OEHHA Draft Recommendation

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Draft Recommendations for Nitrogen Dioxide

- Retain Nitrogen Dioxide as the indicator for nitrogen oxide air pollutants
- Lower the current 1-hr standard of 0.25 ppm, to 0.18 ppm, not to be exceeded
- Establish a new annual average standard of 0.030 ppm, not to be exceeded
- Retain the chemiluminescence monitoring method

Existing Standards and Recommendations

Averaging time	CA (1992)	Federal (1995)	OEHHA (Proposed)
1-hour	0.25 ppm (470 μg/m^3)	--	0.18 ppm
Annual average	--	0.053 ppm (100 μg/m^3)	0.030 ppm

Evidence on the Health Effects of Nitrogen Dioxide Provided by Different Types of Studies

- Controlled human exposure
- Animal toxicology
- Epidemiology

Controlled Human Exposure Studies

- Exposures of human volunteers in a laboratory setting
- Responses studied: respiratory symptoms, lung function, inflammation (lung or blood), cardiovascular effects
- Typical subjects: healthy adults or mild asthmatics

Controlled Human Exposure Studies

- Advantages
  - Precise measures of exposure and response
- Limitations
  - Few studies on more vulnerable populations
  - Small sample size and studied doses
  - Few studies of pollutant mixtures
  - Cannot predict effects of chronic exposures

Controlled Human Studies of NO_2 : Lowest Concentrations Showing Effects

- Healthy Subjects: no effects below 1 ppm
- Asthmatics
  - Enhanced airway response to allergen at 0.26 ppm (15-30 min)
  - Increased airway reactivity at 0.2 – 0.3 ppm (30 min-2 hr)
    - ➢ Potential to increase asthma symptoms and medication use

Observations from Low Doses in Clinical Studies, I

1. Mixed evidence based on endpoint, protocol, subjects, phase.
2. Fairly consistent evidence for enhanced allergic response

Many different markers of NO_2 enhanced allergic response

0.1, 0.4 ppm x 1hr then allergen	↓FEV1 (early & late phase) at 0.4 ppm Tunicliffe 94
0.26 ppm x 30 min then allergen at 4 hr	↓ Pk flow late phase Strand '97
0.26 ppm x 30 min then allergen at 4 hr daily x 4d	↓FEV1 (early & late phase) Strand 98
0.26 ppm x 30 min then allergen at 4 hr, BAL @ 19h	↑PMN, ↑ECP in BAL Barck 2002
0.26 ppm x 15 min allergen at 4h D1,D2;	↑ECP (blood/sputum) Barck 2005

Observations from Low Doses in Clinical Studies, II

3. Mixed findings on Airway Reactivity (AR) between 0.1 and 0.3 ppm.
4. Evidence of AR between 0.1 – 0.3 ppm:
   - Orehek et al (1976) @ 0.1 ppm (1 hr) in 13/20 asthmatics
   - Ahmed et al (1992, abs) @ 0.1 ppm (1 hr) in 13/20
   - Bylin et al (1988) @ 0.26 ppm (30 mins) & tendency @ 0.13 ppm (p = 0.052)

- **Kleinman et al (1983): @ 0.2 ppm (2 hrs) 2/3 of subjects had ↑ in AR**
- **Strand et al (1996): @ 0.26 ppm (30 mins) slight increase (p = 0.08) but stat signif at 5 hrs.**
- **Jorres & Magnussen (1990) @ 0.25 ppm (30 mins)**
- **Bauer et al (1990) @ 0.30 ppm (30 mins)**
- **Follinsbee (1992) meta analysis indicates ~76% positive AR response at rest between 0.2- 0.3 ppm**

Observations from Low Doses in Clinical Studies, III

5. Variability in response among subjects
6. Some evidence for non-attenuation after 4 days of NO_2 & allergen (Strand et al., 1998)
7. Some larger responders:
   - 3/15 in Solomon et al. (2004)
   - 3/20 in Orehek (1976); 3/15 in Hazucha (1983)

