Environmental Tobacco Smoke: Abstracts of DART Studies Published After Completion of the 2005 OEHHA Review

February 2006

Reproductive and Cancer Hazard Assessment Branch

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

Environmental Tobacco Smoke: Abstracts of DART Studies Published After Completion of the 2005 OEHHA Review

Office of Environmental Health Hazard Assessment

February 2006

This document compiles abstracts of studies of the developmental and reproductive toxicity of environmental tobacco smoke (ETS) published since the completion of the document "Health Effects Assessment for Environmental Tobacco Smoke," released by the Office of Environmental Health Hazard Assessment (OEHHA) in 2005. That document is being provided to the Developmental and Reproductive Toxicant (DART) Identification Committee as the Committee considers the possible listing under Proposition 65 of ETS as "known to cause reproductive toxicity." Chapters 3, 4 and 5 address the reproductive toxicity of ETS (i.e., male and female reproductive and developmental toxicity). The OEHHA ETS document generally includes articles published before late 2003. The present compilation is of abstracts of recent relevant studies not included in the OEHHA 2005 document. The OEHHA 2005 document was an update to a 1997 OEHHA document entitled "Health Effects Assessment for Environmental Tobacco Smoke[1]."

OEHHA is the lead agency for the implementation of the Safe Drinking Water and Toxic Enforcement Act of 1986[2] (Proposition 65). The DART Identification Committee of OEHHA's Science Advisory Board advises and assists OEHHA in compiling the Proposition 65 list of chemicals known to the State to cause reproductive toxicity, as required by Health and Safety Code section 25249.8. The Committee serves as the State's qualified experts for determining whether a chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause reproductive toxicity (Title 22, Cal. Code of Regs., section 12305(b)(1)).

ETS has been previously considered for Proposition 65 listing by the DART Identification Committee. At a meeting held on May 12, 1995, the Committee concluded that ETS had not been clearly shown to cause reproductive toxicity. Since that time, a substantial number of additional studies of its potential developmental and reproductive toxicity have been completed and published, and members of the Committee have subsequently requested that ETS be brought back to the Committee for reconsideration.

The 2005 OEHHA health effects assessment of ETS was finalized as part of the Toxic Air Contaminant program.[3] Additional information concerning OEHHA's air program can be found at: http://www.oehha.ca.gov/air.html. The document was finalized September 30, 2005 and

[1] The OEHHA 1997 assessment was also published as: National Cancer Institute. Health Effects of Exposure to Environmental Tobacco Smoke: The Report of the California Environmental Protection Agency. Smoking and Tobacco Control Monograph no. 10. Bethesda, MD. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, NIH Pub. No. 99-4645, 1999.
[2] Health and Safety Code section 25249.5 et seq.
[3] Health and Safety Code section 39606

made available to the public. This compilation, along with the 2005 OEHHA review and an earlier 1997 OEHHA review of the health effects of ETS, are being provided to the Committee as the hazard identification materials for consideration of ETS. These materials are available from the Proposition 65 Implementation Office at (916) 445-6900 and through the Internet at the following address: **http://www.oehha.ca.gov/.**

Table of Contents

I. Epidemiologic DART Studies

A. Studies reporting increased risk of adverse developmental or reproductive outcomes

Effect of environmental tobacco smoke on levels of urinary hormone markers.
Chen C, Wang X, Wang L, Yang F, Tang G, Xing H, Ryan L, Lasley B, Overstreet JW, Stanford JB Xu X.
Environ Health Perspect 2005,113(4):412-7

Our recent study showed a dose-response relationship between environmental tobacco smoke (ETS) and the risk of early pregnancy loss. Smoking is known to affect female reproductive hormones. We explored whether ETS affects reproductive hormone profiles as characterized by urinary pregnanediol-3-glucuronide (PdG) and estrone conjugate (E1C) levels. We prospectively studied 371 healthy newly married nonsmoking women in China who intended to conceive and had stopped contraception. Daily records of vaginal bleeding, active and passive cigarette smoking, and daily first-morning urine specimens were collected for up to 1 year or until a clinical pregnancy was achieved. We determined the day of ovulation for each menstrual cycle. The effects of ETS exposure on daily urinary PdG and E1C levels in a +/-10 day window around the day of ovulation were analyzed for conception and nonconception cycles, respectively. Our analysis included 344 nonconception cycles and 329 conception cycles. In nonconception cycles, cycles with ETS exposure had significantly lower urinary E1C levels (beta = -0.43, SE = 0.08, $p < 0.001$ in log scale) compared with the cycles without ETS exposure. There was no significant difference in urinary PdG levels in cycles having ETS exposure (beta = -0.07, SE = 0.15, $p = 0.637$ in log scale) compared with no ETS exposure. Among conception cycles, there were no significant differences in E1C and PdG levels between ETS exposure and nonexposure. In conclusion, ETS exposure was associated with significantly lower urinary E1C levels among nonconception cycles, suggesting that the adverse reproductive effect of ETS may act partly through its antiestrogen effects.

Antioxidant status of neonates exposed in utero to tobacco smoke.
Fayol L, Gulian JM, Dalmasso C, Calaf R, Simeoni U Millet V.
Biol Neonate 2005,87(2):121-6

To investigate the influence of maternal smoke exposure on neonatal and maternal antioxidant status, 39 mothers who were active smokers, 14 mothers exposed to environmental tobacco smoke (ETS), 17 controls, and their newborns were included in a prospective, controlled study. Plasma total antioxidant capacity, measured as total radical-trapping antioxidant parameter (TRAP) and ferric reducing antioxidant power (FRAP), and concentrations of specific antioxidants were measured in cord and in maternal blood. A similar, significant increase in ceruloplasmin concentration was observed in neonates born to actively smoking mothers and in those born to ETS exposed mothers. Uric acid and TRAP concentrations were significantly increased in ETS-exposed newborns and their mothers, compared to newborns and mothers from

the active smoking and no-exposure groups with a trend towards increased uric acid, TRAP and FRAP concentrations being observed in the active smokers group. Neonatal and maternal antioxidant concentrations correlated significantly, except for ceruloplasmin. Cord blood vitamin A, E and C concentrations were unaffected by smoke exposure. These results show that maternal active smoking as well as ETS exposure significantly affect neonatal and maternal antioxidant status.

