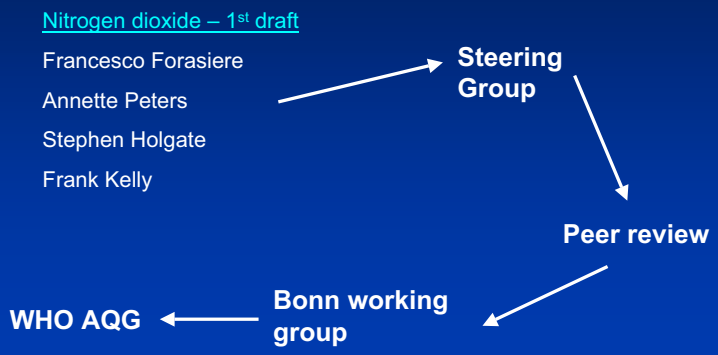
NO_2 - a surrogate for traffic or a pollutant in its own right?

Frank J Kelly
Environmental Research Group
King's College London, UK

WHO AQG, Global Update 2005



NO_2: evaluations undertaken

- 1987: WHO AQG for Europe, 1st Edition
- 1997: IPCS, Report for the Environmental Health Criteria → annual mean of 40 µg/m³
- 2000: WHO AQG for Europe (completed 1997), 2nd Edition → one hour mean of 200 µg/m³
- 2003: Report on a WHO WG: Health Aspects of Air Pollution with PM, O_3 & NO_2
- 2004: Report on a WHO WG meeting: Health Aspects of Air Pollution with PM, O_3 & NO_2 – answers to follow-up questions from CAFE
- 2006: WHO AQG, Global Update 2005

NO_2 and health effects

Evidence from …

- Animal toxicology
- Controlled human exposures
- Observational epidemiology
  - Indoors
  - Outdoors

NO_2 animal toxicology
- pulmonary metabolism -

• Lung oedema • Lipid changes • ↑ antioxidant metabolism • ↑ lung enzymes	>3160 µg/m³ (acute & subchronic)	Rats
• ↑ lipid peroxidation	752 µg/m³ (18 mo; TBARS) 75 µg/m³ (9 mo; ethane) exhalation	Rats

• *Lipid & antioxidant metabolism show response pattern dependent on conc. & exposure duration*

NO_2 animal toxicology
- pulmonary structure -

Cell changes (type I alveolar epithelial to type II; ciliated epithelial to non-ciliated) in tracheobronchial & alveolar regions	640 µg/m³ (7d)	Rats
Cytoplasm changes & hypertrophy in replaced cells	940 µg/m³ (10 d)	Rats
Human-type emphysema	15000-37000 µg/m³ (chronic)	Rats/ rabbits

• *Both conc. & time of exposure important, but pattern is complex*

NO_2 animal toxicology
airway inflammation/responsiveness

↑ epithelial damage, baseline smooth muscle tone & airway neutrophilia; ↓ mucin expression	3760 µg/m^3 (24 h) aerosolised OVA on d13 & 14	BALB/c mice sensitised to OVA
↓ TNF-α; ↑ IL-10, IL-6 & suppressor of cytokine signalling-3 mRNA	18800 µg/m^3 (1,3,20 d)	Rats

- *In vitro, depleted antioxidants defences, cell injury & inflammation confirm reactivity of NO_2*

NO_2 animal toxicology
- host defence -

↓ Antibacterial defence	940 µg/m^3 - 6 mo 3760 µg/m^3 - 3 h	Mice

- *Effects due more to concentration than duration or total dose*
- *Peak exposures and patterns of exposures important*

Animal toxicology
- summary -

- Exposure to above ambient concentrations: effects on lung metabolism, structure, function, inflammation & increased susceptibility to infection
- Very high concentrations: emphysema-like changes

NO_2 animal toxicology
- extrapolation to humans -

Inherent differences between mammalian species

- Is NO_2 an inhalant toxicant at ambient concentrations in humans?
- Exactly what exposures would lead to effects in humans?
- Would some effects seen in animals occur in humans at all?

