SULFUR DIOXIDE

This is a compilation of abstracts of articles identified during the preliminary toxicological evaluation of evidence on the developmental and reproductive toxicology of sulfur dioxide. Sulfur dioxide (CAS# 7446-09-5) has a variety of industrial uses including as a captive intermediate in the production of sulfuric acid, a fumigant, preservative, bleach, and steeping agent for grain in food processing; catalyst or extraction solvent in the petroleum industry; flotation depressant for sulfide ores in the mining industry; intermediate for bleach production; and reducing agent in several industrial processes. Sulfur dioxide in the air comes mainly from activities such as the burning of coal and oil at power plants or from copper smelting.

Compiled are abstracts from developmental and reproductive epidemiologic and animal toxicity studies and other relevant investigations. This information was used in a screen to select appropriate chemicals for presentation to the Developmental and Reproductive Toxicant Identification Committee as possible candidates for Committee consideration. The criterion for passing this screen is the existence of two or more analytical epidemiologic studies judged to be of adequate quality that reported increased risk of adverse developmental or reproductive outcomes. The epidemiologic studies report on developmental and reproductive sequelae related to environmental exposures to sulfur dioxide. Based on a review of abstracts of the following studies, the chemical passed the epidemiologic screen.

- Eighteen epidemiologic studies of sulfur dioxide reporting increased risk of adverse developmental or reproductive outcomes were identified, seven of which were analytical studies of adequate quality. One meeting abstract reporting increased risk of adverse developmental or reproductive outcomes was also identified. One epidemiologic study reporting no increased risk of adverse developmental or reproductive outcomes was identified, as well as one related article.

- Six animal studies of sulfur dioxide reporting reproductive or developmental toxicity were identified, as well as two studies reporting no reproductive or developmental toxicity. Four related articles were also identified.

Contents

I. Epidemiologic DART Studies

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

[*] Exposures to air pollutants during pregnancy and preterm delivery.
Leem JH, Kaplan BM, Shim YK, Pohl HR, Gotway CA, Bullard SM, Rogers JF, Smith MM, Tylenda CA.
Environ Health Perspect. 2006 Jun;114(6):905-10.

The association between preterm delivery (PTD) and exposure to air pollutants has recently become a major concern. We investigated this relationship in Incheon, Republic of Korea, using spatial and temporal modeling to better infer individual exposures. The birth cohort consisted of 52,113 singleton births in 2001-2002, and data included residential address, gestational age, sex, birth date and order, and parental age and education. We used a geographic information system and kriging methods to construct spatial and temporal exposure models. Associations between exposure and PTD were evaluated using univariate and multivariate log-binomial regressions. Given the gestational age, birth date, and the mother's residential address, we estimated each mother's potential exposure to air pollutants during critical periods of the pregnancy. The adjusted risk ratios for PTD in the highest quartiles of the first trimester exposure were 1.26 [95% confidence interval (CI), 1.11-1.44] for carbon monoxide, 1.27 (95% CI, 1.04-1.56) for particulate matter with aerodynamic diameter < or = 10 microm, 1.24 (95% CI, 1.09-1.41) for nitrogen dioxide, and 1.21 (95% CI, 1.04-1.42) for sulfur dioxide. The relationships between PTD and exposures to CO, NO2, and SO2 were dose dependent ($p < 0.001$, $p < 0.02$, $p < 0.02$, respectively) . In addition, the results of our study indicated a significant association between air pollution and PTD during the third trimester of pregnancy. In conclusion, our study showed that relatively low concentrations of air pollution under current air quality standards during pregnancy may contribute to an increased risk of PTD. A biologic mechanism through increased prostaglandin levels that are triggered by inflammatory mediators during exposure periods is discussed.

The association between low level exposures to ambient air pollution and term low birth weight: a retrospective cohort study.
Dugandzic, R., Dodds, L., Stieb, D. Smith-Doiron, M.,
Environ Health. 2006 Feb 17;5(3).

BACKGROUND: Studies in areas with relatively high levels of air pollution have found some positive associations between exposures to ambient levels of air pollution and several birth outcomes including low birth weight (LBW). The purpose of this study was to examine the association between LBW among term infants and ambient air pollution, by trimester of

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exposure, in a region of lower level exposures. METHODS: The relationship between LBW and ambient levels of particulate matter up to 10 um in diameter (PM10), sulfur dioxide (SO2) and ground-level ozone (O3) was evaluated using the Nova Scotia Atlee Perinatal Database and ambient air monitoring data from the Environment Canada National Air Pollution Surveillance Network and the Nova Scotia Department of Environment. The cohort consisted of live singleton births (> or =37 weeks of gestation) between January 1, 1988 and December 31, 2000. Maternal exposures to air pollution were assigned to women living within 25 km of a monitoring station at the time of birth. Air pollution was evaluated as a continuous and categorical variable (using quartile exposures) for each trimester and relative risks were estimated from logistic regression, adjusted for confounding variables. RESULTS: There were 74,284 women with a term, singleton birth during the study period and with exposure data. In the analyses unadjusted for year of birth, first trimester exposures in the highest quartile for SO2 and PM10 suggested an increased risk of delivering a LBW infant (relative risk = 1.36, 95% confidence interval = 1.04 to 1.78 for SO2 exposure and relative risk = 1.33, 95% confidence interval = 1.02 to 1.74 for PM10). After adjustment for birth year, the relative risks were attenuated somewhat and not statistically significant. A dose-response relationship for SO2 was noted with increasing levels of exposure. No statistically significant effects were noted for ozone. CONCLUSION: Our results suggest that exposure during the first trimester to relatively low levels of some air pollutants may be associated with a reduction in birth weight in term-born infants. These findings have implications for the development of effective risk management strategies to minimize the public health impacts for pregnant women.

[Relationship between low birthweight and air pollution in the city of Sao Paulo, Brazil].
Medeiros, A. Gouveia, N.,
Rev Saude Publica. 2005 Dec;39(6): 965-72.

