Latest evidence on health impacts of nitrogen dioxide

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First some history!

- The first WHO Guidelines for NO_2 were published in 2000
- Short term 1-hour guideline 200 ug/m^3
- Annual average guideline 40 ug/m^3
- Unchanged since then
- Both values incorporated in EU Directives 1999/30/EC and Directive 2008/50/EC
- The 1-hour LV not to be exceeded more than 18 times in a calendar year

NO_2, health and the Limit Values

- Annual LV based on WHO Guideline (2000)
- WHO Guideline used IPCS Environmental Health Criteria report (1997)
- Based on meta-analysis of 9 indoor studies
- 4 studies measured NO_2 by Palmes tubes
- 5 studies used ‘gas or electric stoves?’ as the only exposure measure
- The IPCS report stated “On the basis of a background level of 15 $\mu g/m^3$ and the fact that significant adverse health effects occur with an additional level of 28.2 $\mu g/m^3$ or more, an annual guideline of 40 $\mu g/m^3$ is proposed.”

WHO, AQ Guidelines 2000

Although there is no particular study or set of studies that clearly support selection of a specific numerical value for an annual average guideline, the database nevertheless indicates a need to protect the public from chronic nitrogen dioxide exposure. For example, indoor air studies with a strong nitrogen dioxide source, such as gas stoves, suggest that an increment of about 30 μg/m^3 (2-week average) is associated with a 20% increase in lower respiratory illness in children aged 5–12 years. However, the affected children had a pattern of indoor exposure that included peak exposures higher than those typically encountered outdoors. Thus the results cannot be readily extrapolated quantitatively to the outdoor situation. Outdoor epi-

WHO AQ Guidelines 2000 (2)

ide be established. Selecting a well supported value based on the studies reviewed has not been possible, but it has been noted that a prior review conducted for the Environmental Health Criteria document on nitrogen oxides recommended an annual value of 40 $\mu g/m^3$ *(5)*. In the absence of support for an alternative value, this figure is recognized as an air quality guideline.

The EU CAFE process asked WHO ‘What is the basis for maintaining the WHO annual specific guideline for NO_2?

- **WHO response :**
  - “Uncertainty remains over the significance of NO_2 as a pollutant with a direct impact on human health at current ambient air concentrations in the European Union, and there is ***still no firm basis for selecting a particular concentration as a long-term guideline for NO_2.***”
  - “In recent studies....NO_2 has been associated with adverse effects even when the annual mean is within a range that includes 40µg/m^3. However we are unable to establish an alternative AQG from these studies. We therefore recommend that the WHO AQG should be retained or lowered.”

