Evaluations of the health effects of long-term exposure to $\text{NO}_2$ – a European perspective

Dr Heather Walton
Presentation to HEI conference
2nd May 2017
Number of publications “air pollution” or “(nitrogen dioxide or NO₂)” or “(particulate matter or PM₁₀ or PM₂.5 or black smoke or sulphate or nitrate or secondary particles)” and health (PubMed)

![Graph showing the number of publications over time for air pollution, nitrogen dioxide (NO₂), and particulate matter (PM) from 1980 to 2017.](image-url)
WHO Review of Evidence on Health Aspects of Air Pollution (REVIHAAP) 2013

Is there sufficient new evidence to justify revising the guidelines for each pollutant? (But not setting new guidelines) (answer was yes)

Series of other questions

Only studies since 2004, cut off for 2005 guidelines published in 2006
Some key influences

Systematic reviews of chamber study data (for EPA),
Microenvironment concentrations can be at levels that show effects in chamber studies
Time-series studies (including multipollutant models)
Multipollutant models in cohort studies
Long-term studies respiratory morbidity (lung function, asthma)
Cardiovascular evidence sparse – some studies of interest e.g. Channell et al 2012, some no effect
A bit of toxicology – see later
Justification for updating guidelines

Short-term associations remain after adjustment for PM mass (sometimes black smoke)

Does not mean completely attributable to NO$_2$ *per se* (other traffic pollutants)

Reasonable to infer some direct short-term effects (mechanistic support, particularly respiratory)
Long-term harder to judge independence
Close spatial correlations
Chamber studies less applicable, less toxicology
Mortality, respiratory symptoms, lung function
  independent of PM mass but maybe not other traffic pollutants
Despite this, mechanistic evidence (respiratory) and short-term evidence mean suggestive of causality
“What concentration–response functions for key pollutants should be included in cost–benefit analysis supporting the revision of EU air quality policy?”

Group A: pollutant–outcome pairs for which enough data are available to enable reliable quantification of effects;

Group B: pollutant–outcome pairs for which there is more uncertainty about the precision of the data used for quantification of effects.

Recognised mp models for correlated pollutants in the presence of measurement error could be subject to bias (and fewer studies than with sp models) but overlap using sp models

mp = multipollutant, sp = single pollutant
HRAPIE NO$_2$

Limited set (A) –
All cause mortality (short-term), adjusted
Respiratory hospital admissions, single

Extended set (B) –
all cause mortality (long-term), single, above 20 μg/m$^3$, notes 33% reduction adjusted for PM;
bronchitic symptoms in asthmatics, adjusted
Evidence associating NO$_2$ with health effects has strengthened substantially in recent years and we now think that, on the balance of probability, NO$_2$ itself is responsible for some of the health impact found to be associated with it in epidemiological studies.
Supplemental Table S3. Sensitivity analyses to explain heterogeneity

Pooled effects of NO₂ (10μg/m³) on total and CV mortality.

<table>
<thead>
<tr>
<th>NO₂ (10μg/m³)</th>
<th>Total or natural mortality</th>
<th>Cardio-vascular mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N studies</td>
<td>RR</td>
</tr>
<tr>
<td>All countries</td>
<td>12</td>
<td>1.04</td>
</tr>
<tr>
<td>excluding at-risk groups</td>
<td>9</td>
<td>1.02</td>
</tr>
<tr>
<td>Europe</td>
<td>6</td>
<td>1.07</td>
</tr>
<tr>
<td>excluding at-risk groups</td>
<td>5</td>
<td>1.03</td>
</tr>
<tr>
<td>America</td>
<td>5</td>
<td>1.03</td>
</tr>
<tr>
<td>excluding at-risk groups</td>
<td>3</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Coefficient of 1.025 (1.01–1.04) (single pollutant) with additional comment on the evidence that there is likely to be substantial overlap between NO₂ and PM₂.₅ when single-pollutant models are used in the same analysis.

