

Reactions of ozone with human skin lipids: Sources of carbonyls, dicarbonyls, and hydroxycarbonyls in indoor air

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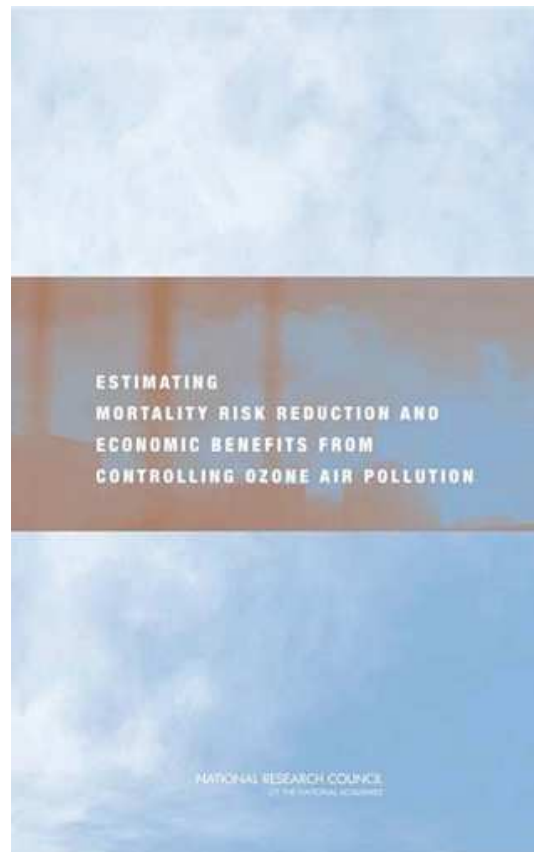
Environmental and Occupational Health Sciences Institute
University of Medicine and Dentistry of New Jersey and Rutgers University
and
Technical University of Denmark



*International Centre for
Indoor Environment and Energy*



Short-term ozone exposure: morbidity and mortality



National Research Council (2008)

OVERALL CONCLUSIONS

The committee concludes from its review of the health-based evidence that short-term exposure to ambient ozone is likely to contribute to premature deaths.

Human chamber and toxicologic studies have yielded strong evidence indicating that short-term exposure to ozone can exacerbate lung conditions, causing illness and hospitalization, and can potentially lead to death.

On the basis of its review of the evidence, the committee concludes that the association between short-term changes in ozone concentrations and mortality is generally linear throughout most of the concentration range, although uncertainties make it difficult to determine whether there is a threshold for the association at the lower end of the range.

Long-term ozone exposure: mortality

N ENGL J MED 360;11 NEJM.ORG MARCH 12, 2009

Long-Term Ozone Exposure and Mortality

Michael Jerrett, Ph.D., Richard T. Burnett, Ph.D., C. Arden Pope III, Ph.D.,
Kazuhiko Ito, Ph.D., George Thurston, Sc.D., Daniel Krewski, Ph.D.,
Yuanli Shi, M.D., Eugenia Calle, Ph.D., and Michael Thun, M.D.

cardiovascular causes, whereas ozone was associated with the risk of death from respiratory causes. The estimated relative risk of death from respiratory causes that was associated with an increment in ozone concentration of 10 ppb was 1.040 (95% confidence interval, 1.010 to 1.067). The association of ozone with the risk of death from respiratory causes was insensitive to adjustment for confounders and to the type of statistical model used.

Indoor ozone

Environmental Health Perspectives • VOLUME 114 | NUMBER 10 | October 2006

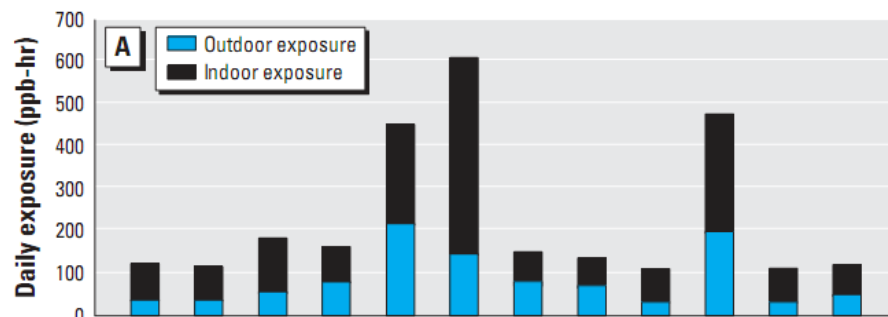
Review

Ozone's Impact on Public Health: Contributions from Indoor Exposures to Ozone and Products of Ozone-Initiated Chemistry

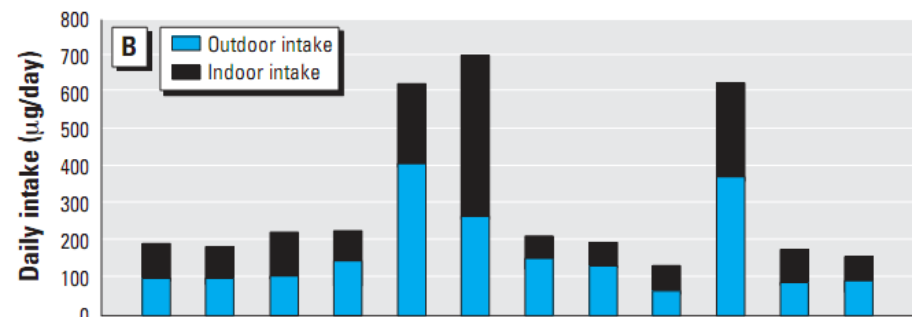
Charles J. Weschler^{1,2}

- main source of indoor ozone is outdoor-to-indoor transport
- indoor ozone levels are 10-50 % of outdoor values
- people spend 80-90 % of their time indoors

Indoor O₃ exposure: 43-76 % (avg. 60 %)



Indoor O₃ intake: 27- 60 % (avg. 40 %)

