CHROMIUM (hexavalent)

This is a compilation of abstracts of articles identified during the preliminary toxicological evaluation of evidence on the developmental and reproductive toxicology of hexavalent chromium (CAS# 18540-29-2). Hexavalent chromium compounds are used in dyes, paints, inks, anticorrosive agents, surface coatings and electroplating baths. Occupational exposure can occur in performing "hot work" such as welding on stainless steel or melting chromium metal. Groundwater aquifers can be contaminated with hexavalent chromium which persists in water. Releases to the air during use and manufacturing can also result in exposures to the general population.

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 occupational and environmental exposures to hexavalent chromium. Based on a review of abstracts of the following studies, the chemical passed the epidemiologic screen.

- Five epidemiologic studies of hexavalent chromium reporting increased risk of adverse developmental or reproductive outcomes were identified, all of which were analytical studies of adequate quality. Eight epidemiologic studies reporting no increased risk of adverse developmental or reproductive outcomes were identified.

- Twenty-one animal studies of hexavalent chromium and three meeting abstracts reporting reproductive or developmental toxicity were identified, as well as one animal study that did not report reproductive or developmental toxicity.

Contents

I. Epidemiologic DART Studies

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

*** Semen quality of industrial workers occupationally exposed to chromium.**
Kumar S, Sathwara NG, Gautam AK, Agarwal K, Shah B, Kulkarni PK, Patel K, Patel A, Dave LM, Parikh DJ, Saiyed HN.
J Occup Health 2005 Sep;47(5):424-30.

A total of sixty-one subjects occupationally exposed to chromium in an industry which manufactures chromium sulphate and fifteen control subjects from a nearby industry which does not manufacture any chromium related compounds were studied. The history of each subject was recorded on pre-designed form through interview and a routine medical examination was carried out. Blood samples (5-6 ml) were collected for the estimation of chromium and semen samples were collected for semen analysis and the determination of copper and zinc levels in the seminal plasma. Clinical examination revealed nasal perforation in 10 subjects (out of 61) in the exposed group as compared to none in the control group. A significantly higher level of chromium was observed in the blood of the exposed workers as compared to the control. The concentration of zinc in seminal plasma was lower while the level of copper was higher in the exposed group as compared to the control. However, these changes were not statistically significant. Statistically significant higher numbers of morphologically abnormal sperms were noticed in the exposed group with respect to the control. Further analysis of the data indicated that about 53% of the exposed subjects showed less than 30% normal forms as compared to 10% in control subjects. However, no significant alterations in semen volume, liquefaction time, mean pH value, sperm viability, concentration or motility, were noticed between chromium exposed and unexposed workers. The data also indicates that exposure to chromium has some effect on human sperm as a significant positive correlation (r=0.301) was observed between percentages of abnormal sperm morphology and blood chromium levels (p=0.016) after pooling all the data of the control and exposure groups.

*** Semen quality of Indian welders occupationally exposed to nickel and chromium.**
Danadevi K, Rozati R, Reddy PP, Grover P.
Reprod Toxicol. 2003 Jul-Aug;17(4):451-6.

The semen quality of 57 workers from a welding plant in South India and 57 controls was monitored. Blood nickel and chromium concentrations were determined by ICP-MS. Analysis of semen samples was performed in accordance with World Health Organization criteria. The blood level of nickel and chromium for the 28 exposed workers was 123.3 +/- 35.2 and 131.0 +/- 52.6 microg/l, respectively, which was significantly higher than the 16.7 +/- 5.8 and 17.4 +/- 8.9

* 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.

microg/l for the control group (n=27). Sperm concentrations of exposed workers were 14.5 +/- 24.0 millions/ml and those of the control group were 62.8 +/- 43.7 millions/ml. Rapid linear sperm motility was decreased in exposed workers compared to controls. There was a significant positive correlation between the percentage of tail defects and blood nickel concentration in exposed workers. The sperm concentration showed a negative correlation with blood chromium content in workers. More abnormal characteristics were found in the semen of exposed workers. Semen abnormalities correlated with the number of years of exposure to welding fumes containing nickel and chromium.

*** Effect of Cr(VI) exposure on sperm quality: human and animal studies.**
Li H, Chen Q, Li S, Yao W, Li L, Shi X, Wang L, Castranova V, Vallyathan V, Ernst E, Chen C.
Ann Occup Hyg. 2001 Oct;45(7):505-11.

The semen status of male workers occupationally exposed to hexavalent chromium(VI) was investigated. Sperm counts from exposed workers were 47.05+/-2.13 x 10^6/ml and those from control group 88.96+/-3.40 x 10^6/ml. Sperm motility decreased from 81.92+/-0.41% for the control group to 69.71+/-0.93% for the exposed workers. The levels of zinc, lactate dehydrogenase (LDH), and lactate dehydrogenase C4 isoenzyme (LDH-x) in seminal plasma for the exposed workers were 1.48+/-0.07 micromol/ml, 1.05+/-0.02 x 10^3 U, and 0.47+/-0.01 x 10^3 U, respectively, which were significantly lower than those of 5.72+/-0.15 micromol/ml, 1.49+/-0.02 x 10^3 U, and 0.78+/-0.15 x 10^3 U for the control group, respectively. Follicle stimulating hormone (FSH) (7.34+/-0.34 x 10^{-3} IU/ml) in serum from the exposed workers was significantly higher than that (2.41+/-0.08 x 10^{-3} IU/ml) from the control group. On the other hand, there were no significant differences in semen volume, semen liquefaction time, luteinizing hormone (LH) level in serum, and Cr concentration in both serum and seminal plasma between the exposed workers and the control group. Feeding Cr(VI) to rats significantly reduced the epididymal sperm counts from 87.40+/-3.85 x 10^6/g epididymis in control group to 21.40+/-1.20 x 10^6/g epididymis at a CrO_3 dose of 10 mg/kg body weight and to 17.48+/-1.04 x 10^6/g epididymis at a CrO_3 dose of 20 mg/kg body weight. Exposure of rats to Cr(VI) also significantly increased the sperm abnormality from 2.75+/-0.06% in the control group to 6.68+/-0.32% in the exposed group at a CrO_3 dose of 10 mg/kg body and to 7.6+/-0.15% at a CrO_3 dose of 20 mg/kg body weight. In exposed rats, there was visible disruption in germ cell arrangement near the walls of the seminiferous tubules. The diameters of seminiferous tubules in exposed rats were smaller. These results suggest that occupational exposure to chromium(VI) leads to alteration of semen status and may affect the reproductive success of exposed workers.

* 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.

*** Male-mediated spontaneous abortion among spouses of stainless steel welders.**
Hjollund NH, Bonde JP, Jensen TK, Henriksen TB, Andersson AM, Kolstad HA, Ernst E, Giwercman A, Skakkebaek NE, Olsen J.
Scand J Work Environ Health. 2000 Jun;26(3):187-92.