Observations from Low Doses in Clinical Studies, IV

8. Subjects with chronic lung disease
   - Decreased lung function at 0.3 ppm
9. Limited data for children, elderly and those with cardiovascular disease, longer exposure duration

Animal NO2 Toxicology Studies

- Oxidant damage mechanism consistent with both animal and human studies
- Evidence for airway epithelium and alveolar macrophage effects with acute/short-term exposure at low levels (≥ 0.5-0.8 ppm)
- In animal models of allergic asthma, exposure to high concentrations of NO_2 (≥ 5 ppm) produce increased markers of allergic inflammation
- Prolonged repeated exposure of young animals during lung development show changes in lung structure (≥ 0.25 ppm)

Epidemiologic Studies, I

- **Advantages**
  - **Evaluate exposures and responses of free-living populations over a wide range of individuals, behaviors, and subgroups, including susceptible individuals**
  - **Examine both short and long-term exposures**
- **Limitations**
  - **Difficult to determine specific exposure averaging time**
  - **Need to account for other factors, particularly co-pollutants (i.e., PM, UF, EC, VOCs)**

Epidemiologic Studies, II

- Study Designs/Exposures
  1. Outdoor time-series studies
  2. Outdoor panel studies
  3. Traffic Studies
  4. Outdoor chronic studies
  5. Indoor studies

Findings From Epi Studies

Outdoor studies short term exposure (24-hr to several days)

- **Associations reported for mortality, cardiovascular and respiratory-related hospital admissions and ER visits, cardiac arrhythmias, asthma symptoms and lung fn**

- **Respiratory effects, especially for asthma, most consistent for both adults and children.**

Associations between NO2 and mortality reported in multi-city studies

- 90 US (Samet 2000) (11- 40; 26 ppb)
- 29 European (Samoli 2006) (14 – 50; 28 med ppb)
- 8 Italian (Biggeri 2001) (31- 46; 39 ppb)
- 11 Canadian (Burnett 1998) (14-28; 24 ppb)
- 7 Spanish (Saez 2002) (17 – 38; 28 ppb)
  - Katsouyanni (2001) shows effect modification of PM

Associations between NO2 and respiratory disease appear robust

- Peel (05): Asthma ERV in children in Atlanta (23 ppb)
- Galan (03): Asthma HA in Madrid (34)
- Atkinson (99): ER asthma in children in London (50)
- Hajat (99): MD asthma calls for children in London (34)
- Anderson (98): Asthma HA in London (57)
- Sunyer (97): HA asthma in children in 3 Euro cities (19-37 med)

Asthma panel studies show effect of NO2

- Delfino (2002, 2003, 2004): Symptoms and wheeze in SoCal children
- Mortimer (2002): PEF in 8 US cities
- Ostro (2001): Symptoms
- Boezen (1999): Symptoms among Dutch children with BHR and IgE
- Linaker (2000): Symptoms after respiratory infection

Findings From Epi Studies

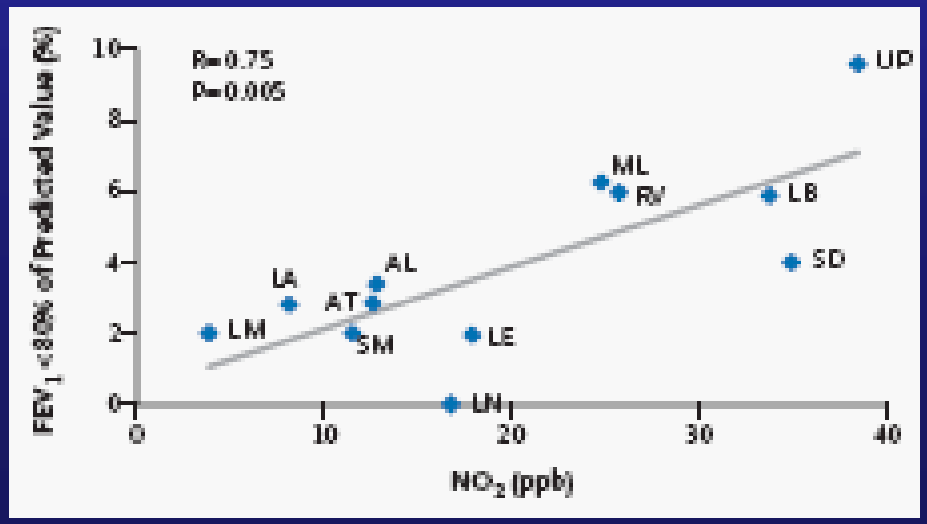
Outdoor studies (including traffic)