Qualitatively and quantitatively similar effects of active and passive maternal tobacco smoke exposure on in utero mutagenesis at the HPRT locus.
Grant SG.
BMC Pediatr 2005, June 29;5(20)

BACKGROUND: Induced mutagenesis in utero is likely to have life-long repercussions for the exposed fetus, affecting survival, birth weight and susceptibility to both childhood and adult-onset diseases, such as cancer. In the general population, such exposures are likely to be a consequence of the lifestyle choices of the parents, with exposure to tobacco smoke one of the most pervasive and easily documented. Previous studies attempting to establish a direct link between active smoking and levels of somatic mutation have largely discounted the effects of passive or secondary exposure, and have produced contradictory results. METHODS: Data from three studies of possible smoking effects on in utero mutagenesis at the HPRT locus were compiled and reanalyzed, alone and in combination. Where possible, passive exposure to environmental tobacco smoke was considered as a separate category of exposure, rather than being included in the non-smoking controls. Molecular spectra from these studies were reanalyzed after adjustment for reported mutation frequencies from the individual studies and the entire data set. RESULTS: A series of related studies on mutation at the X-linked HPRT locus in human newborn cord blood samples has led to the novel conclusion that only passive maternal exposure to tobacco mutagens has a significant effect on the developing baby. We performed a pooled analysis of the complete data from these studies, at the levels of both induced mutation frequency and the resulting mutational spectrum. CONCLUSION: Our analysis reveals a more commonsensical, yet no less cautionary result: both active maternal smoking and secondary maternal exposure produce quantitatively and qualitatively indistinguishable increases in fetal HPRT mutation. Further, it appears that this effect is not perceptibly ameliorated if the mother adjusts her behavior (i.e. stops smoking) when pregnancy is confirmed, although this conclusion may also be affected by continued passive exposure.

Environmental tobacco smoke exposure among pregnant women: impact on fetal biometry at 20-24 weeks of gestation and newborn child's birth weight.
Hanke W, Sobala W Kalinka J.
Int Arch Occup Environ Health 2004,77(1):47-52

AIM: While there are sufficient data regarding the negative effect of exposure to the constituents of tobacco smoke on newborn infants' birth weights, it is still unclear whether this effect may originate in early pregnancy. The aim of the present study was to evaluate the impact of exposure to tobacco smoke components in early pregnancy (20-24 weeks) on fetal biometry. METHODS: The study population comprised 183 women consecutively enrolled at 20-24 weeks of pregnancy

at the two antenatal care units. Ultrasound biometric measurements of fetal bi-parietal diameter (BPD), abdominal circumference (AC) and femur length (FL) were performed at the time of enrollment. Serum cotinine concentration was determined at 20-24 weeks of gestation by gas chromatography with mass spectrometry detector (GC/MS) to assess environmental tobacco smoke (ETS) exposure during the previous evening and the morning of the same day (blood collection at 1200-1300 h). ETS exposure (passive smoking) was assumed to occur when the level of serum cotinine ranged from 2-10 ng/ml. RESULTS: In a multiple regression model for bi-parietal diameter (BPD), after adjustment for pregnancy duration at the time of ultrasound examination, fetal gender, and maternal pre-pregnancy weight, a statistically significant negative association was found between the BPD and serum cotinine concentration. A similar association was identified for subjects with serum cotinine concentrations below 10 ng/ml (corresponding to passive smoking) (P=0.06). After controlling for pregnancy duration, maternal pre-pregnancy weight and infant's gender, we found that serum cotinine levels at 20-24 weeks of gestation was inversely associated with infant birth weight (P=0.004). For the subjects with serum cotinine levels below 10 ng/ml, a borderline association (P=0.09) with infant birth weight was found. CONCLUSIONS: Maternal exposure to tobacco smoke in early pregnancy, as measured by serum cotinine concentrations at 20-24 weeks of gestation, adversely affects fetal BPD. Preventive measures need to be undertaken to encourage pregnant women to stop smoking and avoid passive exposure to tobacco smoke from the very beginning of pregnancy.

Effects of the GSTM1 and GSTT1 polymorphisms on the relationship between maternal exposure to environmental tobacco smoke and neonatal birth weight.
Hong YC, Lee KH, Son BK, Ha EH, Moon HS, Ha M
J Occup Environ Med 2003, May,45(5):492-8

The purpose of the investigation was to determine whether genetic polymorphisms in enzymes that metabolize exogenous chemicals modulate the effects of environmental tobacco smoke (ETS) exposure on birth weight. A survey was conducted from 2000 to 2001 among 266 pregnant women who were hospitalized for delivery and on their singleton live births. We determined maternal GSTM1 and GSTT1 polymorphisms by polymerase chain reaction and measured the urinary cotinine of pregnant women at delivery by radioimmunoassay. Birth weight was found to decrease significantly with increasing concentrations of maternal urinary cotinine ($P < 0.05$). The interactive effect of exposure to ETS and the presence of the GSTT1 polymorphism was found to be significant by multivariate analysis ($P < 0.01$), whereas the interactive effect of exposure to ETS and the presence of GSTM1 polymorphism did not reach statistical significance ($P = 0.21$). A combination of the GSTM1-null and the GSTT1 null-genotypes was found to exacerbate the effect of maternal exposure to ETS on birth weight more than the presence of either genotype alone. Our data indicate that maternal exposure to ETS negatively affects neonatal birth weight, and the adverse effect of maternal exposure to ETS on neonatal birth weight could be modified by the maternal metabolic genotypes, GSTM1 and GSTT1.