OBJECTIVES: Male-mediated spontaneous abortion has never been documented for humans. The welding of stainless steel is associated with the pulmonary absorption of hexavalent chromium, which has genotoxic effects on germ cells in rodents. Clinical and early subclinical spontaneous abortions were examined among spouses of stainless-steel welders. METHODS: A cohort of first-pregnancy planners was recruited from members of the union of metal workers and 3 other trade unions. The cohort was followed for 6 menstrual cycles from the cessation of contraceptive use. Altogether, 280 pregnancies were conceived, of which 35 were detected by human chorionic gonadotrophic hormone analysis and did not survive to a clinically recognized pregnancy. Information on exposure was collected prospectively in relation to the outcome and was available for all cycles resulting in a pregnancy. Information on pregnancy outcome was collected for all 245 clinically recognized pregnancies. RESULTS: Increased risk of spontaneous abortion was found for pregnancies with exposure to paternal stainless-steel welding (adjusted relative risk 3.5, 95% confidence interval 1.3-9.1). The results were consistent in analyses of both biochemically and clinically recognized abortions. There was no increased risk for spontaneous abortion in pregnancies with paternal exposure to the welding of metals other than stainless steel. CONCLUSIONS: Male welding of stainless steel was associated with an increased risk of spontaneous abortion in spouses. A mutagenic effect of hexavalent chromium has been found previously in both somatic and germ cells, and the findings could be due to mutations in the male genome.

The results of the following study are also contained in the Li et al., (2001) article presented above. However, specific information concerning measurement of exposure to Cr (VI) is included only in the article presented below.

***[Studies on male reproductive toxicity caused by hexavalent chromium]**
[Article in Chinese]
Li H, Chen Q, Li S, Xu Y, Yao W, Chen C.
Zhonghua Yu Fang Yi Xue Za Zhi. 1999 Nov;33(6):351-3.

OBJECTIVE: To study male reproductive toxicity caused by hexavalent chromium ((Cr(VI +)). METHODS: Morphology of semen and spermatozoa was observed and chromium level in blood, chromium and zinc level in sperm plasma, leuteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in serum were determined for male workers exposed to (Cr(VI +)) (CrO(3)X = 0.0195 mg/m(3)) with occupational epidemiologic investigation and laboratory analysis. RESULTS: For the exposed workers, their seminal counting was (52.21 +/- 45.51) x 10(9)/L, and zinc level in seminal plasma (4,811.85 +/- 1,401.88) micromol/L, significantly

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lower than those in controls (88.96 +/- 74.82) x 10(9)/L and (5 718.49 +/- 2 827.90) micromol/L, respectively, P < 0.05. Serum FSH was (7.34 +/- 6.88) IU/L in the exposed groups, significantly higher than that of controls (2.41 +/- 1.69) IU/L, P < 0.01. There were no significant difference in semen volume, semen liquefaction time, prevalence of teratospermia, serum Cr(VI +) and LH level in seminal plasma between exposed group and control group (P > 0.05). Prevalence of teratospermia was 0.24 +/- 0.09, and serum LH and FSH were (7.94 +/- 2.67) IU/L and FSH (9.33 +/- 6.47) IU/L, respectively, in workers exposed to high concentration of Cr(VI +) (CrO(3)X = 0.2351 mg/m(3)) significantly higher than those exposed to lower concentration of Cr(VI +) (CrO(3)X = 0.0172 mg/m(3)), with 0.17 +/- 0.06 of prevalence of teratospermia, (5.05 +/- 3.05) IU/L of LH, and (3.74 +/- 3.04) IU/L of FSH, respectively (P < 0.05). CONCLUSION: The results suggested that damage to convoluted seminiferous tubule epithelium, reduction of spermatozoa formation and increase in prevalence of teratospermia could be caused by exposure to certain concentration of Cr(VI +).

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

Spontaneous abortion in IVF couples--a role of male welding exposure.
Hjollund NH, Bonde JP, Ernst F, Lindenberg S, Andersen AN, Olsen J.
Hum Reprod. 2005 Jul;20(7):1793-7. Epub 2005 Mar 10.

BACKGROUND: Fume from welding of stainless steel contains hexavalent chromium, which in animal studies can induce paternally mediated spontaneous abortion. Human studies have shown conflicting results. The best studies include early pregnancy experience, but these are expensive to conduct. In vitro fertilization (IVF) provides new design opportunities. Our aim was to study pregnancy survival in IVF treated women with respect to paternal welding exposure. METHODS: We mailed a questionnaire to 5879 couples from the Danish IVF register that covers all IVF treatments after 1993 (response ratio 68.2%). A subgroup of male metal workers received a second questionnaire on exposure to welding (n = 319 men, response ratio 77%). Information on outcome was collected from national health registers. Survival of the first hCG-positive pregnancy was analysed using Cox regression. RESULTS: The proportion of pregnancies terminated by spontaneous abortion before 28 gestational weeks was 18% (n = 91 pregnancies) and 25% (n = 128) in pregnancies with paternal exposure to stainless steel welding and mild steel welding, respectively. In the reference group of 2925 pregnancies the abortion ratio was 28%. The risk ratio for pregnancies with paternal exposure to stainless steel was 0.6 (95% CI 0.4-1.0). CONCLUSIONS: We found no increased risk of spontaneous abortion in IVF treated women, who became pregnant by a man exposed to welding of any sort. Since the process of fertilization and selection of IVF pregnancies differs from natural pregnancies the negative results need not apply to other pregnancies.

Congenital anomalies in Glasgow between 1982 and 1989 and chromium waste.
Eizaguirre-Garcia D, Rodriguez-Andres C, Watt GC.
J Public Health Med. 2000 Mar;22(1):54-8.

BACKGROUND: The former site of a factory in Glasgow and nearby areas were found to be heavily polluted by chromium waste. This gave rise to local concern on possible health effects. As part of a wider study answering this concern, congenital malformations were investigated. METHODS: A descriptive geographical study was carried out. A 10 km circle centred on the factory site was designated as the study area and subdivided into one circle of 2 km radius and eight 1 km wide rings. Significant differences in relative risk between the circle and rings and a decreasing trend of risk with distance from the centre would point towards a teratogenic role of the chromium waste. Relative risks by rings were obtained by Poisson regression. Relative risks by deprivation categories were also obtained, with most results adjusted by these categories. RESULTS: Significant differences in risk appeared, with the area containing the polluted soil having the lowest risk. Aggregations of rings showed a central area with a relatively low risk, followed by an intermediate one with the highest risk and an external area with risk also high. Relative risk appeared to increase sharply between the most affluent category and the rest, then growing steadily with increasing deprivation but decreasing slightly for the most deprived. CONCLUSIONS: Relative risk shows a significant peak in an area 2-4 km away from the pollutant, which does not point towards a possible teratogenic effect of the chromium waste. Relative risk of congenital malformations for the more affluent sector of the population appeared to be markedly lower than that for the rest.