OBJECTIVE: Air pollution has been investigated as a potential determinant for low birthweight. The aim of the present study was to study the effect of air pollution on birthweight. METHODS: We analyzed all deliveries by mothers living in the municipality of Sao Paulo, Southeastern Brazil, between 1998 and 2000. We estimated the prevalence of low birthweight according to newborn, mother, and delivery characteristics. Only births occurring in the most central districts of the city were analyzed, totaling 311.735 events. For the evaluation of the effects of air pollution, we excluded preterm and multiple deliveries. Pollutants analyzed were ozone (O3), sulfur dioxide (SO2), nitrogen dioxide (NO2), suspended particles (PM10), and carbon monoxide (CO). The effect of maternal exposure to air pollution on birthweight was evaluated using linear and logistic regression. RESULTS: A total of 4.6% of newborns weighed less than 2,500 g at birth. Maternal exposure to CO, PM10, and NO2 during the first trimester of pregnancy was significantly associated with decreased birthweight. CONCLUSIONS: Our results reinforce the notion that maternal exposure to air pollution during the first trimester of pregnancy may contribute to lesser weight gain in the fetus.

[*] Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997-2000.
Gilboa, S. M., Mendola, P., Olshan, A. F., Langlois, P. H., Savitz, D. A., Loomis, D., Herring, A. H. Fixler, D. E.,
Am J Epidemiol. 2005 Aug 1;162(3): 238-52.

A population-based case-control study investigated the association between maternal exposure to air pollutants, carbon monoxide, nitrogen dioxide, ozone, sulfur dioxide, and particulate matter <10 microm in aerodynamic diameter during weeks 3-8 of pregnancy and the risk of selected cardiac birth defects and oral clefts in livebirths and fetal deaths between 1997 and 2000 in seven Texas counties. Controls were frequency matched to cases on year of birth, vital status, and maternal county of residence at delivery. Stationary monitoring data were used to estimate air pollution exposure. Logistic regression models adjusted for covariates available in the vital record. When the highest quartile of exposure was compared with the lowest, the authors observed positive associations between carbon monoxide and tetralogy of Fallot (odds ratio = 2.04, 95% confidence interval: 1.26, 3.29), particulate matter <10 microm in aerodynamic diameter and isolated atrial septal defects (odds ratio = 2.27, 95% confidence interval: 1.43, 3.60), and sulfur dioxide and isolated ventricular septal defects (odds ratio = 2.16, 95% confidence interval: 1.51, 3.09). There were inverse associations between carbon monoxide and isolated atrial septal defects and between ozone and isolated ventricular septal defects. Evidence that air pollution exposure influences the risk of oral clefts was limited. Suggestive results support a previously reported finding of an association between ozone exposure and pulmonary artery and valve defects.

A time-series analysis of air pollution and preterm birth in Pennsylvania, 1997-2001.
Sagiv, S. K., Mendola, P., Loomis, D., Herring, A. H., Neas, L. M., Savitz, D. A. Poole, C.,
Environ Health Perspect. 2005 May;113(5): 602-6.

Preterm delivery can lead to serious infant health outcomes, including death and lifelong disability. Small increases in preterm delivery risk in relation to spatial gradients of air pollution have been reported, but previous studies may have controlled inadequately for individual factors. Using a time-series analysis, which eliminates potential confounding by individual risk factors that do not change over short periods of time, we investigated the effect of ambient outdoor particulate matter with diameter < or = 10 microm (PM10) and sulfur dioxide on risk for preterm delivery. Daily counts of preterm births were obtained from birth records in four Pennsylvania counties from 1997 through 2001. We observed increased risk for preterm delivery with exposure to average PM10 and SO2 in the 6 weeks before birth [respectively, relative risk (RR) = 1.07; 95% confidence interval (CI), 0.98-1.18 per 50 microg/m3 increase; RR = 1.15; 95% CI, 1.00-1. 32 per 15 ppb increase], adjusting for long-term preterm delivery trends, co-pollutants, and offsetting by the number of gestations at risk. We also examined lags up to 7 days before the birth and found an acute effect of exposure to PM10 2 days and 5 days before birth (respectively,

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RR = 1.10; 95% CI, 1.00-1.21; RR = 1.07; 95% CI, 0.98-1.18) and SO2 3 days before birth (RR = 1.07; 95% CI, 0.99-1.15), adjusting for covariates, including temperature, dew point temperature, and day of the week. The results from this time-series analysis, which provides evidence of an increase in preterm birth risk with exposure to PM10 and SO2, are consistent with prior investigations of spatial contrasts.

[*] **First two months of pregnancy--critical time for preterm delivery and low birthweight caused by adverse effects of coal combustion toxics.**
Mohorovic, L.,
Early Hum Dev. 2004 Nov;80(2): 115-23.

OBJECTIVE: The objective of this study was to define the most critical gestation period for adverse effects of environmental toxics in terms of preterm delivery (<37 weeks) and low birthweight (<2500 g) in humans. STUDY DESIGN: From January 1, 1987 to December 31, 1989, 704 women were included in a retrospective epidemiological study. All were from the district of Labin and lived in the vicinity of a coal power plant Plomin 1, Croatia. This plant is the single large source of air pollution in the area. The coal used for fuel is extremely rich with sulfur, 9-11%. Daily, weekly, and monthly consumption of coal and related SO2 emissions were calculated for each pregnant woman from the beginning to the end of pregnancy. RESULTS: We found that a greater and longer exposure to SO2 emissions during the initial two months of pregnancy resulted in a significantly shorter gestation (end of the first month: -0.0914, p=0.008, end of the second month: -0.0806, p=0.016) and in lower body mass of a newborn (end of the first month: -0.0807, p=0.016, end of the second month -0.0733, p=0.026). CONCLUSION: The results of this study confirm the role of inhaled environmental toxics in the early development of human embryo and in adverse pregnancy course caused by permanent oxidative stress, misbalanced production of reactive oxygen species (ROS), reactive nitrogen species (RNS), reactive sulfur species (RSS), and other unfavorable metabolic processes on early embryogenesis, resulting in growth-arrested cells.

[*] **Association between maternal exposure to elevated ambient sulfur dioxide during pregnancy and term low birth weight.**
Lin, C. M.; Li, C. Y.; Yang, G. Y., and Mao, I. F.
Environ Res. 2004 Sep; 96(1):41-50.

