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

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

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33   **TOC Graphic**

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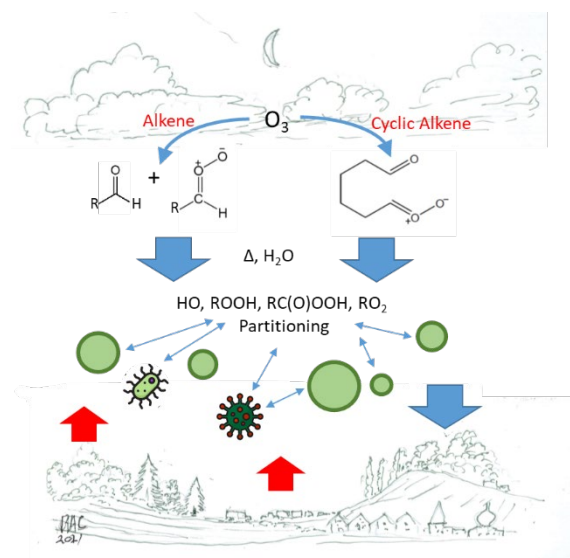
1 The history of the Open Air Factor

36   The public health benefits of fresh air have been recognized since ancient times (Brimblecombe, 1995; Hobday, 2019).

37   In the 20th century, knowledge has especially evolved during major medical emergencies, such as in wartime (Souttar,

38   1915; Nelson, 1915; Hobday, 1997), during the 1918 influenza pandemic (Hobday and Cason, 2009) or in the

39   treatment of tuberculosis (Ransome, 1958; Ransome and Delphine, 1894). Fresh air was considered as a potential

40   mass treatment for burns during a nuclear war (Blocker et al., 1951; Artz et al., 1953). Germicidal effects of fresh air

41   were investigated as part of biodefence research in the 1970s (Hood, 2009). Fresh air has been considered an option

42   in dealing with antimicrobial resistance (Wang et al., 2020). Phytotoxic and germicidal effects were related to the

43   presence of pollutants produced during photochemical smog episodes in Los Angeles (Arnold, 1959; Druett and

44   Packman, 1968). In experiments carried out at the Microbiological Research Establishment at Porton Down (MREPD)

45   in southern England, Druett and May (1968) reported detection of a reactive airborne species in rural air, which

46   possessed powerful germicidal properties and called this the Open Air Factor (OAF). Flowing ambient air over

47   microorganisms supported on spiders-web filaments resulted in a loss of viability, which was reduced to zero after ~3

48   hours of exposure unless the air was first passed through a brass tube, which removed the germicidal agent (hence the

49   term Open Air). Laboratory experiments exposing *Escherichia coli* to ozone, sulphur dioxide (SO_2), nitrogen oxides

50   (NO_X), formaldehyde (HCHO), and ionised air at ambient levels showed that none of these were the responsible agent,

51   and fluctuations of temperature and RH were also ruled out. Exposure to direct sunlight did however kill the

52   microorganisms, so the experiments were carried out at night-time.

53   Druett and May (1968) postulated that the OAF was identical, or closely related, to the "ozone-olefin complex"

54   identified earlier in phytotoxic air pollution. This postulate was supported by additional laboratory work at MREPD

55   by Dark and Nash (1970) who showed that the ozonolysis of a series of alkenes resulted in significant, but variable,

56   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 (Harada, 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, Rijswike, 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-O_3 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 O_3-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-O_3 reactions has been demonstrated experimentally, it is likely that the same species (and/or similar species) are also formed from additional pathways in ambient air (e.g. HO or NO_3 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

93   in oxidation pathways and in OAF yields. A key result from Dark and Nash was the observation that (through their

94   ozonolysis) cycloalkenes appeared to be more lethal to the microorganisms than linear acyclic alkenes, which, in turn,

95   had a greater impact than branched acyclic alkenes. It is noted that the cycloalkenes are structurally similar to some

96   common environmental terpenoid VOCs (e.g. α-pinene, limonene). The relative efficiency (expressed as an effective

97   loss rate coefficient, k_{loss} for the *E. coli*) of selected alkene-O_3 mixtures is summarised in Fig. 1, illustrating the

98   observed range of impacts. The derivation of k_{loss} from the original data is described in the SI (section 2). These may

99   be compared with a value of $k_{loss} \approx 0.03$ min^{-1} that can be inferred for open air for the typical conditions of the Druett

100   and May (1968) study, based on information presented in Fig. 1 of their paper. The average values of k_{loss} for the three

101   ozone regimes in the Dark and Nash (1970) experiments, based on the data for the alkenes shown in Fig. 1, are about

102   0.04, 0.09 and 0.2 min^{-1} for the 4, 11 and 33 ppb ozone experiments respectively. In approximate terms, this suggests

103   that the germicidal agent is formed, on average, at comparable levels to the ambient level in the 4 ppb experiments,

104   and approaching an order of magnitude higher in the 33 ppb experiments – although with substantial variation between

105   the different alkene-O_3 systems.