Semen quality and sex hormones with reference to metal welding.
Hjollund NH, Bonde JP, Jensen TK, Ernst E, Henriksen TB, Kolstad HA, Giwercman A, Skakkebaek NE, Olsen J.
Reprod Toxicol. 1998 Mar-Apr;12(2):91-5.

Welding may involve hazards to the male reproductive system, but previous studies of semen quality have produced inconsistent results. We studied the effects of welding on markers of semen quality in a Danish nationwide sample of 430 first-time pregnancy planners without earlier reproductive experience. Couples were recruited among members of the union of metal workers and three other trade unions and were followed from termination of birth control until pregnancy for a maximum of six menstrual cycles. The males provided semen samples in each cycle. Median sperm density for welders was 56 x 10(6)/mL (52.5 x 10(6)/mL and 50.0 x 10(6)/mL in two reference groups). No statistically significant differences attributable to welding were found in proportions of morphologically normal sperm, sperm motility assessed by computer-aided sperm analysis, or sex hormones (testosterone, follicle-stimulating hormone, and luteinizing hormone). These negative findings may not apply to populations with high-level exposure to welding fume or to welders exposed to other putative hazards, e.g., heat.

Male-mediated risk of spontaneous abortion with reference to stainless steel welding.
Hjollund NH, Bonde JP, Hansen KS.
Scand J Work Environ Health. 1995 Aug;21(4):272-6.

OBJECTIVES: It was hypothesized that the welding of stainless steel involves a risk of male-mediated developmental toxicity because of exposure to mutagenic substances, including hexavalent chromium. The purpose of the present study was to corroborate or refute earlier findings that spouses of stainless steel welders have an increased risk of spontaneous abortion. METHODS: The occurrence of spontaneous abortion among 2520 pregnancies of spouses of 1715 married metal workers from 1977 through 1987 was examined. Occupational histories were collected with a postal questionnaire in a previous study. Information on children born live, spontaneous abortion, and induced abortion was obtained from national medical registers. RESULTS: The proportion of spontaneous abortions was not increased for pregnancies at risk from stainless steel welding when compared with pregnancies not at risk (odds ratio 0.78, 95% confidence interval 0.55-1.1). The risk estimate was robust to adjustment for potential confounding effects of maternal age and parity and male smoking and alcohol consumption. CONCLUSIONS: This study does not corroborate earlier findings that spouses of stainless steel welders have increased risk of spontaneous abortion. A reanalysis indicated that earlier findings were probably biased because the job exposure of male metal workers is apparently modified by the outcome of their partners' first pregnancy.

Quality of community drinking water and the occurrence of late adverse pregnancy outcomes.
Aschengrau A, Zierler S, Cohen A.
Arch Environ Health. 1993 Mar-Apr;48(2):105-13.

The relationship between community drinking water quality and the occurrence of late adverse pregnancy outcomes was investigated by conducting a case-control study among women who delivered infants during August 1977 through March 1980 at Brigham and Women's Hospital in Massachusetts. The water quality indices were compared among 1,039 congenital anomaly cases, 77 stillbirth cases, 55 neonatal death cases, and 1,177 controls. Trace element levels were gathered from routine analyses of public water supplies from the communities in which the women resided during pregnancy. It was observed that, after adjustment for confounding, the frequency of stillbirths was increased for women exposed to chlorinated surface water (OR 2.6 95% CI 0.9-7.5) and for women exposed to detectable lead levels (OR 2.1; 95% CI 0.6-7.2); the frequency of cardiovascular defects was increased relative to detectable lead levels (OR 2.2, 95% CI 0.9-5.7); and the frequency of central nervous system defects was increased relative to the highest tertile of potassium (OR 6.3, 95% CI 1.1-37.3). The frequency of ear, face, and neck anomalies was increased in relation to detectable silver levels (OR 3.3, 95% CI 0.9-12.2), but the frequency decreased relative to high potassium levels (OR 0.2, 95% CI 0.1-0.7). The frequency of neonatal deaths was decreased relative to detectable fluoride levels (OR 0.4, 95% CI 0.2-1.0), and the frequency of musculoskeletal defects was decreased relative to detectable chromium

levels (OR 0.4, 95% CI 0.2-1.0). The majority of these associations were not stable statistically. Further research is needed to corroborate these findings.

Sex hormones and semen quality in welders exposed to hexavalent chromium.
Bonde JP, Ernst E.
Hum Exp Toxicol. 1992 Jul;11(4):259-63.

Recent experimental studies in rodents document the spermatotoxic effects of water-soluble hexavalent chromium. Welders comprise, worldwide, a major occupational group with acknowledged exposure to chromium. This study examines the relationship between semen quality and chromium in the urine and blood of a population of 30 tungsten inert gas (TIG) stainless steel welders, 30 mild steel welders and 47 non-welding workers. Each subject provided two to three semen samples. The chromium concentration ranged from 0.17 to 4.74 nmol mmol1 creatinine (median 1.08) in post-shift spot urine and from 6.0 to 46.4 nmol l-1 in blood. None of several semen parameters deteriorated with increasing level of internal exposure to chromium. Low-level exposure to hexavalent chromium associated with TIG stainless steel and mild steel welding do not appear to be a major hazard for human spermatogenesis.

Adverse pregnancy outcome and childhood malignancy with reference to paternal welding exposure.
Bonde JP, Olsen JH, Hansen KS.
Scand J Work Environ Health. 1992 Jun;18(3):169-77.

Welding may deteriorate spermatogenesis and increase reproductive failures. This study examines reproductive end points in a Danish cohort of 10,059 metalworkers who fathered 3,569 children in 1973 through 1986. Occupational histories were gathered by postal questionnaires. Information on pregnancy outcomes and offspring was obtained by record linkage to medical registers. The occurrence of reduced birthweight, preterm delivery, infant mortality, and congenital malformation was not increased among children at risk from paternal welding exposure in comparison with children not at risk. The overall incidence of childhood malignancies among 23,264 children born in 1968 through 1986 with a total of 259,113 person-years of follow-up was equal to national rates (relative risk 0.97, 95% confidence interval 0.63-1.42). However, pregnancies preceding a birth at risk from paternal exposure to stainless steel welding were more often terminated by spontaneous abortion (odds ratio 1.9, 95% confidence interval 1.1-3.2). This finding needs cautious interpretation and should be further investigated in future studies.

Stainless steel welding and semen quality.
Reprod Toxicol. 1988;2(3-4):213-5.
Jelnes JE, Knudsen LE.