Scientific and methodological challenges to consider, including interpreting the extent of the independence of the associations of mortality with concentrations of NO₂ and PM.
Simulations – arbitrary values for now (PhD Dimitris Evangelopoulos, not in interim statement)

Categorisation of the scenarios

1. Correlations between the errors (1 → weak / 2 → strong)

Red line represents the assumed true effect of the two pollutants. The dots are the biased estimates from every scenario.
## COMEAP Interim Statement on Long-term Average NO₂ Concentrations and Mortality (extract)

**Table 1: Hazard ratios (HRs) from single- and two-pollutant models for NO₂ and PM₂.₅ (HRs are expressed per interquartile range, IQR)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Corr NO₂/PM₂.₅</th>
<th>NO₂ IQR (µg/m³)</th>
<th>NO₂ LCL</th>
<th>NO₂ UCL</th>
<th>NO₂ adj PM₂.₅ LCL</th>
<th>NO₂ adj PM₂.₅ UCL</th>
<th>PM₂.₅ IQR (µg/m³)</th>
<th>PM₂.₅ LCL</th>
<th>PM₂.₅ UCL</th>
<th>PM₂.₅ adj NO₂ LCL</th>
<th>PM₂.₅ adj NO₂ UCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesaroni et al (2013)</td>
<td>0.79</td>
<td>10.7</td>
<td>1.029</td>
<td>1.022</td>
<td>1.036</td>
<td>1.015</td>
<td>1.037</td>
<td>5.7</td>
<td>1.023</td>
<td>1.016</td>
<td>1.031</td>
</tr>
<tr>
<td>Carey et al (2013)¹</td>
<td>0.85</td>
<td>10.7</td>
<td>1.022</td>
<td>0.995</td>
<td>1.049</td>
<td>1.001</td>
<td>0.959</td>
<td>1.9</td>
<td>1.023</td>
<td>1.000</td>
<td>1.460</td>
</tr>
<tr>
<td>Beelen et al (2014)²</td>
<td>0.2←&lt;0.7</td>
<td>10.0</td>
<td>1.012</td>
<td>0.993</td>
<td>1.031</td>
<td>1.01</td>
<td>0.97</td>
<td>1.05</td>
<td>1.07</td>
<td>1.01</td>
<td>1.13</td>
</tr>
<tr>
<td>Fischer et al (2015)³</td>
<td>0.58⁴</td>
<td>10.0</td>
<td>1.027</td>
<td>1.023</td>
<td>1.030</td>
<td>1.015</td>
<td>1.023</td>
<td>2.4</td>
<td>1.029</td>
<td>1.025</td>
<td>1.033</td>
</tr>
<tr>
<td>Krewski et al (2000)⁵</td>
<td>−0.08</td>
<td>43.3</td>
<td>0.95</td>
<td>0.89</td>
<td>1.01</td>
<td>0.90</td>
<td>0.84</td>
<td>24.5</td>
<td>1.15</td>
<td>1.05</td>
<td>1.25</td>
</tr>
<tr>
<td>Jerrett et al (2013)</td>
<td>0.55</td>
<td>7.7</td>
<td>1.031</td>
<td>1.008</td>
<td>1.056</td>
<td>1.025</td>
<td>0.997</td>
<td>5.3</td>
<td>1.032</td>
<td>1.002</td>
<td>1.062</td>
</tr>
</tbody>
</table>

**Notes:**
1. PM₂.₅ results – personal communication
2. Based on 14 cohorts
3. PM₂.₅ results scaled from PM₁₀ (0.66 and assuming all toxicity within PM₂.₅ fraction)
4. Correlation with PM₁₀
5. HR (95% CI) for min-max range of average concentrations in fine particulate cohort (41 cities)

Additional significant figures for the HRs obtained from the authors
Hazard Ratio per IQR comparison within study sum multipollutant models with single pollutant models, example of range