Glutathione S transferase deficiency and passive smoking increase childhood asthma.
Kabesch M, Hoefler C, Carr D, Leupold W, Weiland SK von Mutius E.
Thorax 2004,59(7):569-73

BACKGROUND: It has been suggested that the genetically determined deficiency of glutathione S transferase (GST) enzymes involved in the detoxification of environmental tobacco smoke (ETS) components may contribute to the development of asthma. METHODS: A large population of German schoolchildren (n = 3054) was genotyped for deficiencies of the GST isoforms M1 and T1. The association between GSTM1 and GSTT1 genotypes and asthma as well as atopy was investigated with respect to current and in utero ETS exposure. RESULTS: In children lacking the GSTM1 allele who were exposed to current ETS the risk for current asthma (OR 5.5, 95% CI 1.6 to 18.6) and asthma symptoms such as wheeze ever (OR 2.8, 95% CI 1.3 to 6.0), current wheezing (OR 4.7, 95% CI 1.8 to 12.6) and shortness of breath (OR 8.9, 95% CI 2.1 to 38.4) was higher than in GSTM1 positive individuals without ETS exposure. Hints of an interaction between ETS exposure and GSTM1 deficiency were identified. In utero smoke exposure in GSTT1 deficient children was associated with significant decrements in lung function compared with GSTT1 positive children not exposed to ETS. CONCLUSIONS: GSTM1 and GSTT1 deficiency may increase the adverse health effects of in utero and current smoke exposure.

Impact of prenatal tobacco smoke exposure, as measured by midgestation serum cotinine levels, on fetal biometry and umbilical flow velocity waveforms.
Kalinka J, Hanke W Sobala W.
Am J Perinatol 2005,22(1):41-7

The aim of this prospective cohort study was to evaluate the impact of tobacco smoke exposure, measured by maternal serum concentration of cotinine, on fetal midgestation biometric parameters and umbilical artery (UA) qualitative blood flow indices. The study population consisted of 114 healthy women in 20 to 24 weeks gestation who were recruited from the patients of two antenatal care units in Lodz, Poland. Significant negative correlation was found between fetal biparietal diameter (BPD) and serum cotinine concentration. Serum cotinine positively correlated with all blood flow indices under study (systolic/diastolic index [S/D], resistance index, and pulsatility index) after controlling for gestational age, gender, and femur length. The midgestation UA S/D ratio > 3 was found to be a significant risk factor for decreased birthweight. Tobacco smoke exposure is a significant factor inducing increased resistance of umbilical blood flow as measured in 20 to 24 weeks gestation. This could be one of the main mechanisms leading to decreased birthweight observed among infants with prenatal exposure to tobacco smoke.

Parental and neonatal risk factors for cryptorchidism.
Kurahashi N, Kasai S, Shibata T, Kakizaki H, Nonomura K, Sata F Kishi R.
Med Sci Monit 2005,11(6):CR274-83

BACKGROUND: Cryptorchidism is one of the most common congenital malformations in males. As male sexual differentiation is critically dependent on normal androgen concentrations,

increased exposure to environmental factors affecting androgen homeostasis during fetal life may cause cryptorchidism. We investigated the relation between cryptorchidism and lifestyle, occupational exposure and the characteristics of parents and/or the perinatal and delivery characteristics. MATERIAL/METHODS: Case-control study conducted among the eligible 96 cases underwent orchiopexy between 1990 and 2003 and 116 controls were enrolled among boy outpatients born in between 1985 and 2001 and who were determined by pediatricians not to have genitourinary malformation. All the cases and controls were surveyed between 1999 and 2003 in Japan. RESULTS: We found significant positive associations between cryptorchidism and cesarean section (OR=2.19, 95% CI=1.09-4.40), paternal smoking before and during pregnancy (OR=1.87, 95% CI=1.03-3.37 and OR=1.94, 95% CI=1.08-3.50, respectively) and paternal exposure to diesel exhaust before and during pregnancy (OR=2.42, 95% CI=1.06-5.55 and OR=2.35, 95% CI=0.99-5.59, respectively). CONCLUSIONS: We found associations of cryptorchidism with unusual delivery and paternal smoking during pregnancy. These findings suggested that cryptorchidism might be associated with not only genetic factors but also increased parental exposure to environmental factors. In the future, prospective study is needed to do risk assessment accurately in the hormone-dependent stages of pregnancy critical for testicular descent.

Obstetric and perinatal effects of active and/or passive smoking during pregnancy.
Nakamura MU, Alexandre SM, Kuhn dos Santos JF, de Souza E, Sass N, Auritscher Beck AP, Trayna E, Andrade CM, Barroso T Kulay Junior L.
Sao Paulo Med J 2004,122(3):94-8

CONTEXT: Cigarette smoke, whether inhaled voluntarily or not, causes damage to the mother-infant pair. The antenatal period may present the best opportunity for performing effective anti-smoking campaigns. OBJECTIVE: To study the obstetric and perinatal effects of smoking on pregnancy and the infant. TYPE OF STUDY: Prospective study, interviewing pregnant women who were randomly selected at the maternity hospital as they were being discharged after giving birth. SETTING: Hospital Municipal Vereador Jose Storopolli, Sao Paulo, Brazil. METHODS: 758 patients were interviewed regarding smoke inhalation before being discharged from the maternity hospital. The groups were formed by 42 active smokers, 272 passive smokers, 108 who inhaled smoke both actively and passively, and 336 non-smokers. The groups were compared regarding age, parity, school education, incidence of spontaneous abortion, rate of caesarian births, average gestational age at birth, rate of low birth weight and adequacy of weight in relation to the gestational age of newborn infants. For all variables we considered $p < 0.05$ as statistically significant. RESULTS: There was a high rate (55.7%) of pregnant smokers, including 5.5% active, 35.9% passive and 14.3% active-passive smokers. Active and active-passive smokers were older and had higher parity. Active smokers had lower education levels and higher rates of previous spontaneous abortion. The weights of newborn babies were lower for smoking mothers. DISCUSSION: The study was performed among patients that were mostly of low economic, social and cultural levels, thus possibly explaining the high incidence of smokers. Worse still was that 35.9% of the non-smokers were actually passive smokers. These rates we report were similar to those from the literature. The typical receptiveness of teenage girls to unrestricted advertising in the media contributes towards an early start to acquiring the habit of smoking, including during pregnancy in our country. We emphasize the difficulties in quantifying exposure to cigarettes even among active smokers. CONCLUSIONS: Cigarette

smoke, whether inhaled voluntarily or not, has an unfavorable effect on the mother-infant pair.