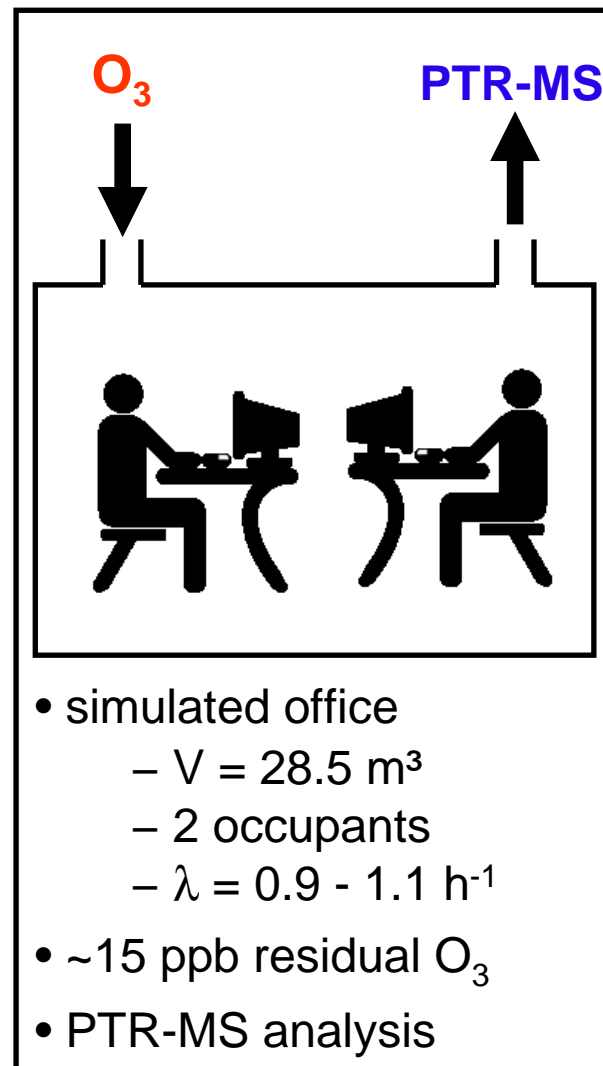
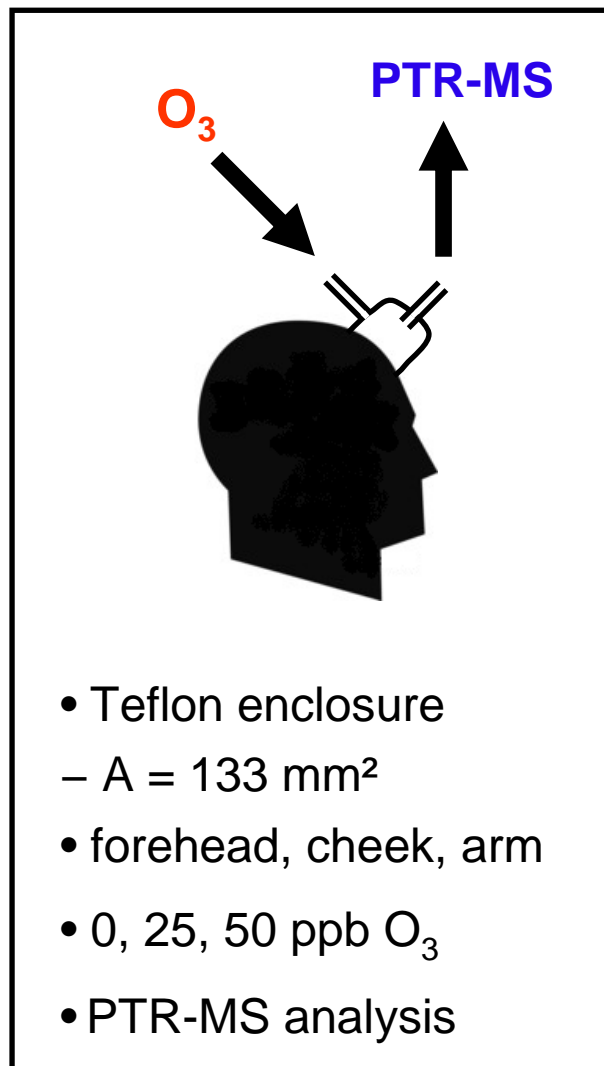
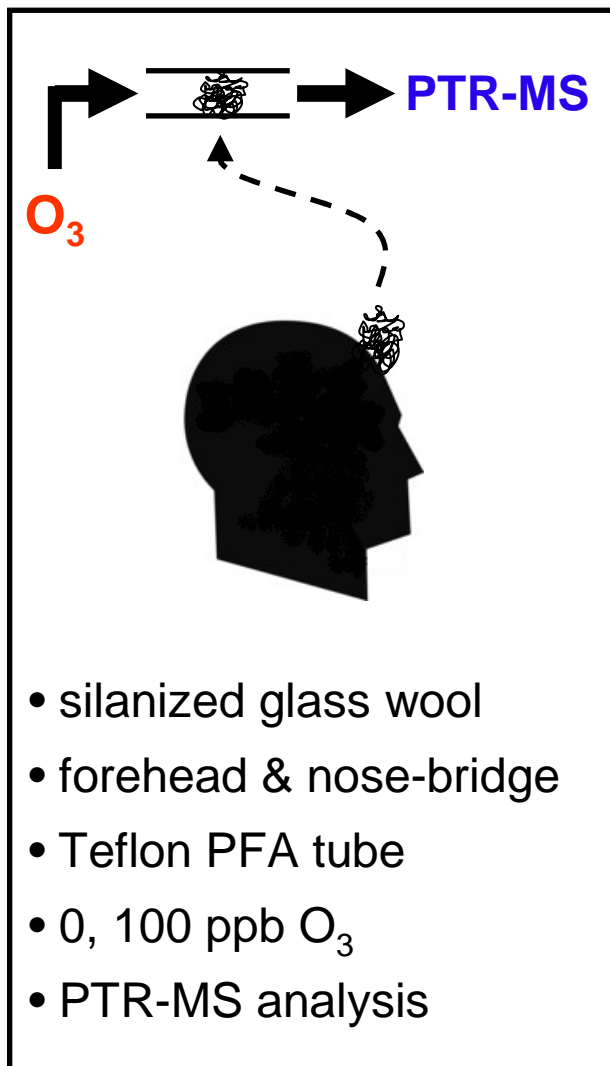


12 studies in the U.S. and Canada

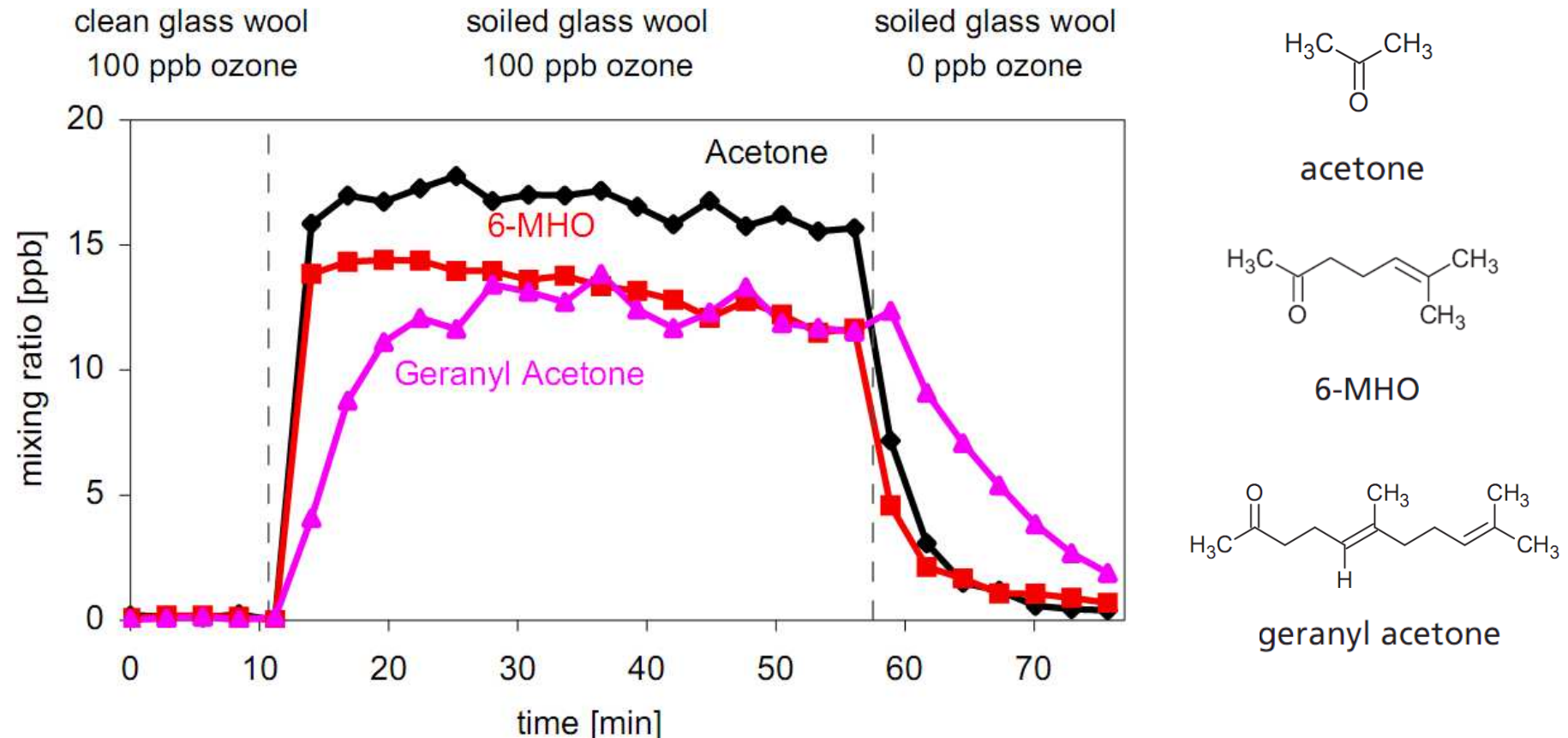
Reactive loss of indoor ozone

- Indoor ozone is primarily lost due to surface reactions:
 - Carpets (e.g. *Weschler et al.*, 1992; *Morrison and Nazaroff*, 2002; *Wang and Morrison*, 2006)
 - Latex paint (e.g. *Reiss et al.*, 1995a,b; *Wang and Morrison*, 2006)
 - HVAC materials (e.g. *Morrison et al.*, 1998; *Hyttinen et al.*, 2003; *Hyttinen et al.*, 2006; *Zhao et al.*, 2007)
- Only selected aspects of the interaction of ozone with the human envelope have been investigated:
 - Clothing (*Wisthaler et al.*, 2005; *Coleman et al.*, 2008)
 - Aircraft passengers (*Weschler et al.*, 2007)
 - Hair (*Pandrangi et al.*, 2008)
 - CFD simulation (*Rim et al.*, 2009)
- No systematic study of the reactive interaction of ozone with the human envelope

