further examined the effect of containment and found that the minimum rate of ventilation required to preserve OAF



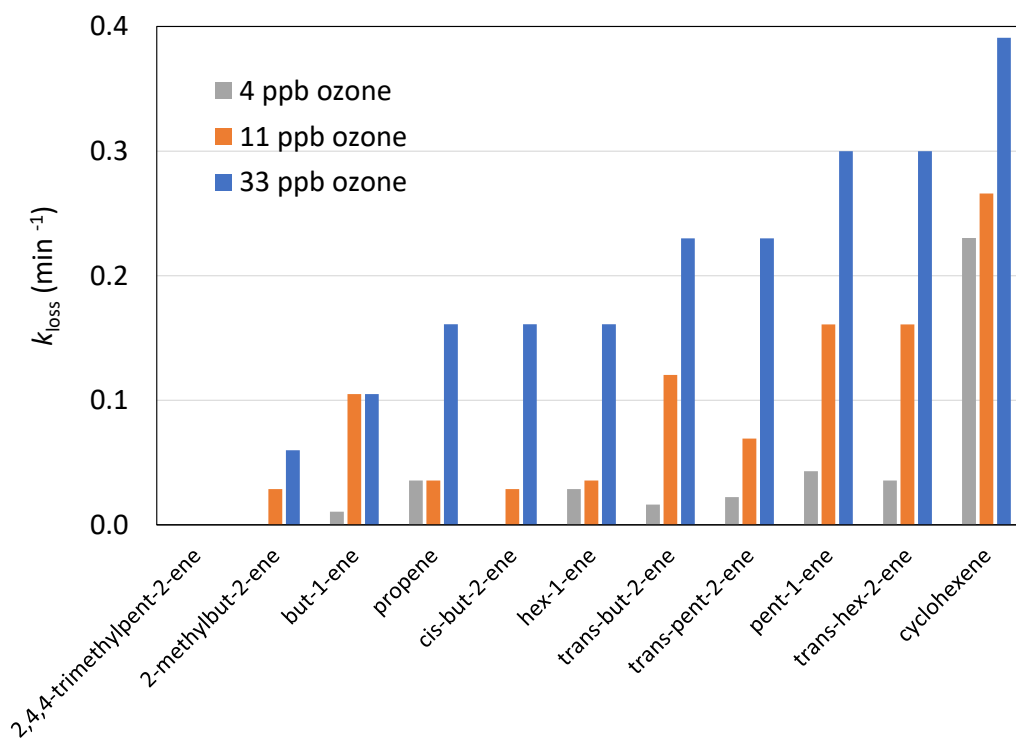
was correlated with the surface-to-volume area of the vessels used, consistent with Druett and May's idea that the OAF was removed at surfaces. Treating the OAF as a single or a small set of molecules in the gas phase enabled estimation of the diffusion coefficient of the elusive species to be made and thus the constraint of its molecular weight to the range 50-150. De Mik and De Groot (1978) at the Medical Biological Laboratory (TNO, Rijksweike, The Netherlands) found substantial damage to the DNA in aerosolized *E. coli* after exposure to air containing ozonized cyclohexene, indicating that OAF(s) could enter the outer lipid/or fatty- acid protective layer(s) of the microorganisms and that they or free radicals deriving from them are accessing and interacting chemically with DNA within the cell. Note that DNA may additionally be protected by histone proteins (Willenbrock and Ussery, 2004). Very little additional work related to the OAF has been performed since the 1970s (Hobday, 2019). A few recent studies have attempted to generate OAF to act against aerosolized microbes in the context of food preservation (Bailey et al., 2007; Nicholas et al., 2013) without providing new insight into the identity of the active agent. Based on recent advances in our understanding of the formation and fate of Criegee intermediates in alkene-O₃ reactions (Cox et al., 2020) we show here that, contrary to previous speculation, neither Criegee intermediates, nor the HO radicals formed in their decomposition, are directly responsible for the germicidal activity attributed to the OAF but identify other potential candidates, which are formed from O₃-alkene reactions and which have known germicidal properties. The overall sequence of processes involved in the germicidal action of OAF is expected to be initiated by the reaction of ozone with alkenes producing oxygenated products in the gas phase that undergo transfer to the lipid membrane of the microorganism, where they may produce free radicals that initiate and propagate lipid phase oxidation processes. While the formation of the key species from alkene-O₃ reactions has been demonstrated experimentally, it is likely the same species (and/or similar species) are also formed from additional pathways in ambient air (e.g. HO or NO₃ initiated oxidation of volatile organic compounds) with a number of sources therefore contributing to OAF.

