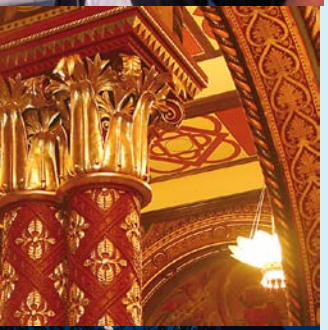
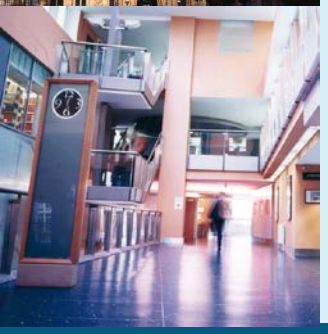




KING'S College LONDON

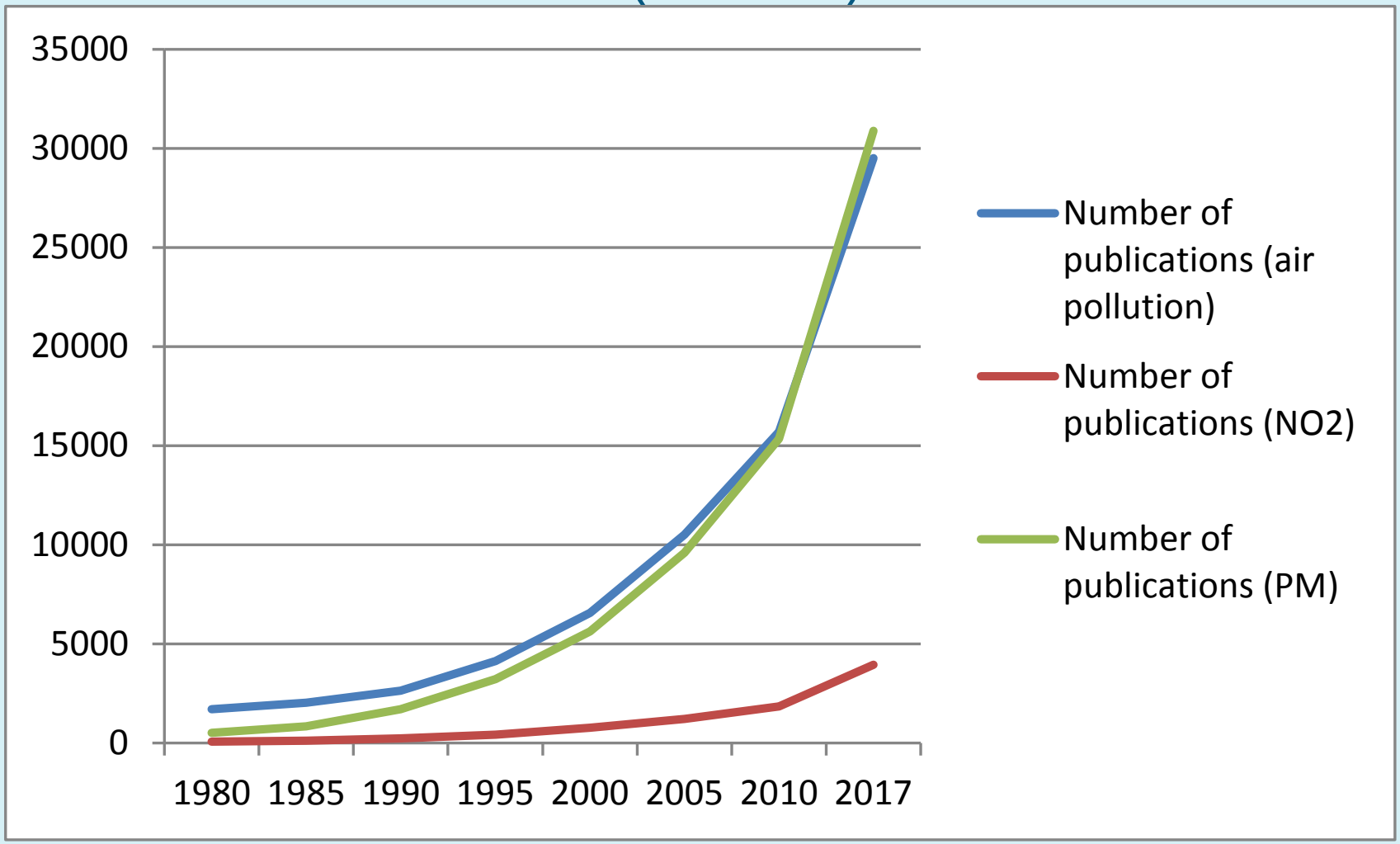
Evaluations of the health effects of long-term exposure to NO_2 – a European perspective

