URANIUM

This is a compilation of abstracts of articles identified during the preliminary toxicological evaluation of evidence on the developmental and reproductive toxicity of uranium (CAS# 7440-61-1). Uranium is a heavy metal that is weakly radioactive and occurs naturally in forms with very long half-lives[1]. It is used in nuclear reactors because it can be artificially induced to produce a chain reaction that generates energy as well as highly radioactive byproducts. Commercially, uranium is used in an enriched form (higher percentage of the fissile isotope ^{235}U) and a depleted form (low percentage of ^{235}U). Enriched uranium is used in nuclear reactors, while depleted uranium is used for military applications in munitions and armor. Uranium has low gastrointestinal absorption; absorbed uranium takes the form of uranyl ion for circulation and tissue distribution.

The abstracts compiled below are from animal toxicity and epidemiologic studies reporting on developmental and reproductive sequelae related to exposure to uranium, as well as other relevant investigations (e.g., *in vitro* studies or studies in non-mammalian animal species). This information was used to screen chemicals to propose for listing consideration by the Developmental and Reproductive Toxicant Identification Committee. The criteria for passing the current screen are the existence of the following number of reports of an increase in adverse developmental or reproductive toxicity outcomes in mammalian species:

1) a total of 15 or more reports across all of the endpoints (developmental toxicity, female reproductive toxicity, male reproductive toxicity); or
2) 10 or more reports for any one category of the following three categories: developmental toxicity, female reproductive toxicity, or male reproductive toxicity.

There were a total of 109 studies identified in the literature search on uranium (some studies may have reported more than one adverse effect). The table below shows how uranium passed the screen.

Endpoints	Reports of adverse effects		Reports of no adverse effects	
	Animal	Human	Animal	Human
Developmental	7	1	1	2
Female reproductive	5	0	1	0
Male reproductive	11	1	2	0
Total	23	2	4	2

[1] The three isotopes in natural uranium - ^{234}U, ^{235}U, and ^{238}U - emit α-particles. While ^{235}U and ^{238}U have half-lives of the order of billions of years. ^{234}U, with its shorter half-life (~250,000 years) contributes most to the (low level) radioactivity of natural uranium, even though it is present in very small concentrations.

In addition to the reports enumerated in the table, the search identified:

- 7 other related studies or meeting presentations (titles of reports only provided below)
- 4 publications with a relevant title but no abstract.

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I. Animal Developmental and Reproductive Toxicity Studies

A. Studies reporting developmental or reproductive toxicity

i. Developmental toxicity

a. Studies identified in the open literature search

Two-generation reproductive toxicity study of implanted depleted uranium (DU) in CD rats.
Arfsten D. P., Still K. R., Wilfong E. R., Johnson E. W., McInturf S. M., Eggers J. S., Schaeffer D. J. and Bekkedal M. Y.
J Toxicol Environ Health A. 2009;72(6):410-27.

Depleted uranium (DU) munitions and armor plating have been used in several conflicts over the last 17 yr, including the Persian Gulf War and the Iraq War. Because of its effectiveness and availability, DU will continue to be used in military applications into the foreseeable future. There is much controversy over the use of DU in weapons and equipment because of its potential radiological and toxic hazards, and there is concern over the chronic adverse health effects of embedded DU shrapnel in war veterans and bystanders. This study evaluated the effects of long-term implantation of DU on the reproductive success of F0 generation adults and development and survival of subsequent F1 and F2 generations in a two-generation reproductive toxicity study. F0 generation Sprague-Dawley rats, 8 wk of age, were surgically implanted with 0, 4, 8, 12, or 20 DU pellets (1 x 2 mm). Inert implant control animals were implanted with 12 or 20 tantallum (Ta) pellets. The F0 generation was then mated at 120 d post DU implantation. In the F0 generation, when measured on postimplantation d 27 and 117, uranium was present in the urine of DU-implanted animals in a dose-dependent manner. F0 reproductive success was similar across treatment groups and the maternal retrieval test revealed no changes in maternal behavior. DU implantation exerted no effect on the survival, health, or well-being of the F0 generation. Necropsy results of F0 animals were negative with the exception of a marked inflammatory response surrounding the implanted DU pellets. For the F1 generation, measures of F1 development through postnatal day (PND) 20 were unremarkable and no gross abnormalities were observed in F1 offspring. No uranium was detected in whole-body homogenates of PND 4 or PND 20 pups. Necropsy findings of F1 PND 20 pups were negative and no instances of ribcage malformation were observed in F1 PND 20 pups. Body weight and body weight gain of F1 rats through PND 120 were similar across treatment groups. Eight of 414 F1 animals observed from PND 20 to 120 died of unknown causes; 7 were from litters of DU-implanted F0 mating pairs. F1 mating success at 10 wk of age was an overall 70% compared with 91% for F0 mating pairs. Mating success was similar between F1 animals derived from DU-implanted F0 adults and those derived from F0 implant control adults suggesting that the comparatively low mating success was not due to F1 DU exposure. The gestational index of F1 animals derived from mid-dose F0 mating pairs was found to be lower compared with F1