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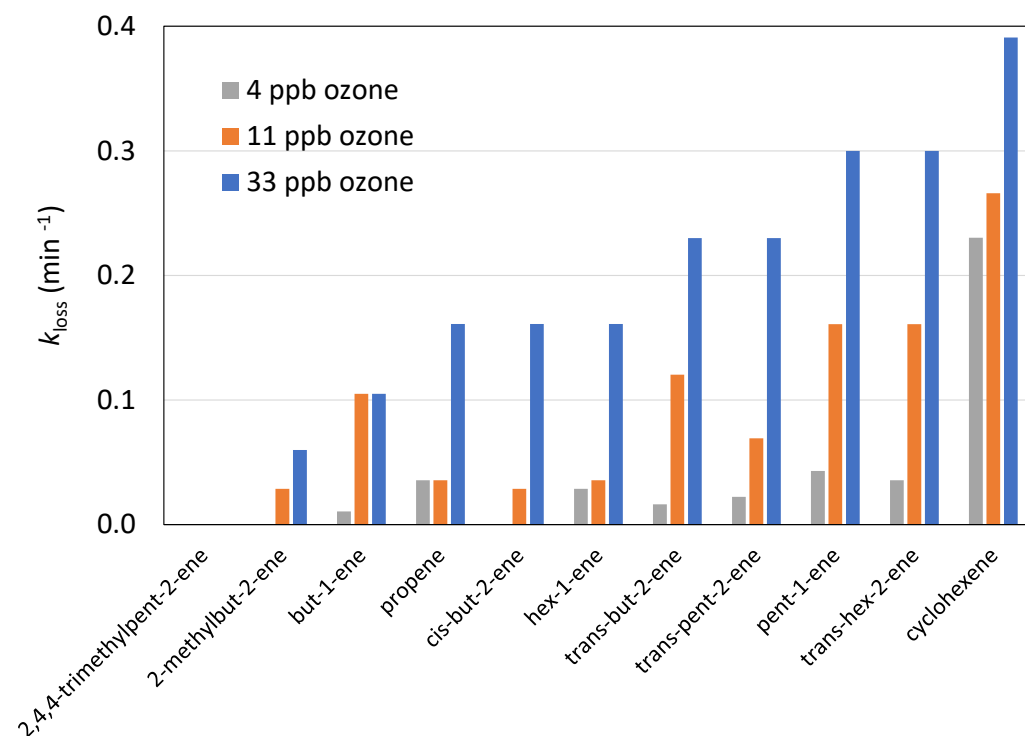

108   **Figure 1**. Average *E. coli* loss rate (k_{loss}) during the ozonolysis of selected alkenes in the experiments of Dark and

109   Nash (1970), illustrating the variation of loss efficiency with alkene structure and ozone mixing ratio.

110

111   It is now well understood that the highly exothermic reaction of ozone with alkenes produces nascent Criegee

112   intermediates (R1CR2OO*) with substantial internal excitation. These can either be stabilized by transferring energy

113   in collisions with other gas phase atmospheric species (mainly N_2 and O_2) or undergo rapid unimolecular

114   decomposition or internal rearrangement (Donahue et al., 2011). The yield of stabilized Criegee intermediates varies

115   greatly (Cox et al., 2020). In the case of the reactions of O_3 with cyclopentene, cyclohexene and cycloheptene, the

116   yield is reported to be close to zero (Hatakeyama et al., 1984; Drozd and Donahue, 2011) and systematically lower

117   than those for similarly sized acyclic alkenes. The observation by Dark and Nash that cycloalkenes are the most potent

118   source of OAF, combined with our current understanding that there is a limited yield of stabilized Criegee

119   intermediates formed in these systems, therefore rules out gas-phase Criegee intermediates as being the germicidal

120   agent(s) in the OAF.

