EVIDENCE ON THE DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF ENVIRONMENTAL TOBACCO SMOKE

Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment (OEHHA)
California Environmental Protection Agency (Cal/EPA)
May 24, 2006

Definition of Environmental Tobacco Smoke (ETS)

- Emitted by combustion of tobacco products and from smoke exhaled by the smoker
  - minor contributions from smoke that escapes as the smoker inhales
- Complex mixture of thousands of gases and fine particles
  - nicotine, carbon monoxide, nitrosamines, polycyclic aromatic hydrocarbons, cadmium
  - particles ranging in size from 0.01 to 1 micrometer

Adverse Effects of ETS

- A number of constituents have been found to cause cancer
- ETS found to be carcinogenic (IARC, EPA, OEHHA and under Proposition 65)
- Adverse non-cancer health effects such as heart disease, sudden infant death syndrome, respiratory infections, etc.

Prevalence of Exposure

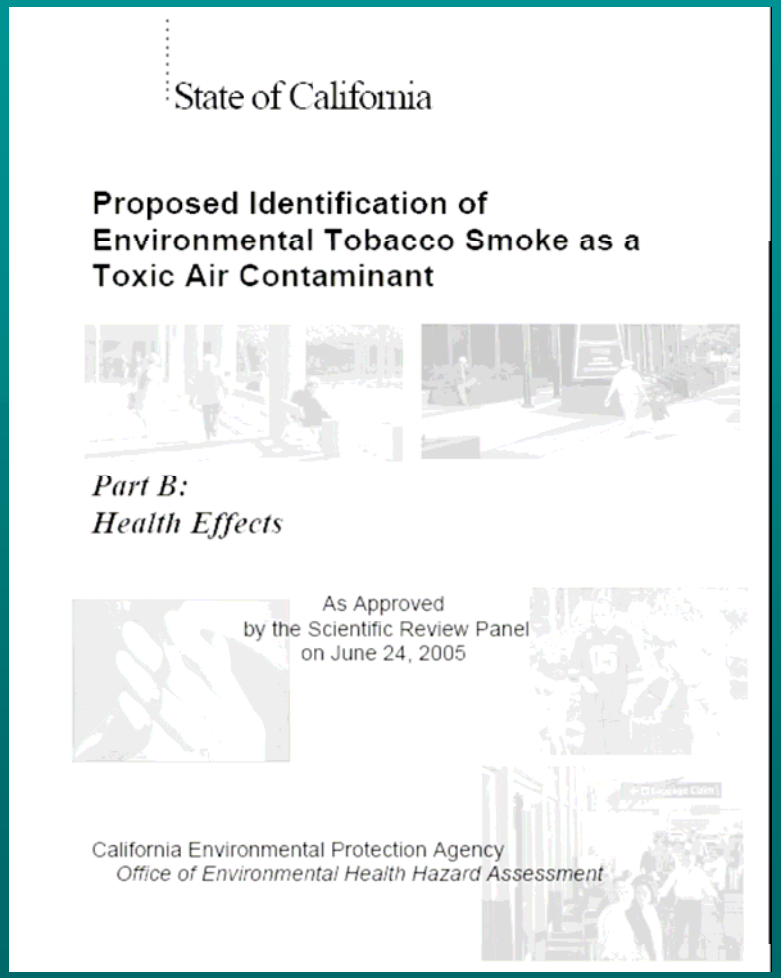
- 14% of California adults smoke
- 22% of child-bearing women in California are exposed to ETS (OEHHA 1997)
- ~ 50% of pregnant women in California are exposed to ETS

Hazard Identification Materials

- Health Effects Assessment for ETS - 1997 Report (prepared by OEHHA)
  - Adopted by National Cancer Institute
- Update (2005) to the report on the Health Effects Assessment for ETS (prepared by OEHHA)
  - Summarizes the findings of the 1997 publication
  - Reviews the literature since the 1997 report
- Recent studies - published after completion of the 2005 report

Health Effects of Exposure to Environmental Tobacco Smoke

Office of Environmental Health Hazard Assessment (OEHHA)