controls. The average gestation duration of F1 animals derived from high-dose F0 mating pairs was found to be significantly longer than F1 controls. F1 sperm motility analyses did not differ among experimental groups and no gross abnormalities were identified at necropsy among surviving F1 animals at PND 120. Histopathology of kidneys, spleen, thymus, bone marrow, ovaries, and testes of F1 high-dose animals did not differ from F1 controls. F1 high-dose females had significantly higher mean relative liver and heart weights compared with F1 controls; the biological relevance of this finding could not be determined. For the F2 generation, measures of F2 development through PND 20 were unremarkable and no gross abnormalities were observed in F2 offspring. Necropsy findings of F2 PND 20 pups were negative and no instances of ribcage malformation were observed in F2 PND 20 pups. Body weight and body weight gain of F2 rats through PND 90 were similar across treatment groups. Mean relative heart weights of males derived from high-dose F0 parents were significantly lower compared with F2 controls. Sperm motility and concentration analysis of F2 males at PND 90 were similar across F2 groups. Overall, the consistent absence of positive findings in this study seems to suggest that DU is not a significant reproductive or developmental hazard, particularly when one considers that mid- and high-dose rats were implanted with the equivalent of 0.3 and 0.5 lb of DU in a 70-kg human, respectively. However, the findings that seven of eight F1 adults that died postweaning were from DU-implanted F0 mating pairs, and that mean relative heart weights were elevated in high-dose F1 and F2 pups, suggest conservatism is warranted in characterizing the reproductive and teratogenic hazards of embedded DU until further studies are completed.

Restraint stress does not enhance the uranium-induced developmental and behavioral effects in the offspring of uranium-exposed male rats.
Albina M. L., Belles M., Linares V., Sanchez D. J. and Domingo J. L.
Toxicology 2005, 215(1-2):69-79.

The influence of stress on postnatal development and behavior was assessed in the offspring of male rats exposed to uranium (U). Eight groups of adult animals received uranyl acetate dihydrate (UAD) in the drinking water at doses of 0, 10, 20 and 40 mg/kg/day during 3 months. One half of rats in each group were concurrently subjected to restraint stress during 2 h per day throughout the study. At the end of the experimental period, male rats were mated with untreated females (1:2). On gestation day 14, one half of pregnant rats were euthanized in order to evaluate maternal toxicity and gestational parameters. The remaining dams were allowed to deliver and wean their offspring. Pups were evaluated for physical development, neuromotor maturation, as well as for behavioral effects. Restraint significantly increased the gravid uterine weight at 40 mg/kg/day. However, no significant interactions between restraint and U could be established in the remaining parameters of maternal toxicity. In the offspring, no remarkable effects of U, restraint or their combination were noted on developmental landmarks, or in the passive avoidance and water maze test. It is concluded that at the current U doses, restraint stress did not enhance the few uranium-induced physical, neuromotor and behavioral changes in the offspring of UAD-exposed male rats.