This retrospective cohort study investigated whether the risk of delivering full term (37-44 completed weeks of gestation) low birth weight (LBW) infants is associated with differences in exposure to air pollutants in different trimesters. Full-term infants (37 completed weeks of gestation) with a birth weight below 2500 g were classified as term LBW infants. The study

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infants comprised 92,288 full-term live singletons identified from the Taiwan birth registry and born in the city of Taipei or Kaoshiung in Taiwan between 1995 and 1997. Maternal exposures to various air pollutants including CO, SO_2, O_3, NO_2, and PM10 in each trimester of pregnancy was estimated as the arithmetic means of all daily measurements taken by the air quality monitoring station nearest to the district of residence of the mother at birth. The multivariable logistic regression model with adjustment for potential confounders was used to assess the independent effect of specific air pollutants on the risk of term LBW. This study suggested a 26% increase in term LBW risk given maternal ambient exposure to SO_2 concentration exceeding 11.4 ppb during pregnancy compared to low exposure (<7.1 ppb) (OR=1.26, 95% CI=1.04-1.53). Since the relative risk of term LBW was reassessed according to exposure level in each trimester, mothers exposed to >12.4 ppb of SO_2 in the last trimester showed 20% higher risk (OR=1.20, 95% CI=1.01-1.41) of term LBW delivery than mothers with lower exposure (<6.8 ppb). No significant elevation ORs was observed for other air pollutants.

Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada.
Liu, S.; Krewski, D.; Shi, Y.; Chen, Y., and Burnett, R. T.
Environ Health Perspect. 2003 Nov; 111(14):1773-8.

The association between ambient air pollution and adverse health effects, such as emergency room visits, hospitalizations, and mortality from respiratory and cardiovascular diseases, has been studied extensively in many countries, including Canada. Recently, studies conducted in China, the Czech Republic, and the United States have related ambient air pollution to adverse pregnancy outcomes. In this study, we examined association between preterm birth, low birth weight, and intrauterine growth retardation (IUGR) among singleton live births and ambient concentrations of sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone in Vancouver, Canada, for 1985-1998. Multiple logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for such effects. Low birth weight was associated with exposure to SO_2 during the first month of pregnancy (OR = 1.11, 95% CI, 1.01-1.22, for a 5.0 ppb increase). Preterm birth was associated with exposure to SO_2 (OR = 1.09, 95% CI, 1.01-1.19, for a 5.0 ppb increase) and to CO (OR = 1.08, 95% CI, 1.01-1.15, for a 1.0 ppm increase) during the last month of pregnancy. IUGR was associated with exposure to SO_2 (OR = 1.07, 95% CI, 1.01-1.13, for a 5.0 ppb increase), to NO2 (OR = 1.05, 95% CI, 1.01-1.10, for a 10.0 ppb increase), and to CO (OR = 1.06, 95% CI, 1.01-1.10, for a 1.0 ppm increase) during the first month of pregnancy. In conclusion, relatively low concentrations of gaseous air pollutants are associated with adverse effects on birth outcomes in populations experiencing diverse air pollution profiles.

Effects of air pollution on birth weight among children born between 1995 and 1997 in Kaohsiung, Taiwan.
Yang, C. Y.; Tseng, Y. T., and Chang, C. C.
J Toxicol Environ Health A. 2003 May 9; 66(9):807-16.

Recent studies have suggested that exposure to air pollution might be associated with low birth weight. The effects of sulfur dioxide (SO(2)) and particulate matter less than 10 microm (PM(10)) were examined on birth weight in each trimester of pregnancy. The study group included all full-term singleton live births during 1995-1997 to women living within about 2 km of an air pollution monitoring site in Kaohsiung. Measurements of SO(2) and PM(10) collected at six air quality monitoring stations were used to estimate the influence of exposures on different pregnancy trimesters. This was done by averaging daily ambient air pollution concentrations during the corresponding days based on the birth date and gestational age of each child. Multiple linear regression analysis was used to estimate the effects of air pollution on birth weight adjusting for possible confounders including maternal age, season, marital status, maternal education, and infant gender. The estimated reduction in birth weight was 0.52 g for 1 microg/m (3) increase in either SO(2) or PM(10) in the first trimester of pregnancy. Data provide further support for the hypothesis that air pollution can affect the outcome of pregnancy.

Exposure to air pollution during different gestational phases contributes to risks of low birth weight.
Lee, B. E., Ha, E. H., Park, H. S., Kim, Y. J., Hong, Y. C., Kim, H. Lee, J. T.,
Hum Reprod. 2003 Mar;18(3): 638-43.

BACKGROUND: Although there have been growing concerns about the adverse effects of air pollution on birth outcomes, little is known about which specific exposure times of specific pollutants contribute to low birth weight (LBW). METHODS: We evaluated the relationships between LBW and air pollution exposure levels in Seoul, Korea. Using the air pollution data, we estimated the exposure during each trimester and also during each month of pregnancy on the basis of the gestational age and birth date of each newborn. Generalized additive logistic regression analyses were conducted considering infant sex, birth order, maternal age, parental education level, time trend, and gestational age. RESULTS: The monthly analyses suggested that the risks for LBW tended to increase with carbon monoxide (CO) exposure between months 2-5 of pregnancy, with exposure to particles <10 micro m (PM(10)) in months 2 and 4, and for sulphur dioxide (SO(2)) and nitrogen dioxide (NO(2)) exposure between months 3-5. CONCLUSIONS: This study suggests that exposure to CO, PM(10,) SO(2) and NO(2) during early to mid pregnancy contribute to risks for LBW.

Is air pollution a risk factor for low birth weight in Seoul?
Ha, E. H.; Hong, Y. C.; Lee, B. E.; Woo, B. H.; Schwartz, J., and Christiani, D. C.
Epidemiology. 2001 Nov; 12(6):643-8.

Environmental factors contributing to reduced birth weight are of great concern because of the well-known relation of birth weight to infant mortality and adverse effects in later life. We examined the associations between air pollution exposures during pregnancy and low birth weight among all full-term births (gestational age 37-44 weeks) for a 2-year period (January 1996 through December 1997) in Seoul, South Korea. We evaluated these associations with a generalized additive logistic regression adjusting for gestational age, maternal age, parental educational level, parity, and infant sex. We used smoothing plots with generalized additive models to analyze the exposure-response relation for each air pollutant. The adjusted relative risk of low birth weight was 1.08 [95% confidence interval (CI) = 1.04-1.12] for each interquartile increase for carbon monoxide concentrations during the first trimester of pregnancy. The relative risks were 1.07 (95% CI = 1.03-1.11) for nitrogen dioxide, 1.06 (95% CI = 1.02-1.10) for sulfur dioxide, and 1.04 (95% CI = 1.00-1.08) for total suspended particles also for interquartile increase in exposure. Carbon monoxide, nitrogen dioxide, sulfur dioxide, and total suspended particle concentrations in the first trimester of pregnancy period are risk factors for low birth weight.