long term exposure (months to years)

- **Asthma exacerbations**
- **Reduced lung function and lung growth**
- **Low birth weight**
- **Respiratory symptoms**

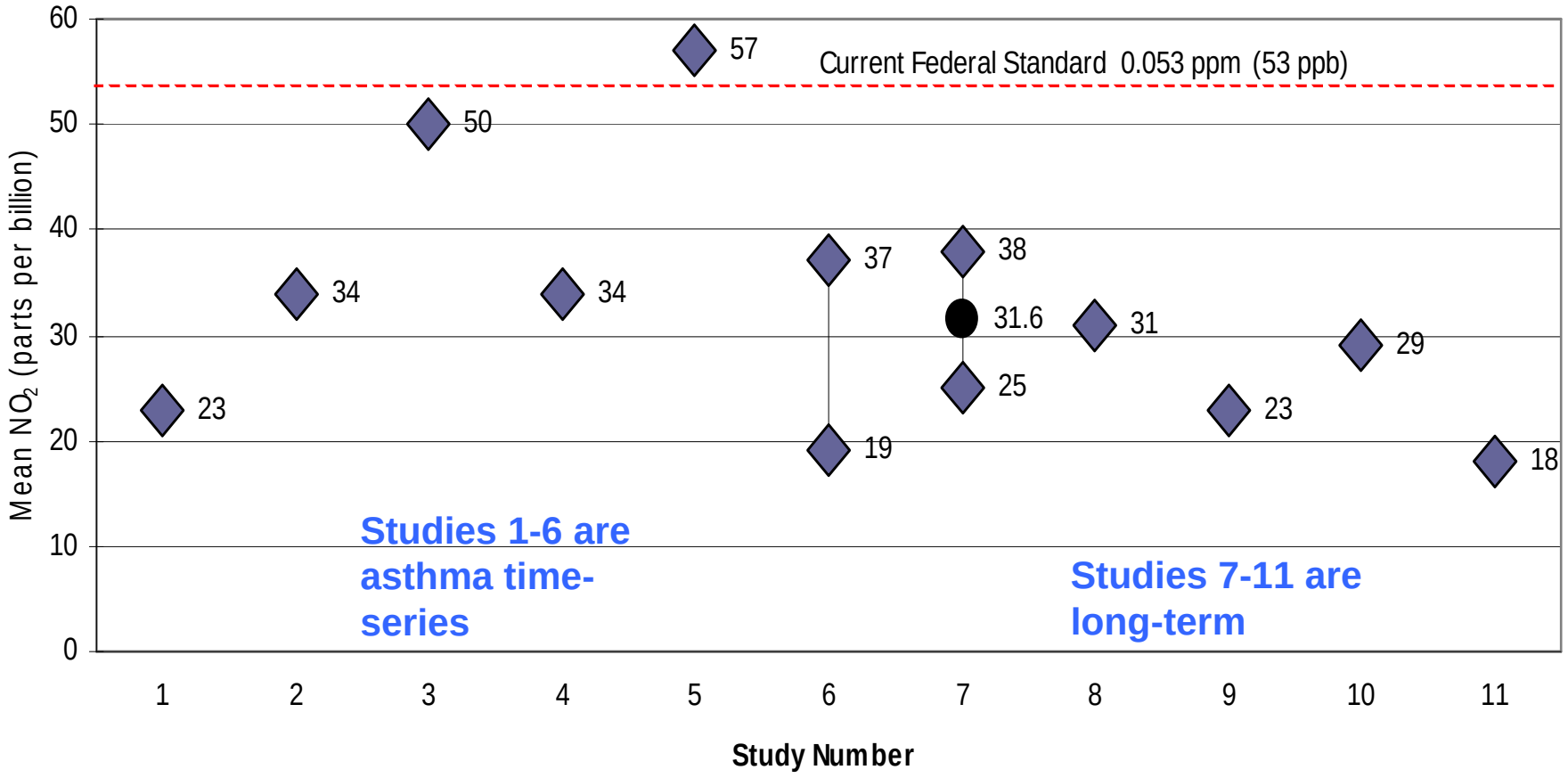
Outdoor studies: long term exposure on children