Questionnaire studies of patients from fertility clinics suggest that welders may have an increased risk of reduced semen quality. In this study, welders and nonwelders from the same plants were asked to provide blood, urine, and semen samples. Urine was analyzed for chromium and nickel, and for mutagenic activity and metal concentration; blood for metal concentrations, immunoglobulin G, total protein, and measures of genotoxicity in lymphocytes; and semen was evaluated by standard semen analysis. Results of the semen evaluation, presented here, showed no difference in semen quality between welders and nonwelders. Because the metal dust exposure of nonwelders in the plant may be higher than that in the general population, welders were also compared to referents not working in the metal industry. Again, no decrease in semen quality associated with welding was demonstrated.

II. Animal DART Studies

A. Studies reporting developmental or reproductive toxicity

Reproductive toxicity of chromium in adult bonnet monkeys (Macaca radiata Geoffrey). Reversible oxidative stress in the semen.
Subramanian, S., Rajendiran, G., Sekhar, P., Gowri, C., Govindarajulu, P., Aruldhas M.M.
Toxicol Appl Pharmacol. 2006, Sep 15; 215(3):237-49.

The present study was designed to test the hypothesis that oxidative stress mediates chromium-induced reproductive toxicity. Monthly semen samples were collected from adult monkeys (Macaca radiata), which were exposed to varying doses (50, 100, 200 and 400 ppm) of chromium (as potassium dichromate) for 6 months through drinking water. Chromium treatment decreased sperm count, sperm forward motility and the specific activities of antioxidant enzymes, superoxide dismutase and catalase, and the concentration of reduced glutathione in both seminal plasma and sperm in a dose- and duration-dependent manner. On the other hand, the quantum of hydrogen peroxide in the seminal plasma/sperm from monkeys exposed to chromium increased with increasing dose and duration of chromium exposure. All these changes were reversed after 6 months of chromium-free exposure period. Simultaneous supplementation of vitamin C (0.5 g/L; 1.0 g/L; 2.0 g/L) prevented the development of chromium-induced oxidative stress. Data support the hypothesis and show that chronic chromium exposure induces a reversible oxidative stress in the seminal plasma and sperm by creating an imbalance between reactive oxygen species and antioxidant system, leading to sperm death and reduced motility of live sperm.

In vivo spermatotoxic effect of chromium as reflected in the epididymal epithelial principal cells, basal cells, and intraepithelial macrophages of a nonhuman primate (Macaca radiata Geoffroy).
Aruldhas M.M., Subramanian, S., Sekhar, P., Vengatesh, G., Govindarajulu, P., Akbarsha, M.A.
Fertil Steril. 2006, Oct; 86 Suppl 4:1097-105.

OBJECTIVE: To understand, through a simulation experiment in a nonhuman primate model, the potential in vivo spermatotoxic toxic effect of hexavalent chromium (CrVI) in men who are occupationally or environmentally exposed to it. DESIGN: Controlled laboratory study. SETTING: Research laboratory in a department of endocrinology in a university in India. ANIMAL(S): Male bonnet monkey, Macaca radiata Geoffroy. INTERVENTION(S): Monkeys were exposed ad libitum to 100, 200, and 400 ppm CrVI, dissolved in drinking water, for a chronic period of 180 days. MAIN OUTCOME MEASURE(S): Examination of epididymis with a transmission electron microscope and assessment of the effect of CrVI in terms of accumulation of sperm-derived lipofuscin (LF) material in the principal cells, basal cells, and intraepithelial macrophages of the epithelium. RESULT(S): The abundance of basal cells and intraepithelial macrophages and the content of LF material in these cell types increased. The principal cells phagocytosed from the lumen the dead sperm resulting from CrVI exposure and

processed them partially into LF material, which was acquired by the basal cells and intraepithelial macrophages and processed further. The LF material-laden basal cells and intraepithelial macrophages appeared to leave the epithelium, accompanied by recruitment of fresh basal cells and intraepithelial macrophages. CONCLUSION(S): Occupational or environmental exposure to CrVI, as would occur in the tannery, soap, and other industries in developing and underdeveloped countries, can be toxic in vivo to spermatozoa.

Testicular dysfunction and antioxidative defense system of Swiss mice after chromic acid exposure.
Acharya, U.R., Mishra, M., Tripathy, R.R., Mishra, I. Reprod Toxicol. 2006, Jul; 22(1):87-91.

Chromic acid (CrO(3)), a hexavalent compound of chromium (Cr) that is widely used in different industries, has been associated with reproductive abnormalities in male Swiss mice. The mechanism of male reproductive toxicity is not clear. Metal-induced reactive oxygen species (ROS) may impair spermatogenesis or alter sperm morphology. Therefore, in the present study we investigated the induction of oxidative stress in the testes of mice over time (5th-8th weeks) after a single intraperitoneal dose (1mg/kg body weight) of CrO(3). Exposed animals showed significantly decreased sperm counts and markedly increased rates of sperm abnormality. Oxidative stress was measured in terms of malondialdehyde content, the activities of superoxide dismutase, peroxidase, and catalase, and non-enzymatic antioxidants such as ascorbic acid. The significant changes in exposed groups relative to controls suggest that CrO(3) exposure suppressed antioxidant enzymes and ascorbic acid with a concomitant increase in the level of lipid peroxidation and H(2)O(2) to adversely affect testicular function.

Chronic chromium exposure-induced changes in testicular histoarchitecture are associated with oxidative stress: study in a non-human primate (Macaca radiata Geoffroy).
Aruldhas, M.M., Subramanian, S,. Sekar, P., Vengatesh, G., Chandrahasan, G., Govindarajulu, P., Akbarsha, M.A.
Hum Reprod. 2005, Oct; 20(10):2801-13.

BACKGROUND: Reproductive toxicity of chromium is in dispute despite positive findings in rodents. Recently we reported epididymal toxicity of hexavalent chromium (CrVI) in bonnet monkeys and in this paper we report its testicular toxicity. METHODS: Adult monkeys (Macaca radiata) were given drinking water containing CrVI (100, 200, 400 p.p.m.) for 6 months and testes were removed for ultrastructural and biochemical analyses. RESULTS: CrVI treatment disrupted spermatogenesis, leading to accumulation of prematurely released spermatocytes, spermatids and uni- and multinucleate giant cells in the lumen of seminiferous tubules. Transmission electron microscopy revealed granulation of chromatin and vacuolation between acrosomal cap and manchette microtubules of elongated spermatids and in the Golgi area of round spermatids. Pachytene spermatocytes had fragmented chromatin and swollen mitochondria with collapsed cristae. Spermatocytes and spermatogonia in the basal compartment were unaffected. Macrophages containing phagocytosed sperm and dense inclusions in Sertoli cells

were seen. Specific activities of the antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and glucose-6-phosphate dehydrogenase and concentrations of the non-enzymatic antioxidants glutathione, vitamins A, C and E decreased, while concentrations of H(2)O(2) and hydroxyl radicals increased in the testis of chromium-treated monkeys. Withdrawal of chromium treatment for 6 months normalized spermatogenesis and the status of pro- and antioxidants in the testis. CONCLUSIONS: CrVI disrupts spermatogenesis by inducing free radical toxicity, and supplementation of antioxidant vitamins may be beneficial to the affected subjects.