Dr Heather Walton

Presentation to HEI conference

2nd May 2017

Number of publications "air pollution" or "(nitrogen dioxide or NO_2)" or "(particulate matter or PM_{10} or $PM_{2.5}$ or black smoke or sulphate or nitrate or secondary particles)" and health (PubMed)



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

REVIHAAP answer extract (i)

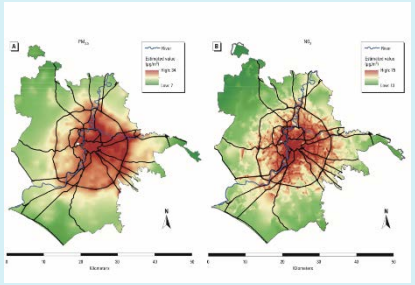
Justification for updating guidelines

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)

REVIHAAP answer extract (ii)



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

WHO Health Risks of Air Pollution in Europe (HRAPIE) late 2013

"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 $\mu g/m^3$, notes 33% reduction adjusted for PM;

bronchitic symptoms in asthmatics, adjusted

COMEAP STATEMENT ON THE EVIDENCE FOR THE EFFECTS OF NITROGEN DIOXIDE ON HEALTH March 2015

https://www.gov.uk/government/publications/nitrogen-dioxide-health-effects-of-exposure

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.

COMEAP = Committee on the Medical Effects of Air Pollutants

Faustini et al European Respiratory Journal 2014; DOI: 10.1183/09031936.00114713

Supplemental Table S3. Sensitivity analyses to explain heterogeneity

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

	Total or natural mortality					Cardio-vascular mortality				
	N studies	RR	95% CIs		I^2	N studies	RR	95% CIs		I^2
NO_2 (10µg/m3)										
All countries	12	1.04	1.02	1.06	89%	18	1.13	1.09	1.18	98%
excluding at-risk groups	9	1.02	1.01	1.02	87%	16	1.13	1.09	1.19	98%
Europe	6	1.07	1.03	1.10	72%	9	1.06	1.03	1.09	79%
excluding at-risk groups	5	1.03	1.02	1.04	50%	8	1.06	1.03	1.09	77%
America	5	1.03	0.99	1.07	95%	7	1.03	1.00	1.07	67%
excluding at-risk groups	3	1.00	0.99	1.01	94%	6	1.03	1.00	1.05	55%

COMEAP Interim Statement on Long-term Average NO_2 Concentrations and Mortality

https://www.gov.uk/government/publications/nitrogen-dioxide-interim-view-on-long-term-average-concentrations-and-mortality

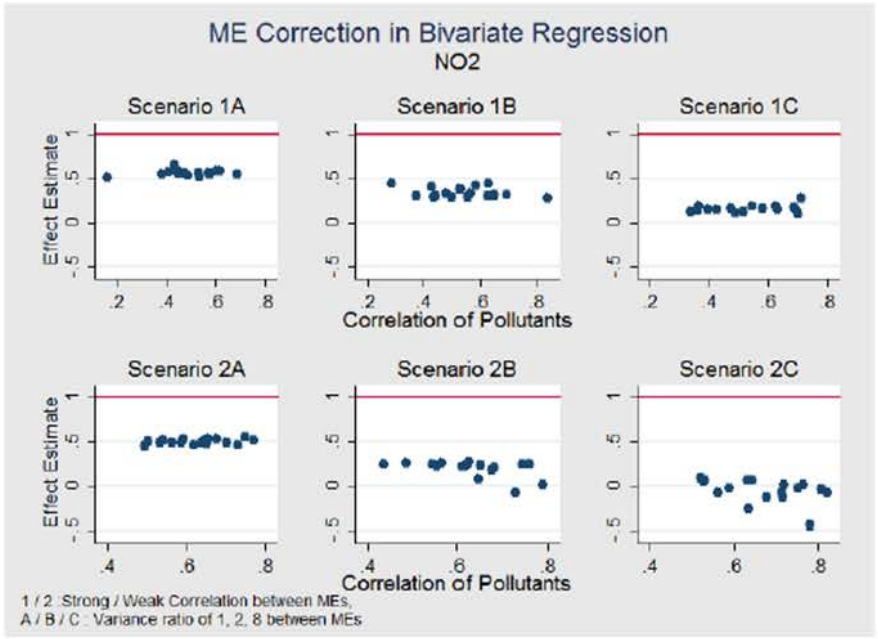
Coefficient of 1.025 (1.01–1.04) (single pollutant) with additional comment on the evidence that there is likely to be substantial overlap between NO_2 and $PM_{2.5}$ when single-pollutant models are used in the same analysis.