Sidestream smoking is equally as damaging as mainstream smoking on IVF outcomes.
Neal MS, Hughes EG, Holloway AC Foster WG.
Hum Reprod 2005,20(9):2531-5

BACKGROUND: Cigarette smoking (CS) is a widely recognized health hazard, yet it remains prevalent in society and the effects of environmental tobacco smoke exposure on fertility are unknown. Our objective was to measure the effects of CS on the fertility of mainstream (MS) or sidestream (SS) smoke-exposed women compared to their non-smoking (NS) counterparts. METHODS: This retrospective study investigated 225 female patients undergoing IVF (n = 97) or ICSI (n = 128). Patients were grouped based on their smoking status for comparison. This included: 39 MS (18 IVF and 21 ICSI); 40 SS (16 IVF and 24 ICSI); and 146 NS (63 IVF and 83 ICSI) women. Fertility treatment outcomes including embryo quality, implantation and pregnancy rate were measured. RESULTS: No difference in embryo quality between the three groups was observed. However, there was a significant difference in implantation rate (MS = 12.0%, SS = 12.6%, and NS = 25.0%) and pregnancy rate (MS = 19.4%, SS = 20.0%, and NS = 48.3%) per embryo transfer. CONCLUSIONS: Despite similar embryo quality there was a striking difference in implantation and pregnancy rates of MS and SS smokers when compared with NS. Our data demonstrate that the effects of SS smoking are equally as damaging as MS smoke on fertility.

Molecular evidence of an interaction between prenatal environmental exposures and birth outcomes in a multiethnic population.
Perera FP, Rauh V, Whyatt RM, Tsai WY, Bernert JT, Tu YH, Andrews H, Ramirez J, Qu L Tang D.
Environ Health Perspect 2004,112(5):626-30

Inner-city, minority populations are high-risk groups for adverse birth outcomes and also are more likely to be exposed to environmental contaminants, including environmental tobacco smoke (ETS), benzo[a]pyrene (BaP), and other polycyclic aromatic hydrocarbons (PAHs) found in urban air. In a sample of nonsmoking African-American and Dominican women, we evaluated the effects on birth outcomes of prenatal exposure to ETS, using questionnaire data and plasma cotinine as a biomarker of exposure, and environmental PAHs using BaP-DNA adducts as a molecular dosimeter. We previously reported that among African Americans, high prenatal exposure to PAHs estimated by prenatal personal air monitoring was associated with lower birth weight ($p = 0.003$) and smaller head circumference ($p = 0.01$) after adjusting for potential confounders. In the present analysis, self-reported ETS was associated with decreased head circumference ($p = 0.04$). BaP-DNA adducts were not correlated with ETS or dietary PAHs. There was no main effect of BaP-DNA adducts on birth outcomes. However, there was a significant interaction between the two pollutants such that the combined exposure to high ETS and high adducts had a significant multiplicative effect on birth weight ($p = 0.04$) and head circumference ($p = 0.01$) after adjusting for ethnicity, sex of newborns, maternal body mass index, dietary PAHs, and gestational age. This study provides evidence that combined exposure to environmental pollutants at levels currently encountered in New York City adversely affects

fetal development.

Maternal and paternal risk factors for cryptorchidism and hypospadias: a case-control study in newborn boys.
Pierik FH, Burdorf A, Deddens JA, Juttmann RE Weber RF.
Environ Health Perspect 2004,112(15):1570-6

Little is known on environmental risk factors for cryptorchidism and hypospadias, which are among the most frequent congenital abnormalities. The aim of our study was to identify risk factors for cryptorchidism and hypospadias, with a focus on potential endocrine disruptors in parental diet and occupation. In a case-control study nested within a cohort of 8,698 male births, we compared 78 cryptorchidism cases and 56 hypospadias cases with 313 controls. The participation rate was 85% for cases and 68% for controls. Through interviews, information was collected on pregnancy aspects and personal characteristics, lifestyle, occupation, and dietary phytoestrogen intake of both parents. Occupational exposure to potential endocrine disruptors was classified based on self-reported exposure and ratings of occupational hygienists based on job descriptions. Our findings indicate that paternal pesticide exposure was associated with cryptorchidism [odds ratio (OR) = 3.8; 95% confidence interval (95% CI), 1.1-13.4]. Smoking of the father was associated with hypospadias (OR = 3.8; 95% CI, 1.8-8.2). Maternal occupational, dietary, and lifestyle exposures were not associated with either abnormality. Both abnormalities were associated with suboptimal maternal health, a lower maternal education, and a Turkish origin of the parents. Being small for gestational age was a risk factor for hypospadias, and preterm birth was a risk factor for cryptorchidism. Because paternal pesticide exposure was significantly associated with cryptorchidism and paternal smoking was associated with hypospadias in male offspring, paternal exposure should be included in further studies on cryptorchidism and hypospadias risk factors.

Developmental effects of exposure to environmental tobacco smoke and material hardship among inner-city children.
Rauh VA, Whyatt RM, Garfinkel R, Andrews H, Hoepner L, Reyes A, Diaz D, Camann D Perera FP.
Neurotoxicol Teratol 2004,26(3):373-85

Because of the growing concern that exposures to airborne pollutants have adverse effects on fetal growth and early childhood neurodevelopment, and the knowledge that such exposures are more prevalent in disadvantaged populations, we assessed the joint impact of prenatal exposure to environmental tobacco smoke (ETS) and material hardship on the 2-year cognitive development of inner-city children, adjusted for other sociodemographic risks and chemical exposures. The purpose was to evaluate the neurotoxicant effects of ETS among children experiencing different degrees of socioeconomic disadvantage, within a minority population. The sample did not include children exposed to active maternal smoking in the prenatal period. Results showed significant adverse effects of prenatal residential ETS exposure and the level of material hardship on 2-year cognitive development, as well as a significant interaction between material hardship and ETS, such that children with both ETS exposure and material hardship exhibited the greatest cognitive deficit. In addition, children with prenatal ETS exposure were

twice as likely to be classified as significantly delayed, as compared with nonexposed children. Postnatal ETS exposure in the first 2 years of life did not contribute independently to the risk of developmental delay, over and above the risk posed by prenatal ETS exposure. The study concluded that prenatal exposure to ETS in the home has a negative impact on 2-year cognitive development, and this effect is exacerbated under conditions of material hardship in this urban minority sample.