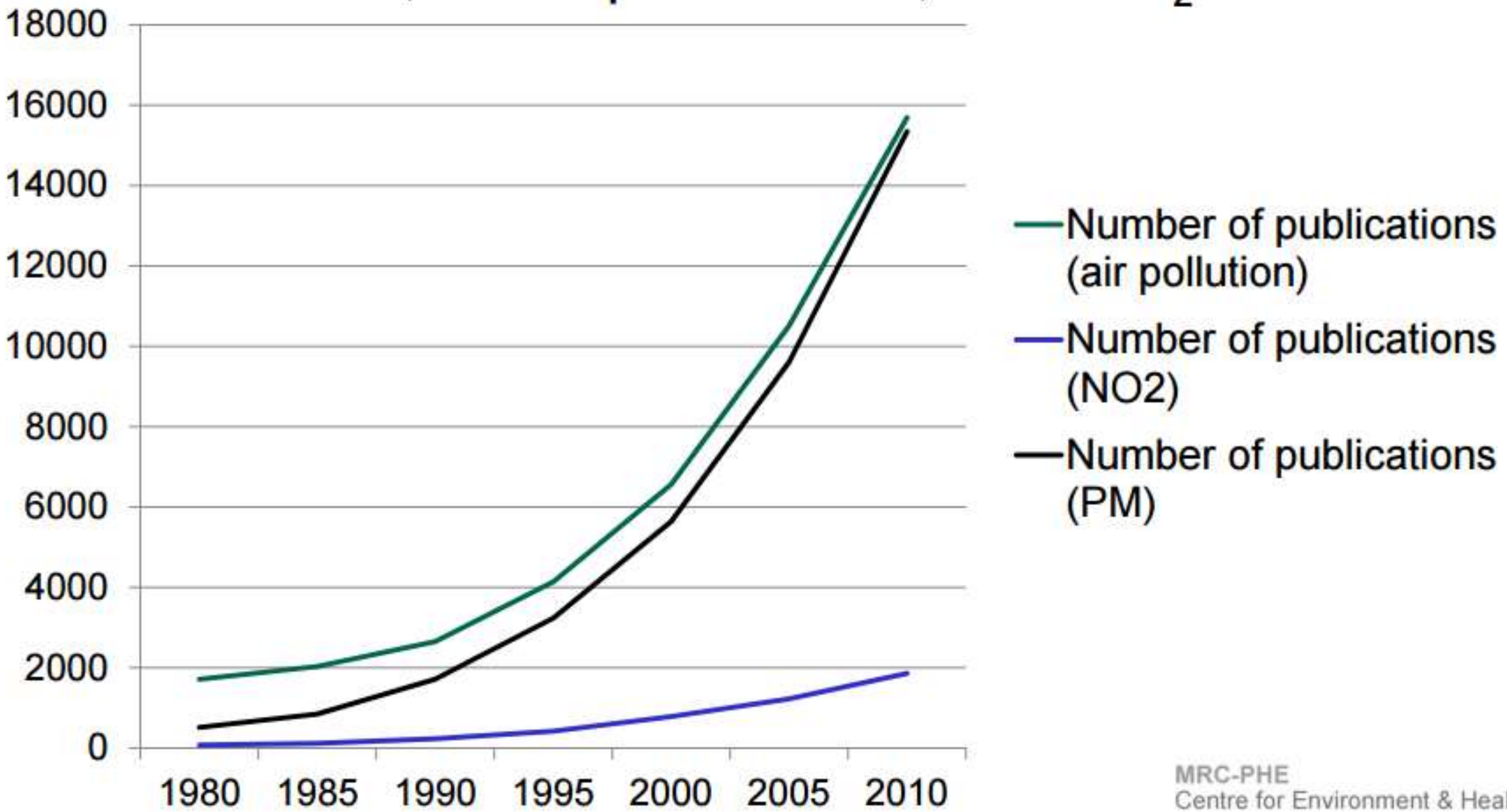
- WHO further response:
  - - "We have been asked to comment on our confidence in this guideline. Our reply is that it remains ***difficult to provide solid scientific support for the numerical value of the guideline. There still is no robust basis for setting an annual average guideline value for*** $\boldsymbol{NO_2}$ through any direct toxic effect."

WHO Global Update 2005

- “In population studies, NO_2 has been associated with adverse health effects even when the annual average concentration complied with the WHO annual average guideline of 40 μg/m^3.
- “These results (with indoor studies) suggest a lowering of the annual average guideline.”
- “However since NO_2 is...highly correlated with other primary and secondary combustion products, it is unclear to what extent the health effects observed in epi studies are attributable to NO_2 itself or to other correlated pollutants.”