Microcanalization in the epididymis to overcome ductal obstruction caused by chronic exposure to chromium - a study in the mature bonnet monkey (Macaca radiata Geoffroy).
Aruldhas, M.M., Subramanian, S., Sekhar, P., Hasan, G.C., Govindarajulu, P., Akbarsha, M.A.
Reproduction. 2004, Jul; 128(1):127-37.

In order to apprehend the toxic effects of chromium, an occupational/environmental pollutant, on the epididymis, adult bonnet monkeys were exposed to chromium (VI) in their drinking water at concentrations of 100, 200 and 400 p.p.m. for a chronic period of 180 days. At the end of the experimental period, testicles and segments of epididymis from control and treated monkeys were subjected to light microscopic (resin-embedded semi-thin sections) and transmission electron microscopic analyses. Among the various changes undergone by the epididymal epithelium, the present paper describes the origin of two different kinds of microcanals, probably caused by ductal obstruction. The first type of microcanal, which appears to provide passage for spermatozoa to bypass the obstructed main duct, is comparable with the one already reported in carbendazim-treated efferent ductules of the rat. The second type of microcanal, which is novel, consisted of a lumen in the epithelium enclosed by four to five cells, which are either modified basal cells, principal cells or a hitherto unknown cell type. This novel type of microcanal is suggested to be a device to entrap the spermatozoa which reach the core of the epithelium and may be a mechanism to prevent extravasation of sperm so as to avoid an autoimmune response of spermatic granuloma formation. Thus, the present study has shown that chronic exposure to chromium (VI) through drinking water can produce pathological manifestations in the epididymal epithelium but the epididymis, being a versatile organ, is capable of overcoming such adverse situations through novel devices.

Potential role of vitamins in chromium induced spermatogenesis in Swiss mice.
Acharya, U.R., Mishra, M., Mishra, I., Tripathy, R.R.
Environmental Toxicology and Pharmacology 2004 Jan;15(2-3):53-9

ABSTRACT: Chromium (Cr) (VI) compounds are known carcinogens and mutagens. The mechanism of carcinogenicity and mutagenicity caused by chromium(VI) compounds remained unclear for several years. However, in the recent past chromium-induced carcinogenicity and/or mutagenicity was known to happen due to the generation of reactive oxygen species (ROS). In the present context, chromic acid (CrO3), a potential Cr(VI) compound could be able to generate

reactive oxygen radicals in the testes of Swiss mice as evidenced from significantly higher lipid peroxidation compared to untreated controls. The cytotoxic effects of the compound on the testes are depicted in terms of significantly reduced sperm count level accompanied with increased abnormal sperm population in treated mice. Supplementation of vitamins like Vitamin C and Vitamin E (Vit C and Vit E) to CrO3 injected mice groups could partially prevent the incidence of abnormal sperm population and increased the sperm count. Of the two vitamins, taken for the study, Vit C happens to be more effective in ameliorating germ cells from degeneration and from mutation to abnormal sperm. Possible antioxidative role of both the vitamins have been studied for significant decrease in lipid peroxidation associated with marked elevation in sperm count level and significant decrease in the percentage of abnormal sperm formation in CrO3-treated mice.

Effect of Cr(VI) exposure on sperm quality: human and animal studies
Li, H., Chen, Q., Li, S., Yao, W., Li, L., Shi, X., Wang, L., Castranova, V., Vallyathan, V., Ernst, E., and Chen, C.
Ann Occup Hyg 2001;45(7):505-11

The semen status of male workers occupationally exposed to hexavalent chromium(VI) was investigated. Sperm counts from exposed workers were 47.05+/-2.13 x 10(6)/ml and those from control group 88.96+/-3.40 x 10(6)/ml. Sperm motility decreased from 81.92+/-0.41% for the control group to 69.71+/-0.93% for the exposed workers. The levels of zinc, lactate dehydrogenase (LDH), and lactate dehydrogenase C4 isoenzyme (LDH-x) in seminal plasma for the exposed workers were 1.48+/-0.07 micromol/ml, 1.05+/-0.02 x 10(3) U, and 0.47+/-0.01 x 10(3) U, respectively, which were significantly lower than those of 5.72+/-0.15 micromol/ml, 1.49+/-0.02 x 10(3) U, and 0.78+/-0.15 x 10(3) U for the control group, respectively. Follicle stimulating hormone (FSH) (7.34+/-0.34 x 10(-3) IU/ml) in serum from the exposed workers was significantly higher than that (2.41+/-0.08 x 10(-3) IU/ml) from the control group. On the other hand, there were no significant differences in semen volume, semen liquefaction time, luteinizing hormone (LH) level in serum, and Cr concentration in both serum and seminal plasma between the exposed workers and the control group. Feeding Cr(VI) to rats significantly reduced the epididymal sperm counts from 87.40+/-3.85 x 10(6)/g epididymis in control group to 21.40+/-1.20 x 10(6)/g epididymis at a CrO(3) dose of 10 mg/kg body weight and to 17.48+/-1.04 x 10(6)/g epididymis at a CrO(3) dose of 20 mg/kg body weight. Exposure of rats to Cr(VI) also significantly increased the sperm abnormality from 2.75+/-0.06% in the control group to 6.68+/-0.32% in the exposed group at a CrO(3) dose of 10 mg/kg body and to 7.6+/-0.15% at a CrO(3) dose of 20 mg/kg body weight. In exposed rats, there was visible disruption in germ cell arrangement near the walls of the seminiferous tubules. The diameters of seminiferous tubules in exposed rats were smaller. These results suggest that occupational exposure to chromium(VI) leads to alteration of semen status and may affect the reproductive success of exposed workers.