Pregnant women quit smoking; what about fathers? Survey study in Bursa Region, Turkey.
Uncu Y, Ozcakir A, Ercan I, Bilgel N Uncu G.
Croat Med J 2005,46(5):832-7

AIM: To evaluate maternal and paternal smoking habits during pregnancy and determine their correlation with pregnancy complications and newborn status. METHODS: The study included 499 pregnant women who delivered at the Department of Obstetrics and Gynecology in Uludag University School of Medicine, over a period of one year. Women were interviewed about their smoking habits before and during pregnancy. They were also asked about the smoking habits of their spouses. The relationship between smoking habits and pregnancy complications and newborn status was researched. The outcomes measured included pregnancy complications, gestational age at the onset of labor, Apgar scores during labor, and fetal birth weight and height. RESULTS: The percentage of maternal smoking before pregnancy was 26.5% (n=132) and decreased to 9.8% (n=49) at the end of pregnancy, with 52.5% (n=262) of the fathers who continued to smoke at home during their wife's pregnancy. Low birth weight and preterm delivery rate were significantly higher in maternal (n=15 [30.6%], and n=12 [24.5%], respectively) and paternal smoking groups (n=52 [22.4%] and n=54 [23.3%], respectively). Paternal smoking had no effect on intrauterine growth retardation (n=10 [4.3%]) and prenatal death (n=4 [1.7%]), although maternal smoking had such an effect (n=7 [14.3%] and n=3 [6.1%], respectively). CONCLUSION: Maternal smoking is a major risk factor for preterm delivery, low birth weight, intrauterine growth retardation, and intrauterine death, but paternal smoking also carries risk for the fetus. During perinatal care, we should educate the expectant parents about the side effects, not only of maternal, but also of paternal smoking.

Paternal smoking and pregnancy loss: a prospective study using a biomarker of pregnancy.
Venners SA, Wang X, Chen C, Wang L, Chen D, Guang W, Huang A, Ryan L, O'Connor J, Lasley B, Overstreet J, Wilcox A Xu X.
Am J Epidemiol 2004,159(10):993-1001

Results of studies on paternal smoking and spontaneous abortions have been inconsistent. The authors examined the effect of paternal smoking on the risk of pregnancy loss in a prospective cohort of 526 newly married, nonsmoking, female textile workers in China between 1996 and 1998. Upon stopping contraception, subjects provided daily urine specimens and records of vaginal bleeding for up to 1 year or until clinical pregnancy. Daily urinary human chorionic gonadotropin was assayed to detect conception and early pregnancy losses, and pregnancies were followed to detect clinical spontaneous abortions. Subjects were grouped by the number of cigarettes that husbands reported smoking daily: nonsmokers (group 1, n = 216), fewer than 20

cigarettes (group 2, n = 239), and 20 or more cigarettes (group 3, n = 71). Compared with that for group 1, the adjusted odds ratio of early pregnancy loss of any conception for group 2 was 1.04 (95% confidence interval (CI): 0.67, 1.63) and for group 3 was 1.81 (95% CI: 1.00, 3.29). The adjusted hazard ratio of conception for group 2 was 0.90 (95% CI: 0.70, 1.18) and for group 3 was 0.96 (95% CI: 0.66, 1.39), while the adjusted hazard ratio of clinical pregnancy for group 2 was 0.93 (95% CI: 0.72, 1.20) and for group 3 was 0.78 (95% CI: 0.55, 1.12). The authors conclude that heavy paternal smoking increased the risk of early pregnancy loss through maternal and/or paternal exposure.

B. Studies reporting no increased risk of adverse developmental or reproductive outcomes

[The socio-economic status of women smoking during pregnancy and birth weight of their newborns].
Adamek R, Florek E, Piekoszowski W Breborowicz GH.
Przegl Lek 2004,61(10):1006-11

In this survey, socio-economic status of pregnant women smoking during pregnancy and influence of this status on birth weight of their newborn were assessed. The research was done on the group of 1328 pregnant women. Smoking habit was declared by 18.6% of women and passive exposure to tobacco smoke was stated by 30.6% of respondents. Significant association between active and passive smoking and socioeconomic status of respondents was observed. Cigarette smoking during pregnancy was the main cause of lower birth weight of newborns. The newborns of actively smoking mothers were lighter of about 357 g according to those ones of mothers who did not smoke and were not exposed to passive smoking, and were lighter than newborns of mothers who were not exposed to passive smoking of about 330 g. The passive exposure to the tobacco smoke was not significant considering effect on the birth weight.

Limb deficiency defects, MSX1, and exposure to tobacco smoke.
Carmichael SL, Shaw GM, Yang W, Lammer EJ, Zhu H Finnell RH.
Am J Med Genet A 2004,125(3):285-9

There is increasing evidence from epidemiologic studies that genetic susceptibilities may modify the teratogenic effects of smoking. A previous study suggested that maternal smoking in the presence of a dinucleotide repeat polymorphism for MSX1 produced an almost fivefold increased risk for limb anomalies, providing evidence for a gene-environment interaction. The current study examined this potential interaction, using case-control data with several methodologic improvements, including a larger sample size and more detailed information on cigarette smoke exposures. Cases (n = 92) were ascertained from pregnancies ending in 1987-1989, and controls (n = 180) were randomly selected from eligible liveborn infants. In telephone interviews, women reported smoking behaviors during the month before pregnancy through the end of the first trimester. Odds ratios (OR) for maternal and paternal smoking ranged from 1.0 to 1.4, risk estimates were imprecise; for example, the OR for maternal smoking >or=20 cigarettes per day, versus none, was 1.3 (95% confidence interval (CI) 0.5-3.4). Relative to the homozygous wildtype, the OR was 1.5 (95% CI 0.7-3.5) for the homozygous variant genotype

and 0.8 (95% CI 0.5-1.4) for the heterozygous variant genotype. There was no evidence that maternal smoking or both parents smoking, in combination with a susceptible MSX1 genotype, conferred an additional increase in risk of limb defects. This study did not find a gene-environment interaction between maternal smoking, infant MSX1 CA repeat polymorphism, and risk of limb deficiency defects. This finding contrasts with results of a previous study, which provided initial evidence for such an interaction. Several important methodological differences may have contributed to the differences in findings between the two studies.