State of California

Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant

Part B:
Health Effects

As Approved
by the Scientific Review Panel
on June 24, 2005

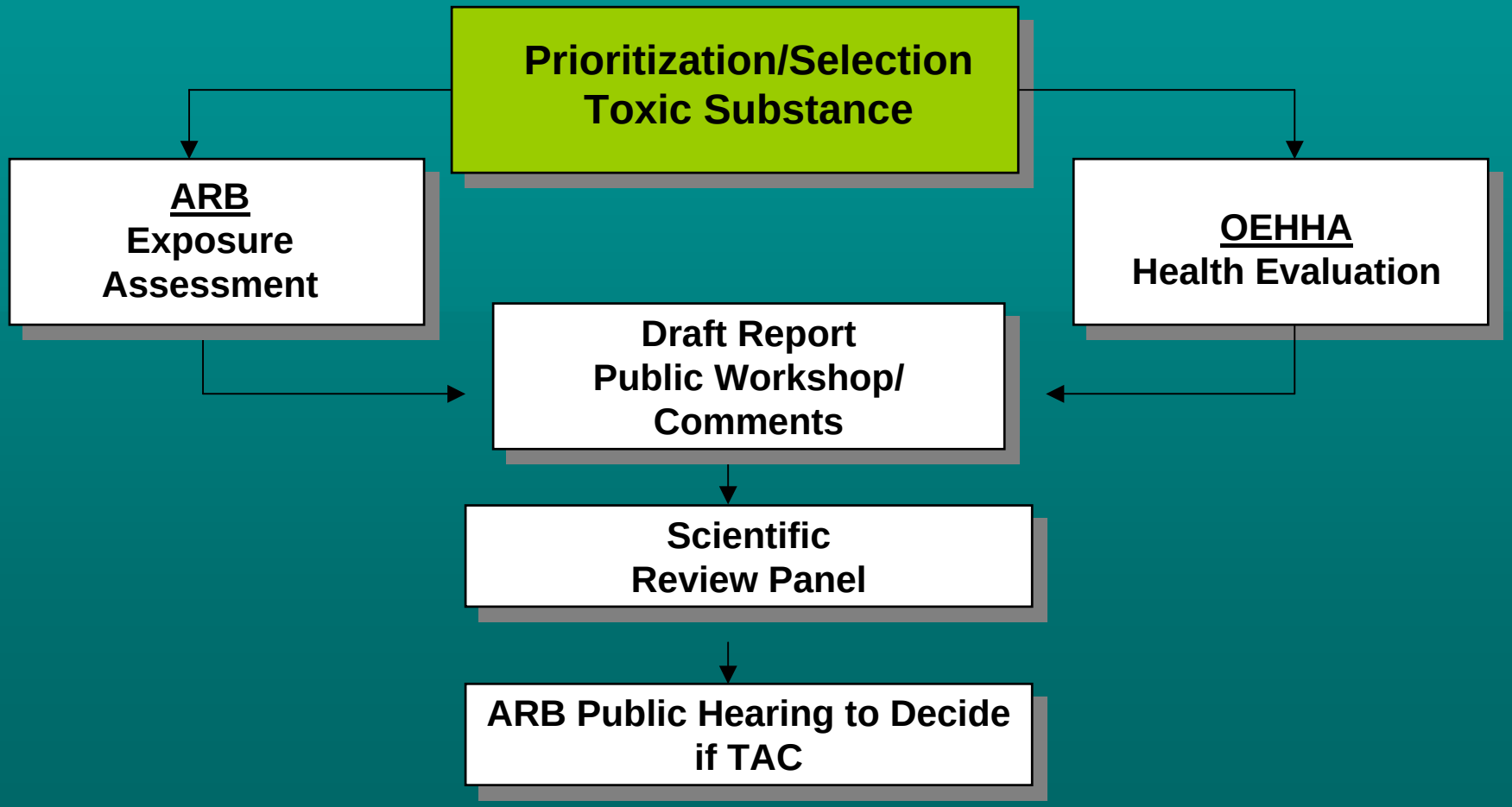
California Environmental Protection Agency
Office of Environmental Health Hazard Assessment

TAC Identification
Health & Safety Code Requirements

- Exposure assessment (ARB)
  - properties, emissions, ambient concentrations, indoor/total exposure, persistence
- Requires OEHHA to use all available scientific data to assess health effects
- SB 25 requires ARB and OEHHA to consider special exposure patterns and susceptibility for children and infants

Toxic Air Contaminants Program

Identification



Scientific Review Panel on Toxic Air Contaminants

- **John R. Froines, Ph.D.**, Chairman
  Director, Center of Occupational and Environmental Health UCLA
  Toxicology

- **Roger Atkinson, Ph.D.**
  Director, Air Pollution Research Center, UC Riverside
  Atmospheric Science

- **Paul D. Blanc, M.D.**
  Chief, Division of Occupational and Environmental Medicine UCSF
  Occupational Environmental Medicine

- **Craig V. Byus, Ph.D.**
  UC Riverside
  Professor of Biomedical Science
  and Biochemistry
  Biochemistry/Molecular Biology

- **Gary D. Friedman, M.D.,**
  Consulting Professor Stanford, Kaiser
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- **Stanton A. Glantz, Ph.D.**
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- **Joseph R. Landolph, Ph.D.**
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  Molecular Pharmacology and Toxicology
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  Oncology / Carcinogenesis

- **Charles G. Plopper, Ph.D.**
  Professor, Department of Anatomy, Physiology and Cell Biology
  UC Davis
  Pathology

OEHHA 1997 and 2005 Reports on Health Effects of ETS

- OEHHA 1997 document underwent public review and comment and peer review by Scientific Review Panel
- Also published by the National Cancer Institute as a monograph in 1999
- ARB entered ETS into the TAC process in 2001, triggering an update of the 1997 report
- OEHHA conducted an exhaustive literature search of studies published since the 1997 report
- Information in the 1997 report and the update the basis of conclusions in the 2005 report

ETS – Potential Mechanisms of Developmental Toxicity

- Numerous chemicals in tobacco smoke are known to cause developmental toxicity (e.g., carbon monoxide, nicotine, cadmium)
- Potential mechanisms for toxicity include:
  - Inhibition of copper enzyme lysyl oxidase decreases collagen formation that may result in preterm delivery
  - Decrease in Vitamin C caused by oxidative gases is associated with PROM and preterm delivery
  - Constituents of tobacco smoke inhibit fibronectin and platelet activating factor (PAF) acetylhydrolase and may lead to preterm labor
  - Changes are found in many hormone levels necessary for pregnancy maintenance, e.g., estrogen, HCG, prolactin.

ETS and Pregnancy Outcomes: Comparison of OEHHA (1997) and 2005 Update

Outcome	Number of Studies in 1997	Number of Additional Studies in Update	Evidence of causal association?	
			OEHHA 1997 Findings	Update Findings
Reduced Birth Weight	24	18	Conclusive	Conclusive (strengthened)
Low Birth Weight (<2500gms)	13	9	Conclusive	Conclusive (strengthened)
Pre-term Delivery	6	7	Suggestive	Conclusive
Intrauterine Growth Retardation	5	8	Suggestive	Suggestive (strengthened)
Spontaneous Abortion	5	4	Suggestive*	Suggestive*
Malformations	5	6	Inconclusive	Inconclusive

*possible role of paternal smoking.