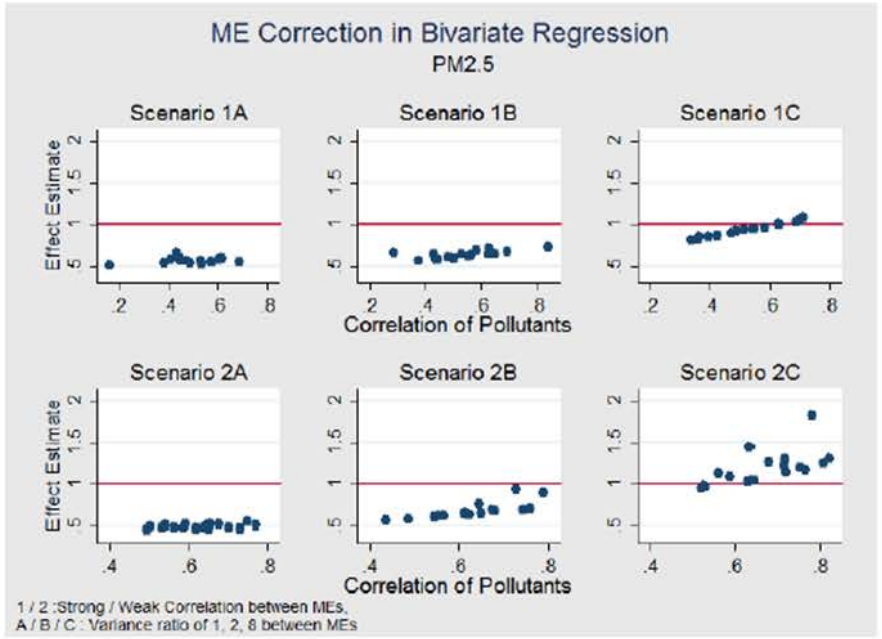
Scientific and methodological challenges to consider, including interpreting the extent of the independence of the associations of mortality with concentrations of NO_2 and PM.

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)
2. Variance ratio of the errors (A → 1 / B → 2 / C → 8)





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 NO_2 Concentrations and Mortality (extract)

Table 1: Hazard ratios (HRs) from single- and two-pollutant models for NO_2 and $PM_{2.5}$ (HRs are expressed per interquartile range, IQR)

Study	Corr $NO_2/PM_{2.5}$	NO_2 IQR ($\mu g/m^3$)	NO_2	LCL	UCL	NO_2 adj $PM_{2.5}$	LCL	UCL	$PM_{2.5}$ IQR ($\mu g/m^3$)	$PM_{2.5}$	LCL	UCL	$PM_{2.5}$ adj NO_2	LCL	UCL
Cesaroni et al (2013)	0.79	10.7	1.029	1.022	1.036	1.026	1.015	1.037	5.7	1.023	1.016	1.031	1.004	0.994	1.015
Carey et al (2013)[1]	0.85	10.7	1.022	0.995	1.049	1.001	0.959	1.044	1.9	1.023	1.000	1.460	1.023	0.989	1.060
Beelen et al (2014)[2]	0.2–<0.7	10.0	1.012	0.993	1.031	1.01	0.97	1.05	5.0	1.07	1.01	1.13	1.06	0.98	1.15
Fischer et al (2015)[3]	0.58[4]	10.0	1.027	1.023	1.030	1.019	1.015	1.023	2.4	1.029	1.025	1.033	1.015	1.011	1.020
Krewski et al (2000)[5]	–0.08	43.3	0.95	0.89	1.01	0.90	0.84	0.96	24.5	1.15	1.05	1.25	1.22	1.11	1.33
Jerrett et al (2013)	0.55	7.7	1.031	1.008	1.056	1.025	0.997	1.054	5.3	1.032	1.002	1.062	1.015	0.980	1.050

Corr correlation, IQR interquartile range, LCL lower confidence interval, UCL upper confidence interval, adj adjusted for

Notes:

1 $PM_{2.5}$ results –personal communication

2 Based on 14 cohorts

3 $PM_{2.5}$ results scaled from PM_{10} (0.66 and assuming all toxicity within $PM_{2.5}$ fraction)

4 Correlation with PM_{10}

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[a]

	NO_2 adj $PM_{2.5}$	$PM_{2.5}$ adj NO_2	sum	NO_2 alone	$PM_{2.5}$ alone
Carey et al 2013	1.001	1.023	1.024	1.022	1.023
Jerrett et al 2013	1.025	1.015	1.04	1.031	1.032

Quote from interim statement – combined effects ‘either similar to or only a little higher than for NO_2 or $PM_{2.5}$ 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/m^3 $PM_{2.5}$, 9.5 ppb Ozone, 8.1 ppb Nitrogen dioxide

$PM_{2.5} + O_3$: 1.038 (1.032, 1.044) weaker than $PM_{2.5} + NO_2$: 1.070 (1.062, 1.078) or $O_3 + NO_2$: 1.074 (1.065, 1.083)

? Ozone capturing regional pollution, NO_2 capturing local pollution.