Sexual maturation and fertility of male and female mice exposed prenatally and postnatally to trivalent and hexavalent chromium compounds
Al-Hamood, M. H., Elbetieha, A., and Bataineh, H.
Reprod Fertil Dev 1998;10(2):179-83

The reproductive toxicity of trivalent and hexavalent chromium compounds was investigated in male and female mice exposed to 1000 ppm chromium chloride and potassium dichromate via their mother during gestational and lactational periods. Fertility was reduced in male offspring exposed to either trivalent or hexavalent chromium compounds. Body weights and weights of testes, seminal vesicles and preputial glands were reduced in trivalent-exposed male offspring. The exposure of female mice offspring to trivalent and hexavalent chromium compounds delayed sexual maturation. Fertility was reduced in female offspring exposed to either trivalent or hexavalent chromium compounds. The exposure of female mice to hexavalent chromium compound reduced the number of implantations and viable fetuses respectively. Body weight and weights of ovaries and uteri were reduced in trivalent-exposed female offspring. The results indicate that under our experimental conditions, the exposure of male and female mice offspring to either trivalent or hexavalent chromium compounds during gestational and lactational periods impair reproductive functions and fertility in adulthood.

Embryo and fetotoxicity of hexavalent chromium: a long-term study
Kanojia, R. K., Junaid, M., and Murthy, R. C.
Toxicol Lett 1998;95(3):165-72

Ingestion of chromium(VI) (250, 500 or 750 ppm as potassium dichromate, K2Cr2O7) through drinking water by female rats for 3 months prior to gestation was toxic to embryo and fetus. There was a significant reduction in number of implantations and number of fetuses and an increase in number of resorptions and pre-implantation and post-implantation losses. No significant visceral abnormality was found. The increase in the number of subdermal hemorrhagic patches on the thorax and abdomen was significant. Skeletal abnormality in the form of reduced ossification in parietal, interparietal and caudal bones was observed in fetuses. Chromium levels in the blood of mothers, placenta and fetuses showed a significant increase. Duration of the estrous cycle was also increased significantly. The study revealed that long-term chromium exposure in rats did not cause embryo and fetotoxicity in a duration-dependent manner compared to short-term treatment as observed earlier. A possible explanation could be that, in the 90-day study, the female rats did not mate for three estrous cycles, thus giving time for clearance of a sizable amount of chromium from their bodies.

Effect of long-term ingestion of chromium compounds on aggression, sex behavior and fertility in adult male rat
Bataineh, H., al-Hamood, M. H., Elbetieha, A., and Bani Hani, I.
Drug Chem Toxicol 1997;20(3):133-49

The effects of long-term ingestion of chromium chloride (trivalent compound) and potassium dichromate (hexavalent compound) was investigated on sexual behavior, aggressive behavior and fertility in male rats. Adult male rats were exposed to chromium chloride and potassium dichromate in drinking water at a concentration of 1000 ppm for 12 weeks. The exposure of male rats to chromium chloride and potassium dichromate reduced the number of mounts. The exposure of male rats to potassium dichromate increased the time to ejaculation. On the other hand, the exposure of male rats to chromium chloride and potassium dichromate increased the post ejaculatory interval. The number of animals ejaculating were reduced in chromium chloride and potassium dichromate exposed male rats. The exposure of male rats to chromium chloride and potassium dichromate decreased lateralizations, boxing bouts and fights with stud male. The exposure of male rats to chromium chloride and potassium dichromate had no effect on fertility. Testes, seminal vesicle and preputial gland weights were significantly reduced in chromium chloride- and potassium dichromate-exposed males. In conclusion, the long-term ingestion of chromium chloride and potassium dichromate would have adverse effects on sexual behavior and territorial aggression in adult male rat.

Long-term exposure of male and female mice to trivalent and hexavalent chromium compounds: effect on fertility
Elbetieha, A. and Al-Hamood, M. H.
Toxicology 1997;116(1-3):39-47

Sexually mature male and female mice at 50 days of age were exposed to trivalent (Chromium chloride) or hexavalent (potassium dichromate) chromium compounds in drinking water for 12 weeks. The effects of the direct chromium exposure on fertility was assessed at day 140 of age. Fertility was significantly reduced in males exposed to the trivalent chromium compound. The number of implantation sites and the number of viable fetuses was significantly reduced in females impregnated by males exposed to the hexavalent chromium compound. The number of resorptions and dead fetuses was increased in females impregnated by males exposed to trivalent and hexavalent chromium compounds. The exposure of female mice to trivalent and hexavalent chromium compounds significantly reduced the number of implantation sites and the number of viable fetuses. The number of females with resorptions was significantly increased in hexavalent chromium exposed females. The number of resorptions was increased in trivalent and hexavalent exposed females. Body, seminal vesicles and preputial gland weights were significantly reduced in males exposed to trivalent and hexavalent chromium, whereas testes weight was significantly increased in males exposed to these compounds. Furthermore, ovarian weight was significantly increased in females exposed to trivalent and hexavalent chromium, whereas uterine weight was significantly decreased in trivalent chromium exposed females. In conclusion, the ingestion of trivalent and hexavalent chromium compounds by adult male and female mice would cause

adverse effects on fertility and reproduction.

Embryotoxicity of orally administered chromium in mice: exposure during the period of organogenesis
Junaid, M., Murthy, R. C., and Saxena, D. K.
Toxicol Lett 1996;84(3):143-8

Administration of chromium (VI)(250, 500 and 750 ppm as potassium dichromate) via drinking water during organogenesis (days 6-14 of gestation) in mice revealed embryo- and fetotoxic effects. Reduced fetal weight, retarded fetal development, number of fetuses (live and dead) per mother and high incidences of dead fetuses and resorptions in treated mothers in the highest dosed group were evident. No significant gross structural abnormalities were observed in any of the fetuses of chromium (VI)-treated mothers. Significant incidences of reduced ossification were found in the highest dosed group. Chromium levels were increased in a dose-dependent manner in maternal blood, placenta and fetuses. The present study suggests a risk to the developing embryo if the mother is exposed to a sufficiently high concentration of chromium (VI) through drinking water during the period of organogenesis.

Chromium induced teratogenicity in female rat
Kanojia, R. K., Junaid, M., and Murthy, R. C.
Toxicol Lett 1996;89(3):207-13

Exposure to chromium (VI) (250, 500 and 750 ppm as potassium dichromate) via drinking water pregestationally in rats revealed embryo- and fetotoxic effects in the form of a significant reduction in the number of implantations and number of fetuses. An increase in the number of resorptions, pre-implantation and post-implantation loss in chromium (VI)-treated mothers was also observed. No significant visceral abnormality was found. A significant increase in sub-dermal hemorrhagic patches on thoracic and abdominal areas was found. Skeletal abnormality in the form of reduced ossification in parietal, interparietal and caudal bones was found in the fetuses of chromium (VI)-treated mothers. Chromium levels in blood, placenta and fetuses were found to be significantly increased in the 500 ppm and 750 ppm dosed groups. The duration of estrus cycle was significantly altered after chromium (VI) exposure. This study suggests that chromium exposure in rat causes a lower degree of toxicity than in mice as observed in our earlier studies.