2 Revisiting the Open Air Factor

The experiments of Dark and Nash (1970) provide a basis for examining germicidal agent formation in relation to what is currently known about the mechanism of alkene ozonolysis. Dark and Nash investigated the effect of a series of reactive ozone/alkene mixtures on both *E. coli* and *Micrococcus albus* suspended on micro-threads produced by spiders, to mimic airborne particles, in a 670 litre aluminium box. They selected a series of terminal alkenes, internal alkenes and cycloalkenes (and some unsaturated oxygenates). Experiments were carried out with 4 ppb, 11 ppb, and 33 ppb ozone, with alkene concentrations chosen such that 75 % ozone decay occurred over a period of 10 minutes. As shown in the supporting information (section 1), the rate coefficients for reactions of ozone with alkenes inferred from the data reported by Dark and Nash are generally consistent with current recommended kinetic data (Cox et al., 2020) so that the relationship between germicidal effects and structure of the alkene precursor reflected the differences in oxidation pathways and in OAF yields. A key result from Dark and Nash was the observation that (through their ozonolysis) cycloalkenes appeared to be more lethal to the microorganisms than linear acyclic alkenes, which, in turn, had a greater impact than branched acyclic alkenes. It is noted



that the cycloalkenes are structurally similar to some common environmental terpenoid VOCs (e.g. α -pinene, limonene). The relative efficiency (expressed as an effective loss rate coefficient, k_{loss} for the *E. coli*) of selected alkene- O_3 mixtures is summarised in Fig. 1, illustrating the observed range of impacts. The derivation of k_{loss} from the original data is described in the SI (section 2). These may be compared with a value of $k_{\text{loss}} \approx 0.03 \text{ min}^{-1}$ that can be inferred for open air for the typical conditions of the Druett and May (1968) study, based on information presented in Fig. 1 of their paper. The average values of k_{loss} for the three ozone regimes in the Dark and Nash (1970) experiments, based on the data for the alkenes shown in Fig. 1, are about 0.04, 0.09 and 0.2 min^{-1} for the 4, 11 and 33 ppb ozone experiments respectively. In approximate terms, this suggests that the germicidal agent is formed, on average, at comparable levels to the ambient level in the 4 ppb experiments, and approaching an order of magnitude higher in the 33 ppb experiments – although with substantial variation between the different alkene- O_3 systems.



95 **Figure 1.** Average *E. coli* loss rate (k_{loss}) during the ozonolysis of selected alkenes in the experiments of Dark and Nash (1970), illustrating the variation of loss efficiency with alkene structure and ozone mixing ratio.

It is now well understood that the highly exothermic reaction of ozone with alkenes produces nascent Criegee intermediates (R1CR2OO^*) with substantial internal excitation. These can either be stabilized by transferring energy in collisions with other gas phase atmospheric species (mainly N_2 and O_2) or undergo rapid unimolecular decomposition or internal rearrangement



(Donahue et al., 2011). The yield of stabilized Criegee intermediates varies greatly (Cox et al., 2020). In the case of the reactions of O₃ with cyclopentene, cyclohexene and cycloheptene, the yield is reported to be close to zero (Hatakeyama et al., 1984; Drozd and Donahue, 2011) and systematically lower than those for similarly sized acyclic alkenes. The observation by Dark and Nash that cycloalkenes are the most potent source of OAF, combined with our current understanding that there is a limited yield of stabilized Criegee intermediates formed in these systems, therefore rules out gas-phase Criegee intermediates as being the germicidal agent(s) in the OAF.