Relation between ambient air pollution and low birth weight in the Northeastern United States.
Maisonet, M.; Bush, T. J.; Correa, A., and Jaakkola, J. J.
Environ Health Perspect. 2001 Jun; 109 Suppl 3:351-6.

We evaluated the relation between term low birth weight (LBW) and ambient air levels of carbon monoxide (CO), particulate matter up to 10 microm in diameter (PM(10)), and sulfur dioxide (SO(2)). The study population consisted of singleton, term live births (37-44 weeks of gestation) born between 1 January 1994 and 31 December 1996 in six northeastern cities of the United States: Boston, Massachusetts; Hartford, Connecticut; Philadelphia, Pennsylvania; Pittsburgh, Pennsylvania; Springfield, Massachusetts; and Washington, DC. Birth data were obtained from National Center for Health Statistics Natality Data Sets. Infants with a birth weight < 2,500 g were classified as LBW. Air monitoring data obtained from the U.S. Environmental Protection Agency were used to estimate average trimester exposures to ambient CO, PM(10), and SO(2). Our results suggest that exposures to ambient CO and SO(2) increase the risk for term LBW. This risk increased by a unit increase in CO third trimester average concentration [adjusted odds ratio (AOR) 1.31; 95% confidence interval (CI) 1.06,1.62]. Infants with SO(2) second trimester exposures falling within the 25 and < 50th (AOR 1.21; CI 1.07,1.37), the 50 to < 75th (AOR 1.20; CI 1.08,1.35), and the 75 to < 95th (AOR 1.21; CI 1.03,1.43) percentiles were also at increased risk for term LBW when compared to those in the reference category (< 25th percentile). There was no indication of a positive association between prenatal exposures to PM(10) and term LBW. Increased ambient levels of air pollution may be associated with an increased risk for LBW.

Fecundability and parental exposure to ambient sulfur dioxide
Dejmek, J.; Jelinek, R.; Solansky', I.; Benes, I., and Sram, R. J.
Environ Health Perspect. 2000 Jul; 108(7):647-54.

Recently it has been observed that birth rates in Teplice, a highly polluted district in Northern Bohemia, have been reduced during periods when sulfur dioxide levels were high. This study, which is based on data from 2,585 parental pairs in the same region, describes an analysis of the impact of SO(2) on fecundability in the first unprotected menstrual cycle (FUMC). We obtained detailed personal data, including time-to-pregnancy information, via maternal questionnaires at delivery. We estimated individual exposures to SO(2) in each of the 4 months before conception on the basis of continual central monitoring. Three concentration intervals were introduced: < 40 microg/m(3)(reference level); 40-80 microg/m(3); and [greater than or equal to] 80 microg/m(3). We estimated adjusted odds ratios (AORs) of conception in the FUMC using logistic regression models. Many variables were screened for confounding. AORs for conception in the FUMC were consistently reduced only for couples exposed in the second month before conception to SO(2) levels as follows: 40-80 microg/m(3), AOR 0.57 [95% confidence interval (CI), 0.37-0.88; $p < 0.011$]; [greater than or equal to] 80 microg/m(3), AOR 0.49 (CI, 0.29-0.81; $p < 0.006$). The association was weaker in the second 2 years of the study, probably due to the gradual decrease of SO(2) levels in the region. The relationship between SO(2) and fecundability was greater in couples living close to the central monitoring station (within 3.5 km). The timing of these effects is consistent with the period of sperm maturation. This is in agreement with recent findings; sperm abnormalities originating during spermatid maturation were found in young men from Teplice region who were exposed to the increased levels of ambient SO(2). Alternative explanations of our results are also possible.

[*] Association of very low birth weight with exposures to environmental sulfur dioxide and total suspended particulates.
Rogers, J. F.; Thompson, S. J.; Addy, C. L.; McKeown, R. E.; Cowen, D. J., and Decoufle, P.
Am J Epidemiol. 2000 Mar 15; 151(6):602-13.

This paper presents results of a population-based case-control study of the association between maternal exposures to environmental sulfur dioxide and total suspended particulates (TSP) and risk for having a very low birth weight (VLBW) baby, i.e., one weighing less than 1,500 g at birth. The study, which took place between April 1, 1986 and March 30, 1988, comprised 143 mothers of VLBW babies and 202 mothers of babies weighing 2,500 g or more living in Georgia Health Care District 9. Environmental exposure estimates (microg/m3) were obtained through environmental transport modeling that allowed us to assign environmental sulfur dioxide and TSP exposure estimates at the birth home of each study subject. Exposures less than or equal to 9.94 microg/m3, the median of TSP and sulfur dioxide exposures for the controls, were considered as referent exposures. Exposures to atmospheric TSP and sulfur dioxide above the

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95th percentile (56.75 microg/m3) yielded an adjusted odds ratio of 2.88 (95% confidence interval (CI): 1.16, 7.13), that from above the 75th to the 95th percentile (25.18-56.75 microg/m3) yielded an adjusted odds ratio of 1.27 (95% CI: 0.68, 2.37), and that from above the median (9.94 microg/m3) to the 75th percentile, an adjusted odds ratio of 0.99 (95% CI: 0.51, 1.72). The trend demonstrated in these adjusted estimates suggests an association between VLBW and maternal exposures to high levels of air pollution.

Outdoor air pollution, low birth weight, and prematurity.
Bobak, M.
Environ Health Perspect. 2000 Feb; 108(2):173-6.

