Quantification methods for health effects of \( \text{NO}_2 \)

2nd July 2015
Outline

(Focussing on long-term exposure and mortality)

- Long term exposure studies on PM$_{2.5}$ and NO$_2$
- WHO discussions on causality
- WHO discussions on concentration-response functions
- Counterfactuals (baselines), cessation lags, scale of modelling
- Different approaches for different types of exposure assessment
Six Cities Study (PM)

Lippmann 1998 (Figure 5, page 87).

P= Portage, Wisconsin; T= Topeka, Kansas; W= Watertown, Massachusetts; L= St Louis, Missouri; H= Harriman, Tennessee; and S= Steubenville, Ohio
Within city contrasts (PM$_{2.5}$, NO$_2$) (Cesaroni et al (2013) Rome)
<table>
<thead>
<tr>
<th>Study name</th>
<th>Central estimate % change per 10 µg/m³</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands cohort study</td>
<td>8</td>
<td>0</td>
<td>16</td>
<td>Beelen et al (2008)</td>
</tr>
<tr>
<td>German cohort (Ruhr) (women)</td>
<td>11</td>
<td>4</td>
<td>18</td>
<td>Heinrich et al (2013)</td>
</tr>
<tr>
<td>PAARC (France)</td>
<td>14</td>
<td>3</td>
<td>25</td>
<td>Filleul et al (2005)</td>
</tr>
<tr>
<td>Danish cohort</td>
<td>8</td>
<td>2</td>
<td>13</td>
<td>Rasschou Nielsen et al (2012)</td>
</tr>
<tr>
<td>US truckers (men)</td>
<td>5</td>
<td>3</td>
<td>7</td>
<td>Hart et al (2011)</td>
</tr>
<tr>
<td>Rome longitudinal study</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>Cesaroni et al (2013)</td>
</tr>
<tr>
<td>California Teachers Study (women)</td>
<td>-3</td>
<td>-9</td>
<td>4</td>
<td>Lipsett et al (2011)</td>
</tr>
<tr>
<td>Shizuoka elderly cohort</td>
<td>2</td>
<td>-4</td>
<td>8</td>
<td>Yorifujii et al (2010)</td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
<td><strong>5.5</strong></td>
<td><strong>3.1</strong></td>
<td><strong>8</strong></td>
<td></td>
</tr>
</tbody>
</table>

Excludes between city studies and district mean studies and NOx study.
Figure 1: Relative risks (RR) of natural mortality with increasing chronic exposure to nitrogen dioxide (NO₂). df: degrees of freedom; I²: inconsistency.
Table 4. ESs for NO$_2$ from single- and multipollutant models on all-cause (natural) mortalit

<table>
<thead>
<tr>
<th>Reference pollutant</th>
<th>Parameter</th>
<th>All-cause (natural) mortality estimate</th>
<th>% reduction on adjustment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gehring et al. (2006a)</td>
<td>NO$_2$ single (per 16 µg/m$^3$)</td>
<td>Rate ratio</td>
<td>1.19</td>
<td>1.02</td>
</tr>
<tr>
<td>With traffic indicator</td>
<td>No change with traffic indicator (data not shown)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jerrett et al. (2009b)</td>
<td>NO$_2$ single (per 4 ppb)</td>
<td>Rate ratio</td>
<td>1.17</td>
<td>1.00</td>
</tr>
<tr>
<td>with traffic indicator</td>
<td>1.13</td>
<td>0.97</td>
<td>1.32</td>
<td>24%</td>
</tr>
<tr>
<td>Hart et al. (2011)</td>
<td>NO$_2$ single (per 8 ppb)</td>
<td>Percentage increase</td>
<td>8.20</td>
<td>4.50</td>
</tr>
<tr>
<td>with PM$_{10}$ and sulphur dioxider</td>
<td>7.40</td>
<td>2.40</td>
<td>12.50</td>
<td>9.8%</td>
</tr>
<tr>
<td>Cao et al. (2011)</td>
<td>NO$_x$ single (per 10 µg/m$^3$)</td>
<td>Percentage increase</td>
<td>1.50</td>
<td>0.40</td>
</tr>
<tr>
<td>with total suspended particles</td>
<td>1.40</td>
<td>0.30</td>
<td>2.50</td>
<td>6.7%</td>
</tr>
<tr>
<td>Cesaroni et al. (2013)</td>
<td>NO$_2$ single (per 10 µg/m$^3$)</td>
<td>Rate ratio</td>
<td>1.03</td>
<td>1.02</td>
</tr>
<tr>
<td>with PM$_{2.5}$</td>
<td>1.02</td>
<td>1.01</td>
<td>1.03</td>
<td>33%</td>
</tr>
<tr>
<td>with traffic indicator</td>
<td>No change (data not shown)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jerrett et al. (2013)</td>
<td>NO$_2$ (per 4.1167 ppb)</td>
<td>Rate ratio</td>
<td>1.031</td>
<td>1.008</td>
</tr>
<tr>
<td>With PM$_{2.5}$</td>
<td>1.025</td>
<td>0.997</td>
<td>1.054</td>
<td>19%</td>
</tr>
</tbody>
</table>
NO$_2$ cohort studies controlling for PM (ii)