121   This conclusion can also be drawn from a kinetic perspective when examining the experiment by Druett and May

122   (1968). If the germicidal agent were tied to the concentration of Criegee intermediates entering the tube from the

123   atmosphere, it would be in steady state given by a balance between production from ozonolysis and removal via loss

124   by unimolecular decomposition, reaction with trace gases and particles present in the air, and loss at the tube walls.

125   As shown in the supporting materials (section 3), the lifetimes of common Criegee Intermediates with respect to gas

126   phase sinks are < 60 ms. The same kinetic argument also holds for HO radicals, generated from decomposition of

127   (excited or stabilized) Criegee intermediates, which are removed by gas-phase reaction with most atmospheric trace

128   species. The typical lifetime of HO radicals in clean background UK air is about 200 ms (Lee et al., 2009; Ingham et

129   al., 2009). Thus, the species controlling the lifetime of the bacteria in the Druett and May experiment must be related

130   to the precursors (O_3) or the oxidation products that are lost to the walls. The kinetics of loss of viability observed in

131   the brass tube experiments of Druett and May (Fig. S2) may provide indications for the chemical properties of the

132   OAF, when assuming that these are volatile gas phase molecules taken up to the bacteria in a reactive process, and

133   that the loss of these species at the wall controls the observed decay of germicidal activity. As shown in the SI (section

134   4), based on the experimental gas flow rates and making reasonable assumptions about the properties of the brass tube,

135   the uptake coefficient (γ, the probability per collision that the OAF is irreversibly lost at the cylindrical wall), falls in

136   the range of 10^{-4} to 10^{-2}. One possible explanation for the observed loss of bactericidal activity along the flow tube is

137   loss of the precursor O_3 to the brass walls. However, γ values for O_3 are much lower than 10^{-4} (Crowley et al., 2010),

138   especially when considering passivation effects over the several hours of the experiment. Peroxides, which are

139   important products formed in alkene ozonolysis (and present in outside air from a variety of sources: see section 3 of

140   the SI), are well established disinfectants (Kampf et al., 2020), and hence are potential contributors to the OAF.

141   Oxygenated VOCs (such as peroxides) in general strongly partition (reversibly and irreversibly) to tube walls (Deming

142   et al., 2019). As discussed in the SI (section 4), γ values for peroxides indeed fall into the range derived above to

143   explain the wall loss rates of the Druett and May experiment. The same is true for HO_2 and possibly other peroxy

144   radicals that could be precursors for further radicals.

145   To gain insight into the potential contribution of e.g. peroxy radicals and peroxides to the germicidal activity of OAF

146   we simulated the Dark and Nash experiments. Initial scoping simulations used the detailed alkene chemistry in the

147   "Master Chemical Mechanism" [MCM_v3.2: http://mcm.york.ac.uk] for six of the linear acyclic alkene systems

148   studied. The analysis not only generated gas-phase concentrations of product species, but also calculated respective

149   vapour pressures and octanol-water partition coefficients (see SI, section 5). These parameters are important as they

150   impact partitioning to the condensed phase and the ability to penetrate cell membranes (see discussion below in Sect.

151   3). The simulations revealed that the concentrations of HO were suppressed by the high concentrations of alkenes.

152   HO concentrations in the 33 ppb O_3 experiments were $(0.28 - 8.5) \times 10^5$ molecule cm^{-3}, with proportionately lower

153   values in the 11 ppb and 4 ppb O_3 experiments. These were, therefore, generally lower than those typically present in

154   air during daytime, but comparable to those reported at night in UK rural air (Emmerson and Carslaw, 2009).

155   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

156   ppb O_3 experiments, were however significantly higher than reported at night in UK rural air (Emmerson and Carslaw,

157   2009). As expected, some classes of non-radical products were found to be present in much higher concentrations

158   with aldehydes, peroxides and organic acids dominating the product distribution (See Fig. S3). Important, and

159   sometimes major, contributions to these product classes resulted from the secondary chemistry initiated by the

160   reactions of HO with the parent alkenes. The simulations revealed no clear trend when considering the product

161   concentrations (or the concentration scaled by vapour pressures or octanol-water distribution coefficients) with the

162   germicidal activity for each alkene reported by Dark and Nash. These results are summarised in detail in section 5 of

163   the SI.