This study tested the hypothesis, suggested by several recent reports, that air pollution may increase the risk of adverse birth outcomes. This study analyzed all singleton live births registered by the Czech national birth register in 1991 in 67 districts where at least one pollutant was monitored in 1990-1991 (n = 108,173). Maternal exposures to sulfur dioxide (SO(2)), total suspended particles (TSP), and nitrous oxides (NO(x)) in each trimester of pregnancy were estimated as the arithmetic means of all daily measurements taken by all monitors in the district of birth of each infant. Odds ratios of low birth weight (< 2,500 g), prematurity (< 37 weeks of gestation), and intrauterine growth retardation (IUGR; < 10th percentile of birth weight for gestational age and sex) were estimated by robust logistic regression. The median (and 25th and 75th percentile) trimester exposures were 32 (18, 56) microg/m(3) for SO(2); 72 (55, 87) microg/m(3) for TSP; and 38 (23, 59) microg/m(3) for NO(x). Low birth weight (prevalence 5.2%) and prematurity (prevalence 4.8%) were associated with SO(2) and somewhat less strongly with TSP. IUGR was not associated with any pollutant. The effects on low birth weight and prematurity were marginally stronger for exposures in the first trimester, and were not attenuated at all by adjustment for socioeconomic factors or the month of birth. Adjusted odds ratios of low birth weight were 1.20 [95% confidence interval (CI), 1.11-1.30] and 1.15 (CI, 1.07-1.24) for a 50 microg/m(3) increase in SO(2) and TSP, respectively, in the first trimester; adjusted odds ratios of prematurity were 1.27 (CI, 1.16-1.39) and 1.18 (CI, 1.05-1.31) for a 50 microg/m(3) increase in SO(2) and TSP, respectively, in the first trimester. Low gestational age accounted for the association between SO(2) and low birth weight. These findings provide further support for the hypothesis that air pollution can affect the outcome of pregnancy.

Pregnancy outcomes and outdoor air pollution: an ecological study in districts of the Czech Republic 1986-8.
Bobak, M. Leon, D. A.,
Occup Environ Med. 1999 Aug;56(8): 539-43.

OBJECTIVES: Outdoor air pollution has consistently been shown to predict mortality. The finding that this association is stronger in infants than in children or adults raises the question whether air pollution could also be related to pregnancy outcomes--such as birthweight and stillbirth. The association between outdoor air pollution and stillbirths and low birthweight in the

Czech Republic, where air pollution was high, was examined. METHODS: An ecological study was conducted, with routinely collected data on stillbirths and low birthweight (< 2500 g), air pollution (total suspended particulates, sulphur dioxide (SO2), and nitrogen oxides (NOx)), and socioeconomic factors (mean income, car ownership, divorce rate, etc). The analyses were restricted to 45 districts on which data on air pollution were available for the period 1986-8. The effects of exposure variables on frequency of pregnancy outcomes were estimated by logistic regression with district-years as the units of analysis. RESULTS: Stillbirth rate (4.2/1000 births in monitored districts) was not significantly associated with any indicator of air pollution, and was weakly related to mean income and proportion of births outside marriage. Crude prevalence of low birthweight (prevalence 5.5%) showed highly significant associations with several socioeconomic factors; after controlling for these, odds ratios (ORs)/50 micrograms/m3 increase in pollutant were: 1.04 (95% confidence interval (95% CI) 0.96 to 1.12) for total suspended particles, 1.10 (1.02 to 1.17) for SO2, and 1.07 (0.98 to 1.16) for NOx. When all pollutants were included in one model, SO2 remained related to low birthweight (OR 1.10 (1.01 to 1.20), p = 0.033). CONCLUSION: These results are consistent with a recent study in China where birthweight was also associated with total suspended particles and SO2 but ecological studies must be interpreted cautiously. Residual confounding by socioeconomic factors cannot be ruled out. The association between air pollution and birthweight requires further investigation.

***Association between air pollution and low birth weight: a community-based study.**
Wang, X.; Ding, H.; Ryan, L., and Xu, X.
Environ Health Perspect. 1997 May; 105(5):514-20.

The relationship between maternal exposure to air pollution during periods of pregnancy (entire and specific periods) and birth weight was investigated in a well-defined cohort. Between 1988 and 1991, all pregnant women living in four residential areas of Beijing were registered and followed from early pregnancy until delivery. Information on individual mothers and infants was collected. Daily air pollution data were obtained independently. The sample for analysis included 74,671 first-parity live births were gestational age 37-44 weeks. Multiple linear regression and logistic regression were used to estimate the effects of air pollution on birth weight and low birth weight (< 2,500 g), adjusting for gestational age, residence, year of birth, maternal age, and infant gender. There was a significant exposure-response relationship between maternal exposures to sulfur dioxide (SO2) and total suspended particles (TSP) during the third trimester of pregnancy and infant birth weight. The adjusted odds ratio for low birth weight was 1.11 (95% CI, 1.06-1.16) for each 100 micrograms/m3 increase in SO_2 and 1.10 (95% CI, 1.05-1.14) for each 100 micrograms/m3 increase in TSP. The estimated reduction in birth weight was 7.3 g and 6.9 g for each 100 micrograms/m3 increase in SO_2 and in TSP, respectively. The birth weight distribution of the high-exposure group was more skewed toward the left tail (i.e., with higher proportion of births < 2,500 g) than that of the low-exposure group. Although the effects of other unmeasured risk factors cannot be excluded with certainty, our data suggests that TSP and SO_2,

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or a more complex pollution mixture associated with these pollutants, contribute to an excess risk of low birth weight in the Beijing population.

***Acute effects of total suspended particles and sulfur dioxides on preterm delivery: a community-based cohort study.**
Xu X, Ding H, Wang X.
Arch Environ Health. 1995 Nov-Dec;50(6):407-15.

The acute effects of air pollution on preterm delivery were examined in a prospective cohort in Beijing, China. From early pregnancy until delivery in 1988, we followed all registered pregnant women who lived in four residential areas of Beijing. Information for both mothers and infants was collected. Daily air pollution and meteorological data were obtained independently. The sample for analysis included 25,370 resident women who gave first live births in 1988. Multiple linear regression and logistic regression were used to estimate the effects of air pollution on gestational age and preterm delivery (i.e., < 37 wk), with adjustment for outdoor temperature and humidity, day of the week, season, maternal age, gender of child, and residential area. Very high concentrations of ambient sulfur dioxide (mean = 102 micrograms/m3, maximum = 630 micrograms/m3) and total suspended particulates (mean = 375 micrograms/m3, maximum = 1 0003 micrograms/m3) were observed in these areas. There was a significant dose-dependent association between gestational age and sulfur dioxide and total suspended particulate concentrations. The estimated reduced duration of gestation was 0.075 wk (12.6h) and 0.042 wk (7.1 h) for each 100-micrograms/m3 increase in sulfur dioxide and total suspended particulates 7-d lagged moving average, respectively. The adjusted odds ratio for preterm delivery was 1.21 (95% CI = 1.01-1.46) for each in micrograms/m3 increase in sulfur dioxide, and was 1.10 (95% CI = 1.01-1.20) for each 100-micrograms/m3 increase in total suspended particulates. In addition, the gestational age distribution of high-pollution days was more skewed toward the left tail (i.e., very preterm and preterm), compared with low-pollution days. We concluded that high levels of total suspended particulates and sulfur dioxide, or of a more complex pollution mixture associated with these pollutants, appear to contribute to excess risk of preterm delivery in this population. Further work need to be carried out, with more detailed information on personal exposure and effect modifiers.