This conclusion can also be drawn from a kinetic perspective when examining the experiment by Druett and May (1968). If the germicidal agent were tied to the concentration of Criegee intermediates entering the tube from the atmosphere, it would be in steady state given by a balance between production from ozonolysis and removal via loss by unimolecular decomposition, reaction with trace gases and particles present in the air, and loss at the tube walls. As shown in the supporting materials (section 3), the lifetimes of common Criegee Intermediates with respect to gas phase sinks are < 60 ms. The same kinetic argument also holds for HO radicals, generated from decomposition of (excited or stabilized) Criegee intermediates, which are removed by gas-phase reaction with most atmospheric trace species. The typical lifetime of HO radicals in clean background UK air is about 200 ms (Lee et al., 2009; Ingham et al., 2009). Thus, the species controlling the lifetime of the bacteria in the Druett and May experiment must be related to the precursors (O₃) or the oxidation products that are lost to the walls. The kinetics of loss of viability observed in the brass tube experiments of Druett and May (Fig. S2) may provide indications for the chemical properties of the OAF, when assuming that these are volatile gas phase molecules taken up to the bacteria in a reactive process, and that the loss of these species at the wall controls the observed decay of germicidal activity. As shown in the SI (section 4), based on the experimental gas flow rates and making reasonable assumptions about the properties of the brass tube, the uptake coefficient (γ , the probability per collision that the OAF is lost at the cylindrical wall), falls in the range of 10⁻⁴ to 10⁻². One possible explanation for the observed loss of bactericidal activity along the flow tube is loss of the precursor O₃ to the brass walls. However, γ values for O₃ are much lower than 10⁻⁴ (Crowley et al., 2010), especially when considering passivation effects over the several hours of the experiment. Peroxides, which are important products formed in alkene ozonolysis (and present in outside air from a variety of sources), are well established disinfectants (Kampf et al., 2020), and hence are potential contributors to the OAF. As discussed in the SI (section 4), γ values for peroxides indeed fall into the range derived above to explain the wall loss rates of the Druett and May experiment. The same is true for HO₂ and possibly other peroxy radicals that could be precursors for further radicals.

To gain insight into the potential contribution of e.g. peroxy radicals and peroxides to the germicidal activity of OAF we simulated the Dark and Nash experiments. Initial scoping simulations used the detailed alkene chemistry in the “Master Chemical Mechanism” [MCM v3.2: <http://mcm.leeds.ac.uk/MCMv3.2/>] for six of the linear acyclic alkene systems studied. The analysis not only generated gas-phase concentrations of product species, but also calculated respective vapour pressures and octanol-water partition coefficients (see SI, section 5). These parameters are important as they impact partitioning to the condensed phase and the ability to penetrate cell membranes (see discussion below in Sect. 3). The simulations revealed that the concentrations of HO were suppressed by the high concentrations of alkenes. HO concentrations in the 33 ppb O₃



135 experiments were $(0.28 - 8.5) \times 10^5$ molecule cm^{-3} , with proportionately lower values in the 11 ppb and 4 ppb O_3 experiments. These were, therefore, generally lower than those typically present in air during daytime, but comparable to those reported at night in UK rural air (Emmerson and Carslaw, 2009). Simulated respective concentrations of HO_2 and RO_2 , $(1.3 - 1.8) \times 10^9$ and $(6.7 - 21) \times 10^9$ molecule cm^{-3} in the 33 ppb O_3 experiments, were however significantly higher than reported at night in UK rural air (Emmerson and Carslaw, 2009). As expected, some classes of non-radical products were found to be present in

140 much higher concentrations with aldehydes, peroxides and organic acids dominating the product distribution (See Fig. S3). Important, and sometimes major, contributions to these product classes resulted from the secondary chemistry initiated by the reactions of HO with the parent alkenes. The simulations revealed no clear trend when considering the product concentrations (or the concentration scaled by vapour pressures or octanol-water distribution coefficients) with the germicidal activity for each alkene reported by Dark and Nash. These results are summarised in detail in section 5 of the SI.