Meta-analyses of ETS and Birth Weight

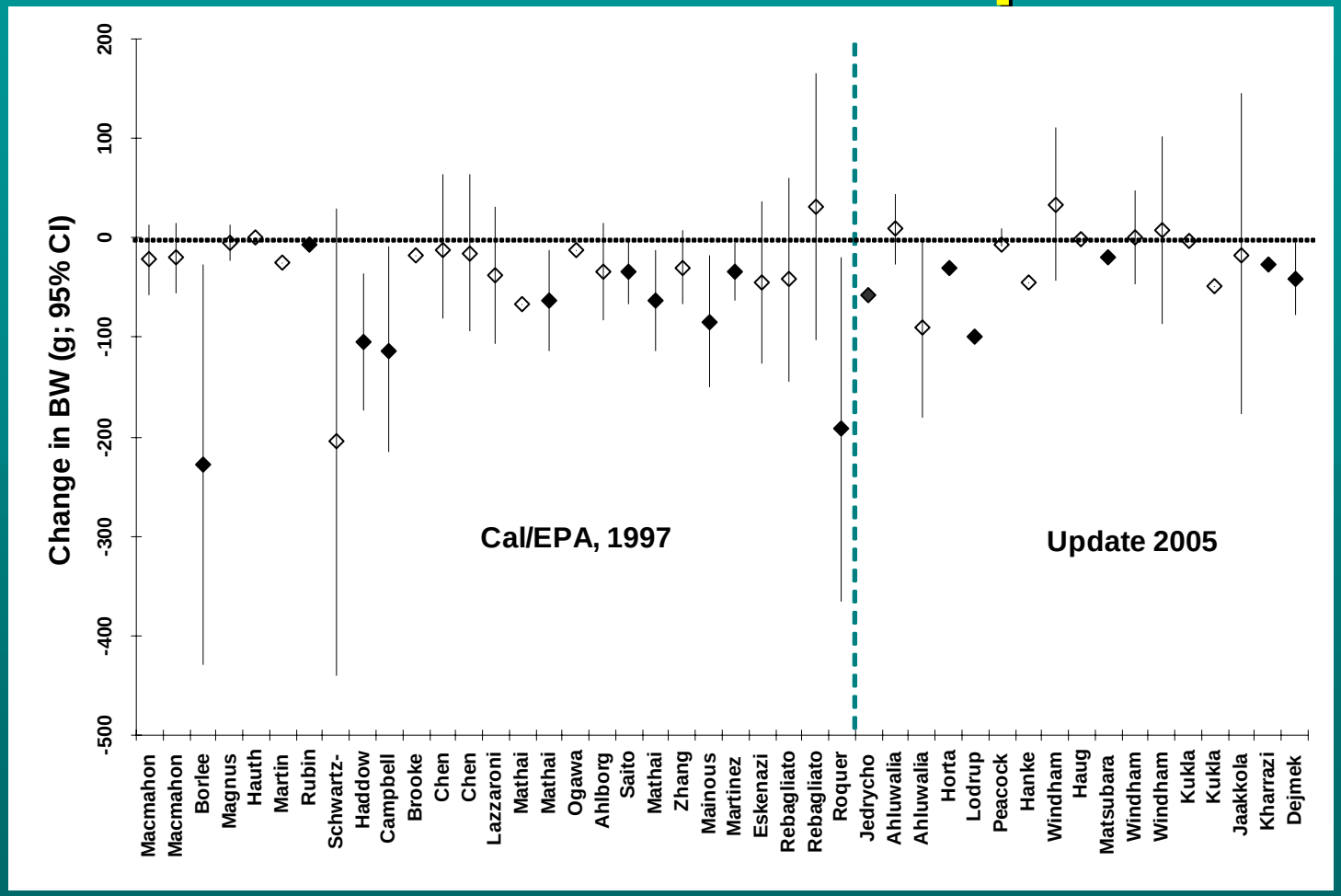
- Windham et al. 1999 pooled risk estimate using adjusted estimates from 8 studies for decrease in BW.

  -24 g (95% CI -39.3;-8.6)

- Peacock et al. 1998 pooled estimate using adjusted estimates from 11 studies for decrease in BW.