* denotes that, from review of the abstract, the study is considered to have met the criteria for evidence of an adverse developmental or reproductive effect associated with exposure to the chemical.

B. Meeting abstracts reporting increased risk of adverse developmental or reproductive outcomes

A Time Series Analysis Of Air Pollution And Preterm Birth In Pennsylvania, 1997-2001.
Herring, A.; Neas, L.; Savitz, D.; Poole, C.; Sagiv, S.; Mendola, P., and Loomis, D.
Epidemiology. 2004 Jul; 15(4):S53; ISSN: 1044-3983.

Introduction: Small increases in risk for preterm delivery in relation to air pollution have been reported, but prior investigations may have inadequately controlled for individual factors, such as maternal smoking. To eliminate confounding by known and unknown individual risk factors that do not vary over short periods of time, we conducted a times-series analysis to investigate the effect of ambient outdoor particulate matter with diameter of 10 micrometers or less (PM10) and sulfur dioxide (SO_2) on risk for preterm delivery. Methods: Daily counts of preterm births were obtained from birth records in four Pennsylvania counties (Allegheny, Beaver, Lackawanna and Philadelphia) between January 1, 1997 and December 31, 2001. PM10 and SO_2 levels were averaged over a six-week window directly preceding birth. Full, adjusted models controlled for long-term seasonal trends, co-pollutants (nitrogen dioxide, carbon monoxide and SO_2 in the PM10 analysis/PM10 in the SO_2 analysis), and were offset by the number of live births in the population. Long-term seasonal trends were adjusted using county-specific parametric splines and county-level information was incorporated using a mixed model with a random intercept. Results: Of 187,997 singleton births, 21,450 (11.4%) were born preterm. Mean six-week air pollution for the four counties ranged from 8.67 to 68.85 ug/m3 for PM10 and from 0.79 to 17.02 parts per billion (ppb) for SO_2. In full, adjusted models, we observed approximately 1 excess preterm birth for every 100 births exposed to a 50 ug/m3 increase in PM10 (Risk Ratio=1.09; 95% CI: 1.01, 1.19) and 2 excess preterm birth for every 100 births exposed to a 15 ppb SO2 increase (RR =1.20%, 95% CI: 1.04, 1.39). Discussion: These findings provide evidence of small absolute increases in preterm birth risk with exposure to both PM10 and SO_2 in the six weeks preceding birth. Results from this time-series analysis of air pollution and preterm delivery are consistent with prior investigations using conventional analyses. This suggests that confounding at the individual level is probably not explaining the observed association between air pollution and preterm delivery. Further analyses are planned to disentangle the effects of PM10 and SO_2 and to investigate a possible acute effect of these pollutants in the seven days preceding birth.

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

Community study of spontaneous abortions: relation to occupation and air pollution by sulfur dioxide, hydrogen sulfide, and carbon disulfide.
Hemminki K, Niemi ML.
Int Arch Occup Environ Health. 1982;51(1):55-63.

Spontaneous abortions were analyzed in an industrial community in Finland in relation to the

occupation of women and their husbands, and to the level of air pollution in the family's residential area. Information on abortions and births was obtained from the hospital discharge register; information on the women and their families was obtained from the files of the population and housing census. Women who were employed in rayon textile jobs and paper products jobs had an increased rate (P less than 0.10) of spontaneous abortions; the wives of men employed in transport and communication, in rayon textile jobs, and in chemical process jobs also had an increased rate of spontaneous abortions. In material stratified for age, parity, and socioeconomic class no evidence was found that the level of sulfur dioxide or carbon disulfide could be associated with a risk of spontaneous abortions. More spontaneous abortions were noted in all socioeconomic classes in areas where the mean annual level of hydrogen sulfide exceeded 4 micrograms m-3. However, the difference (total rates 7.6 and 9.3, respectively) was not significant statistically.

D. Related articles

The level of maternal methemoglobin during pregnancy in an air-polluted environment.
Mohorovic, L.
Environ Health Perspect. 2003 Dec; 111(16):1902-5.

The objective of this prospective study was to determine if a correlation could be established between the ground-level concentrations of sulfur dioxide and methemoglobin concentrations in pregnant women when a coal-powered thermoelectric power plant was in operation ("dirty" period) and when it was closed ("clean" period). The location of the power plant, Plomin 1, in Labin, Croatia, was taken into consideration. Blood and urine samples of each pregnant woman in the study were tested three times in the clean period (n = 138) and three times in the dirty period (n = 122), with 1 month between each test. I observed a correlation between the increase in mean values of methemoglobin and the ground-level concentration of SO(2) on corresponding dates during the dirty period (r = 0.72, p < 0.01). In the clean period, the negative mean value of methemoglobin was significant (r = -0.60, p <or=0.05), whereas in the dirty period, the positive mean value of methemoglobin was significant (r = 0.73, p 0.01). The increase of maternal methemoglobin could be a useful biomarker to determine when the health of pregnant women is threatened by toxic substances in the environment.

II. Animal DART Studies

A. Studies reporting developmental or reproductive toxicity

[Study of toxicity on male reproductive system of mice induced by SO2 inhalation]
Zhang B; Liu CY; Meng ZQ
Wei Sheng Yan Jiu. 2005, Mar; 34(2):167-9. [Wei sheng yan jiu = Journal of hygiene research] [Chinese]

OBJECTIVE: In this paper, toxicity of SO2 on male reproductive system of mice was studied. METHODS: 40 mice were divided to 4 groups (10/group): a group for control, the other 3 groups for SO2 inhalation (28, 56, 112mg/m3), 4h/d, 7d. RESULTS: The activities of GST and G-6-PD, as well as the content of GSH decreased significantly with SO2 increased. The content of MDA increased evidently with SO2 increased. CONCLUSION: SO2 can influence GSH oxidation-deoxidation system and cause DNA damage in male reproductive system of mice.