Experiments

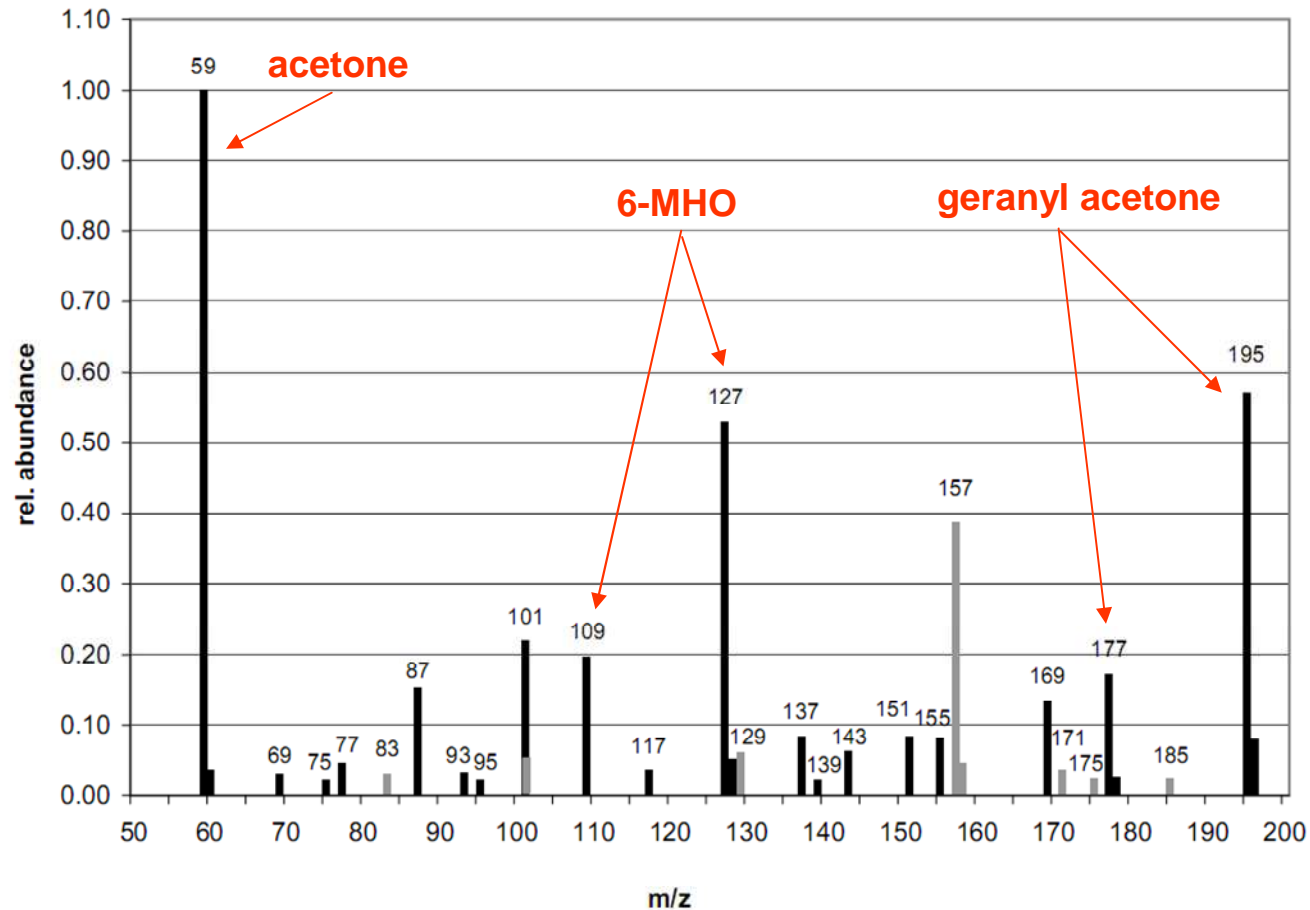


Major products of skin oil ozonolysis



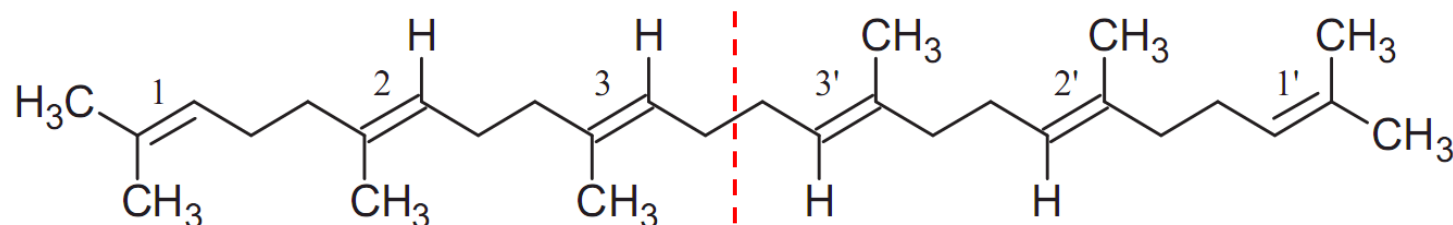
Fruekilde et al, 1998: squalene ozonolysis

Skin oil / squalene ozonolysis



- peaks observed during both skin oil and squalene ozonolysis
- peaks observed only during skin oil ozonolysis

