



Perspectives on Ozone Effects on Chronic Exposure A Tribute to David Bates



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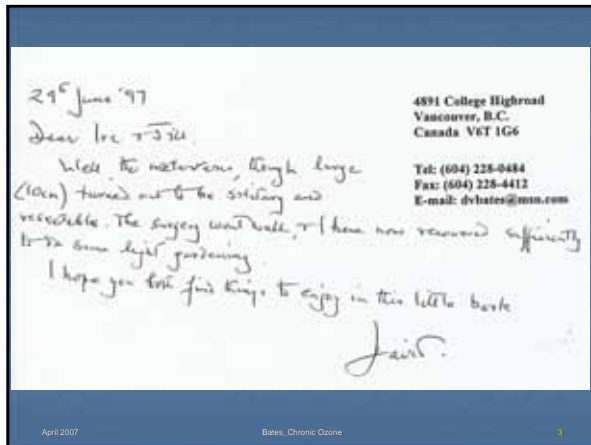


Perspectives on Ozone Effects on Chronic Exposure A Tribute to David Bates



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David Bates On:
CREATIVITY:

- "But then, after about 5 minutes and fifteen seconds..., there occur nine bars... our world has completely changed."

RESEARCH:

- "The analogy that I have always preferred is between research and ...path-making... Research consists of making new paths."

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Last Stanza of A Poem Written Four Days After the Death of David's Wife, Margaret, July 11, 1996

*I am still awaiting
Your footfall on the stairs
Up to the kitchen
How long does it last?
Yesterday there was a Monarch
On the heliotrope; and a new
Chickadee exploring the deck.
Today the young swallow flew from the box
That you used to watch
From the kitchen window.
Never to return
Never even a backward look.
There's no-one to tell.
No one to tell.*

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David's Guiding Hand in My Work on Effects of Chronic Exposure to Ozone

- Bates DV: Review Ozone—Myth and Reality, Environ Res, 1989
 - 3 phenomena we should be studying in human populations exposed to O₃
 - ↑ prevalence of lung infections
 - *Premature loss of elastic recoil possibly associated with small airway changes due to lung remodeling*
 - ↑ airway reactivity

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David's Guiding Hand in My Work on Effects of Chronic Exposure to Ozone

- Bates DV, Sizto R: The Ontario Air Pollution Study: Identification of a Causal Agent. Environ Res, 1989
 - "It is concluded that neither ozone nor SO₂ alone is responsible for the observed acute respiratory admissions...or some pattern of sequential or cumulative exposure is responsible for the observed mortality"

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David's Guiding Hand in My Work on Effects of Chronic Exposure to Ozone

- Sherwin RP, Richters V. Centriacinar Region (CAR) Disease in the Lungs of Young Adults – A Preliminary Report, 1991
 - Defined as "frequent extension of respiratory bronchiolitis into proximal acinar structures"
 - Odds ratio (95%CI) for LA residents
 - 4.0 (1.4, 11.3)

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David's Guiding Hand in My Work on Effects of Chronic Exposure to Ozone

- Bates, DV: Detection of Chronic Respiratory Bronchiolitis in Oxidant Exposed Populations: Analogy to Tobacco Smoke Exposure, EHP, '93
 - Non-human primate studies suggest respiratory bronchiolitis as the lesion of chronic O₃ exposure
 - Consistent with human dosimetry studies
 - Analogy with respiratory bronchiolitis in young smokers (age 20-30 years)
 - Lung function tests of small airways function consistent abnormalities in small airways.

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Respiratory Bronchiolitis



Sherwin, 1991



Niewoehner, 1974

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Study of Effects of Chronic Exposure to Ambient O₃ In Adolescents

- Test the hypothesis that long-term exposure to ambient O₃ is associated, preferentially, with changes in lung function measures that reflect "small airways"
 - O₃ as a marker for complex photochemical mixture

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Study of Effects of Chronic Exposure to Ambient O₃ In Adolescents

- Rationale:
 - Studies in primates indicate that the primary effect of cyclical O₃ exposure on the lung is on remodeling of respiratory bronchioles
 - Human dosimetry of O₃
 - Major site of pulmonary deposition is at level of respiratory bronchioles
 - Our previous pilot study

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Study of Effects of Chronic Exposure to Ambient O₃ In Adolescents