Prenatal sulfur dioxide exposure induces changes in the behavior of adult male mice during agonistic encounters.
Fiore M; Petruzzi, S; Dell'Omo, G, and Alleva, E.
Neurotoxicol Teratol. 1998; 20(5):543-8.

Sulfur dioxide (SO2) is one of the most important pollutants of the western countries, responsible for several cardiopulmonary diseases in humans. SO2 affects both young and adult people, causing low work productivity with social and economical costs extremely high for the communities. To test whether or not SO2 produces changes in social and/or agonistic behavior of laboratory animals, outbred CD-1 male mice were prenatally exposed to different SO2 concentrations (0, 5, 12, or 30 ppm) up to pregnancy day 14. At adulthood, following a 4-week isolation period, they underwent an aggressive encounter with CD-1 male opponents of the same age, body weight, and isolation condition (single 20-min session). The levels of several responses such as tail rattling, freezing, and defensive postures were reduced by the treatment, particularly during the initial period of the agonistic encounter, whereas offensive and attack behaviors were not significantly modified. In addition, rearing and social investigation increased. Overall, the present results indicate that prenatal SO2 exposure can alter mouse social/agonistic behavior, apparently acting on the approach phase toward the opponent and suggestive of changes in the animals' capability to cope with threatening dangerous situations.

Neonatal development altered by maternal sulfur dioxide exposure.
Singh J.
Neurotoxicology. 1989; 10(3):523-7.

Sulfur dioxide (SO2) is one of the commonly encountered environmental contaminants.

Experiments were carried out to test for neonatal behavioral alterations associated with maternal SO2 exposure. Pregnant CD-I mice were exposed to 0, 32, or 65 PPM SO2 in environmental chambers from gestation day 7 to 18 (plug = day 1). The SO2 air flow was set at 500 ml/min. Food and water were available at all times. The dams were allowed to deliver and neonatal behavioral development of the pups was studied. Maternal SO2 exposure did not affect the mean number of live pups born/litter; however, the exposure at the high level significantly decreased the mean pup weight on day 1 of birth. SO2 exposure at both levels significantly increased the time required for the righting reflex on day 1 of birth and negative geotaxis on day 10 of birth. The SO2 exposure did not affect the aerial righting score of the pups on day 12 of birth. The data suggest that maternal SO2 exposure can affect the neuromuscular coordination and may produce deficits in the functional capability of the developing offspring. The functional deficits appear to be associated with the birth weight of the offspring.

Embryotoxicity of inhaled sulfur dioxide and carbon monoxide in mice and rabbits.
Murray F J; Schwetz B A; Crawford A A; Henck J W; Quast J F, and Staples R E.
J Environ Sci Health C. 1979; 13(3):233-50.

The embryotoxic and teratogenic potential of sulfur dioxide (SO2) was evaluated in CF-1 and New Zealand rabbits exposed to SO2 alone or in combination with carbon monoxide (CO). The animals inhaled filtered room air (controls), SO2 (mice, 25 ppm; rabbits, 70 ppm), or SO2 plus CO (250 ppm) for 7 hr/day from days 6 through 15 (mice) and from days 6 through 18 (rabbits) of gestation. In both species, inhalation of SO2 resulted in slight toxicity in the dams and an increased incidence of minor skeletal variants among their offspring; exposure to the combination did not potentiate the increased incidence of these variants. A teratogenic effect was not discerned in either mice or rabbits exposed to SO2 alone or in combination with carbon monoxide, but the fetuses of mice exposed to the combination were significantly smaller than those exposed only to SO2.

[Effect of low concentrations of sulfur and nitrogen dioxides on the estrual cycle and reproductive functions of experimental animals] [translated from Russian].
Shalamberidze O P. and Tsereteli N T.
Hyg Sanit. 1971; 36(7-9):178-182. [Translated from Gig Sanit 1971; 36(8):13-17]

(Conclusions) 1. Long-term exposure to low concentrations of sulfur and nitrogen dioxides, separately or in combination, produced disturbances in the estrual cycle, manifesting themselves in a prolongation and in a diminished number of normal and total cycles. 2. Exposure to these gases, separately or together, for 3 months affected the reproductive functions of albino rats, resulting in lower fertility and a reduced weight of fetuses.

[On the detrimental effect of carbon monoxide and sulfur dioxide on the fertility of female rats] [Translated from Russian].
Mamatsashvili M I.
Hyg Sanit. 1970; 35(4-6):277-279. [Translated from Gig Sanit 1970;35(5):100-101]

(Concluding paragraphs) Thus, SO2 and CO have a detrimental effect on the estral cycle and fertility of animals and a stimulating influence on the endocrine system.
The strongest effect was produced by a mixture of high concentrations of CO and SO2.
The approved mean diurnal maximum permissible concentration of CO2 in outdoor air (1 mg/m3) was not without effects on the experimental animals. The revision of this standard, however, will need further investigation.

B. Studies reporting no developmental or reproductive toxicity

Behavioural disturbances in adult CD-1 mice and absence of effects on their offspring upon SO2 exposure.
Petruzzi S; Dell'Omo G; Fiore M; Chiarotti F; Bignami G, and Alleva E.
Arch Toxicol. 1996; 70(11):757-66.

Adult male and female CD-1 mice were exposed to different SO2 concentrations (0,5,12, or 30 ppm) for 24 days, from 9 days before the formation of breeding pairs to pregnancy day 12-14. This exposure was near-continuous, covering about 80% of the total time indicated. The offspring of exposed dams were cross-fostered shortly after birth to dams not previously exposed. Videorecordings of the adult subjects' activities during the first hour after the start of exposure showed marked, acute transient behavioural effects such as increase of rearing and social interactions, which were more pronounced in males than in females. Subsequent activity tests on exposure days 3, 6, and 9 showed subacute effects including a dose-dependent decrease of grooming and an increase of digging as well as changes in chamber crossing and wall-rearing which were not dose-dependent; most of these effects were more pronounced in females than in males. Food and water consumption and body weight declined in a dose-dependent fashion only after the formation of breeding pairs, when consummatory responses were enhanced in the controls. Reproductive performance as well as postnatal somatic and neurobehavioural development of the offspring (the latter assessed by an observational test battery including eight reflexes and responses) were not affected by SO2. Passive avoidance acquisition and retention at the young adult stage (60 days) and response changes produced by repeated apparatus exposure in non-reinforced animals (habituation) were similarly unaffected. Overall, the data indicate that SO2 produces transient, acute behavioural disturbances and more subtle subacute response changes in adult mice which may be due, at least partly, to a functional interference with olfactory modulation of mouse behaviour. The absence of effects on reproductive performance and neurobehavioural development of the offspring suggests that the risk to the developing organism from gestational SO2 exposure is low.