• REVIHAAP:
‘Adjustment of NO$_2$ associations for PM10 or PM$_{2.5}$ may not be sufficient, as there is often a closer correlation between NO$_2$ and traffic pollutants, such as primary PM and its constituents.’
So also need to consider causality from other types of evidence.
NO$_2$ causality (short term)

- Criticism: Chamber study responses are variable and well above ambient concentrations
- The time series study effects are all due to particles anyway
- REVIHAAP responded to these points
# NO$_2$ causality (Chamber studies)

<table>
<thead>
<tr>
<th></th>
<th>Effect level starting concentrations</th>
<th>Micro-environments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy</td>
<td>Asthmatics</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Yes &gt; 1 ppm ? 0.2-0.6 ppm</td>
<td>Peaks outdoors polluted cities Kerbside 0.2-0.3ppm 1 hr ave on occasion In car can be similar.</td>
</tr>
<tr>
<td>Allergen-induced inflammation</td>
<td></td>
<td>Ambiguous, yes 0.26 ppm, no 0.3-0.4 ppm</td>
</tr>
<tr>
<td>Non-specific airway responsiveness</td>
<td>1.5 – 2 ppm</td>
<td>0.2 – 0.6 ppm</td>
</tr>
<tr>
<td></td>
<td>No clear dose response 0.1-0.5 ppm but responders at all doses</td>
<td>Other sites 0.1ppm 1 hr ave often exceeded across Europe</td>
</tr>
</tbody>
</table>
Variation in response (Jenkins et al 1999)

![Graph showing variation in response to different exposures.](image)

**Figure 1.** The effect of 6 h exposure to 100 ppb O$_3$, 200 ppb NO$_2$, and 100 ppb O$_3$ + 200 ppb NO$_2$, compared with air, on allergen PD$_{20}$FEV$_1$ in mild asthmatics. Squares represent geometric means.
NO$_2$ time series mortality (Mills et al 2015)
Forest plot for cardiac admissions NO$_2$ with and without adjustment for PM$_{10}$

COMEAP (2006)

- NO2 SINGLE ESTIMATES
- Wong et al 2002 [London]
- Wong et al 2002 [Hong Kong]
- Moolgavkar 2000 [Cook County, USA]

- NO2 CONTROLLING FOR PM10
- Wong et al 2002 [London]
- Wong et al 2002 [Hong Kong]
- Moolgavkar 2000 [Cook County, USA]

Percentage change for a 10 unit change
Cardiovascular endpoints (REVIAHAP)

• Only two since 2008/9 (EPA etc), neither suggestive of effects
• 8 studies of biomarkers of cardiovascular disease with mixed results
• Chanell et al 2012 plasma from volunteers exposed to 0.5ppm NO₂ for 2 hours activated cultured coronary artery endothelial cells
• 2 recent rat studies showing effects on endothelial function and on recovery from stroke at 2-10 ppm
• Too little for conclusion on causality of cv endpoints one way or the other
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)