- Convenience Sample of 252 UCB freshman
 - Lifetime residents of "LA" or "SFBA"
 - Lifetime non-smokers
 - No chronic respiratory disease (1 exception)
- Initial Evaluation ("springtime"—February-May)
 - Detailed residential and health history
 - Spirometry
 - Skin prick tests
 - Blood or buccal smears for DNA
- Second Evaluation ("post summer"—Aug.- Sept.)
- Controlled O₃ exposure

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Brief Description of Study Population



- Sex: 108 males; 147 females
- Age: 95% 18 or 19 years
 - Total residential history: 18 years
- Region: 40% SFBA (by design)
- Race: ~50% Asian, <10% Hispanic, <10% Black
- Respiratory History:
 - Inactive asthma
 - 4% M, 1% F
 - LRI <age 2: 16%
- SHS exposure: 16%
- Atopic by IgE: 30%

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Methods of Exposure Assessment

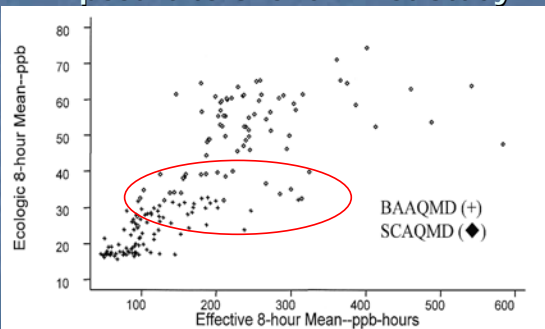
- "Ecological" Model
 - Residence-specific O₃, PM₁₀, NO₂
 - Inverse distance-squared interpolation from up to 3 monitors (all within 50 km, most within 8 km)
 - Weighted average over all residential assignments in ppb/month
- "Time Outdoors" Model (ozone only)
 - First two steps as above
 - Median time spent outdoors from ARB survey by Wiley, *et al.* or based on questionnaire data from study
 - Account for indoor-outdoor O₃ ratio
 - Weighted average over all residential assignments in ppb-hours/month

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Distribution of Estimated Lifetime Exposure to Ozone—Pilot Study

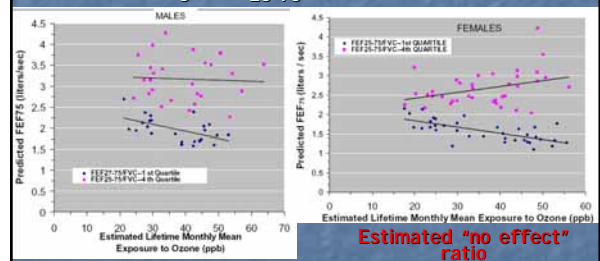


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Modification of Association of Lifetime Exposure to O₃ and FEF₇₅ By FEF₂₅₋₇₅/FVC Ratio



Effects not confounded by estimated lifetime exposure to PM₁₀ or NO₂ and not due to measurement errors

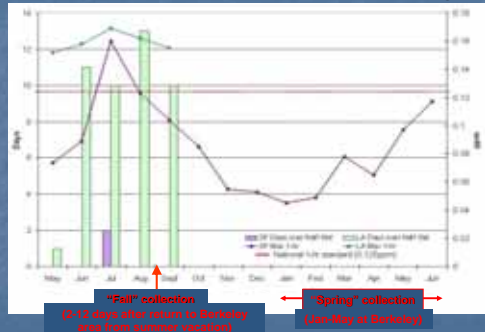
Males: 1.17
Female: 1.04

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Ozone-Induced Cytogenetic Damage and Long-Term Exposure to O₃

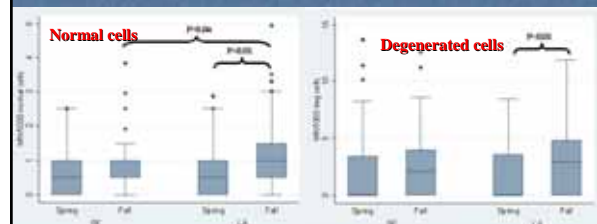


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Frequency of Occurrence of Micronuclei in Exfoliated Buccal Cells



Fall refers to "post summer"

Micronuclei in buccal cells associated only with geographical location of subjects and not with daily, weekly or estimated lifetime exposure

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Controlled O₃ Exposure Protocol