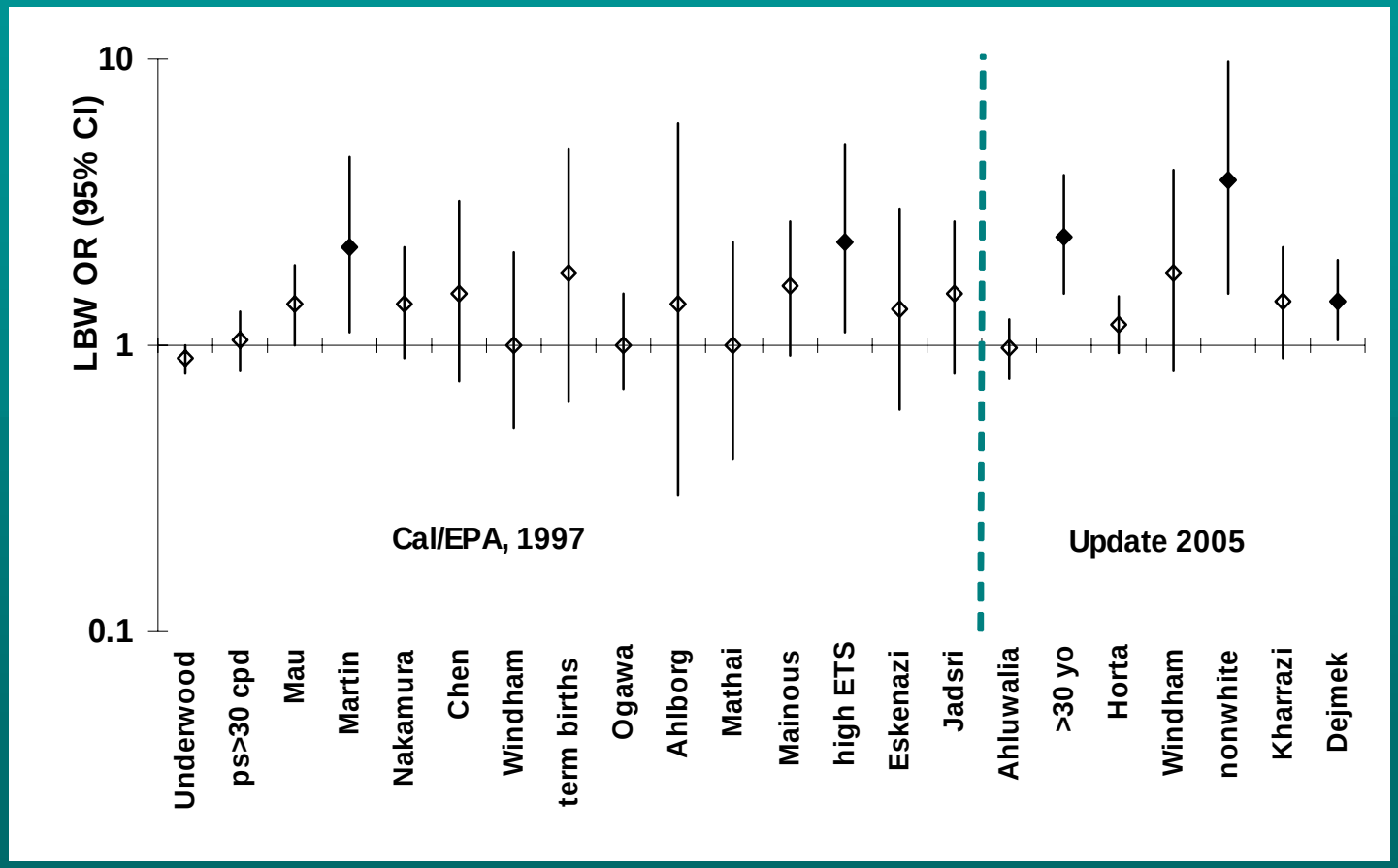
  -31 g (95% CI -44;-19)

Mean Change in Birth Weight with Maternal ETS Exposure



◆ Statistically significant
◇ Statistically non-significant

ETS and Risk of Low Birth Weight



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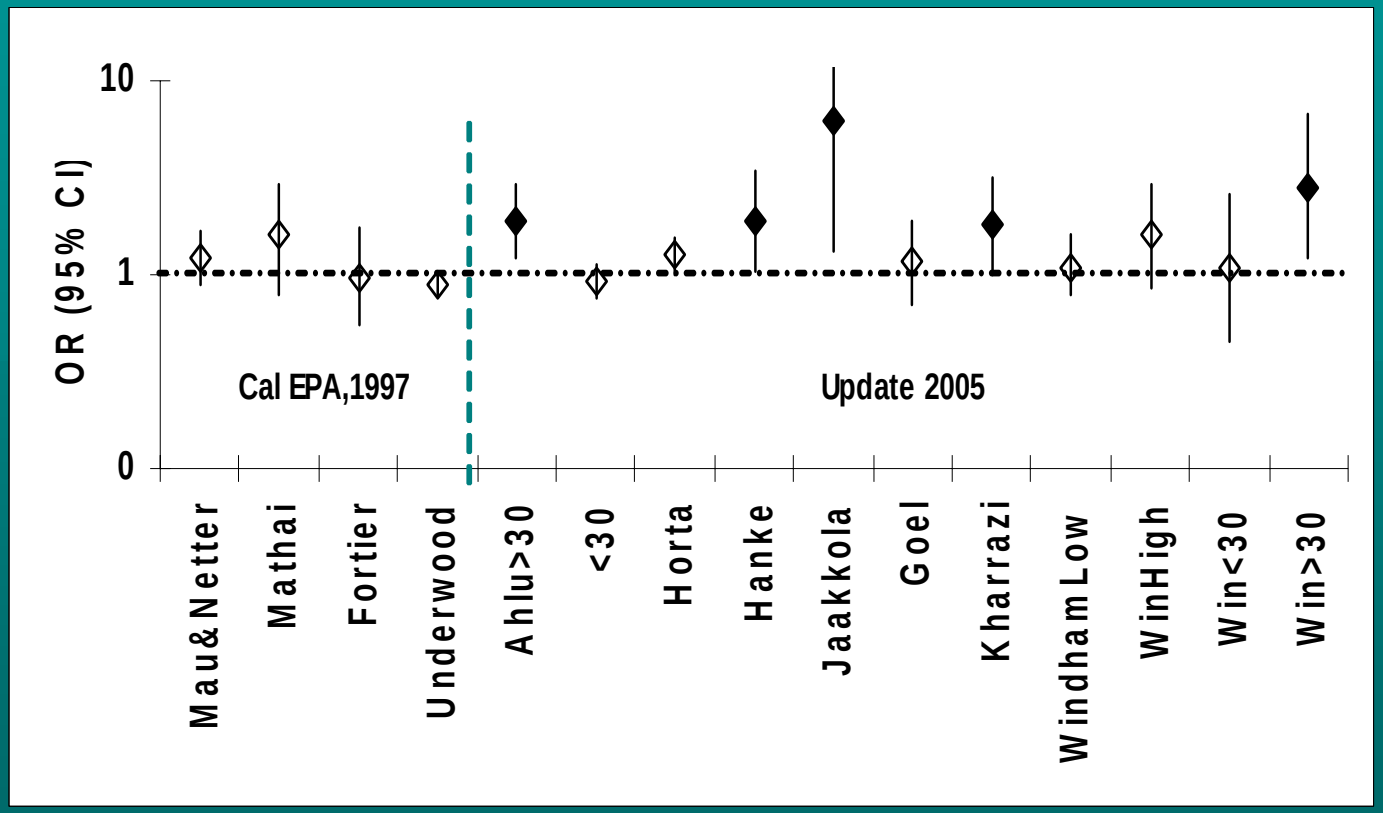
ETS and Risk of Preterm Delivery