Risk of childhood germ cell tumors in association with parental smoking and drinking.
Chen Z, Robison L, Giller R, Krailo M, Davis M, Gardner K, Davies S Shu XO.
Cancer 2005,103(5):1064-71

BACKGROUND: The etiology of childhood germ cell tumors (GCT) is not well understood. The Children's Oncology Group conducted the largest case-control study of childhood GCT to investigate whether parental exposures to smoking and alcohol contributed to the disease. METHODS: Cases included 274 children with GCT diagnosed between January 1, 1993 and December 31, 2001 who were age <15 years. Controls (n=421) were selected by random digit dialing and were frequency matched based on gender, age (+/-1 year), and geographic area. Exposure information was collected from subjects' parents using independent telephone interviews and self-administrated questionnaires. RESULTS: No association was found between parental smoking or drinking alcohol and risk of childhood GCT (for smoking: odds ratio [OR]=1.0, 95% confidence interval [95% CI], 0.8-1.3 and OR = 1.2, 95% CI, 0.9-1.5, for mothers and fathers, respectively; for drinking: OR=0.9, 95% CI, 0.7-1.2 and OR=1.0, 95% CI, 0.8-1.3, for mothers and fathers, respectively). No significant trend was observed for length of maternal exposure to passive smoking during the index pregnancy and GCT risk (for total subject: P=0.77; boys: P=0.52; girls: P=0.93). CONCLUSIONS: The authors found no evidence that childhood GCT was related to prenatal exposure to parental cigarette smoking, alcohol drinking, and maternal passive smoking.

Influence of smoking on maternal and neonatal serum malondialdehyde, superoxide dismutase, and glutathione peroxidase levels.
Ermis B, Ors R, Yildirim A, Tastekin A, Kardas F Akcay F.
Ann Clin Lab Sci 2004,34(4):405-9

This cohort study investigated postnatal serum malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GPx) levels in 14 active-smoking, 14 passive-smoking, and 15 non-smoking mothers and their newborns on day 7 post-partum. No significant differences were noted among the study groups with respect to MDA ($p = 0.63$) or SOD levels ($p = 0.98$) in either the mothers or their infants. However, there were significant differences among the study groups with respect to serum GPx activities in both the mothers ($p = 0.028$) and the infants ($p = 0.039$). When GPx activities were analyzed separately in both mothers and infants, a significant difference was noted only between the infants of smoking mothers and the infants of non-smoking mothers ($p = 0.015$). In conclusion, there was a significant increase in GPx activities of smoking mothers and their infants, suggesting that they may have been exposed to more oxidant stress.

Estimated risk for altered fetal growth resulting from exposure to fine particles during pregnancy: an epidemiologic prospective cohort study in Poland.
Jedrychowski W, Bendkowska I, Flak E, Penar A, Jacek R, Kaim I, Spengler JD, Camann D Perera FP.
Environ Health Perspect 2004,112(14):1398-402

The purpose of this study was to estimate exposure of pregnant women in Poland to fine particulate matter [less than or equal to 2.5 microm in diameter (PM 2.5)] and to assess its effect on the birth outcomes. The cohort consisted of 362 pregnant women who gave birth between 34 and 43 weeks of gestation. The enrollment included only nonsmoking women with singleton pregnancies, 18-35 years of age, who were free from chronic diseases such as diabetes and hypertension. PM 2.5 was measured by personal air monitoring over 48 hr during the second trimester of pregnancy. All assessed birth effects were adjusted in multiple linear regression models for potential confounding factors such as the size of mother (maternal height, prepregnancy weight), parity, sex of child, gestational age, season of birth, and self-reported environmental tobacco smoke (ETS). The regression model explained 35% of the variability in birth weight (beta = -200.8, p = 0.03), and both regression coefficients for PM 2.5 and birth length (beta = -1.44, p = 0.01) and head circumference (HC; beta = -0.73, p = 0.02) were significant as well. In all regression models, the effect of ETS was insignificant. Predicted reduction in birth weight at an increase of exposure from 10 to 50 microg/m3 was 140.3 g. The corresponding predicted reduction of birth length would be 1.0 cm, and of HC, 0.5 cm. The study provides new and convincing epidemiologic evidence that high personal exposure to fine particles is associated with adverse effects on the developing fetus. These results indicate the need to reduce ambient fine particulate concentrations. However, further research should establish possible biologic mechanisms explaining the observed relationship.

Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population.
Perra FP, Rauh V, Tsai WY, Kinney P, Camann D, Barr D, Bernert T, Garfinkel R, Tu YH, Diaz D, Dietrich J, Whyarr RM
Environ Health Perspect 2003, Feb,111(2):201-5

Inner-city, minority populations are high-risk groups for adverse birth outcomes and also are more likely to be exposed to environmental contaminants, including environmental tobacco smoke (ETS), polycyclic aromatic hydrocarbons (PAHs), and pesticides. In a sample of 263 nonsmoking African-American and Dominican women, we evaluated the effects on birth outcomes of prenatal exposure to airborne PAHs monitored during pregnancy by personal air sampling, along with ETS estimated by plasma cotinine, and an organophosphate pesticide (OP) estimated by plasma chlorpyrifos (CPF). Plasma CPF was used as a covariate because it was the most often detected in plasma and was highly correlated with other pesticides frequently detected in plasma. Among African Americans, high prenatal exposure to PAHs was associated with lower birth weight (p = 0.003) and smaller head circumference (p = 0.01) after adjusting for potential confounders. CPF was associated with decreased birth weight and birth length overall (p = 0.01 and p = 0.003, respectively) and with lower birth weight among African Americans (p = 0.04) and reduced birth length in Dominicans (p < 0.001), and was therefore included as a covariate in the model with PAH. After controlling for CPF, relationships between PAHs and

birth outcomes were essentially unchanged. In this analysis, PAHs and CPF appear to be significant independent determinants of birth outcomes. Further analyses of pesticides will be carried out. Possible explanations of the failure to find a significant effect of PAHs in the Hispanic subsample are discussed. This study provides evidence that environmental pollutants at levels currently encountered in New York City adversely affect fetal development.