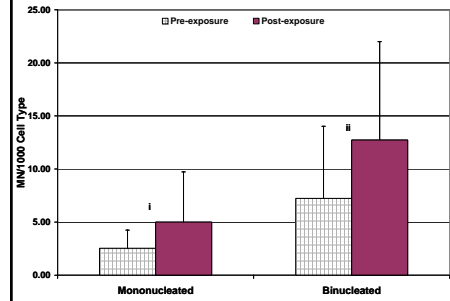
- 15 members of cohort whose FEF₂₅₋₇₅ level below the 10th or above the 90th percentile of the distribution for all subjects
- Exposed to 200 ppb O₃ for 4 hours with 30 minutes of exercise during each hour
- Buccal cells and blood collected pre-exposure
- Bronchoscopy, buccal cells, blood 18 hours post-exposure
- Cytogenetic analysis of pre and post-exposure buccal cells and peripheral blood lymphocytes

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Micronuclei in Peripheral Blood Lymphocytes 18 Hours After Controlled Four-Hour Exposure to 200 ppb O₃



Increase in pycnotic (necrotic) cells post-exposure: [1.6% (95%CI: 0.9-2.7) versus 0.3% (95%CI: -0.1-0.5)]

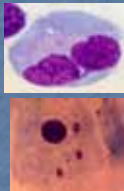
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Associations Between Cytogenetic Markers and Markers From Different Sources

- In binucleate peripheral blood lymphocytes, frequency of nuclear bridges (NB) were correlated with frequency of micronuclei in buccal cells pre- and post-O₃
 - Pre: R = 0.74 (p = 0.02); Post: R = 0.62 (p = 0.05)
- Post-exposure, micronuclei in buccal cells were correlated with MN in peripheral blood lymphocytes
 - Post: R = 0.62 (p = 0.05)

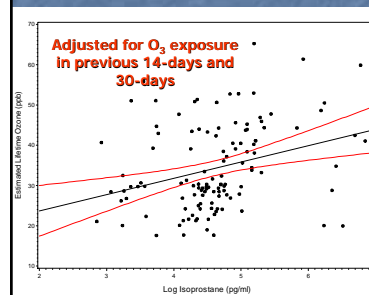


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Association Between Marker of Oxidative Stress and Lifetime Exposure to Ambient Ozone



- Blood collected Feb.-June 2002
- N = 120
 - SF: 59
 - LA: 61
 - Females: 68
- 8-iso-PGF μmol/ml Median (range)
 - SF: 4.4 (2.8-6.5)
 - LA: 4.9 (2.9-6.8)

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Thoughts and CONCLUSIONS

- Our data indicate that long-term exposure to ambient [O₃] is associated with
 - Decreased small airway function as measured by FEF₇₅ and not associated with measures more reflective of lung volume
 - Intrinsic small airway size, as measured by FEF₂₅₋₇₅/FVC, is a susceptibility factor for adverse effects on O₃ on small airway function
 - Evidence of increased systemic oxidative stress
 - Controlled exposure data indicate support for direct contribution of O₃ to systemic effects
- David Bates' ideas made a major contribution to this study!

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THANK YOU
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Estimated Effects of Lifetime Monthly Mean 8-Hour Exposure to Ozone on FEF₇₅ Based on Ecological Model Effects of Measurement Error

Similar Results for males

	Parameter Estimates for Females (±SE)		
	Type of Measurement Error Correction		
	None	PM ₁₀ Before 1987	8-Hour Mean O ₃
Monthly Mean 8-hour O ₃	-0.026 (0.002)	Not applicable	-0.027 (0.002)
Interaction O ₃ +FEF ₂₅₋₇₅ /FVC	+0.023 (0.001)		+0.024 (0.002)
Monthly Mean 8-hour O ₃	-0.024 (0.003)	-0.24 (0.007)	-0.025 (0.003)
Interaction O ₃ +FEF ₂₅₋₇₅ /FVC	+0.025 (0.002)	NA	+0.026 (0.002)
PM ₁₀ before 1988	+1.5*10 ⁻⁴ (0.001)	+9.7*10 ⁻⁴ (0.009)	+1.5*10 ⁻⁴ (0.001)
PM ₁₀ 1988 and later	-0.007 (0.003)	NA	-0.007 (0.003)
Monthly Mean 8-hour O ₃	-0.025 (0.003)		
Interaction O ₃ +FEF ₂₅₋₇₅ /FVC	+0.025 (0.002)		
PM ₁₀ before 1988	+0.001 (0.002)	Not Performed	Not Performed
PM ₁₀ 1988 and later	-0.004 (-0.004)		
NO ₂	-0.004 (0.002)		

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