- Several new studies demonstrated elevated risk of pre-term delivery when mothers were exposed to ETS
- Evidence of increasing risk with increasing exposure
- Some evidence that effect is worse in older (>30 yrs) mothers

ETS and Risk of Preterm Delivery



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Attributable Risks Associated with ETS

Conclusion		
Outcome	**Annual Excess # in CA**	**Annual Excess # in US**
Pregnancy: Low birth weight Pre-term delivery	 1,600 4,700	 24,500 71,900

ETS and Reproduction: Comparison of OEHHA (1997) and Update

Outcome	# Studies 1997	# Additional Studies in Update	Findings OEHHA 1997: Evidence of causal association?	Findings 2005 Update: Evidence of causal association?
Fertility or fecundability	8	7 [1]	Inconclusive	Suggestive
Lower age at Menopause	2	1	Inconclusive	Inconclusive
Male reproductive Dysfunction [2]	0	1	Not assessed	Inconclusive

[1] Includes 2 studies suggestive of menstrual cycle disorders.

[2] The one new study evaluated male reproductive function in adults of mothers who smoked during pregnancy.

Exposure Assessment in Epidemiologic Studies

- Questionnaire
- Biomarkers
  - nicotine
  - cotinine - the major metabolite of nicotine
    - Blood, urine, saliva
    - half life of ~15-19 hours
    - smokers versus non-smokers
    - non-smokers exposed to ETS and those not exposed

ETS Exposure and Birth Weight

42 studies from the 1997 and 2005 reports

- conclusive evidence

Kharrazi et al., 2004

- Prospective, population based cohort (n=2777)
- Serum cotinine taken at 15-19 weeks of gestation
- Sensitive cotinine assay
  - Limit of Detection (LOD) = 0.05 ng/ml
  - Reduced misclassification of exposure
- 3 groups
  - Smokers (> 10 ng/ml)
  - Non-smokers exposed to ETS (0.05 – 10 ng/ml)
  - Non-smokers not exposed to ETS (<0.05 ng/ml)

Results from Kharrazi et al.

- Inverse linear association between cotinine levels and birth weight in a dose-dependent manner
  - For each unit increase in cotinine

    -27.2 g; 95% CI, - 53.7 to – 0.6
  - over the range of cotinine levels (4 levels)

    - 109 grams
- ETS exposure accounted for 12% of adverse pregnancy outcomes (including fetal deaths, preterm deliveries, and term-low birth weight babies).

Association between Serum Cotinine and BW

Serum Cotinine (ng/ml)	# of Women	Change in Birth Weight (grams)
>1.0-10	135	-101
>0.5-1.0	142	-31
>0.1 – 0.5	808	-30
0.05-0.1	652	-15
<0.05	1022	Reference