Teratological evaluation of sulfur dioxide.
Singh J.
Inst Environ Sci Proc. 1982; 28:144-145.

Sulphur dioxide is a common air pollutant gas. Experiments were carried out to evaluate the teratogenicity of sulphur dioxide in mice. Pregnant animals were exposed to 0, 32, 65, 125 and 250 ppm of sulphur dioxide gas from gestation day 7-17. The animals were housed in plexiglass environmental chambers. The environmental chambers were equipped with an airtight see through door and to gascock openings at diagonal ends for quick flushing with gases. The concentrations of the gas was frequently monitored by Beckman Infrared Analyser Model 865. The gas mixture cylinders were obtained from union carbide and the cylinder were equipped with two stage regulators and micrometers. The animals were sacrificed on gestation day 18 and fetuses were studied for any tetratological effects. A careful examination of the fetuses revealed that exposure to sulphur dioxide gas did not produce any significant effect on the number of dead or resorbed fetuses and the live pups did not show any significant teratological changes. However, a significant number of the fetuses had general hematomas at all level of exposure and spinal hematomas at low levels of exposure. [Notes: this is a two page report, grammar as in original.]

C. Related articles

Fetal exposure to low protein maternal diet alters the susceptibility of young adult rats to sulfur dioxide-induced lung injury.
Langley-Evans SC; Phillips GJ, and Jackson AA.
J Nutr. 1997 Feb; 127(2):202-9.

The maternal diet is an important determinant of glutathione-related metabolism in rats. Glutathione (GSH) may play a major role in the detoxification of sulfur dioxide (SO2) within the lungs. The effects of fetal exposure to a low protein maternal diet upon later susceptibility to pulmonary injury induced by chronic SO2 exposure were evaluated in young adult rats. Pregnant rats were fed purified diets containing 180 g casein/kg (control diet) or 120, 90 or 60 g casein/kg (experimental diets). After parturition, all dams were fed a standard non-purified diet (189 g protein/kg diet). The pups thus differed only in terms of protein nutrition during gestation. At seven wk of age the male pups were housed in either room air or 286 microg SO2/m3 for 5 h/d during a 28-d period. At the end of the final SO2 treatment period, the rats exposed to 90 or 60 g casein/kg diets in utero exhibited significantly greater pulmonary injury, as assessed by bronchoalveolar lavage, than did those exposed to control diet in utero. Significant maternal diet-induced differences in activities of enzymes of the gamma-glutamyl cycle were noted in the lungs and livers of rats which had not undergone SO2 treatment. Furthermore, the response of these enzyme activities to SO2 treatment was determined by prior exposure to the maternal diet. SO2-treated rats exposed to control diet (180 g casein/kg) and low protein diet (60 g casein/kg), but not those exposed to 120 or 90 g casein/kg diets, tended to augment the activities, relative to rats not treated with SO2, of enzymes which maintain tissue GSH status either through synthesis or recycling. Differences in susceptibility to SO2-induced tissue injury may be related to

programming of GSH metabolism by the maternal diet. Alternatively, impaired immune and acute phase responses to an inflammatory insult may account for a failure to resolve initial SO2-induced injury in rats exposed to low protein maternal diets.

Distribution, metabolism and toxicity of inhaled sulfur dioxide and endogenously generated sulfite in the respiratory tract of normal and sulfite oxidase-deficient rats.
Gunnison AF; Sellakumar A; Currie D, and Snyder EA.
J Toxicol Environ Health. 1987; 21(1-2):141-62.

We report on the distribution, metabolism, and toxicity of sulfite in the respiratory tract and other tissues of rats exposed to endogenously generated sulfite or to inhaled sulfur dioxide (SO2). Graded sulfite oxidase deficiency was induced in several groups of rats by manipulating their tungsten to molybdenum intake ratio. Endogenously generated sulfite and S-sulfonate compounds (a class of sulfite metabolite) accumulated in the respiratory tract tissues and in the plasma of these rats in inverse proportion to hepatic sulfite oxidase activity. In contrast to this systemic mode of exposure, sulfite exposure of normal, sulfite oxidase-competent rats via inhaled SO2 (10 and 30 ppm) was restricted to the airways. Minor pathological changes consisting of epithelial hyperplasia, mucoid degeneration, and desquamation of epithelium were observed only in the tracheas and bronchi of the rats inhaling SO2, even though the concentration of sulfite plus S-sulfonates in the tracheas and bronchi of these rats was considerably lower than that in the endogenously exposed rats. We attribute this histological damage to hydrogen ions stemming from inhaled SO2, not to the sulfite/bisulfite ions that are also a product of inhaled SO2. In addition to the lungs and trachea, all other tissues examined, except the testes, appeared to be refractory to high concentrations of endogenously generated sulfite. The testes of grossly sulfite oxidase-deficient rats were severely atrophied and devoid of spermatogenic cells.

SO2 and its metabolite: effects on mammalian egg chromosomes.
Jagiello GM; Lin JS, and Ducayen MB.
Environ Res. 1975 Feb; 9(1):84-93.

Abstract: The ubiquity of sulfur dioxide as an air pollutant combined with reports of effects of the gas and its blood metabolite on DNA and chromosomes, prompted a study of possible mutagen action on mammalian oocytes. Utilizing in vitro and in vivo systems, mouse, ewe, and cow oocytes were examined for cytologic evidence of structural or numerical damage in meiosis. Fragmentation with rearrangement seen at M1 and M2 and anaphase lagging seen in vitro in each species are classically known to be etiologic in chromosome abnormalities and must be considered, especially in contaminated areas with foci of fetal loss involving ewe and cow.

A study of the toxicity of sulphite. I.
Lockett MF and Natoff IL.
J Pharm Pharmacol. 1960; 12:488-496.

The effect of sodium metabisulphite, 750 p.p.m. as SO2, in the drinking water, has been studied through three generations of rats in experiments lasting for nearly 3 years. The metabisulphite was without effect on growth, the intake of food and fluid and the output of feces. It did not influence fetility, the weight of the newborn or lactation: neither did it increase the frequency with which tumours developed.