145 As peroxides and peroxyacids (containing the $-\text{OOH}$ group) such as H_2O_2 and peracetic acid are known germicides (Kampf et al., 2020; Kitis, 2004; Becker et al., 2017; Goyal et al., 2014) we examined their potential contribution to OAF in more detail. For this, bespoke mechanisms were written for the extended series of 11 alkenes shown in Fig. 1, which incorporated recent improvements in the current understanding of the ozonolysis chemistry (see supporting material, section 6). The results show that (unlike the OAF) the collective formation of peroxides does not vary greatly from one alkene to the next and total

150 levels are similar in systems with low germicidal activity (e.g., 2,4,4-trimethylpent-2-ene) and in systems with high germicidal activity (e.g., cyclohexene) (Fig. 2a). The peroxide concentrations generated from the gas phase chemistry cannot thus collectively explain the trend in bacterial destruction across the series of O_3 + alkene systems. However, the peroxides formed in the various systems include a structurally diverse set of mono-, bi- and multifunctional peroxide species (see section 6 of the supporting material), which will likely possess different propensities to penetrate the protective membrane of the

155 microorganisms and initiate oxidation (see Sect. 3). These tend to be dominated by simple β -hydroxy peroxides (formed from secondary HO chemistry) in the acyclic systems (Fig. 2c,d). In the case of cyclohexene, however, about 30 % of the simulated peroxide burden is due to a series of highly oxygenated organic molecules (HOMs) containing hydroperoxide and/or peroxy acid groups, along with aldehyde and ketone groups (Fig. 2b). The formation of HOMs occurs via an autooxidation process (Ehn et al., 2014; Hansel et al., 2018), in which peroxy radicals generated sequentially in some alkene systems can isomerize

160 via internal H-shift reactions resulting in rapid formation of a series of products containing increasing numbers of hydroperoxide or peroxy acid groups (Crouse et al., 2013; Crouse et al., 2011; Mutzel et al., 2015; Kirkby et al., 2016). Cyclic alkenes, such as cyclohexene, tend to have higher HOM yields than most acyclic alkenes (Bianchi et al., 2019), with HOM formation mechanisms generally not being operative for small acyclic alkenes. While this idea is consistent with the observation by Dark and Nash that the most effective (or highest concentrations of) germicidal agents were produced in the

165 ozonolysis of endo-cyclic alkenes, we note that several small acyclic alkenes (no HOMs formation) studied still exhibited notable germicidal properties. Nonetheless, given the plethora of (germicidal) peroxide, hydroperoxide and peracid groups in



HOMs, and the fact that they partition readily to the particle phase (Riva et al., 2016; Bianchi et al., 2019), we hypothesize that HOMs may contribute to the OAF.

In spite of the high degree of functionalization of typical HOMs, the remaining vapor pressure could be sufficient that partitioning to the bacteria on the spider webs of the experiments and to the wall of vessels that was deduced by Hood (1974) becomes efficient. The air sampled in the Druett and May experiments certainly contained deliquesced, background aerosol on which condensation or dissolution of HOMs and other lower volatility peroxides would have occurred. At relatively high humidity, the particle – gas equilibration time-scale for an internally mixed aerosol was likely fast enough to enable the brass tube of the Druett and May experiment to act as a denuder for the HOM and other peroxidic species, meaning that the apparent

OAF wall-loss kinetics could possibly have been driven by evaporation from the particles.