Ovarian dysfunction in mice following chromium (VI) exposure
Murthy, R. C., Junaid, M., and Saxena, D. K.
Toxicol Lett 1996;89(2):147-54

Chromium (VI) was given through drinking water in two sets of adult Swiss albino female mice in three doses; 250 ppm, 500 ppm and 750 ppm for 20 days in set 1 and 0.05 ppm, 0.5 ppm and

5.0 ppm in set II for 90 days. At the termination of the treatment, the animals of both the sets were euthanized for histopathology, follicle counting, counting of the superovulated ova, duration of estrus cycle and for ultrastructural studies. Ovaries of the highest dose group (750 ppm) showed large numbers of atretic follicles and congestion in stromal tissue compared to the rest of the treated groups. Also, there was a dose-dependent reduction in the number of follicles at different stages of their maturation. The number of ova recovered from superovulated chromium (VI)-treated animals showed significant decreases in the 500 and 750 ppm dosed groups compared to lower dosed (250 ppm) and control groups. The duration of estrus cycle increased in highest dosed (750 ppm) group. A dose-dependent increase in blood chromium level was also seen in treated mice. Ultrastructural observations revealed disintegrated cell membranes of two layered follicular cells and altered villiform mitochondria in thecal cells of 5 ppm dosed group. From the study it was concluded that ovarian physiology and rate of ovulation might be altered if females are exposed to sufficiently high chromium through oral route.

Chromium fetotoxicity in mice during late pregnancy
Junaid, M., Murthy, R. C., and Saxena, D. K.
Vet Hum Toxicol 1995;37(4):320-3

Female mice received 250, 500 or 750 ppm chromium (VI) as potassium dichromate in drinking water on days 14 to 19 of pregnancy. Gestational weight gain of mothers, fetal weight and crown-rump length decreased in the 500 and 750 ppm groups. The high-dose group also had significantly higher incidences of postimplantation loss. Significant increases in drooping wrists, subdermal hemorrhagic patches, kinky and short tails, and reduced ossification were also found in the 750 ppm group. Chromium levels were increased in a dose-dependent manner in maternal blood and placenta and in fetuses. Our study suggests a risk to the developing fetus if the mother is exposed to high concentrations of chromium (VI) during pregnancy.

Sex hormones and epididymal sperm parameters in rats following sub-chronic treatment with hexavalent chromium
Ernst, E. and Bonde, J. P.
Hum Exp Toxicol 1992;11(4):255-8

Testicular atrophy and reduced epididymal sperm count are known to occur after i.p. administration of high doses of hexavalent chromium to rats. The effect of 0.5 mg kg-1 hexavalent chromium injected i.p. 5 d a week for 8 weeks was investigated in male Wistar rats. A significant reduction in epididymal sperm motility was found at the end of the exposure period. The reduction was reversed after an unexposed period of a further 8 weeks. In addition, a decrease in serum testosterone and an increase in FSH were found at the end of the exposure period. The results indicate that a number of mechanisms may be involved in the deleterious effects of chromate on male fecundity.

Ultrastructural observations in testicular tissue of chromium-treated rats
Murthy, R. C., Saxena, D. K., Gupta, S. K., and Chandra, S. V.
Reprod Toxicol 1991;5(5):443-7

The administration of hexavalent chromium (2 mg/kg, ip as potassium dichromate) in adult rats daily for 15 days produced significant increases in the blood and testicular chromium levels. Although no light microscopic pathologic changes or alterations in epididymal sperm counts and motility were observed, lanthanum perfusion in treated rats revealed leakage of Sertoli-cell tight junctions under EM. A few tubules showed marked ultracellular alterations in the form of vacuolization of cytoplasm and degeneration of mitochondria in the epithelial cells. Late stage spermatids were the most affected germ cells. The mitochondrial sheath of the midpiece was vacuolated, incomplete, swollen, or broken in places. The observed alterations may result in the disruption of normal testicular physiology leading to reproductive impairment after chromium exposure.

Testicular toxicity following short-term exposure to tri- and hexavalent chromium: an experimental study in the rat
Ernst, E.
Toxicol Lett 1990;51(3):269-75

The effect of tri- and hexavalent chromium after intraperitoneal administration for 5 consecutive days on testicular histopathology and epididymal sperm number was assessed. Treatment with hexavalent chromium induced testicular atrophy and a reduction in epididymal sperm number after 60 days. No effect was seen after treatment with trivalent chromium.

Effect of hexavalent chromium on testicular maturation in the rat
Saxena, D. K., Murthy, R. C., Lal, B., Srivastava, R. S., and Chandra, S. V.
Reprod Toxicol 1990;4(3):223-8

Daily intraperitoneal administration of hexavalent chromium (Cr6+; 1, 2, and 3 mg/kg intraperitoneally as potassium dichromate) in weaned rats for an entire duration of 55 and 90 days of age produced dose- and duration-dependent enzymatic and pathologic alterations. At 55 days, the pathologic changes were not seen in testes of Cr6+ treated rats, but the activities of sorbitol dehydrogenase, lactic dehydrogenase, gamma-glutamyl transpeptidase, and glucose-6-phosphate dehydrogenase were significantly altered. When the treatment was prolonged to sexual maturity, that is, 90 days of age, the alterations in enzyme activities were greater, and there were dose-dependent pathologic changes in the testes of Cr(6+)-treated rats. These alterations suggest a risk to growing testes if rats are exposed to Cr6+ during the prepubertal stage of development, which, in turn, may disturb normal testicular physiology at adulthood.

Embryotoxicity and fetotoxicity of orally administered hexavalent chromium in mice
Trivedi, B., Saxena, D. K., Murthy, R. C., and Chandra, S. V.
Reprod Toxicol 1989;3(4):275-8

The embryotoxic and fetotoxic potential of hexavalent chromium (Cr+6) in mice was investigated by administering 250, 500, and 1000 ppm of potassium dichromate daily through drinking water during the entire gestation period. An increase in embryonic deaths was observed; however, in the mothers treated with the highest dose, there was complete absence of implantation sites. No major abnormality was observed in the fetuses except that Cr+6 exposure increased the incidences and types of external and skeletal malformations. It is concluded that oral exposure to Cr+6 causes dose-dependent embryolethal effects in mice.

The effect of the time of administration of chromium trioxide on the embryotoxic response in hamsters
Gale, T. F. and Bunch, J. D. 3rd
Teratology 1979;19(1):81-6

Prior work has demonstrated that chromium trioxide is embryotoxic in hamsters if administered to pregnant animals early on the eighth gestation day. The major manifestations are cleft palate and an increased frequency of resorptions. In the present study a single iv dose (8 mg/kg) of chromium trioxide was injected into pregnant hamsters at 8 A.M. on either day 7, 8, 9, 10 or 11 of gestation in order to determine the effect of altering the time of treatment on embryotoxicity. Fetuses from females treated with chromium or demineralized-distilled water were collected on day 15 of gestation and were examined for the types and frequency of external and internal malformations. The number of resorption sites was recorded. Cleft palate, the major malformation detected, was produced only when chromium was administered on days 7, 8, or 9 of gestation. Since the frequency of resorptions and the incidence of cleft palate varied with the time of treatment it is concluded that the time at which chromium trioxide is injected into the pregnant hamster does influence embryotoxicity. The results suggest that an interference with embryonic growth may be an important factor in chromium-induced cleft palate in hamsters.