Kharrazi et al., 2004

Recent Studies of ETS and BW

5 additional studies were identified

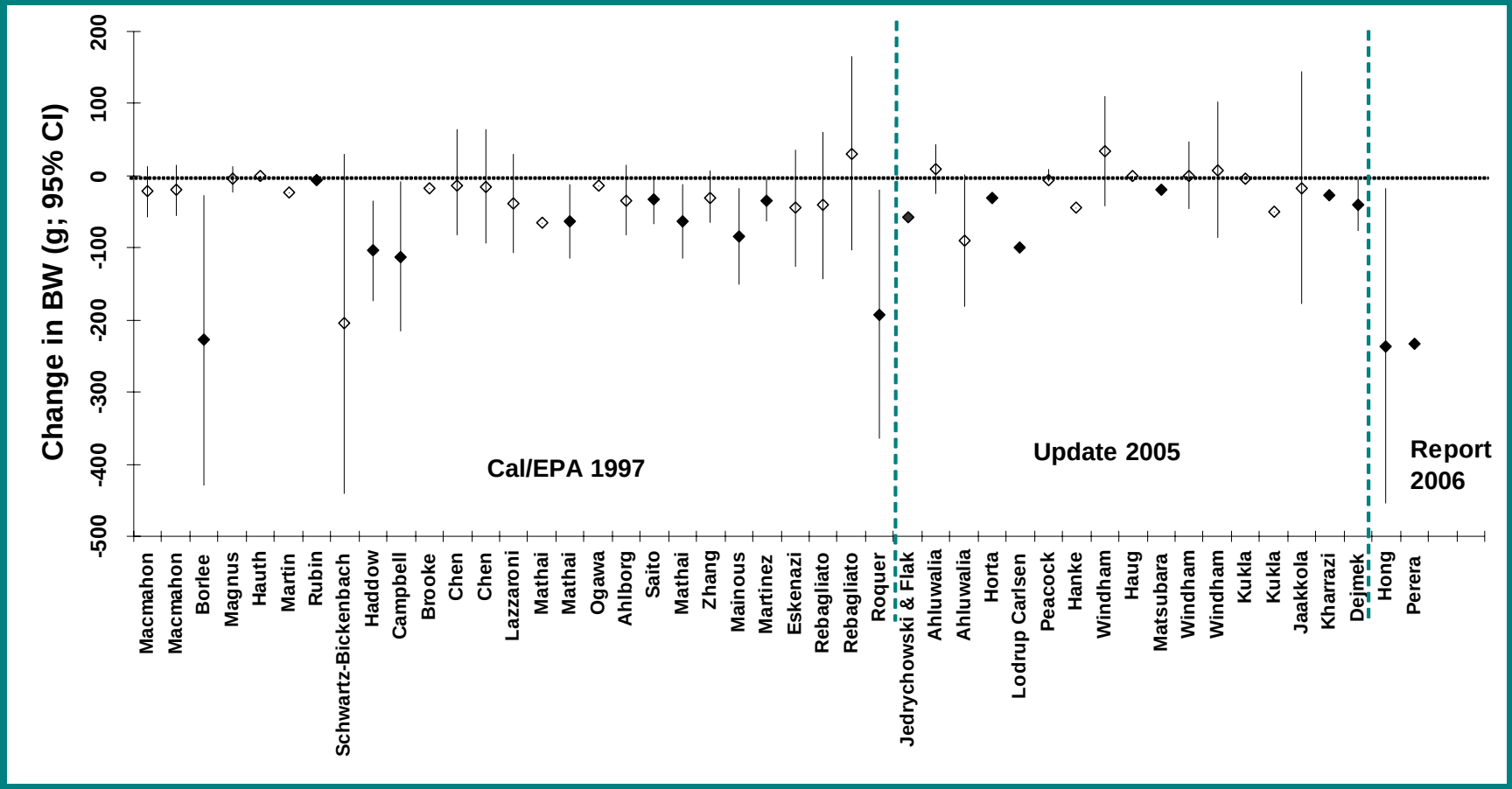
- Adamek et al., 2004
- Perera et al., 2003
- Jedrychowski et al., 2004

- Hong et al., 2003
- Perera et al., 2004

Recent Studies of ETS and BW

Author	Study Type	Outcome	Risk Estimate
Hong et al., 2003	Cohort (n = 266)	BW	Significant interaction between ETS and genetic polymorphisms (GSTT1-null) -236 g (95% CI, -17 to –455)
Perera et al., 2004	Cohort (n = 214)	BW Head circumference	Significant interaction between ETS and BaP-DNA adducts -233 g (p = 0.05) - 1 cm (p = 0.01)

Mean Change in Birth Weight



◆ Statistically significant
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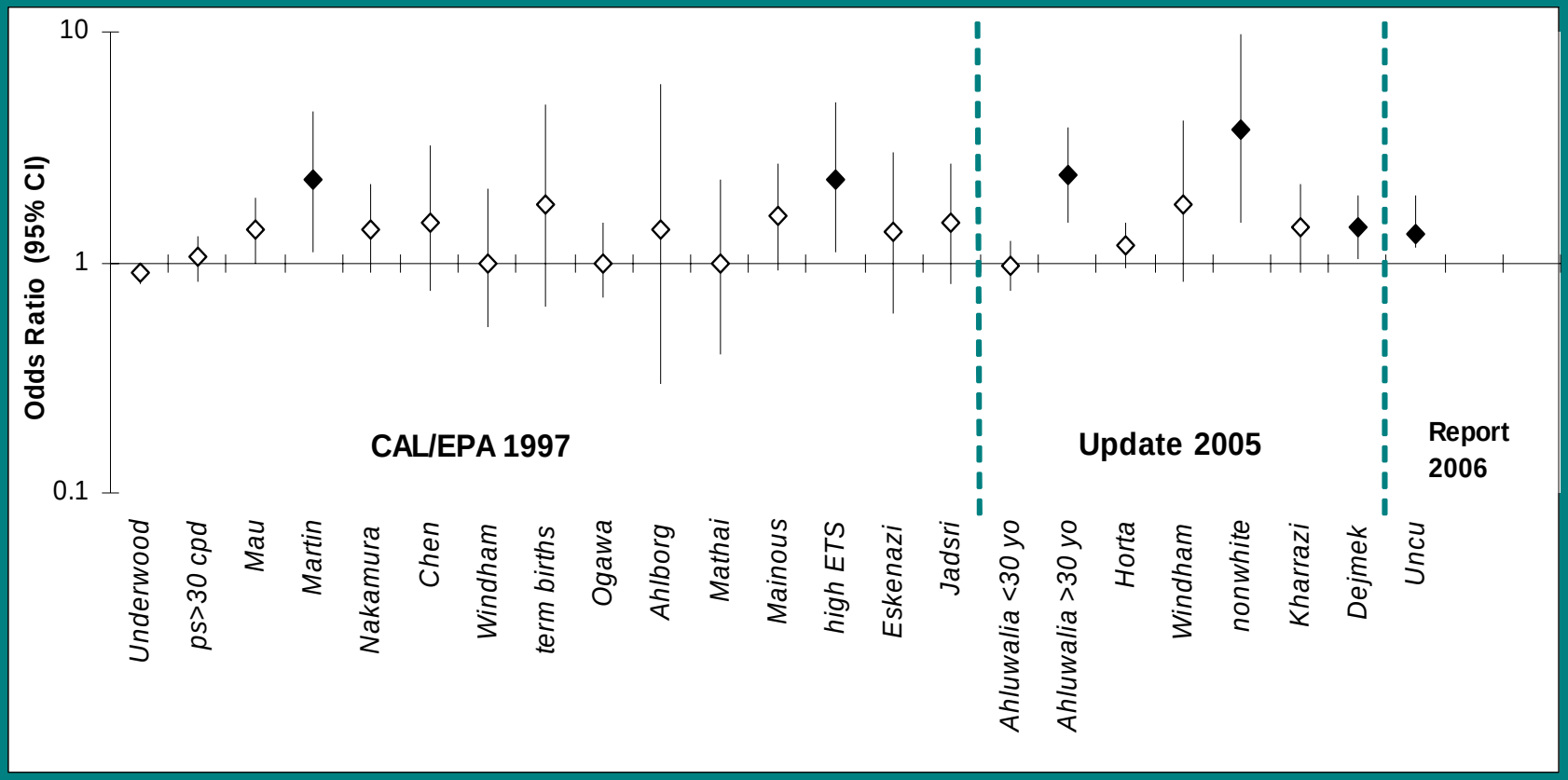
ETS and Odd Ratios for Low Birth Weight