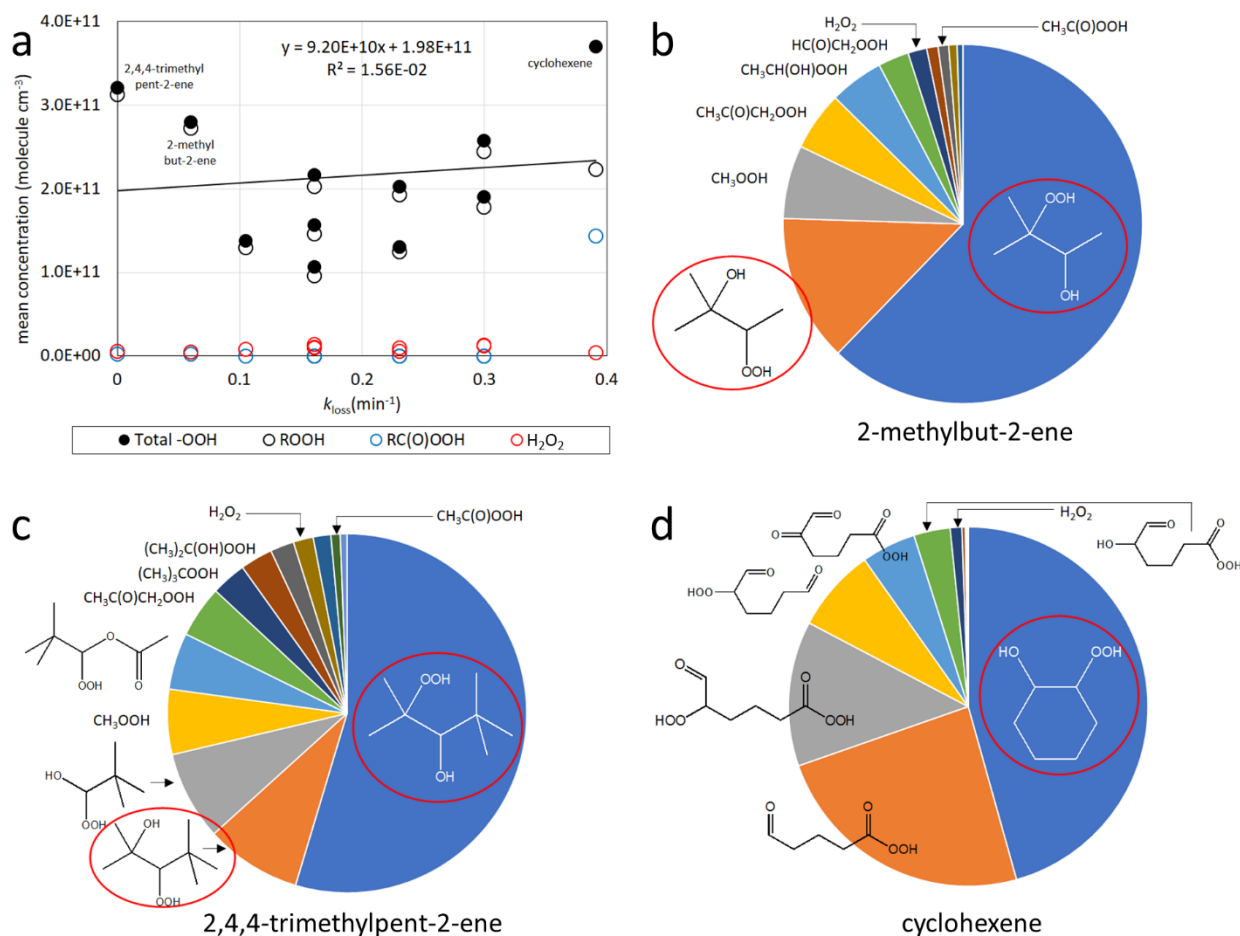


Figure 2. (a) Simulated concentrations of hydroperoxide products vs. k_{loss} for *E. coli* in 33 ppb O₃ experiments for the series of 11 alkenes shown in Fig. 1, showing the concentrations for H₂O₂, ROOH species and RC(O)OOH species and their totals (total -OOH); and linear regression of the total -OOH data. (b,c,d) Simulated speciation of peroxidic compounds generated



from 2-methylbut-2-ene, 2,4,4-trimethylpent-2-ene and cyclohexene in the 33 ppb O₃ experiments. The total -OOH concentrations in the three cases were, 2.8×10^{11} , 3.2×10^{11} and 3.7×10^{11} molecule cm⁻³, respectively. Species in red ellipses are those formed from the HO + alkene reactions.