B. Studies reporting no developmental or reproductive toxicity

Oral chromium(VI) does not affect the frequency of micronuclei in hematopoietic cells of adult mice and of transplacentally exposed fetuses.
De Flora S Iltcheva M Balansky RM
Mutat Res. 2006, Nov 7; 610(1-2):38-47. [Mutation research]

Chromium(VI) compounds are genotoxic in a variety of cellular systems. Their potential carcinogenicity is affected by toxicokinetic patterns restricting bioavailability to certain targets, and by metabolic pathways affecting interaction of chromate-derived reactive species with DNA. Epidemiological data indicate that chromium(VI) can be carcinogenic to the human respiratory tract following inhalation at doses that are only achieved in certain occupational settings.

However, concern has been raised that adverse effects may also result from oral intake. In order to further explore this issue, we performed studies in BDF1 and Swiss mice of both genders and various age. Sodium dichromate dihydrate and potassium dichromate were administered either with the drinking water, up to a concentration of 500 mg chromium(VI)/l for up to 210 consecutive days, or in a single intragastric dose of 17.7 mg/kg body weight. Under these conditions, no increase of the micronucleus frequency was observed in either bone marrow or peripheral blood erythrocytes. Conversely, the same compounds induced a clastogenic damage following intraperitoneal injection, which by-passes detoxification mechanisms. In addition, due to the hypothesis that susceptibility may be increased during the period of embryogenesis, we treated pregnant mice, up to a concentration of 10mg chromium(VI)/l drinking water. There was no effect on the numbers of fetuses/dam and on body weight of fetuses. Again, no toxic or genotoxic effect was observed either in bone marrow of pregnant mice or in liver and peripheral blood of their fetuses. Thus, even at doses that largely exceed drinking water standards (up to 10,000 times) or by massive intragastric administration, chromium(VI) is not genotoxic to hematopoietic cells of either adult mice or transplacentally exposed fetuses. These conclusions are consistent with the poor toxicity and lack of carcinogenicity of oral chromium(VI), and are mechanistically explained by the high efficiency of chromium(VI) detoxification processes in the gastrointestinal tract.

C. Related meeting abstracts

Maternal and neonatal effects of chromated copper arsenic on Sprague-Dawley rats
Ogden, L., Wilson, L., Graham, T., Johnson, F., Knight, Q., Hammersley, M., and DeJan, B.
Int J Toxicol 2002 Nov-Dec;21(6):522
Chromated copper arsenic (CCA) mixture is frequently used to preserve wood. Humans and animals are most often exposed when they come in contact with CCA treated decks, porches, fencing, picnic tables, playground posts, highway barriers, exterior wooden frames, and utility posts. The most common CCA formulation results in a wood concentration of Cr, Cu, and As between 0.1-0.2%. The major objective of this study is to evaluate the effects of low levels of the CCA mixture on various life phases in a mammalian model. Adult female Sprague-Dawley rats were exposed to different levels of the CCA mixture by oral gavage during gestation, lactation, and neonatal periods. Body weight, feed consumption, behavioral changes and clinical signs were monitored. Other groups of rats were given CCA (Type C) wood soaked effluent or ash-effluent for 60 days by oral gavage. Hematological (e.g., RBC, WBC, MCV, MCHC, HCT) and clinical chemistries (e.g., total protein, ALT, BUN, Creatinine) were determined. Liver, kidney, ovary, testicle, spleen, and brain tissues of F0 and F1 generations were evaluated for (arsenic, chromium, and copper levels) and morphological evaluations were conducted. The mutagenic potential of CCA was determined in bone marrow smears and biochemical studies were also conducted in F0 and F1 generations.

Assessment of the teratogenicity of trivalent and hexavalent chromium compounds in female rabbits.
El-Tawil, O.S., Morgan, A.M.
Toxicologist 2000 Mar;54(1):292.

The exposure of pregnant female rabbits to trivalent (chromium chloride) or hexavalent (potassium dichromate) chromium compounds in drinking water (500 ppm) during the organogenesis period (6-18th day of gestation) revealed embryotoxic and fetotoxic effects. Both trivalent and hexavalent compounds induced dwarfism, kinky and short tail and a significant reduction in the number of implantation sites and in the number of viable fetuses. The number of females with resorption was significantly increased in the hexavalent-exposed group. Visceral abnormalities in the form of lung hypoplasia, heart hypertrophy, intrathoracic hemorrhage and dilated nares and brain lateral ventricles were found in the fetuses of both chromium (III, VI) treated mothers. Skeletal anomalies (reduced number of sternal and caudal bones) were also recorded in both chromium groups. Furthermore, reduced ossification in parietal and inerparietal bones was significantly increased in the hexavalent chromium exposed females. Chromium levels in blood, placenta and fetuses significantly increased in both chromium groups. In conclusion, the exposure of pregnant rabbits to trivalent and hexavalent chromium compounds would have adverse effects on the embryonic and fetal development.

Teratogenic effect of trivalent and hexavalent chromium in rabbits.
El-Tawil O.S., Morgan A.M.
Toxicologist 2000 Mar;54(1):32.

Chromium is considered to be an essential nutrient that helps to maintain normal metabolism of glucose, cholesterol, and fat in humans. Studies in the literature indicate that hexavalent chromium (Cr-VI) is more toxic than trivalent chromium (Cr-III) as it is actively transported across the plasma membranes and is reduced via unstable reactive intermediate to Cr-III. Also, the published data indicate that exposure to Cr-VI decrease the number of viable fetuses and increase the number of dead ones. In the current investigation pregnant rabbits were exposed to Cr-III (chromium chloride), or Cr-IV (potassium dichromate) in drinking water at a dose of 500 ppm each during the organogenesis period. Exposure to Cr-IV significantly increased the number of resorption sites and decreased the number of viable fetuses compared to Cr-III and control groups. Exposure to either chemicals induced dwarfism, kinky and short tails, lung hypoplasia, heart hypertrophy, intrathoracic hemorrhage and dilated nares and brain lateral ventricles. Furthermore, reduced ossification in parietal and inerparietal bones was significantly increased in the fetuses from the females exposed to Cr-VI. The results of the current investigation may indicate that both Cr-III and Cr-VI are teratogenic for the tested concentration. However, the severity of effects are higher with the exposure to Cr-VI.