- Gauderman et al. (2004)
  - 12 communities in Southern California
  - Cohort follow-up study examined lung function growth in children ages 10-18
  - Higher percent of children with FEV_1 < 80% in areas with higher NO2, PM, Acid vapor



- **Gauderman (2005): History of asthma, current wheeze and medication use @ 31 ppb**
- **Kim (2004): Exacerbation of asthma, bronchitis in Bay Area children @ 23 ppb**
- **Kramer (2000): Allergic sensitization and allergic symptoms in Dusseldorf children @ 29 ppb**
- **Janssen (2003): Allergic sensitization in Dutch children @ 18 ppb**

Key epidemiologic studies showing associations between NO_2 and respiratory disease



◆ = Average NO_2 in single city study

◆ = Range of averages in multi-city study

● = Overall average NO_2 in multi-city study

Studies showing associations between NO_2 and respiratory disease

Study	Author	Outcome	Location
1	Peel (05)	Asthma ERV, child	Atlanta
2	Galan (03)	Asthma HA	Madrid
3	Atkinson (99)	Asthma ER, child	London
4	Hajat (99)	MD asthma, child	London
5	Anderson (98)	Asthma HA	London
6	Sunyer (97)	Asthma HA, child	3 Euro cities
7	Gauderman (04)	Lung function	So. Calif.
8	Gauderman (05)	Asthma, wheeze	So. Calif.
9	Kim (04)	Asthma, bronchitis	S.F. Bay Area
10	Kramer (00)	Allergic sx	Dusseldorf
11	Janssen (03)	Allergic sensitization	Netherlands

Findings From Epi Studies

- **Indoor studies long term exposure (weeks to months): (gas stoves and measured NO_2):**
  - **Respiratory symptoms among asthmatics and infants at risk of asthma**

Basis for OEHHA NO_2 1-hr standard of 0.18 ppm

1. Includes additional studies since last review in 1992
2. Increased airway reactivity in asthmatics at 0.2 –0.3 ppm 30 min-2 hr
3. Enhanced allergic response in asthmatics at 0.26 ppm for 15-30 min
4. Modest associations in a few studies below 0.2 ppm

Basis for NO_2 1-hr standard (cont.)

5. Add margin of safety for:

   - Children and other susceptible populations (e.g. more severe asthmatics) and other possible endpoints
   - Possible effects at lower concentrations
   - Proposing 1-hr avg standard but effects observed after 15-30 minutes
   - Effects observed in epi studies may be due to short-term exposures

Basis for OEHHA Annual average Standard of 0.030 ppm

1. Potential effects of NO_2 on serious outcomes including mortality, ER, hospitalization for cardio and respiratory disease, arrythmias and lung development
2. Hospital admissions and ER visits for asthma and effects of long-term exposure on lung development, asthma and allergy in areas with annual averages of 0.025 to 0.040 ppm
3. NO_2 likely to be best marker of traffic among criteria pollutants

Basis for Annual average (cont.)

4. Tox shows airway reactivity and enhancement of allergic response and alterations in lung structure in young animals due to long term exposures
5. Important to lower full distribution of exposures not just peak 1-hr

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