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 NO_2



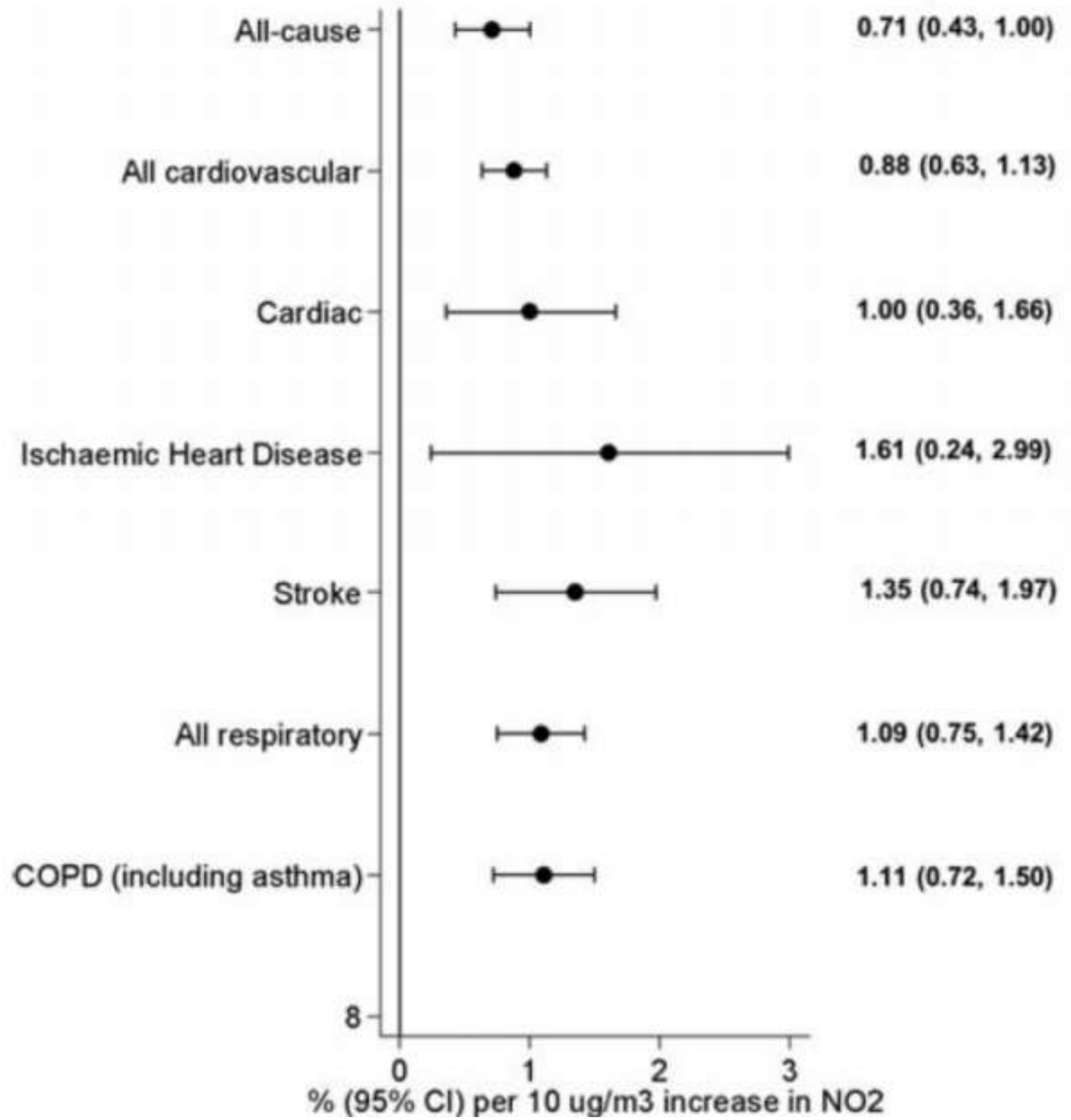
MRC-PHE
Centre for Environment & Health

WHO REVIHAAP Review 2013

- New short and long-term epidemiological studies since 2004 (cut-off for 2005 guidelines)
- Some, notably short-term (time-series) studies, show associations robust to inclusion of other pollutants.
- Supports updating of guidelines to give
- a) an epidemiologically based short-term guideline
- b) an annual average guideline based on newly accumulated evidence from outdoor studies
- Both could result in lower guidelines.
- NO_2, particularly in long-term exposure studies may represent other constituents
- But mechanistic evidence, particularly on respiratory effects, and short-term epidemiological evidence is suggestive of a causal relationship.

New evidence – time series studies

NO_2 time series mortality (Mills et al 2015)



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.
- 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.