Similar to

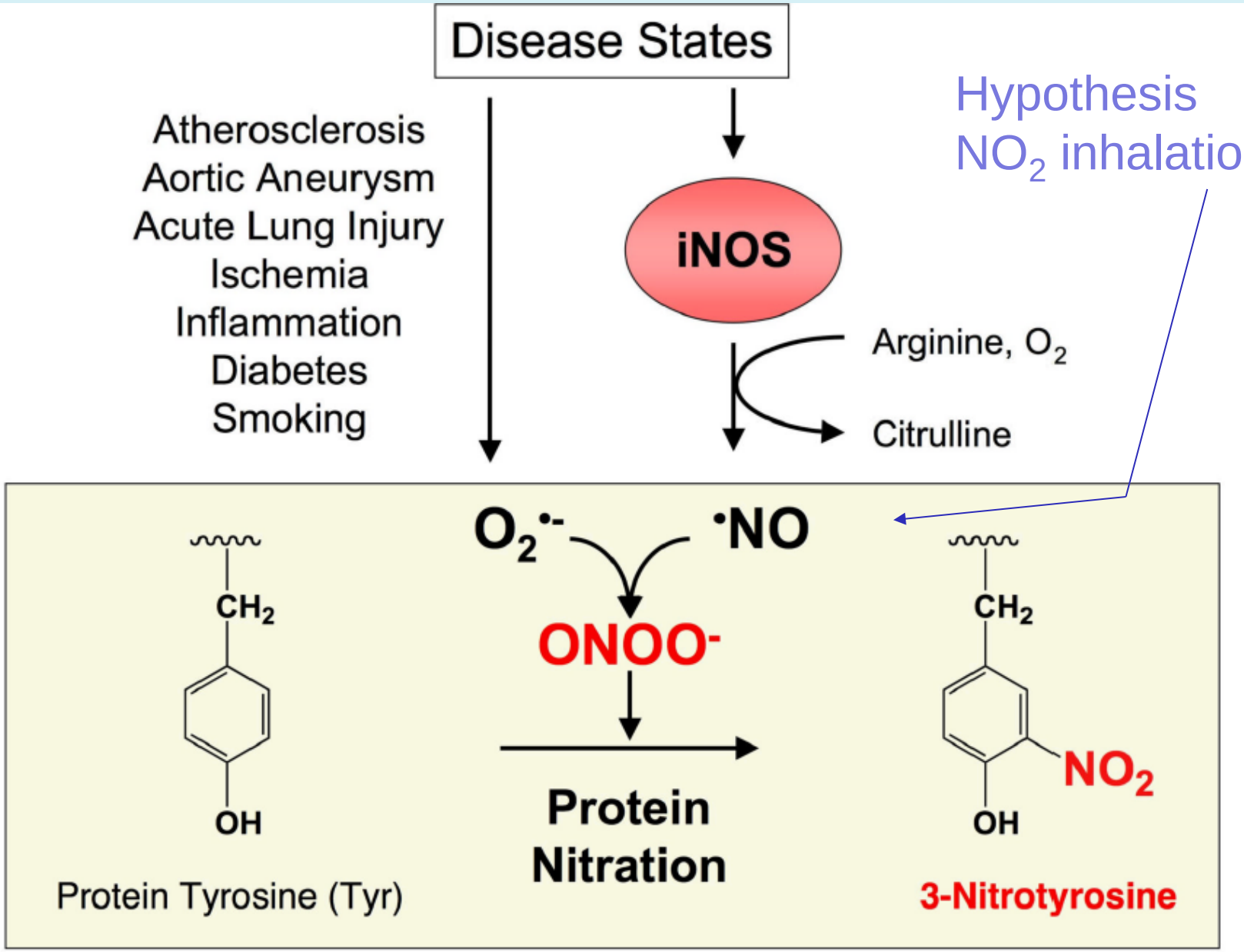
$PM_{2.5} + O_3 + NO_2$: 1.075 (1.067, 1.084)

Poster 19B!

Toxicology – LOAELs

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

LOAEL = lowest-observed-adverse-effect level


Disease States
Atherosclerosis
Aortic Aneurysm
Acute Lung Injury
Ischemia
Inflammation
Diabetes
Smoking
iNOS
Arginine, O_2
Citrulline
Hypothesis
NO_2 inhalation
$O_2^{\bullet-}$
$^{\bullet}NO$
$ONOO^-$
Protein
Nitration
CH_2
OH
Protein Tyrosine (Tyr)
CH_2
NO_2
OH
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