Influence of maternal stress on uranium-induced developmental toxicity in rats.
Albina M. L., Belles M., Gomez M., Sanchez D. J. and Domingo J. L.
Exp Biol Med (Maywood) 2003, Oct; 228(9):1072-7

It has been demonstrated that uranium is an embryo/fetal toxicant when given orally or subcutaneously to pregnant mice. On the other hand, maternal stress has been shown to enhance the developmental toxicity of a number of metals. In this study, maternal toxicity and developmental effects of a concurrent exposure to uranyl acetate dihydrate (UAD) and restraint stress were evaluated in rats. Four groups of pregnant animals were given subcutaneous injections of UAD at 0.415 and 0.830 mg/kg/day on Days 6 to 15 of gestation. Animals in two of these groups were also subjected to restraint for 2 hr/day during the same gestational days. Control groups included restrained and unrestrained pregnant rats not exposed to UAD. Cesarean sections were performed on gestation Day 20, and the fetuses were weighed and examined for malformations and variations. Maternal toxicity and embryotoxicity were noted at 0.830 mg/kg/day of UAD, while fetotoxicity was evidenced at 0.415 and 0.830 mg/kg/day of UAD by significant reductions in fetal body weight and increases in the total number of skeletally affected fetuses. No teratogenic effects were noted in any group. Maternal restraint enhanced uranium-induced embryo/fetal toxicity only at 0.830 mg/kg/day, a dose that was also significantly toxic to the dams. As in previous studies with other metals, maternal stress enhances uranium-induced developmental toxicity at uranium doses that are highly toxic to the dams; however, at doses that are less acutely toxic the role of maternal stress would not be significant.

Effectiveness of sodium 4,5-dihydroxybenzene-1,3-disulfonate (Tiron) in protecting against uranium-induced developmental toxicity in mice.
Bosque M. A., Domingo J. L., Llobet J. M. and Corbella J.
Toxicology. 1993;79(2):149-56.

The effect of Tiron (sodium 4,5-dihydroxybenzene-1,3-disulfonate), a chelating agent used in the treatment of experimental poisoning by a number of heavy metals, on uranium-induced developmental toxicity was evaluated in Swiss mice. A series of four Tiron injections was administered intraperitoneally to pregnant mice immediately after a single subcutaneous injection of 4 mg/kg of uranyl acetate dihydrate given on day 10 of gestation and at 24, 48, and 72 h thereafter. Controls received 0.9% saline with or without uranyl acetate. Tiron effectiveness was assessed at 500, 1000 and 1500 mg/kg per day. Amelioration by Tiron of uranium-induced embryolethality was not noted at the two lower doses. The percentage of dead and resorbed fetuses in the Tiron-treated groups was not statistically different from that in the positive control group. However, treatment at 1500 mg/kg per day showed isolated protective effects against uranium fetotoxicity, such as that evidenced by the lack of differences in fetal body weight between this group and the uranium-untreated group, as well as by a decrease in the number of skeletal defects. According to these results, the ability of Tiron to protect the

developing mouse fetus against uranium-induced developmental toxicity offers only modest encouragement with regard to its possible therapeutic potential for pregnant women exposed to this metal.

Evaluation of the perinatal and postnatal effects of uranium in mice upon oral administration.
Domingo J. L., Ortega A., Paternain J. L. and Corbella J.
Arch Environ Health. 1989;44 (6):395-8.

Perinatal and postnatal studies were performed in Swiss mice given uranium--as uranyl acetate dihydrate--at daily dosages of 0, 0.05, 0.5, 5, and 50 mg/kg from day 13 of pregnancy until weaning of the litters on day 21 post-birth. Postnatal development was monitored after 0, 4, and 21 d of lactation. At doses of 0, 0.05, 0.5, and 5 mg/kg.d, treatment with uranium had no significant effect on sex ratios, mean litter size, pup body weight, or pup body length throughout lactation. Significant decreases in the mean litter size on postnatal day 21, and in the viability and lactation indices were observed at the 50 mg/kg.d dose level. When comparing the “no observable effect level” (NOEL) for reproductive effects of uranium, with the concentrations of the metal usually ingested by men, a safety factor below 1,000 can be estimated.

The developmental toxicity of uranium in mice.
Domingo J. L., Paternain J. L., Llobet J. M. and Corbella J.
Toxicology. 1989;55(1-2):143-52.