NO_2 and health effects

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NO_2 controlled human studies
- pulmonary function -

Healthy subjects	>1800 µg/m^3 9400 µg/m^3 but not at 7000 µg/m^3 2820 – 6580 µg/m^3 (20')	*Generally* ↑ SR_{aw} ↓Mucociliary Cl
Asthmatics	230 & 188 µg/m^3 560 µg/m^3 (30-110' + exercise) 1880-7520 µg/m^3	ns trends Lowest level No response
COPD	560 µg/m^3 (4h) Similar to above (1h + exercise) 3000 µg/m^3	Functional effects No response ↑ SR_{aw}

NO_2 controlled human studies
- airway responsiveness in asthmatics -

560 µg/m³ 488 µg/m³	Cold Histamine
meta-analysis ≥ 200 µg/m³ ≥ 1900 µg/m³ (normals)	Increase in airway responsiveness to a range of constrictor stimuli
800 µg/m³ 500 µg/m³	House-dust mite allergen Pollen allergen
≥ 300 µg/m³ ('road tunnel NO_2')	Greater early response; ↓ function and ↑ symptoms during late response

Mechanistic studies: ↑ neutrophils in BW & BAL; ↑ECP in BW, blood & sputum; ↑eosinophil granule product in BW

NO_2 controlled human studies
- airway inflammation -

Single dose Healthy subjects 1128-7520 µg/m³	↑ neutrophils, IL-8, antiprotease, α_2-macroglobulin ↓/↑ mast cells & lymphocytes ↓ alveolar macrophages & α_1-protease inhibitor activity
Repeated dose Healthy subjects 3600 µg/m³ 4h/d x4	↑ neutrophils ↓ antioxidants Upregulation in expression of IL-5, IL-10, IL-13 & ICAM-1

NO_2 controlled human studies
- host defence -

Healthy subjects 1880-5600 µg/m³ 2h/d x3 Attenuated influenza virus	ns trend for increased infectivity
Healthy subjects 1128 µg/m³ 3h Attenuated influenza virus	↓ inactivation of virus by alveolar macrophages

NO_2 controlled human studies
- summary -

- In healthy subjects, changes in pulmonary function, ↑ airway responsiveness, mild inflammation & ↓ host defences at concentrations (>1800 µg/m³) in excess to those outdoors
- Asthmatics more susceptible to acute effects
- In mild asthmatics, lowest concentration to change pulmonary function: 500 µg/m³ and to enhance effect of allergens: 200 µg/m³

NO_2 and health effects

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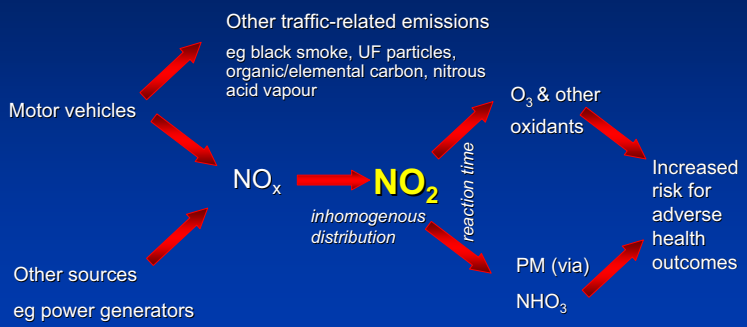
Simplified relationship between NO_x emissions & formation of NO_2 and other harmful reaction products



NO_2 - Epidemiology

Outdoor studies more informative when…

- temporal / spatial distributions of NO_2 and PM are different
- conducted in areas where the daily concentrations of PM and NO_2 are not well correlated or where NO_2 varied more than fine particles
- adjustments for measured particles concentration (PM_{10}, $PM_{2.5}$, black smoke) were possible
- effect of PM is modified by NO_2,

NO_2 – Outdoor population-based studies: short-term effects

Study	Effect	Controlling for other pollutants	Notes
Time-series: Mortality	Sig. association with ↑ overal CV & resp. mortality	↓ effect estimate	European cities: ↑ effect of PM on daily mortality with ↑ NO_2 levels
Time-series: Morbidity in adults	Seems to indicate an effect	• ↓ effect estimate • Effect ns • Some studies, NO_2, not PM, associated	Recent studies provide basis for health risk evaluation

NO_2 – Outdoor population-based studies: short-term effects contd.