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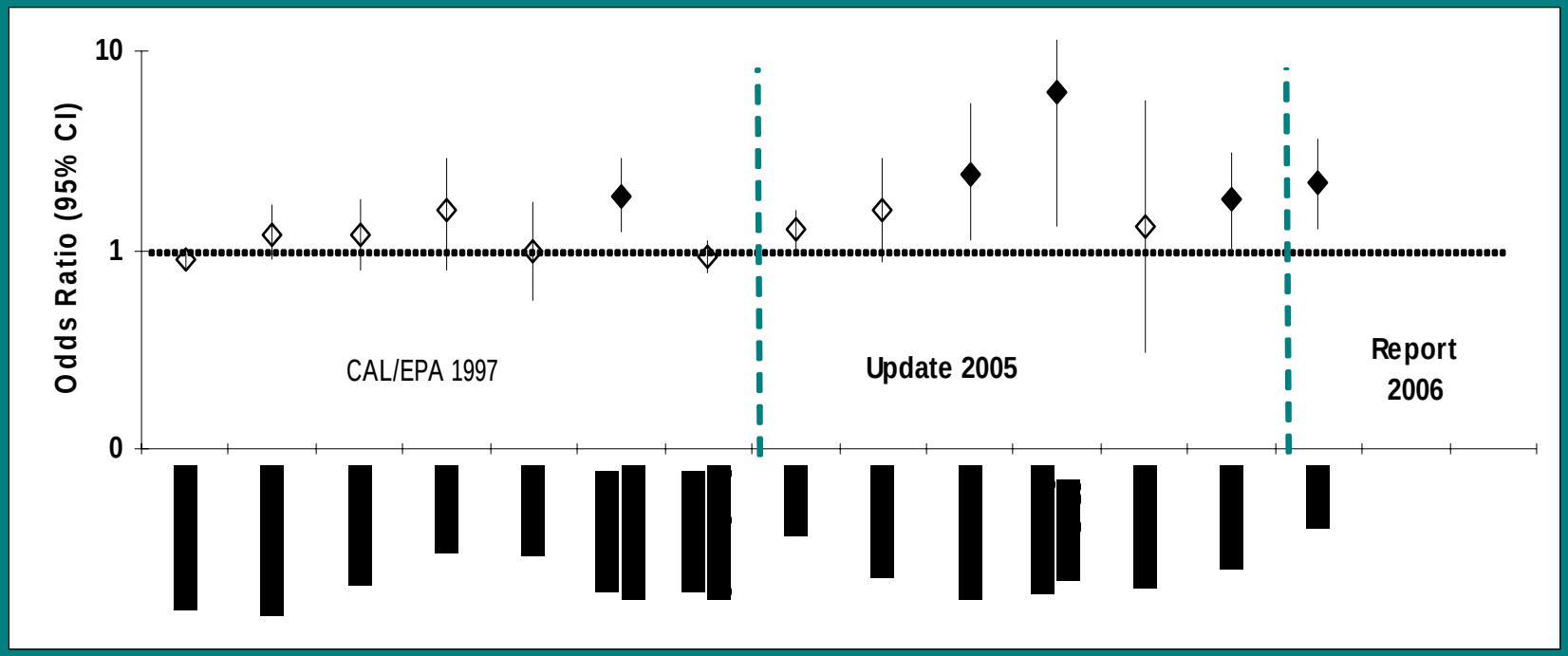
Odd Ratios for Preterm Delivery



◆ Statistically significant
◇ Statistically non-significant

Recent Studies of Various Outcomes

Outcome	Study	Results
Asthma	Skorge et al.	No significant association
Antioxidant Status	Ermis et al. Fayol et al.	No significant association Significant association
Congenital Malformations	Carmichael et al. Kurahashi et al. Pierik et al.	No significant association Significant association Significant association
Cognitive development	Rauh et al.	Significant association
Fetal biometry & blood flow	Kalinka et al.	Significant association
Mutagenesis	Chen et al. Grant et al.	No significant association Significant association

Recent Female ReproductiveToxicity Studies of ETS

- Chen et al., 2005
  - Urinary hormone levels
- Neal et al., 2005
  - IVF (In vitro fertilization) or ICSI (Intracytoplasmic sperm injection) outcomes