164   As peroxides and peroxyacids (containing the –OOH group) such as H_2O_2 and peracetic acid are known germicides

165   (Kampf et al., 2020; Kitis, 2004; Becker et al., 2017; Goyal et al., 2014) we examined their potential contribution to

166   OAF in more detail. For this, bespoke mechanisms were written for the extended series of 11 alkenes shown in Fig.

167   1, which incorporated recent improvements in the current understanding of the ozonolysis chemistry (see supporting

168   material, section 6). The results show that (unlike the OAF) the collective formation of peroxides does not vary greatly

169   from one alkene to the next and total levels are similar in systems with low germicidal activity (e.g., 2,4,4-

170   trimethylpent-2-ene) and in systems with high germicidal activity (e.g., cyclohexene) (Fig. 2a). The peroxide

171   concentrations generated from the gas phase chemistry cannot thus collectively explain the trend in bacterial

172   destruction across the series of O_3 + alkene systems. However, the peroxides formed in the various systems include a

173   structurally diverse set of mono-, bi- and multifunctional peroxide species (see section 6 of the supporting material),

174   which will likely possess different propensities to penetrate the protective membrane of the microorganisms and

175   initiate oxidation (see Sect. 3). These tend to be dominated by simple β-hydroxy peroxides (formed from secondary

176   HO chemistry) in the acyclic systems (Fig. 2c,d). In the case of cyclohexene, however, about 30 % of the simulated

177   peroxide burden is due to a series of highly oxygenated organic molecules (HOMs) containing hydroperoxide and/or

178   peroxy acid groups, along with aldehyde and ketone groups (Fig. 2b). The formation of HOMs occurs via an

179   autooxidation process (Ehn et al., 2014; Hansel et al., 2018), in which peroxy radicals generated sequentially in some

180   alkene systems can isomerize via internal H-shift reactions resulting in rapid formation of a series of products

181   containing increasing numbers of hydroperoxide or peroxy acid groups (Crounse et al., 2013; Crounse et al., 2011;

182   Mutzel et al., 2015; Kirkby et al., 2016). Cyclic alkenes, such as cyclohexene, tend to have higher HOM yields than

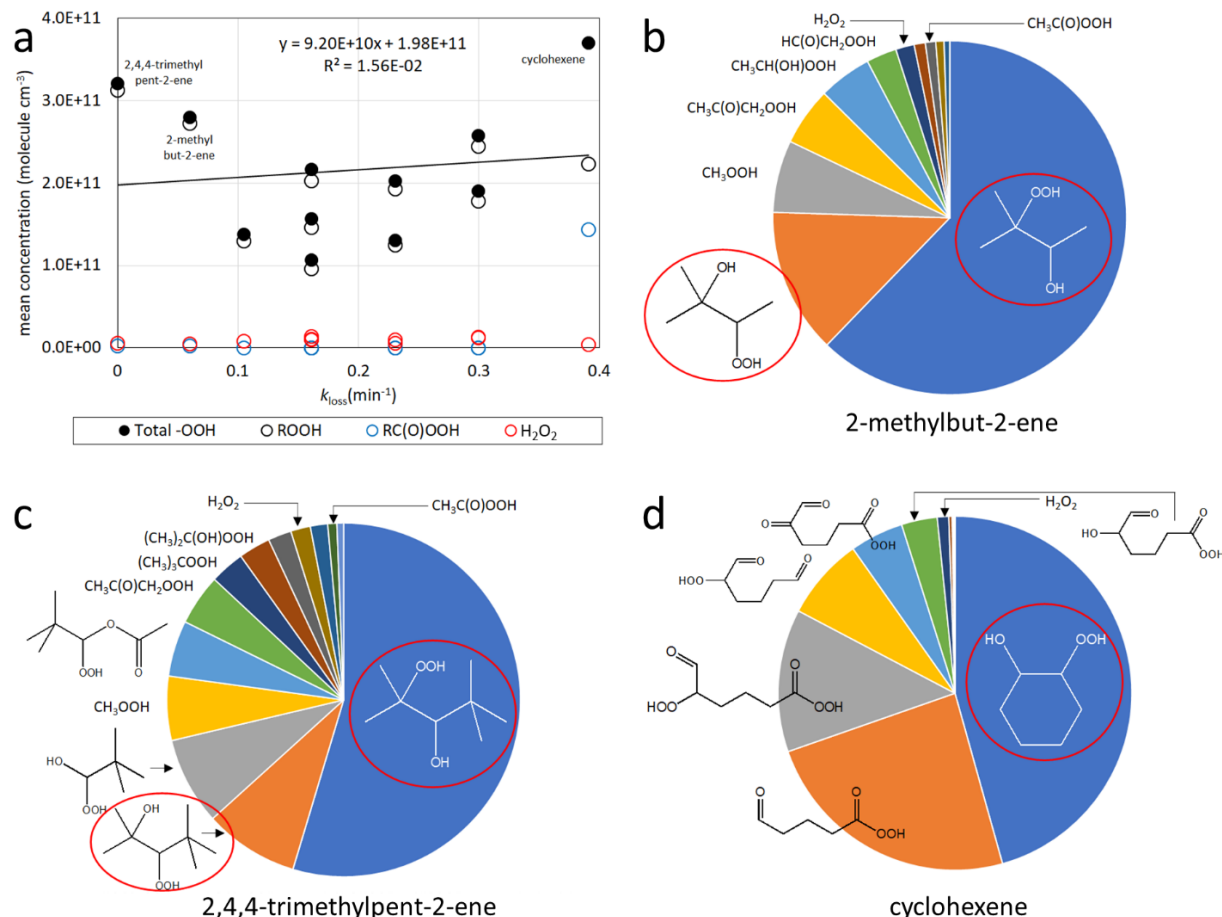
183   most acyclic alkenes (Bianchi et al., 2019), with HOM formation mechanisms generally not being operative for small