3. Implications

185 As mentioned above, the role of hydrogen peroxide (Kampf et al., 2020; Goyal et al., 2014), organic peroxides or peracids
(Becker et al., 2017; Kitis, 2004) as disinfectants for a wide range of pathogens is well established. The work of De Mik and
De Groot demonstrated that DNA damage resulted from primary or secondary attack on the organisms. The organisms are
protected from external damage by oxidizing agents present in the air by external membranes surrounding the internal aqueous
medium containing the key chemical entities controlling the functions in the cell. The chemical nature of the membrane layer
is different in individual microorganisms. *E. coli* are surrounded by a lipid membrane, as are many viruses. Other micro-
190 organisms have chemically different protective layers. The mechanism of action of peroxides and HOMs containing peroxidic
and peroxyacidic groups is likely through their oxidation potential, via their thermal decomposition to yield smaller radicals
as a source of reactive oxygen species that also drives their health impact when inhaled (Tong et al., 2019). The germicidal
effects of ozonated unsaturated oils has been attributed to secondary ozonides and peroxides (Travagli et al., 2010). In a recent
195 experimental investigation of autoxidation of unsaturated lipids initiated by gas phase HO, Zeng et al. (Zeng et al., 2020)
observed substantial amplification of oxidation via lipid autoxidation propagated by Criegee intermediates and free radicals
via pathways specific for the condensed phase, providing an example of how radical precursors, such as HOMs or peroxides
in general may initiate a wealth of oxidative processes in the condensed phase. The finding of lipid membrane degradation
initiated by reactive species fits with the fact that microbes with lipid membranes, including enveloped viruses and vegetative
200 bacteria, are more susceptible to degradation by disinfectant agents than other microbes such as capsid viruses or prion proteins
(Russell, 1999). The amplifying effect of radicals in lipid peroxidation also highlights that even very small amounts of OAF
may have a substantial germicidal effect.

In summary, the discussion above indicates that a range of products formed in the ozonolysis of alkenes could contribute to
the OAF as distinct germicides. Chemical simulations of these chemical systems do not identify a clear individual gas-phase
205 molecule or class of molecules that matches the ranking of bactericidal activity reported in the experiments of Dark and Nash.
However, we need to keep in mind that the gas phase yields of the suspected species may not correlate directly with their
germicidal effects as the response of germs is related to the partitioning of these species to the condensed phase in a highly
non-linear manner and may also depend on their ability to initiate condensed phase free radical chemistry that ultimately kills
pathogens.

210 Although the airborne pathway, i.e., aerosol particles carrying pathogens and infecting a target, is recognised as a major route
of transmission of many infectious diseases, including transmission of SARS-CoV-2 (Prather et al., 2020; Greenhalgh et al.,
2021), the current understanding of the processes involved in the transmission of infection (e.g. during the current pandemic)



is incomplete. An improved understanding of the OAF will help assessing the importance of outdoor air on the transmission of COVID-19, as well as the importance of ventilation in indoor environments (Morawska and Milton, 2020; Morawska et al., 2020). It is therefore of substantial interest to further investigate the role of ambient air in pathogen viability and the mechanisms behind the OAF.

Data availability:

Numbers backing up the arguments of the main text are provided as tables in the SI. MCM simulations were performed with publicly available code as described in the SI. The mechanism extension in terms of reactions and species is provided in tables S4 and S5.

Author contribution:

RAC initiated this study and provided the historic perspective. PTG and RAC performed preliminary analysis. CJP provided the biochemistry perspective. MA and JNC reanalysed the Druett and May brass tube experiment. HH, AT and EH performed the MCM model calculations and the species property estimation work. MEJ contributed the new and updated mechanisms and performed the corresponding model simulations. TJW, MA, MEJ and JNC prepared the manuscript, which was reviewed and refined by all co-authors.

Competing interests:

Markus Ammann is co-editor of *Atmospheric Chemistry and Physics*.

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