Chen et al., 2005

- Prospective cohort study of women textile workers in China (n = 371)
  - All women were non-smokers
  - Women were followed for up to one year
- Daily diary - collected information on ETS exposure, sexual intercourse, etc.
- Hormone levels were determined from 1st morning urine specimens collected daily

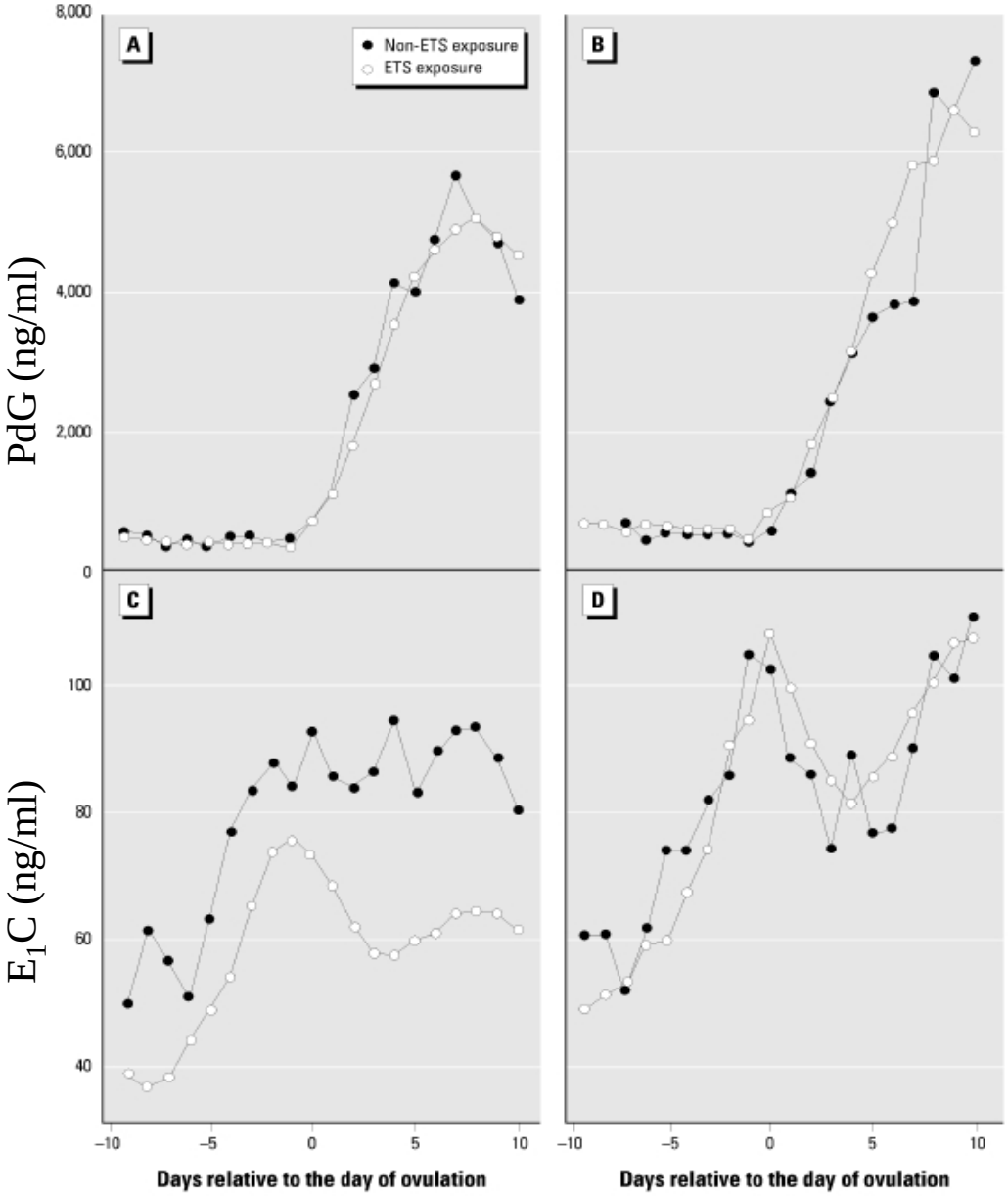


Figure 2. Mean daily PdG (*A,B*) and E_1C (*C,D*) levels in the 20-day window around ovulation by the status of ETS exposure. Of 344 total nonconception cycles (*A,C*), 44 had no ETS exposure and 300 had ETS exposure; of 329 total conception cycles (*B,D*), 32 had no ETS exposure and 297 had ETS exposure.

Neal et al., 2005

- Retrospective cohort study of women undergoing IVF or ICSI (Intracytoplasmic sperm injection) (n = 225)
  - Smoking status from questionnaire data
  - ETS exposure based on partner's smoking

Neal et al., 2005

Outcome	Unexposed non-smokers (n=146)	ETS-exposed non-smokers (n=40)	Smokers (n=39)
Pregnancy rate *	48.3%	20.0%	19.4%
Implantation rate **	25.0%	12.6%	12.0%

* significant difference between groups $p < 0.001$

** significant difference between groups $p < 0.01$

Results from Neal et al.

- No difference in embryo quality between groups
- No difference in fertilization rates between groups
- ETS exposed non-smokers had lower rates of implantation and pregnancy compared with non-smokers unexposed to ETS

Male Reproductive Toxicity of ETS

- One study identified in the 2005 report
  - Study findings were inconclusive due to a paucity of data
- No recent studies were identified