184   acyclic alkenes. While this idea is consistent with the observation by Dark and Nash that the most effective (or highest

185   concentrations of) germicidal agents were produced in the ozonolysis of endo-cyclic alkenes, we note that several

186   small acyclic alkenes (no HOMs formation) studied still exhibited notable germicidal properties. Nonetheless, given

187   the plethora of (germicidal) peroxide, hydroperoxide and peracid groups in HOMs, and the fact that they partition

188 readily to the particle phase (Riva et al., 2016; Bianchi et al., 2019), we hypothesize that HOMs may contribute to the
189 OAF.

190
191 **Figure 2.** (a) Simulated concentrations of hydroperoxide products vs. k_{loss} for *E. coli* in 33 ppb O_3 experiments for the
192 series of 11 alkenes shown in Fig. 1, showing the concentrations for H_2O_2, ROOH species and RC(O)OOH species
193 and their totals (total -OOH); and linear regression of the total -OOH data. (b,c,d) Simulated speciation of peroxidic
194 compounds generated from 2-methylbut-2-ene, 2,4,4-trimethylpent-2-ene and cyclohexene in the 33 ppb O_3
195 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},
196 ^{3}, respectively. Species in red ellipses are those formed from the HO + alkene reactions.

197
198 In spite of the high degree of functionalization of typical HOMs, the remaining vapor pressure could be sufficient that
199 partitioning to the bacteria on the spider webs of the experiments and to the wall of vessels that was deduced by Hood
200 (1974) becomes efficient. The air sampled in the Druett and May experiments certainly contained deliquesced,
201 background aerosol on which condensation or dissolution of HOMs and other lower volatility peroxides would have
202 occurred. At relatively high humidity, the particle – gas equilibration time-scale for an internally mixed aerosol was
203 likely fast enough to enable the brass tube of the Druett and May experiment to act as a sink for the HOM and other
204 peroxidic or oxygenated species (Deming et al., 2019), meaning that the apparent OAF wall-loss kinetics could
205 possibly have been driven by evaporation from the particles.

3. Implications

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-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). These result from the reaction of the stabilized Criegee intermediate (produced by ozonolysis in the condensed phase) with carbonyl compounds (Bailey, 1958; Zahardis and Petrucci, 2007; Pleik et al., 2018). In a recent 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. These two examples emphasise that pathways specific for the condensed phase provide a route 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 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 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.

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.

243 **Data availability:**

244 Numbers backing up the arguments of the main text are provided as tables in the SI. MCM simulations were performed

245 with publicly available code as described in the SI. The mechanism extension in terms of reactions and species is

246 provided in tables S4 and S5.

247 **Author contribution:**

248 RAC initiated this study and provided the historic perspective. PTG and RAC performed preliminary analysis. CJP

249 provided the biochemistry perspective. MA and JNC reanalysed the Druett and May brass tube experiment. HH, AT

250 and EH performed the MCM model calculations and the species property estimation work. MEJ contributed the new

251 and updated mechanisms and performed the corresponding model simulations. TJW, MA, MEJ and JNC prepared the

252 manuscript, which was reviewed and refined by all co-authors.

253 **Competing interests:**

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

255

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