Hoek et al 2013 (NO_2)

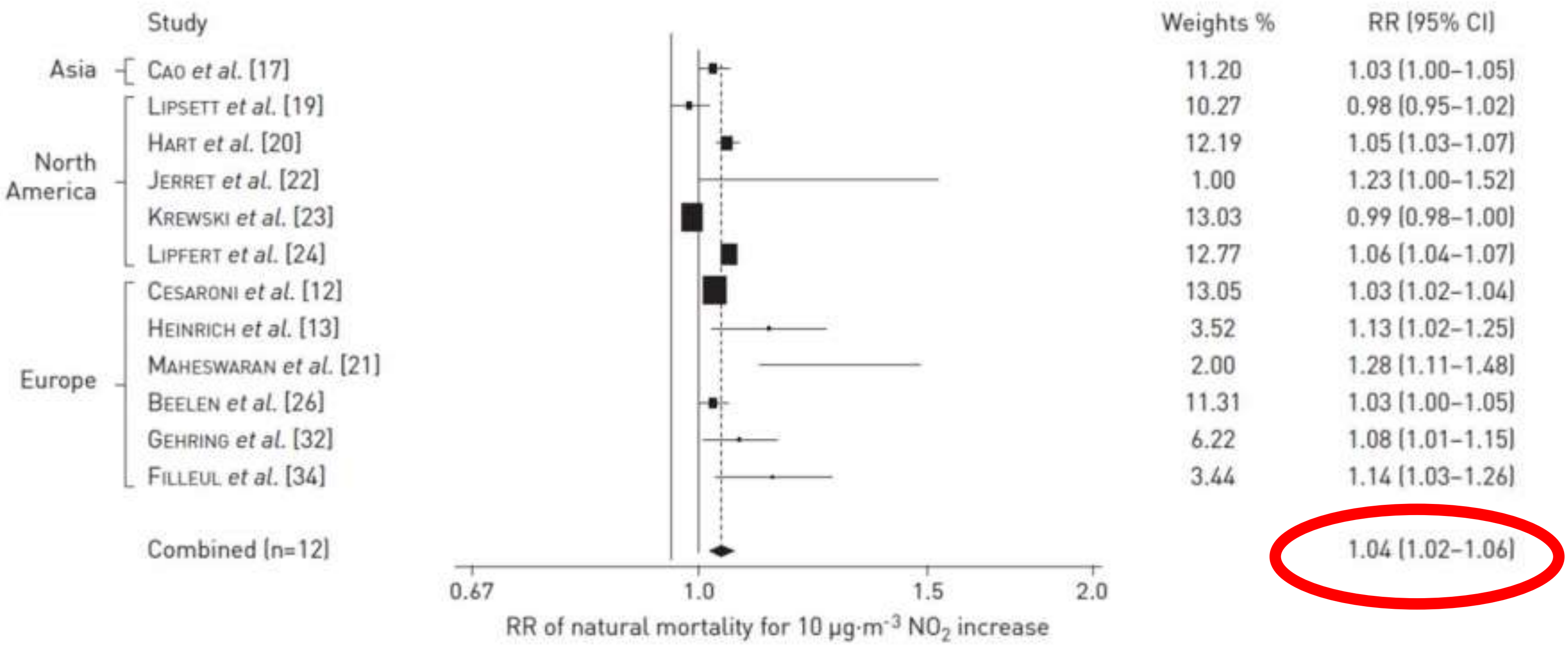
Study name	Central estimate % change per 10 μg/m³	Lower 95% CI	Upper 95% CI	Reference
Oslo cohort (men) (NOx)	*8*	*6*	*11*	*Nafstad et al (2004)*
Netherlands cohort study	8	0	16	Beelen et al (2008)
German cohort (Ruhr) (women)	11	4	18	Heinrich et al (2013)
PAARC (France)	14	3	25	Filleul et al (2005)
Danish cohort	8	2	13	Rasschou Nielsen et al (2012)
US truckers (men)	5	3	7	Hart et al (2011)
Rome longitudinal study	3	2	3	Cesaroni et al (2013)
California Teachers Study (women)	-3	-9	4	Lipsett et al (2011)
Shizuoka elderly cohort	2	-4	8	Yorifuji et al (2010)
Pooled	**5.5**	**3.1**	**8**	

Excludes between city studies and district mean studies and ?NOx study.