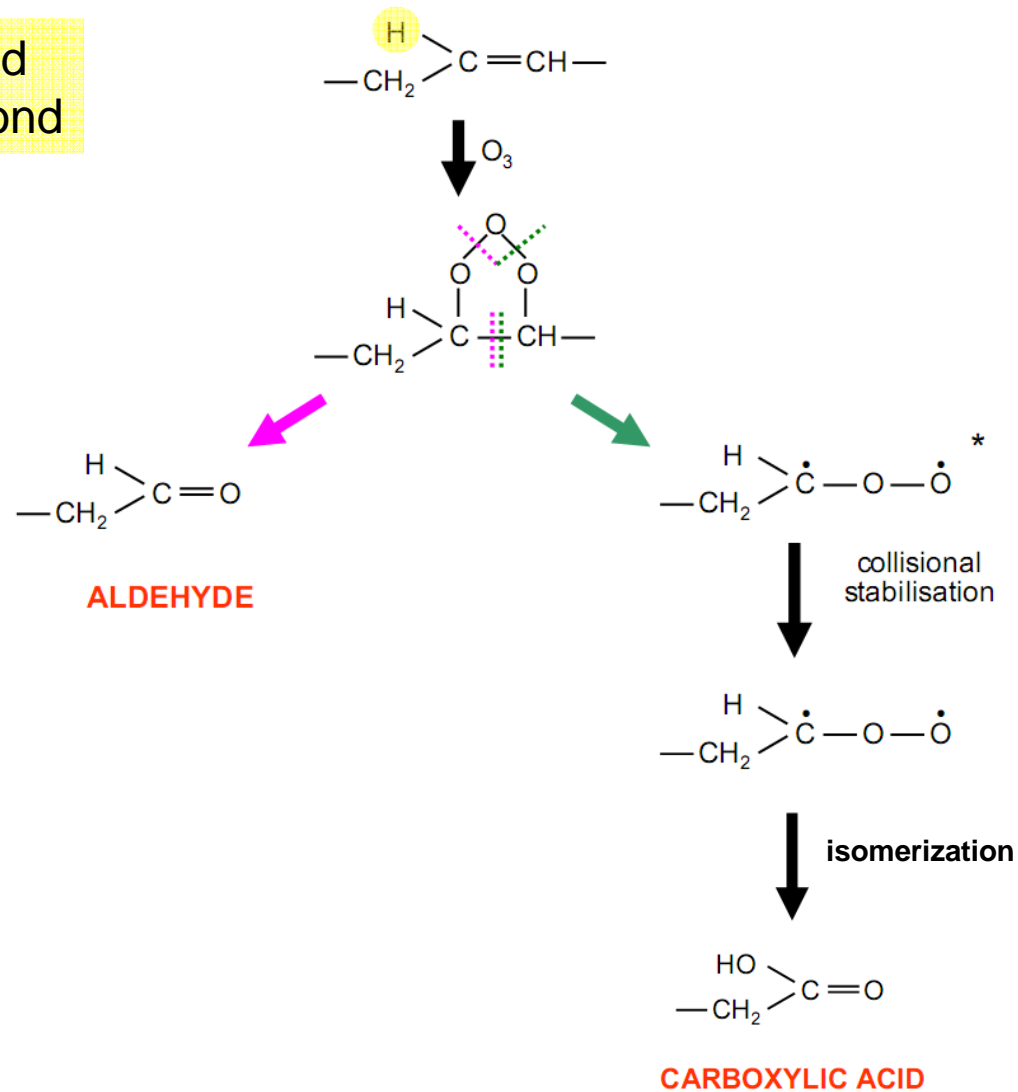
Squalene ozonolysis



- Squalene is the single most abundant ozone-reactive constituent in human skin lipids (~ 12 %, *Nicolaidis*, 1974)
- Initially, ozone attacks one of the double bonds in squalene:
 - primary, monofunctional product
- Subsequently, ozone can attack a double bond in a primary product:
 - secondary, bifunctional product
- Terminal groups formed upon ozonolysis:
 - aldehydic group
 - keto group
 - carboxylic group
 - α -hydroxyketo group

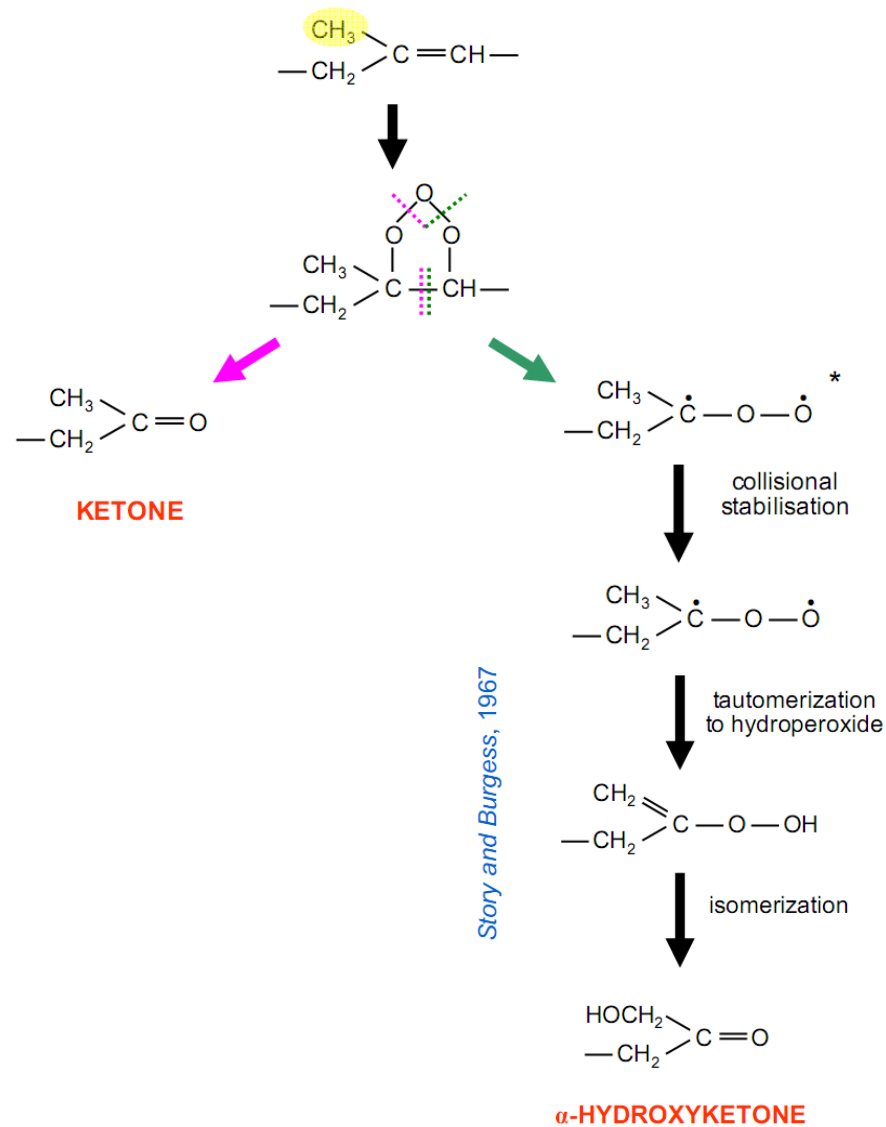
Criegee mechanism

non-substituted
target double bond

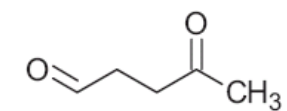
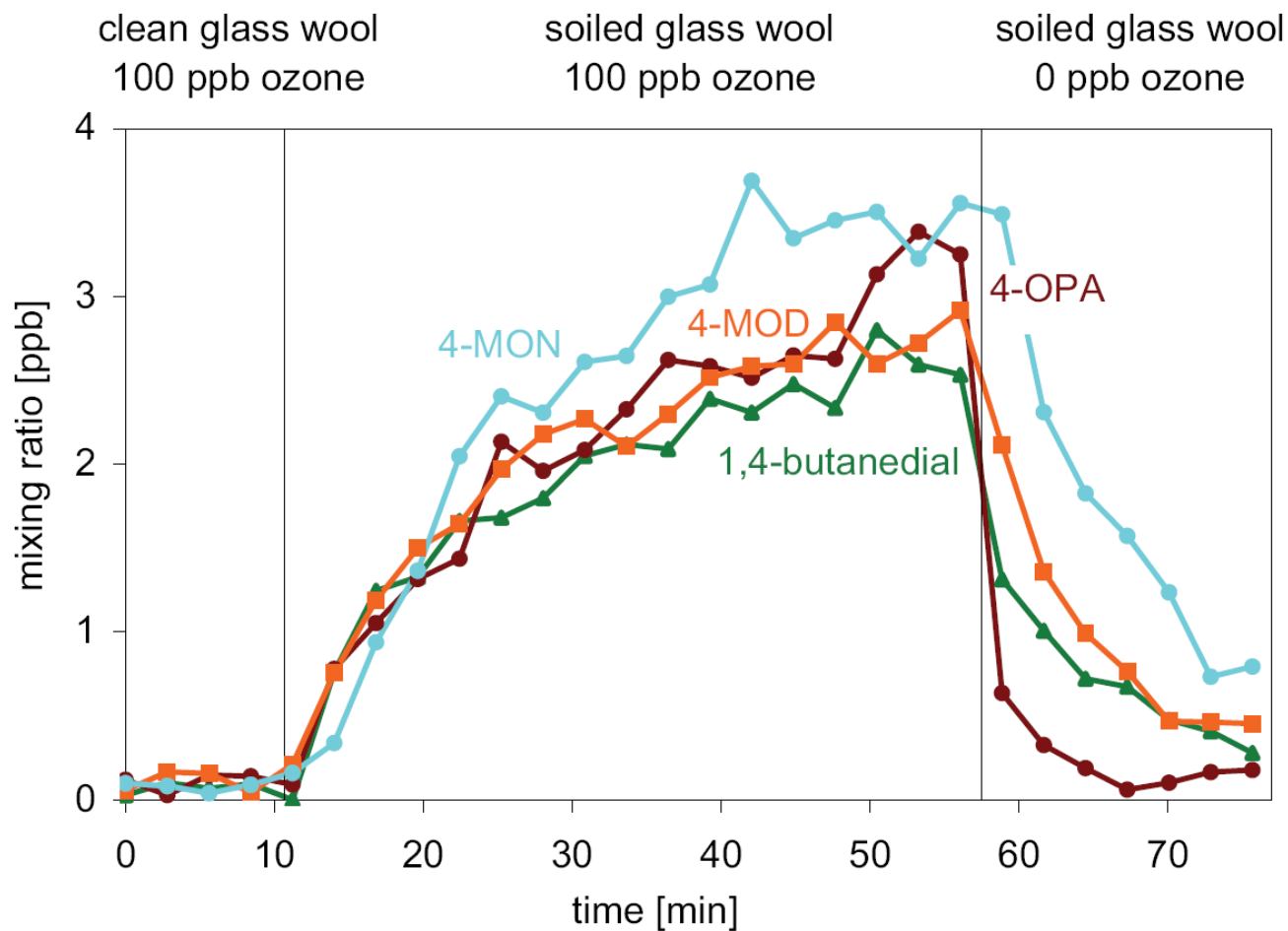