The adult incidence of asthma and respiratory symptoms by passive smoking in uterus or in childhood.
Skorge TD, Eagan TM, Eide GE, Gulsvik A Bakke PS.
Am J Respir Crit Care Med 2005,172(1):61-6

The effects of pre- or postnatal passive smoking on the adult incidence of asthma have not been reported previously. Between 1985 and 1996/1997, we conducted an 11-year community cohort study on the incidence of asthma and respiratory symptoms in Western Norway. The cohort included 3,786 subjects aged 15 to 70 years, of which 2,819 were responders at both baseline and follow-up. The incidence of asthma and five respiratory symptoms by self-reported exposure to maternal smoking in utero and in childhood, as well as smoking by other household members in childhood, was examined. After adjustment for sex, age, education, hay fever, personal smoking, and occupational exposure, maternal smoking was associated with asthma, phlegm cough, chronic cough, dyspnea grade 2, attacks of dyspnea, and wheezing, with odds ratios (95% confidence intervals [CI]) of 3.0 (1.6, 5.6), 1.7 (1.1, 2.6), 1.9 (1.2, 3.0), 1.9 (1.2, 3.0), 2.0 (1.3, 3.0), and 1.4 (0.9, 2.2), respectively. The adjusted attributable fractions (95% CI) of the adult incidence of asthma were 17.3% (5.2, 27.9) caused by maternal smoking and 9.3% (95% CI, -23.2, 33.2) caused by smoking by other household members. Exposure to pre- and postnatal smoking carries a substantial risk for developing adult asthma and respiratory symptoms.

C. Studies with unclear findings

[Prematurity and low birth weight: effects of active and passive smoking during pregnancy]
Badlissi D, Guillemette A, Fadin A.
Can J Public Health 2001 Jul-Aug,92(4):272-5.

Among the risk factors inevitably associated with low birthweights and premature births, tobacco remains the factor most often cited. From 1997 to 1998, a study was conducted in a Quebec City hospital centre in order to determine the prevalence of smoking among pregnant women as well as their exposure to passive smoking at home and at work. The percentage of women who smoke before pregnancy is 40.2%, while that of women who smoke during pregnancy is 37.3%. The analysis of characteristics of pregnant women who smoke and do not smoke shows strong variations according to age, education, matrimonial status and income. The relative risk linked to smoking is 1.54 for premature birth and 2.21 for low birthweight.

[Use of prenatal health care and risk of infants born small-for-gestational-age. Preliminary results of a case-control study in the Lodz voivodeship].
Ciesla B, Hanke W, Grodzicka A, Gulczynska E, Pawlowska B Wasilewska-Wilk E.
Przegl Epidemiol 2004,58(3):537-46

It is well documented that small-for-gestational age (SGA) infants are at an increased risk of perinatal mortality and morbidity. In order to identify the major modifiable risk factors of SGA birth, a case-control study was launched in the area of Lodz voivodeship, Poland. The project was focused on the evaluation of the role of perinatal health services and avoidance of exposure to tobacco smoke in the prevention of SGA births. The study population consisted of mothers of 153 SGA infants (cases) and 93 mothers of control infants. SGA infants were identified as infants with body weight below 10th percentile for gestational age, using Ballarda scale. The controls were non-SGA infants delivered after 37 week of gestation. The infants from both groups were delivered in 26 maternity wards in the Lodz voivodeship within the period of June 1-November 1, 2003. One month after delivery, each mother of SGA and control infants was visited by an interviewer who collected information about her profile of use of perinatal health care and on active and passive exposure to tobacco smoke in pregnancy. Odds ratios and 95% confidence units (CU) were calculated using EpiInfo software developed by CDC, Atlanta, Georgia, US. Late booking for perinatal care (after 12 week of gestation) and less than 5 visits during pregnancy was found to be related to an increased risk of SGA, however, the OR values included unity. About 1/3 of mothers of SGA infants and "of the controls were served mainly by the private health sector. The use of private care was related to a lower risk of SGA: OR= 0.55 95% CI (0.31-0.96). This protective pattern was observed in the population of women aged 19-25 living in rural areas years and with only primary education. The preconception visits to obstetricians and contacts with health educators during pregnancy were also found to have some protective effect, however, the ORs were not statistically significant. The adverse effect of smoking during pregnancy was clearly confirmed in the study population, OR= 2.69 95%CI (1.37-5.33), while the role of passive smoking was difficult to assess due to the small number of nonsmoking women exposed to ETS. There are some indications that the poor use of perinatal health services may account for the elevated risk of SGA births in the Lodz voivodeship. The use of the private health sector is growing and seems to be related to a lower risk of SGA births. More effective tools to prevent maternal smoking have to be developed and implemented in routine perinatal care.

Smoking and orofacial clefts: a United Kingdom-based case-control study.
Little, J., A. Cardy, Arslan MT, Gilmour M, Mossey PA; United Kingdom-based case-control study.
Cleft Palate Craniofac J 2004,41(4):381-6.

OBJECTIVE: To investigate the association between smoking and orofacial clefts in the United Kingdom. DESIGN: Case-control study in which the mother's exposure to tobacco smoke was assessed by a structured interview. SETTING: Scotland and the Manchester and Merseyside regions of England. PARTICIPANTS: One hundred ninety children born with oral cleft between September 1, 1997, and January 31, 2000, and 248 population controls, matched with the cases on sex, date of birth, and region. MAIN OUTCOME MEASURE: Cleft lip with or without cleft palate and cleft palate. RESULTS: There was a positive association between maternal smoking

during the first trimester of pregnancy and both cleft lip with or without cleft palate (odds ratio 1.9, 95% confidence interval 1.1 to 3.1) and cleft palate (odds ratio 2.3, 95% confidence interval 1.3 to 4.1). There was evidence of a dose-response relationship for both types of cleft. An effect of passive smoking could not be excluded in mothers who did not smoke themselves. CONCLUSION: The small increased risk for cleft lip with or without cleft palate in the offspring of women who smoke during pregnancy observed in this study is in line with previous evidence. In contrast to some previous studies, an increased risk was also apparent for cleft palate. In these U.K. data, there was evidence of a dose-response effect of maternal smoking for both types of cleft. The data were compatible with a modest effect of maternal passive smoking, but the study lacked statistical power to detect or exclude such an effect with confidence. It may be useful to incorporate information on the effects of maternal smoking on oral clefts into public health campaigns on the consequences of maternal smoking.