2015 25,000 air pollution/PM, 3000 NO₂
NO₂ one hypothesis for mechanism

• NO₂ inhalation leads to nitrite in the blood
• Following points established in the general literature on nitrative stress but not studied in relation to NO₂ inhalation specifically
• Nitrite can be converted to NO in the tissues
• In normal circumstances NO is beneficial (e.g. vasodilation)
• In disease it can combine with superoxide radical to form peroxynitrite
• Peroxynitrite can nitrate proteins forming 3-nitrotyrosine
• In the wrong place and in too many proteins, this is a problem.
• Increased levels of 3-nitrotyrosine in the blood have been associated with heart disease
REVIHAAP conclusions long-term exposure to NO$_2$ and mortality (edited summary)

- Harder to judge the independent effects of NO$_2$ in long-term studies - correlations between concentrations of NO$_2$ and other pollutants are often high, so that NO$_2$ might represent the mixture of traffic-related air pollutants.

- No chamber studies for long-term effects and toxicological evidence is limited.

- However, some epidemiological studies do suggest associations of long-term NO$_2$ exposures with respiratory and cardiovascular mortality and with children’s respiratory symptoms and lung function that were independent of PM mass metrics.

- The mechanistic evidence, particularly on respiratory effects, and the weight of evidence on short-term associations are suggestive of a causal relationship.
HRAPIE recommendations for NO$_2$

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

Extended set –
• All cause mortality (long-term), single pollutant, above 20 µg/m$^3$;
• Bronchitic symptoms in asthmatics, adjusted
Am. J. Epidemiol. 2007;165:435-443
Update on evidence for quantification of NO$_2$ impacts: Mortality associated with long-term average concentrations
Quantifying the health impacts of ambient air pollutants: recommendations of a WHO/Europe project

International Journal of Public Health 2015:690
DOI: 10.1007/s00038-015-0690-y

MarieEve Héroux, H. Ross Anderson, Richard Atkinson, Bert Brunekreef, Aaron Cohen, Francesco Forastiere, Fintan Hurley, Klea Katsouyanni, Daniel Krewski, Michal Krzyzanowski, Nino Künzli, Inga Mills, Xavier Querol, Bart Ostro and Heather Walton
Evolution of lower limit for quantification in journal article (i)

• We also note that a recent cohort study ....(Raaschou-Nielsen et al. 2012) has shown a significant, almost linear concentration–response relationship between long-term NO2 concentration ...and mortality... throughout the observed range of NO2 concentrations, which in the large majority of subjects was below 20 μg/m³ (minimum 10.5 μg/m³, median 15.1 μg/m³, maximum 59.6 μg/m³).

• This study was included in the Hoek et al. (2013) meta-analysis, but we did not explicitly consider it when discussing lower limits of quantification in the HRAPIE project.
Update on evidence for quantification of NO₂ impacts: Mortality associated with long-term average concentrations
Evolution of lower limit for quantification in journal article (ii)

- All-cause mortality increased by 8% per 10 µg/m³ NO₂ long-term exposure at the residence address in the study by Raaschou-Nielsen et al. (2012), so slightly more than estimated in the Hoek et al. meta-analysis.

- Therefore, the HRAPIE recommendation to calculate the impacts of long-term NO₂ exposure on mortality for levels over 20 µg/m³, ignoring potential impacts at lower concentrations, may be too conservative.
Workshop 26th February 2015

- Involved many people from HRAPIE
- HRAPIE recommendations were not in the context of burden discussions (where counter factuals more crucial)
- Workshop discussed both (i) general concepts regarding thresholds and cut-offs and (ii) specific discussion of counter factuals for NO$_2$
- (ii) described here
- Separate analysis Rome study above and below 20 µg/m$^3$ - steeper below 20 µg/m$^3$ but wide Cis (Cesaroni/Forastiere personal communication)
Figure 1 Model to derive number of cases attributable to air pollution Based on exposure-response function (slope or relative risks, RR, from epidemiological studies), population frequency of the outcome, P (ie, prevalence, incidence, or number of days), ...