Criegee mechanism

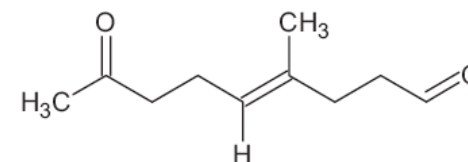
methyl-substituted
target double bond



Secondary dicarbonyls



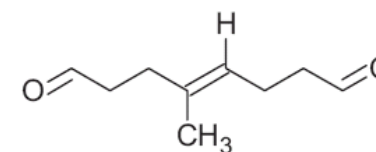
4-oxopentanal (4-OPA)



4-methyl-8-oxo-4-nonenal (4-MON)

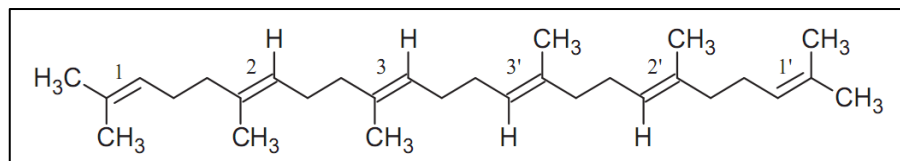


1,4-butanediol (succinic dialdehyde)



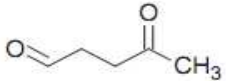
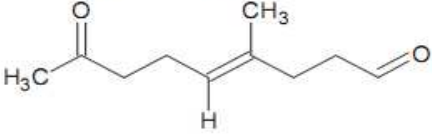
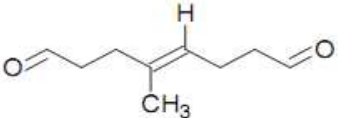

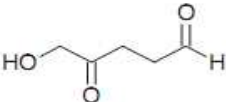
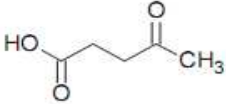
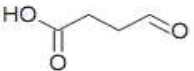
4-methyl-4-octene-1,8-dial (4-MOD)

Overview: primary products



<i>m/z</i>	Product identified in gas phase	Major precursors*	Bond(s) involved†
59	 propan-2-one (acetone)	squalene, C27-pentaenal, C22-tetraenal, C17-trienal, C27-pentaenoic acid, C22-tetraenoic acid, C17-trienoic acid, OH-geranyl acetone, geranyl acetone, OH-6MHO, 6-MHO	1
109, 127	 6-methyl-5-hepten-2-one (6-MHO)	squalene, C27-pentaenal, C22-tetraenal, C17-trienal, C27-pentaenoic acid, C22-tetraenoic acid, C17-trienoic acid, OH-geranyl acetone, geranyl acetone	2
177, 195	 6,10-dimethylundeca-5,9-dien-2-one (geranyl acetone)	squalene, C27-pentaenal, C22-tetraenal, C17-trienal, C27-pentaenoic acid, C22-tetraenoic acid, C17-trienoic acid	3
75	 1-hydroxypropan-2-one (hydroxy acetone)	squalene, C27-pentaenal, C22-tetraenal, C17-trienal, C27-pentaenoic acid, C22-tetraenoic acid, C17-trienoic acid, OH-geranyl acetone, geranyl acetone, OH-6MHO, 6-MHO	1
125, 143	 1-hydroxy-6-methyl-5-hepten-2-one	squalene, C27-pentaenal, C22-tetraenal, C17-trienal, C27-pentaenoic acid, C22-tetraenoic acid, C17-trienoic acid, OH-geranyl acetone, geranyl acetone	2

Overview: secondary products

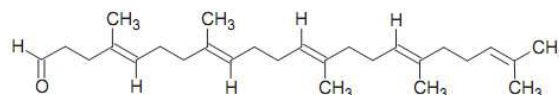
<i>m/z</i>	Product identified in gas phase	Major precursors*	Bond(s) involved†
101	 4-oxopentanal (4-OPA)	C27-pentaenal, C22-tetraenal, geranyl acetone, 6-MHO	1 & 2 2 & 3 2 & 1 3 & 2
151, 169	 4-methyl-8-oxo-4-nonenal (4-MON)	C27-pentaenal, geranyl acetone	1 & 3 3 & 1
137, 155	 4-methyl-4-octene-1,8-dial (4-MOD)	C22-tetraenal, C17-trienal	2 & 3' 3 & 2'
87	 1,4-butanedial (succinic dialdehyde)	C17-trienal	3 & 3'
99, 117	 5-hydroxy-4-oxopentanal	C27-pentaenal, C22-tetraenal, OH-geranyl acetone, OH-6MHO	1 & 2 2 & 3
99, 117	 4-oxopentanoic acid (levulinic acid)	C27-pentaenoic acid, C22-tetraenoic acid, geranyl acetone, 6-MHO	2 & 1 3 & 2
85, 103	 4-oxobutanoic acid	C17-trienal, C17-trienoic acid	3 & 3'

tertiary and higher-order products are not discussed

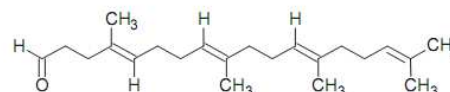
Discussion: squalene ozonolysis

- Full spectrum of volatile (low *mw*) products observed
- Formation of non-volatile (high *mw*) products can be inferred

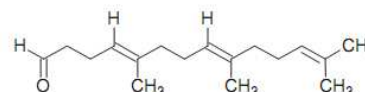
4,8,13,17,21-pentamethyl-docosa-4,8,12,16,20-pentaenal
(C27-pentaenal)



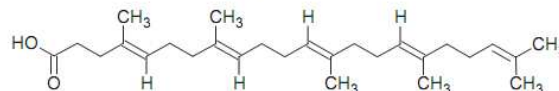
4,9,13,17-tetramethyl-octadeca-4,8,12,16-tetraenal (C22-tetraenal)



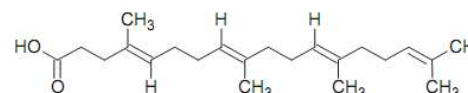
5,9,13-trimethyltetradeca-4,8,12-trienal (C17-trienal)



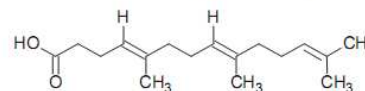
4,8,13,17,21-pentamethyl-docosa-4,8,12,16,20-pentaenoic acid
(C27-pentaenoic acid)



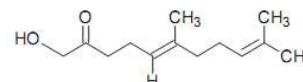
4,9,13,17-tetramethyl-octadeca-4,8,12,16-tetraenoic acid
(C22-tetraenoic acid)