D. Related Studies

Biomarkers in maternal and newborn blood indicate heightened fetal susceptibility to procarcinogenic DNA damage.
Perera FP, Tang D, Tu YH, Cruz LA, Borjas M, Bernert T Whyatt RM.
Environ Health Perspect 2004,112(10):1133-6

Polycyclic aromatic hydrocarbons (PAHs) such as benzo[a]pyrene (BaP) are widespread air contaminants released by transportation vehicles, power generation, and other combustion sources. Experimental evidence indicates that the developing fetus is more susceptible than the adult to carcinogenic effects of PAHs, although laboratory studies in rodents suggest that the dose to fetal tissues is an order of magnitude lower than that to maternal tissues. To assess fetal versus adult susceptibility to PAHs and environmental tobacco smoke (ETS), we compared carcinogen-DNA adducts (a biomarker associated with increased cancer risk) and cotinine (a biomarker of tobacco smoke exposure) in paired blood samples collected from mothers and newborns in New York City. We enrolled 265 nonsmoker African-American and Latina mother-newborn pairs in New York City between 1997 and 2001 (estimated average ambient air BaP concentrations < 0.5 ng/m3). Despite the estimated 10-fold lower fetal dose, mean levels of BaP-DNA adducts as determined by high-performance liquid chromatography-fluorescence were comparable in paired New York City newborn and maternal samples (0.24 adducts per 10(8) nucleotides, 45% of newborns with detectable adducts vs. 0.22 per 10(8) nucleotides, 41% of mothers with detectable adducts). However, by the Wilcoxon signed-rank test, the levels in newborns were higher ($p = 0.02$). Mean cotinine was higher in newborns than in mothers (1.7 ng/mL, 47% detectable vs. 1.28 ng/mL, 44% detectable). Consistent with our prior study in a Caucasian Polish population, these results indicate increased susceptibility of the fetus to DNA damage and reduced ability to clear ETS constituents. The findings have implications for risk assessment, given the need to protect children as a sensitive subset of the population.

II. Animal DART Studies

A. Studies reporting developmental or reproductive toxicity

Gestation stage-specific oxidative deoxyribonucleic acid damage from sidestream smoke in pregnant rats and their fetuses.
Maciag A, Bialkowska A, Espiritu I, Powell D, Alvord WG, Kasprzak KS, Anderson LM, Witschi HR
Arch Environ Health 2003, Apr,58(4):238-44

Transplacental exposure to environmental tobacco smoke (ETS) is a possible cancer risk factor in offspring. The authors exposed pregnant Sprague-Dawley rats to a relevant dose of ETS (1 mg/m3) from gestation day 4 to days 16 or 21. They then assayed tissues for levels of 8-oxo-2'-deoxyguanosine (8-oxo-dG), a marker of oxidative deoxyribonucleic acid damage. ETS exposure ending on gestation day 16 resulted in statistically significant increases in 8-oxo-dG in maternal liver and kidney and in fetal kidney. On gestation day 21, there were significant 8-oxo-dG increases in fetal liver and brain. These gestational stage- and tissue-specific increases of 1.2- to 1.4-fold are similar to the putative relative increases in risk of human cancers related to ETS.

Perinatal environmental tobacco smoke exposure in rhesus monkeys: critical periods and regional selectivity for effects on brain cell development and lipid peroxidation.
Slotkin TA, Pinkerton KE, Seidler FJ.
Environ Health Perspect. 2006 Jan;114(1):34-9.

Perinatal environmental tobacco smoke (ETS) exposure in humans elicits neurobehavioral deficits. We exposed rhesus monkeys to ETS during gestation and through 13 months postnatally, or postnatally only (6-13 months). At the conclusion of exposure, we examined cerebrocortical regions and the midbrain for cell damage markers and lipid peroxidation. For perinatal ETS, two archetypal patterns were seen in the various regions, one characterized by cell loss (reduced DNA concentration) and corresponding increases in cell size (increased protein/DNA ratio), and a second pattern suggesting replacement of larger neuronal cells with smaller and more numerous glia (increased DNA concentration, decreased protein/DNA ratio). The membrane/total protein ratio, a biomarker of neurite formation, also indicated potential damage to neuronal projections, accompanied by reactive sprouting. When ETS exposure was restricted to the postnatal period, the effects were similar in regional selectivity, direction, and magnitude. These patterns resemble the effects of prenatal nicotine exposure in rodent and primate models. Surprisingly, perinatal ETS exposure reduced the level of lipid peroxidation as assessed by the concentration of thiobarbituric acid reactive species, whereas postnatal ETS did not. The heart, a tissue that, like the brain, has high oxygen demand, displayed a similar but earlier decrease (2-3 months) in lipid peroxidation in the perinatal exposure model, whereas values were reduced at 13 months with the postnatal exposure paradigm. Our results provide a mechanistic connection between perinatal ETS exposure and neurobehavioral anomalies, reinforce the role of nicotine in these effects, and buttress the importance of restricting or eliminating ETS exposure in young children.

Prenatal environmental tobacco smoke exposure promotes adult atherogenesis and mitochondrial damage in apolipoprotein E-/-mice fed a chow diet.
Yang Z, Knight CA, Mamerow MM, Vickers K, Penn A, Postlethwait EM, Ballinger SW
Circulation 2004, Dec 14,110(24):3715-20

BACKGROUND: Environmental tobacco smoke (ETS) exposure is recognized as a cardiovascular disease risk factor; however, the impact of prenatal ETS exposure on adult atherogenesis has not been examined. We hypothesized that in utero ETS exposure promotes adult atherosclerotic lesion formation and mitochondrial damage. METHODS AND RESULTS: Atherosclerotic lesion formation, mitochondrial DNA damage, antioxidant activity, and oxidant load were determined in cardiovascular tissues from adult apolipoprotein E-/- mice exposed to either filtered air or ETS in utero and fed a standard chow diet (4.5% fat) from weaning until euthanasia. All parameters were significantly altered in male mice exposed in utero to ETS. CONCLUSIONS: These data support the hypothesis that prenatal ETS exposure is sufficient to promote adult cardiovascular disease development.