HRAPIE Quantification for NO_2 Mortality

Pollutant Metric	Health Outcome	Relative Risk (95% CI per 10 ug/m3)	Comments
NO_2 daily maximum 1-hour mean	All cause mortality	1.0027 (1.0016-1.0038)	
NO_2 Annual Mean	All cause mortality	1.055 (1.031-1.080)	>20 ug/m^3 , up to 33% overlap with $PM_{2.5}$

Faustini et al 2014 (NO_2)



Test for heterogeneity: Chi-squared=102.28 df=11
p=0.001 I^2=89%
Test for overall effect: z=3.632 p=0.001

FIGURE 1 Relative risks (RR) of natural mortality with increasing chronic exposure to nitrogen dioxide (NO_2). df: degrees of freedom; I^2: inconsistency.

WHO meeting May 2014 General principles of health risk assessment (global)

- Described HRAPIE recommendations and provided an update of recent cohort studies on NO_2.

- The three most recent cohort studies, not considered in the original reviews from Hoek *et al* (2013) and Faustini (2014), reported relative risks (per 10 µg/m3 NO_2) lower than those previously reported in the meta-analytical estimates, namely
- 1.031 (1.008, 1.056) for the California study (Jerrett *et al*, 2013),
- 1.02 (1.00–1.05) for the English cohort (Carey *et al*, 2013), and
- 1.01 (0.99-1.04) for the ESCAPE study.

- The HRAPIE recommendation to use single pollutant model results noting up to a 33% overlap was considered to still hold considering the most recent ESCAPE results, since the effect estimate for NO_2 in this study did not change from unadjusted analysis (1.01, 95% 0.99-1.04) to that adjusted for $PM_{2.5}$ (1.01, 95% 0.97-1.05) although the uncertainty of the estimate was larger.

New evidence since 2013?

ORIGINAL ARTICLE

Within- and between-city contrasts in nitrogen dioxide and mortality in 10 Canadian cities; a subset of the Canadian Census Health and Environment Cohort (CanCHEC)

Dan L. Crouse[1], Paul A. Peters[2,3], Paul J. Villeneuve[4], Marc-Olivier Proux[2], Hwashin H. Shin[1], Mark S. Goldberg[5,6], Markey Johnson[7], Amanda J. Wheeler[7], Ryan W. Allen[8], Dominic Odwa Atari[9], Michael Jerrett[10], Michael Brauer[11], Jeffrey R. Brook[12,13], Sabit Cakmak[1] and Richard T. Burnett[1]

COMEAP report long-term exposure and mortality due December 2015

Air Pollution and Mortality in Seven Million Adults: The Dutch Environmental Longitudinal Study (DUELS)

Paul H. Fischer,[1] Marten Marra,[1] Caroline B. Ameling,[1] Gerard Hoek,[2] Rob Beelen,[1,2] Kees de Hoogh,[3,4,5] Oscar Breugelmans,[1] Hanneke Kruize,[1] Nicole A.H. Janssen,[1] and Danny Houthuijs[1]

Systematic review of Chinese studies of short-term exposure to air pollution and daily mortality☆

Yu Shang[a], Zhiwei Sun[b], Junji Cao[c], Xinming Wang[d], Liuju Zhong[e], Xinhui Bi[d], Hong Li[f], Wenxin Liu[g], Tong Zhu[h], Wei Huang[i,*]

Traffic-related pollution and asthma prevalence in children. Quantification of associations with nitrogen dioxide

Graziella Favarato · H. Ross Anderson · Richard Atkinson · Gary Fuller · Inga Mills · Heather Walton

Quantitative systematic review of the associations between short-term exposure to nitrogen dioxide and mortality and hospital admissions

I C Mills,[1] R W Atkinson,[2] S Kang,[2] H Walton,[3,4,5] H R Anderson[2,3]

The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies

G. Bowatte[1], C. Lodge[1], A. J. Lowe[1], B. Erbas[2], J. Perret[1], M. J. Abramson[3], M. Matheson[1*] & S. C. Dharmage[1,4,*]