5,9,13-trimethyltetradeca-4,8,12-trienoic acid (C17-trienoic acid)



1-hydroxy-6,10-dimethylundeca-5,9-dien-2-one (OH-geranyl acetone)



→ secondary
non-volatile
products

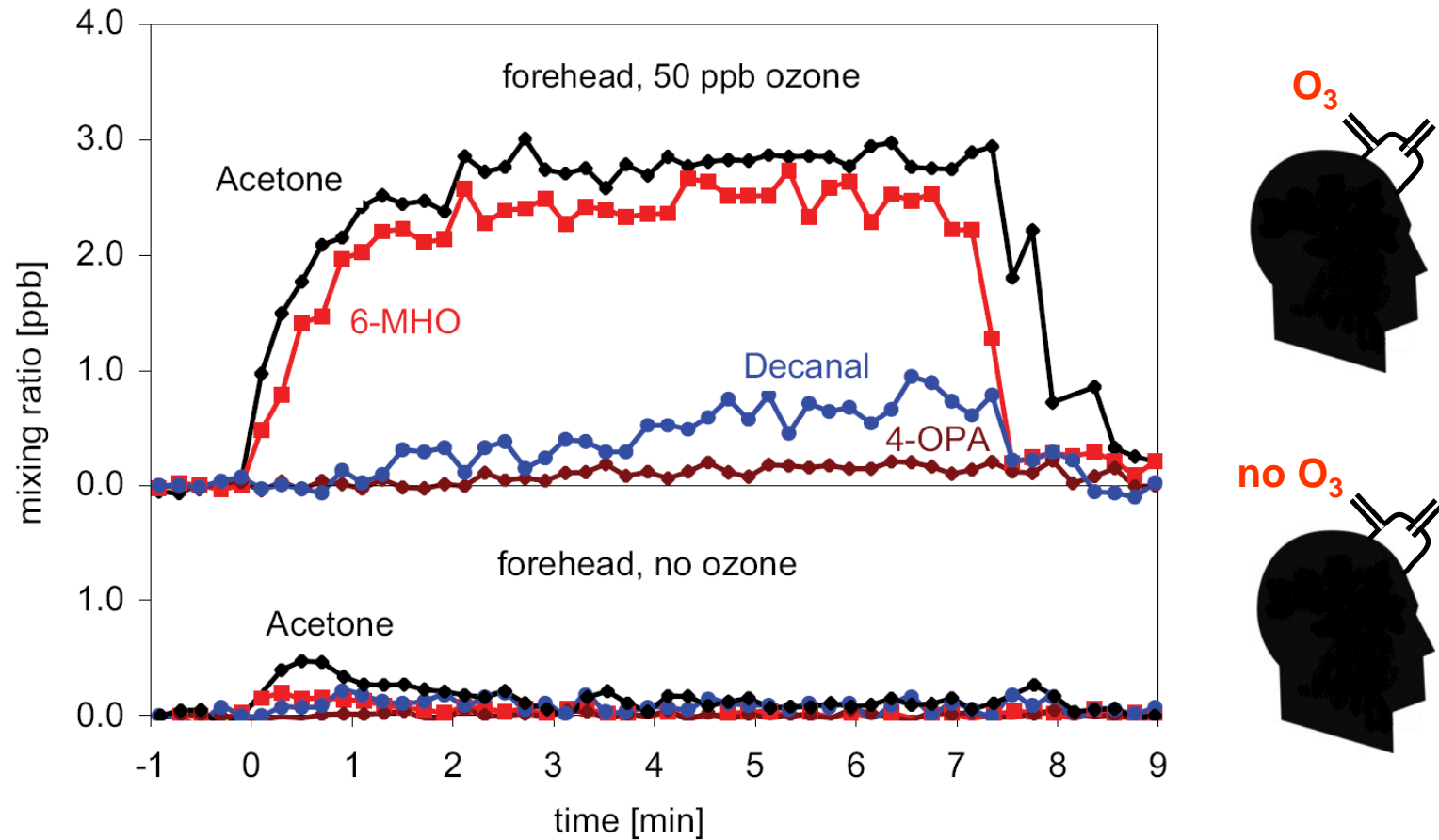
- Skin surface reactions of the SCI's ? (carbonyls, acids, water,..)
 - secondary ozonides, hydroperoxides, diperoxides, acid anhydrides,..

Ozonolysis of fatty acids

	Product identified in gas phase	Major fatty acid precursors*
	 dodecanal	<i>cis</i> -octadec-6-enoic acid
	 undecanal	<i>cis</i> -heptadec-6-enoic acid, <i>cis</i> -14-methylhexadec-6-enoic acid
	 decanal [‡]	<i>cis</i> -hexadec-6-enoic acid, <i>cis</i> -octadec-8-enoic acid, <i>cis</i> -15-methylpentadec-6-enoic acid, octadeca-5,8-dienoic acid
	 nonanal	oleic acid, <i>cis</i> -heptadec-8-enoic acid
	 octanal	<i>cis</i> -tetradec-6-enoic acid
	 hexanal	linoleic acid

