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
• 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)
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*

Prioritization/Selection

*Toxic Substance*

- **ARB**
  - Exposure Assessment
- **OEHHA**
  - Health Evaluation

Draft Report

Public Workshop/
Comments

Scientific
Review Panel

ARB Public Hearing to Decide if TAC
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  
  Epidemiology

• Stanton A. Glantz, Ph.D.  
  Professor of Medicine, UCSF  
  Biostatistics

• S. Katharine Hammond, Ph.D.  
  Professor of Environmental Health Sciences, UC Berkeley  
  Exposure Assessment

• Joseph R. Landolph, Ph.D.  
  Associate Professor, Molecular Microbiology and Immunology, Pathology, and  
  Molecular Pharmacology and Toxicology USC  
  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.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Studies in 1997</th>
<th>Number of Additional Studies in Update</th>
<th>Evidence of causal association?</th>
<th>OEHHA 1997 Findings</th>
<th>Update Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced Birth Weight</td>
<td>24</td>
<td>18</td>
<td>Conclusive</td>
<td>Conclusive</td>
<td>Conclusive (strengthened)</td>
</tr>
<tr>
<td>Low Birth Weight (&lt;2500gms)</td>
<td>13</td>
<td>9</td>
<td>Conclusive</td>
<td>Conclusive</td>
<td>Conclusive (strengthened)</td>
</tr>
<tr>
<td>Pre-term Delivery</td>
<td>6</td>
<td>7</td>
<td>Suggestive</td>
<td>Suggestive</td>
<td>Conclusive</td>
</tr>
<tr>
<td>Intrauterine Growth Retardation</td>
<td>5</td>
<td>8</td>
<td>Suggestive</td>
<td>Suggestive</td>
<td>Suggestive (strengthened)</td>
</tr>
<tr>
<td>Spontaneous Abortion</td>
<td>5</td>
<td>4</td>
<td>Suggestive*</td>
<td>Suggestive*</td>
<td>Suggestive*</td>
</tr>
<tr>
<td>Malformations</td>
<td>5</td>
<td>6</td>
<td>Inconclusive</td>
<td>Inconclusive</td>
<td>Inconclusive</td>
</tr>
</tbody>
</table>

*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

-500 -400 -300 -200 -100 0 100 200

Change in BW (g; 95% CI)

Cal/EPA, 1997
Update 2005

◆ Statistically significant
◇ Statistically non-significant
ETS and Risk of Low Birth Weight

Cal/EPA, 1997

Update 2005

LBW OR (95% CI)

Statistically significant

Statistically non-significant

Underwood
Mau
Martin
Nakamura
Chen
Windham
term births
Ogawa
Ahlborg
Mathai
Mainous
high ETS
Eskenazi
Jadsri
Ahiwaria
>30 yo
Horta
Windham
nonwhite
Kharrazi
Dejmek
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

- Statistically significant
- Statistically non-significant
# Attributable Risks Associated with ETS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Annual Excess # in CA</th>
<th>Annual Excess # in US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>1,600</td>
<td>24,500</td>
</tr>
<tr>
<td>Pre-term delivery</td>
<td>4,700</td>
<td>71,900</td>
</tr>
</tbody>
</table>
### ETS and Reproduction: Comparison of OEHHA (1997) and Update

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertility or fecundability</td>
<td>8</td>
<td>7&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Inconclusive</td>
<td>Suggestive</td>
</tr>
<tr>
<td>Lower age at Menopause</td>
<td>2</td>
<td>1</td>
<td>Inconclusive</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Male reproductive Dysfunction&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0</td>
<td>1</td>
<td>Not assessed</td>
<td>Inconclusive</td>
</tr>
</tbody>
</table>

<sup>1</sup> Includes 2 studies suggestive of menstrual cycle disorders.

<sup>2</sup> 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

<table>
<thead>
<tr>
<th>Serum Cotinine (ng/ml)</th>
<th># of Women</th>
<th>Change in Birth Weight (grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.0-10</td>
<td>135</td>
<td>-101</td>
</tr>
<tr>
<td>&gt;0.5-1.0</td>
<td>142</td>
<td>-31</td>
</tr>
<tr>
<td>&gt;0.1 – 0.5</td>
<td>808</td>
<td>-30</td>
</tr>
<tr>
<td>0.05-0.1</td>
<td>652</td>
<td>-15</td>
</tr>
<tr>
<td>&lt;0.05</td>
<td>1022</td>
<td>Reference</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Type</th>
<th>Outcome</th>
<th>Risk Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong et al., 2003</td>
<td>Cohort (n = 266)</td>
<td>BW</td>
<td>Significant interaction between ETS and genetic polymorphisms (GSTT1-null)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-236 g (95% CI, -17 to –455)</td>
</tr>
<tr>
<td>Perera et al., 2004</td>
<td>Cohort (n = 214)</td>
<td>BW</td>
<td>Significant interaction between ETS and BaP-DNA adducts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Head circumference</td>
<td>-233 g (p = 0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-1 cm (p = 0.01)</td>
</tr>
</tbody>
</table>
Mean Change in Birth Weight

Statistically significant
Statistically non-significant
ETS and Odd Ratios for Low Birth Weight

- Statistically significant
- Statistically non-significant
Odd Ratios for Preterm Delivery

- Statistically significant
- Statistically non-significant
**Recent Studies of Various Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Skorge et al.</td>
<td>No significant association</td>
</tr>
<tr>
<td>Antioxidant Status</td>
<td>Ermis et al.</td>
<td>No significant association</td>
</tr>
<tr>
<td></td>
<td>Fayol et al.</td>
<td>Significant association</td>
</tr>
<tr>
<td>Congenital Malformations</td>
<td>Carmichael et al.</td>
<td>No significant association</td>
</tr>
<tr>
<td></td>
<td>Kurahashi et al.</td>
<td>Significant association</td>
</tr>
<tr>
<td></td>
<td>Pierik et al.</td>
<td>Significant association</td>
</tr>
<tr>
<td>Cognitive development</td>
<td>Rauh et al.</td>
<td>Significant association</td>
</tr>
<tr>
<td>Fetal biometry &amp; blood flow</td>
<td>Kalinka et al.</td>
<td>Significant association</td>
</tr>
<tr>
<td>Mutagenesis</td>
<td>Chen et al.</td>
<td>No significant association</td>
</tr>
<tr>
<td></td>
<td>Grant et al.</td>
<td>Significant association</td>
</tr>
</tbody>
</table>
Recent Female Reproductive Toxicity 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 E1C (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
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unexposed non-smokers (n=146)</th>
<th>ETS-exposed non-smokers (n=40)</th>
<th>Smokers (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy rate *</td>
<td>48.3%</td>
<td>20.0%</td>
<td>19.4%</td>
</tr>
<tr>
<td>Implantation rate **</td>
<td>25.0%</td>
<td>12.6%</td>
<td>12.0%</td>
</tr>
</tbody>
</table>

* 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