N Künzli, R Kaiser, S Medina, M Studnicka, O Chanel, P Filliger, M Herry, F Horak Jr, V Puybonnieux-Tex...

Public-health impact of outdoor and traffic-related air pollution: a European assessment


http://dx.doi.org/10.1016/S0140-6736(00)02653-2
Possible criteria for choosing counterfactuals

• Threshold for effect
• Studied range in epidemiological studies (5th percentile)
• Range over which there is most confidence in the shape of the curve / concentration response function
• Policy-relevant range
• Lowest concentration in the environment (5th percentile)
• Zero

• GBD for PM$_{2.5}$ suggested using the 5th percentile of the exposure distribution of the key epidemiological study or studies as the counter-factual, with the minimum concentration as the lower bound (Lim et al., 2012; Burnett et al., 2014).

<table>
<thead>
<tr>
<th>2002 ($\mu g/m^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO$_2$</td>
</tr>
<tr>
<td>830,429 (99%)</td>
</tr>
<tr>
<td>22.5 (7.4)</td>
</tr>
<tr>
<td>4.5–60.8</td>
</tr>
<tr>
<td>10.7</td>
</tr>
</tbody>
</table>

| No. of patients with pollution linkage (%) | 830,429 (99%) |
| Mean pollution (SD)                      | 22.5 (7.4)    |
| Minimum–maximum range                    | 4.5–60.8      |
| Interquartile range                      | 10.7          |

% increase in mortality per 10 $\mu g/m^3$ (95% CI): 2% (0%, 5%)

But NO$_2$/PM$_{2.5}$ correlation 0.9
Figure 1: Distribution of NO₂. Time-weighted average concentrations of NO₂ at the residential addresses of 52,061 cohort participants from 1971 onwards.

Workshop suggestions for NO$_2$ counter factuals

- [20 µg/m$^3$]
- 15 µg/m$^3$ (median Copenhagen study)
- 10 µg/m$^3$ (minimum Copenhagen study)
- 5 µg/m$^3$ (lowest mean ESCAPE cohorts; minimum Carey study)
- [0 µg/m$^3$] (not favoured as outside data range but minimums in ESCAPE get as low as 1.5 µg/m$^3$ (Umeå))

- Could assign probabilities to each of these sensitivities and do a Monte Carlo analysis.
### Choices for quantification

<table>
<thead>
<tr>
<th></th>
<th>Central</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk</td>
<td>1.055</td>
<td>1.031</td>
<td>1.08</td>
</tr>
<tr>
<td>Adjust for overlap (30%)</td>
<td>1.039</td>
<td>1.022</td>
<td>1.056</td>
</tr>
</tbody>
</table>

#### Counterfactual

Within range 0-20 \( \mu g/m^3 \), 5,10,15 \( \mu g/m^3 \)

#### Cessation lag

As for PM\(_{2.5}\) in absence of evidence to the contrary, ?no long lag for lung cancer

#### Concentration scale

Fine within city scale

Context of health impact assessment (next slide)
Context of health impact assessment

- Is it NO\textsubscript{2} itself being quantified or traffic pollution?
- If traffic pollution, is the proportion of NO\textsubscript{2} similar to that in the original studies? If so, can use single pollutant model.
- Are other pollutants e.g. PM being quantified at the same time? If so, need to think about overlap.
- Is it a burden assessment (total effect) or a health impact assessment (effects of a pollution change)?
- WHO cautioned against adding single pollutant model results for NO\textsubscript{2} to those for PM\textsubscript{2.5} (noted overlap up to 33%)
- Currently no recommendations for PM\textsubscript{2.5} adjusted for NO\textsubscript{2}
- Best to produce a range of results to account for the possibility that other constituents of traffic account for some of the NO\textsubscript{2} effect.
Conclusions

• Evidence for effects of long-term exposure to NO2 is strengthening
• Still uncertainties that need to be explained
• Need to be clear of the context for quantification
• Many choices to be made about inputs, better to choose a variety of options
• Important to scope the implications of the developing evidence for quantification