* Free and esterified

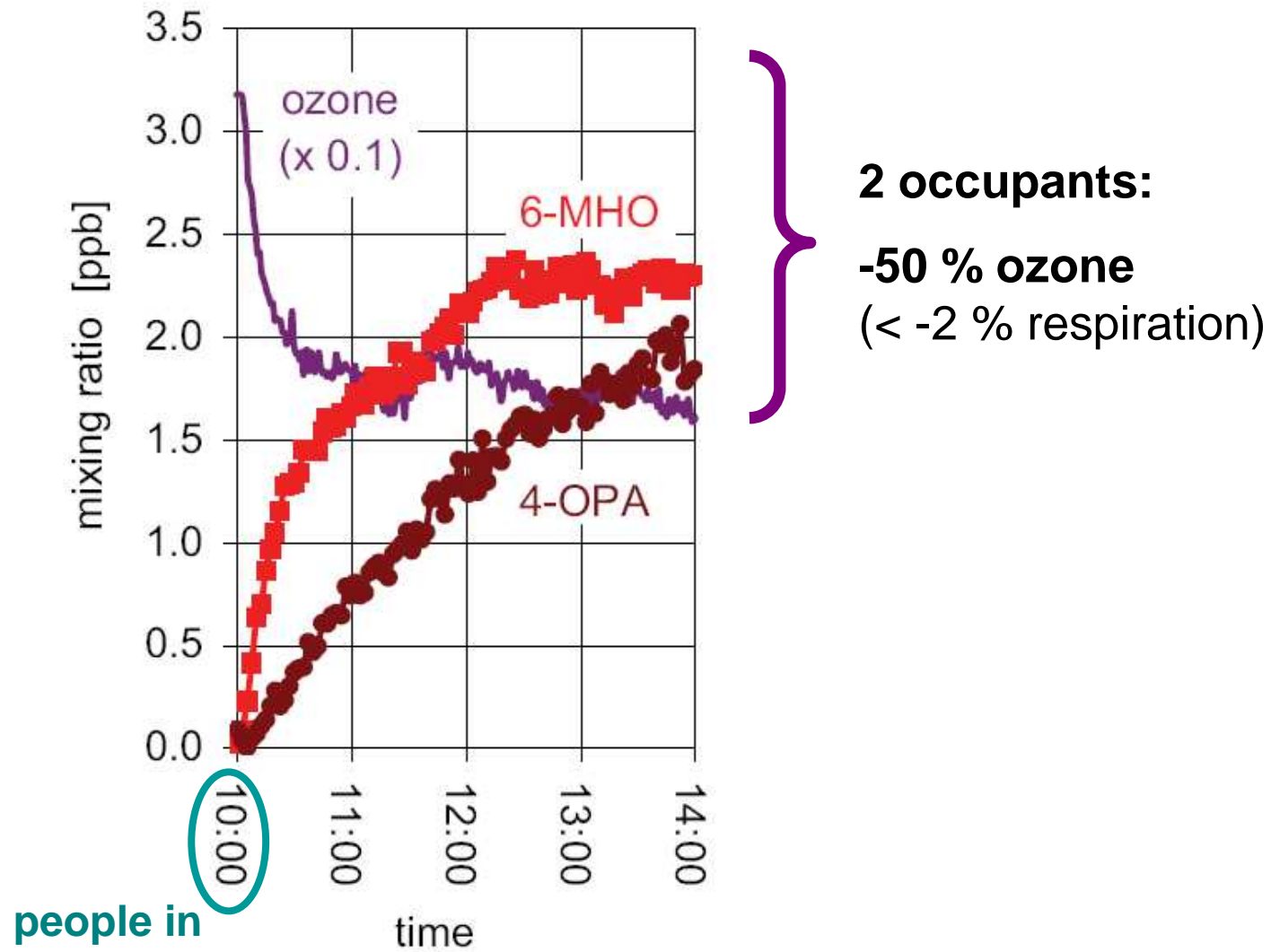
In vivo measurements



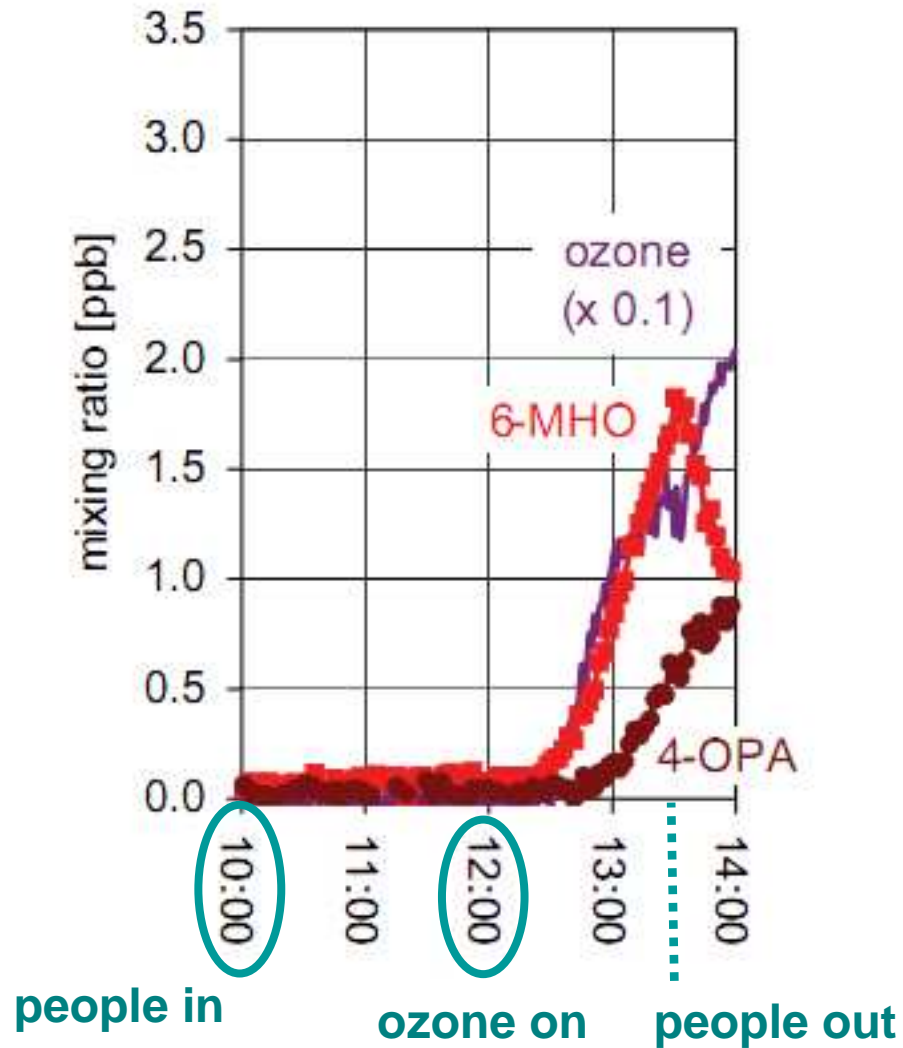
Relative concentrations: forehead (100%), cheek (75%), forearm (65%)

Steady-state concentrations scale linearly with ozone concentrations (25 or 50 ppb)

Office experiment (scenario 1)



Office experiment (scenario 2)



Personal reactive cloud

Indoor Air 2009; 19: 324–334

The influence of chemical interactions at the human surface on breathing zone levels of reactants and products

D. Rim¹, A. Novoselec¹, G. Morrison²

CFD:

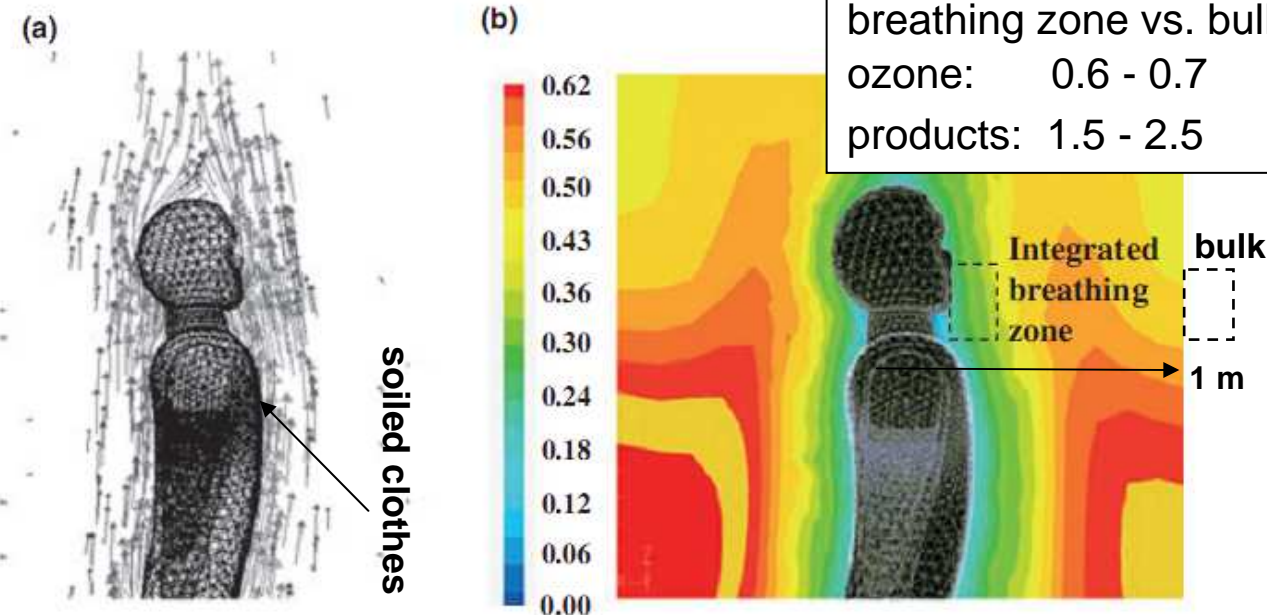
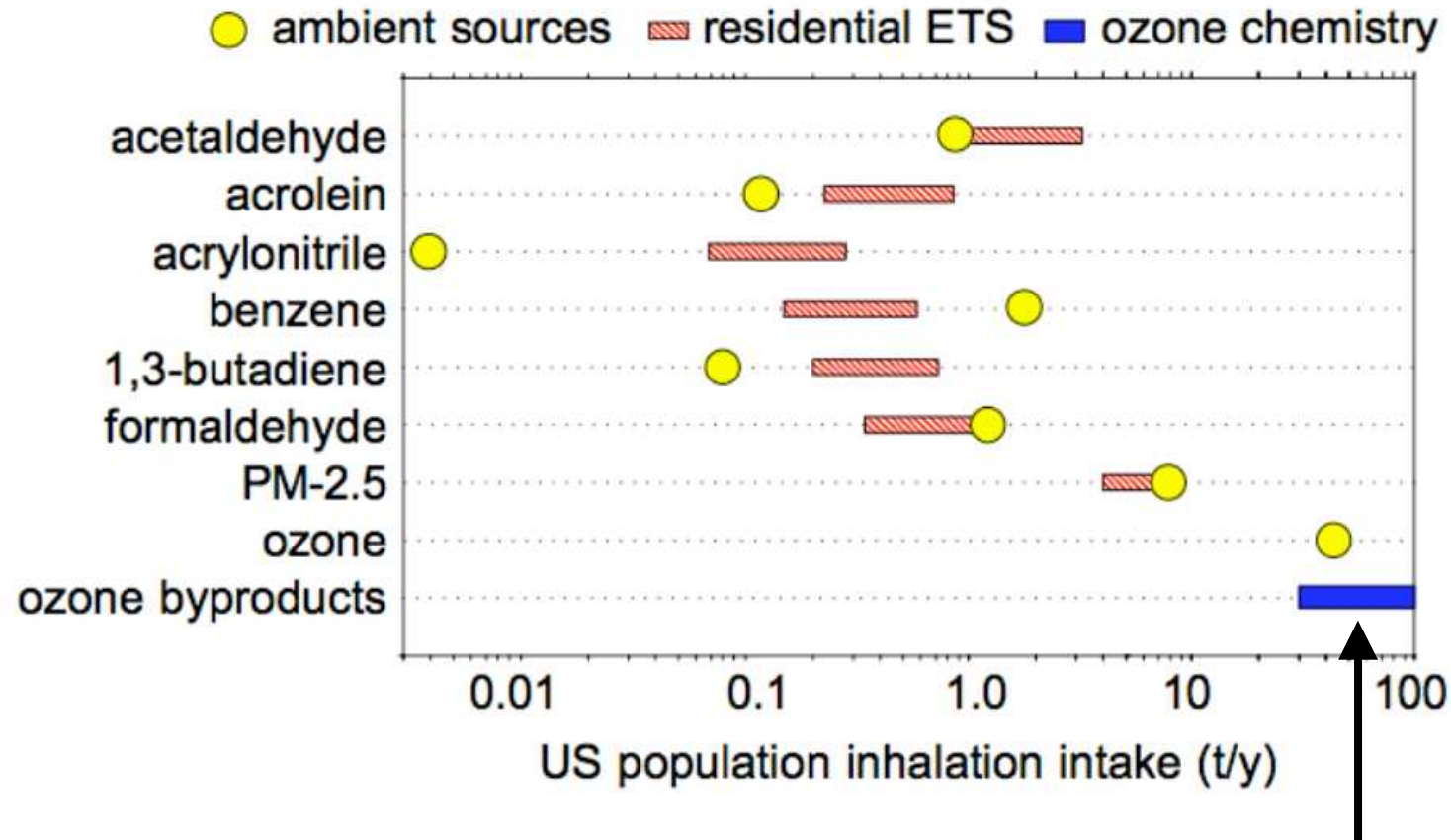