<table>
<thead>
<tr>
<th></th>
<th>NO₂ adj PM₂.₅</th>
<th>PM₂.₅ adj NO₂</th>
<th>sum</th>
<th>NO₂ alone</th>
<th>PM₂.₅ alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carey et al 2013</td>
<td>1.001</td>
<td>1.023</td>
<td>1.024</td>
<td>1.022</td>
<td>1.023</td>
</tr>
<tr>
<td>Jerrett et al 2013</td>
<td>1.025</td>
<td>1.015</td>
<td>1.04</td>
<td>1.031</td>
<td>1.032</td>
</tr>
</tbody>
</table>

Quote from interim statement – combined effects ‘either similar to or only a little higher than for NO₂ or PM₂.₅ alone’ Incorrect to add single pollutant results

a Sum not given in interim statement
COMEAP report aims

To quantify the association between long-term average concentrations of NO$_2$ and mortality

To comment on any associated uncertainty

To comment on the extent to which this should be regarded as additional to the mortality effects of PM$_{2.5}$

*Including new single pollutant meta-analysis to mid 2015, further on % reduction on adjustment, more on uncertainty (very wide range of views)*

*Publication delayed by elections!*
Hazard ratios (95% CIs) for cumulative risk estimates for all-cause mortality in two- and three pollutant models CanCHEC cohort Crouse et al 2015 EHP 123: 1180 (similar approach to Jerrett et al 2013)

Per mean – 5th percentile i.e. 5.0 µg/m³ PM$_{2.5}$, 9.5 ppb Ozone, 8.1 ppb Nitrogen dioxide

\[
\frac{PM_{2.5} + O_3}{1.038} \quad (1.032, 1.044)
\]

weaker than

\[
\frac{PM_{2.5} + NO_2}{1.070} \quad (1.062, 1.078)
\]

or

\[
\frac{O_3 + NO_2}{1.074} \quad (1.065, 1.083)
\]

Similar to

\[
\frac{PM_{2.5} + O_3 + NO_2}{1.075} \quad (1.067, 1.084)
\]

? Ozone capturing regional pollution, NO$_2$ capturing local pollution.

Poster 19B!
## Toxicology – LOAELs

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LOAEL</th>
<th>Duration</th>
<th>Species</th>
<th>Reference/ quoted by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed macrophage function</td>
<td>0.3 – 0.5 ppm</td>
<td>4hrs – 2days</td>
<td>Rabbit, rat</td>
<td>Schlesinger 1987, Robison 1993 /CARB 2007</td>
</tr>
<tr>
<td>Bronchiolar epithelium proliferation</td>
<td>0.8 ppm</td>
<td>1, 3 days</td>
<td>Rat</td>
<td>Barth 1994 /CARB 2007. EPA 2008</td>
</tr>
<tr>
<td>Type II cell hyperplasia</td>
<td>0.25 ppm</td>
<td>6hr/d, 5 d/wk 6 weeks then 6 weeks air</td>
<td>Weanling mice</td>
<td>Sherwin and Richters (1995 a,b)/CARB 2007</td>
</tr>
<tr>
<td>Emphysema, Lung function deteriorated after dose stopped</td>
<td>0.64 ppm (+ 0.25 ppm NO)</td>
<td>5.5 years then 2.5 years air</td>
<td>Dogs</td>
<td>Hyde et al 1978</td>
</tr>
</tbody>
</table>

LOAEL = lowest-observed-adverse-effect level
Hypothesis

NO₂ inhalation

Disease States

Atherosclerosis
Aortic Aneurysm
Acute Lung Injury
Ischemia
Inflammation
Diabetes
Smoking

iNOS

Arginine, O₂
Citrulline

Protein Nitration

3-Nitrotyrosine

O₂⁻ + •NO → ONOO⁻ → Protein Nitration → 3-Nitrotyrosine
Research needs

Interpretation of multipollutant models/understanding of measurement error

Mechanistic research e.g. link with nitrative stress

Comparative toxicology – different pollutants in the same systems to give relative potency to aid epidemiology interpretation