Study	Effect	Controlling for other pollutants	Notes
Time-series: Asthma in children	•Most studies indicate effect of PM and O_3 •Recent studies, NO_2 strongly related	Several instances, effect remained	Recent studies provide basis for health risk evaluation
Panel: Asthmatic children	•Inconsistent results •Indicate an effect on symptoms & defence mechanisms		Results in-keeping with those of asthma hosp. & indoor studies

NO_2 – Outdoor population-based studies: long-term effects

Study	Effect	Effects attributable to NO_2 *per se*
Asthma, respiratory disorders & atopy	Suggested associated between NO_2 conc. At home address and asthma incidence in children	No
Lung function	•Evidence of effect on lung function growth* •Europe: supports effect on lung function in adults	No
Mortality	Recent data suggests association with ↑ risk of all cause mortality	No

**Southern California Children's Health Study*

NO_2 – Indoor studies

*Meta-analysis, 1992	Long-term exposure to NO_2 associated with ↑ prevalence of respiratory symptoms in children < 12 years of age
More recent studies	Among infants & children with or at risk of developing asthma, frequency of respiratory symptoms is associated with ↑ NO_2 concentrations

*
- *Relied on a limited number of heterogeneous studies*
- *Formed the basis of the 40 μg/m³ annual mean, originally adopted from the IPCS in 1997*

NO2 – Epidemiology
- summary-

- Risk estimates in many studies greatly reduced & often became non-significant after adjusting for particles
- In some studies, strongest effect was found for NO_2, itself, whereas PM had a weaker or no effect.
- Stronger indications of an independent effect of NO_2 come from studies on:
  - hospital admission/emergency department visits for respiratory and CV diseases
  - asthma aggravation
  - indoor effects, especially among asthmatics and infants at risk of asthma
- Role of other components (eg organic carbon & nitrous acid vapour) associated with NO_2 cannot be ruled out

AQG Global Update 2005
- NO_2 1-hour mean -

Controlled human exposure studies

Acute health effects at levels higher than 500 μg/m³

Meta-analysis indicate effects exceeding 200 μg/m³

Insufficient accumulated evidence to alter guideline value

Current health-based WHO guidelines for NO_2

- 1-hour mean: 200 μg/m³
- Annual mean: 40 μg/m³

AQG Global Update 2005
- NO_2 annual guideline -

Animal tox: chronic exposure to above ambient concs. has adverse effects

Population studies: adverse health effects at 40 μg/m³

Indoor studies: effects on resp. symptoms in children below 40 μg/m³

Should annual guideline be lowered?

What extent are the health effects observed in epidemiological studies attributed to NO_2 or to other correlated pollutants?

AQG Global Update 2005
- NO_2 annual guideline -

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Current health-based WHO guidelines for NO_2

- Annual mean: 40 μg/m³
- 1-hour mean: 200 μg/m³

AQG Global Update 2005
- NO_2 annual guideline -

- Set to protect the public from health effects of NO_2 itself
- Still no robust basis for setting a value for NO_2 through any direct toxic effect
  - Increased concern over health effects from recent epidemiological studies
  - Possible contribution from unmeasured components (eg organic carbon, nitrous acid vapour)
- Takes into account a potential direct toxic effect of chronic NO_2 exposure at low levels

AQG Global Update 2005
- NO_2 guidelines -

What are the values protecting us from?

NO_2

- Precursor of secondary toxic pollutants
- Marker of traffic-related pollution
- Potential to enhance other environmental pollutants eg allergens

Guideline that limits resulting health effects

↓

Reductions in NO_2 *PLUS* secondary traffic related pollution +/or secondary pollutants

NO_2 - a surrogate for traffic or a pollutant in its own right?

NO_2 - a surrogate for traffic or a pollutant in its own right?

Questions to be addressed:

- Does NO_2 at concentrations achieved outdoors have any detectable toxicity on the human lung ?
- Which aspects or components of combustion mixtures are responsible for the adverse health effects observed in epidemiological studies ?
- Is NO_2 able to synergise with other pollutants eg PM (ie role as an effect modifier) ?

↓

More efficient protection against health effects of complex gas-particle mixtures ?

WHO WG: Bonn October 2005

EUROPE