Fig. 3 (a) Occupant thermal plume for an air exchange rate equal to $0.5/h$ mean velocity magnitude around the body = 0.1 m/s (b) Contour of ozone concentration (normalized by chamber inlet concentration) around the body and sampling region for inhaled concentration

Population burden to ozone by-products



„modern“ burden:

only since people are mostly indoors and since tropospheric ozone levels are elevated

Nazaroff and Weschler, Indoor Air Conference 2008

Implications

- potential health effects:
 - ozone vs. ozone reaction products
 - natural defense mechanism (“anti-oxidant”) vs. aldehyde burden
- potential others effects:
 - surface chemistry occurs on all surfaces that have been touched by humans or to which squalene / fatty acids have redistributed: artwork, books, etc.
- measurement artifacts:
 - ozone measurements
 - OH reactivity measurements
 - VOC measurements (acetone, decanal, others)

Potential health effects

○ Новости



19.08 10:18

Озон раздражает кожу и легкие офисных работников

Ученые из Инсбрукского университета имени Леопольда и Франца (Leopold-Franzens-Universität Innsbruck) (Австрия) и Университета медицины и стоматологии Нью-Джерси (University of Medicine and Dentistry of New Jersey) под руководством доктора Армина Висталера (Armin Wisthaler) нашли еще одно опасное химическое соединение в воздухе офисов. Им оказался озон.

Как говорят авторы работы, этот активный окислитель выделяется при работе ксероксов, пылеуловителей, увлажнителей воздуха, и, что не удивительно, озонаторов. Оказывается, многие приборы, цель которых - улучшить качество воздуха, напротив, создают множество проблем для здоровья людей. Как выяснили Висталер и его коллеги, озон взаимодействует с липидами кожного сала человека.

При этом выделяются вещества, вызывающие раздражение кожи и заболевания верхних дыхательных путей.

Potential health effects

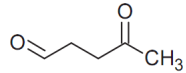
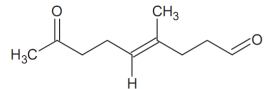
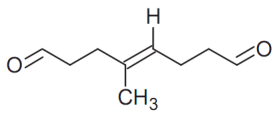
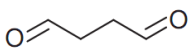
Relationship between chemical structure and the occupational asthma hazard of low molecular weight organic compounds

J Jarvis, M J Seed, R A Elton, L Sawyer, R M Agius

.....
Occup Environ Med 2005;**62**:243–250. doi: 10.1136/oem.2004.016402

- structure-activity relationship (SAR):
 - 78 low-molecular-weight asthmagens and 301 control compounds
- bifunctional reactivity strongly associated with occupational asthma hazard
 - covalent cross-linking of otherwise non-antigenic “self” proteins
- Chemical Asthma Hazard Assessment Program:
 - <http://homepages.ed.ac.uk/jjarvis/research/hazassess/hazassess.html>
 - calculates asthma hazard index (0-1, low to high potential to cause occupational asthma)

Potential health effects of dicarbonyls

Name	Structure	Asthma hazard index	Classification
4-OPA		0.52	This molecule is very probably hazardous.
4-MON		0.81	This molecule is undoubtedly hazardous.
4-MOD		0.93	This molecule is undoubtedly hazardous.
1,4-butanedial		0.78	This molecule is undoubtedly hazardous.

- based on toxicological studies in which exposure was >> than typical indoor levels
 - but: sensitization can occur at low concentrations (no threshold)
 - effects of combined exposure ?

Toxicology studies (high concentrations)

- 4-OPA:

- ongoing work at U.S. NIOSH

Franko et al., 4-Oxopentanal Identified as a Potential Indoor Air Irritant and Allergen [A1509] [abstract]. *Toxicologist* 108(1):313, 2009

- irritant
- extreme sensitizer

- glutaraldehyde (1,5-pentanedial):

- eye, skin, upper respiratory tract irritant
- allergenic contact dermatitis
- headache, nausea and fatigue
- numerous cases of occupational asthma
- low exposure limits: 3 ppb (30 d), 0.6 ppb (180 d)

[Commission on Life Sciences, 1996]

Indirect evidence ?

Indoor Air 2008; 18: 156–170

Outdoor ozone and building-related symptoms in the BASE study

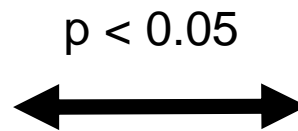
M. G. Apte, I. S. H. Buchanan, M. J. Mendell



100 randomly selected office buildings

4200 self-administered questionnaires

Outdoor
O₃



Building-related symptoms



Dry eyes



Neurological
(fatigue, trouble concentrating)



Headache



Upper respiratory
(nose/sinus congestion, sore throat, sneeze)

Conclusions

- Indoor ozone is scavenged by reaction with human skin oils
- Squalene is the primary ozone target
- Squalene ozonolysis produces a cascade of products:
 - volatile / non-volatile
 - monofunctional / bifunctional
 - carbonyl / carboxyl / α -hydroxyketone groups
- Exposure occurs via inhalation and skin contact
- Dicarbonyls are of potential health concern:
 - respiratory and skin irritation and/or sensitization
 - future studies required

Reactions of ozone with human skin lipids: Sources of carbonyls, dicarbonyls, and hydroxycarbonyls in indoor air

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