Adult lung function and long-term air pollution exposure. ESCAPE: a multicentre cohort study and meta-analysis

Association between Ambient Air Pollution and Diabetes Mellitus in Europe and North America: Systematic Review and Meta-Analysis

Ikenna C. Eze,[1,2] Lars G. Hemkens,[3] Heiner C. Bucher,[3] Barbara Hoffmann,[4,5] Christian Schindler,[1,2] Nino Künzli,[1,2] Tamara Schikowski,[1,2,4] and Nicole M. Probst-Hensch[1,2]

Department
for Environment
Food & Rural Affairs

www.gov.uk/defra

Valuing impacts on air quality:

Updates in valuing changes in emissions o[f] Oxides of Nitrogen (NO_X) and concentratio[n] of Nitrogen Dioxide (NO_2)

September 2015

From our consideration of authoritative reviews and additional evidence we have reached the following conclusions:

i. Evidence of associations of ambient concentrations of NO_2 with a range of effects on health has strengthened in recent years. These associations have been shown to be robust to adjustment for other pollutants including some particle metrics.

ii. Although it is possible that, to some extent, NO_2 acts as a marker of the effects of other traffic-related pollutants, the epidemiological and mechanistic evidence now suggests that it would be sensible to regard NO_2 as causing some of the health impact found to be associated with it in epidemiological studies.

We have not drawn conclusions on specific health outcomes nor looked in detail at the methodological issues relevant to quantification of effects associated with ambient NO_2 at this stage. We intend to do this and, if appropriate, to consider recommendations for coefficients associating NO_2 with specific health effects, as part of separate work items to be addressed later."

COMEAP have provided an interim steer to Defra on how the latest NO_2 evidence should be reflected in policy analysis. On 24 July 2015 a COMEAP working group on NO_2 wrote to Defra recommending that a coefficient of 1.025 per 10 μg/m^3 exposure to NO_2 (within the range 1.01 – 1.04)[4] should be used to assess the link between long term exposure to NO_2 and all-cause mortality.[5]

The US Federal Approach to NO_2

- The Primary National Ambient Air Quality Standard was first ***set in 1971*** as an annual average
- In two subsequent reviews it has ***not been changed***
- It is considerably less stringent than the EU/WHO value at 101 µg/m^3 (in US law it is 0.053ppm; conversion at 20C)
- On 22 January 2010 the EPA introduced an hourly standard of 100ppb assessed as the 3-year average of the 98th%ile of hourly values
- Numerically the same as the EU/WHO hourly LV but less stringent (EU LV allows 18 hours exceedence – a 98th %ile of hours allows 175 exceedences)
- ***But*** US now require roadside monitoring to assess compliance.

US Integrated Science Assessment views have strengthened on health evidence

	2008 ISA	New draft ISA	Reason for change
Respiratory – short-term	Sufficient to infer a likely causal relationship	Causal relationship	Epi evidence, including in copollutant models plus experimental studies on mode of action give consistency, coherence and biological plausibility for NO_2 and asthma exacerbation
Respiratory – long-term	Suggestive but not sufficient to infer a likely causal relationship	Likely to be a causal relationship	Epi evidence residential NO2 exposure and asthma development, biological plausibility from a small body of experimental studies.
Cardiovascular – short-term (all-cause same for new draft)	Inadequate to infer a causal relationship	Suggestive but not sufficient to infer a likely causal relationship	Additional evidence for an array of effects related to the triggering of myocardial infarction. (Independence from traffic pollutants uncertain, experimental evidence limited)
Cardiovascular – long-term (all-cause same for new draft)	Inadequate to infer a causal relationship	Suggestive but not sufficient to infer a likely causal relationship	Large increase in epidemiological studies, including with residential exposure, generally supportive, not entirely consistent. (Independence from traffic pollutants uncertain, experimental evidence limited)

Thank you!

- Thanks to ***Dr Heather Walton*** and other colleagues at King's College London for help in preparing this talk