To evaluate the developmental toxicity of uranium, 5 groups of 20 pregnant Swiss mice were given by gavage daily doses of 0, 5, 10, 25 and 50 mg/kg of uranyl acetate dihydrate on gestational days 6-15. Cesarean sections were performed on all females on gestation day 18. Fetuses were examined for external, visceral, and skeletal abnormalities. The results indicated that such exposure resulted in maternal toxicity as evidenced by reduced weight gain and food consumption during treatment, and increased relative liver weight. There were no treatment-related effects on the number of implantation sites per dam, or on the incidence of postimplantation loss (resorptions plus dead fetuses). The number of live fetuses per litter and the fetal sex ratio were not affected by the treatment. However, dose-related fetal toxicity, consisting primarily of reduced fetal body weight and body length, and an increased incidence of abnormalities was observed. Malformations (cleft palate, bipartite sternebrae) and developmental variations (reduced ossification and unossified skeletal variations) were noted at the 25 and 50 mg/kg per day test levels. Therefore, administration of uranyl acetate dihydrate during organogenesis in mice produced maternal toxicity at 5, 10, 25 and 50 mg/kg per day. The ”no observable effect level” (NOEL) for fetotoxicity including teratogenicity was below 5 mg/kg per day, as some anomalies were observed at this dose. There was no evidence of embryolethality at any dosage level used in this study.

The effects of uranium on reproduction, gestation, and postnatal survival in mice.
Paternain J. L., Domingo J. L., Ortega A. and Llobet J. M.
Ecotoxicol Environ Saf. 1989;17(3):291-6.

Uranyl acetate dihydrate was tested for its effects on reproduction, gestation, and postnatal survival in Swiss mice. Four groups of animals, each of which consisted of 25 males and 25 females, were administered 0, 5, 10, and 25 mg/kg/day of uranyl acetate dihydrate. Mature male mice were treated orally for 60 days prior to mating with mature virgin female mice treated orally for 14 days prior to mating. Treatment of the females continued throughout mating, gestation, parturition, and nursing of the litters. One-half of the dams in each group were sacrificed on Day 13 of gestation and the remaining dams were allowed to deliver and wean their offspring. Postnatal development was monitored after 0, 4, and 21 days of lactation. No adverse effects on fertility were evident at the doses employed in this study. Nevertheless, embryolethality could be observed in the 25 mg/kg/day group. Significant increases in the number of dead young per litter were seen at birth and at Day 4 of lactation in the 25 mg/kg/day group. The growth of the offspring was always significantly lower for the uranium-treated animals. However, the present results suggest that uranium does not cause any adverse effects on fertility, general reproductive parameters, or offspring survival at the concentrations usually ingested by man.

ii. Female reproductive toxicity

a. <u>Studies identified in the open literature search</u>

Two-generation reproductive toxicity study of implanted depleted uranium (DU) in CD rats.
Arfsten D. P., Still K. R., Wilfong E. R., Johnson E. W., McInturf S. M., Eggers J. S., Schaeffer D. J. and Bekkedal M. Y.
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Depleted uranium (DU) munitions and armor plating have been used in several conflicts over the last 17 yr, including the Persian Gulf War and the Iraq War. Because of its effectiveness and availability, DU will continue to be used in military applications into the foreseeable future. There is much controversy over the use of DU in weapons and equipment because of its potential radiological and toxic hazards, and there is concern over the chronic adverse health effects of embedded DU shrapnel in war veterans and bystanders. This study evaluated the effects of long-term implantation of DU on the reproductive success of F0 generation adults and development and survival of subsequent F1 and F2 generations in a two-generation reproductive toxicity study. F0 generation Sprague-Dawley rats, 8 wk of age, were surgically implanted with 0, 4, 8, 12, or 20 DU pellets (1 x 2 mm). Inert implant control animals were implanted with 12 or 20 tantallum (Ta) pellets. The F0 generation was then mated at 120 d post DU implantation. In the F0 generation, when measured on postimplantation d 27 and 117, uranium was present in the urine of DU-implanted animals in a dose-dependent

manner. F0 reproductive success was similar across treatment groups and the maternal retrieval test revealed no changes in maternal behavior. DU implantation exerted no effect on the survival, health, or well-being of the F0 generation. Necropsy results of F0 animals were negative with the exception of a marked inflammatory response surrounding the implanted DU pellets. For the F1 generation, measures of F1 development through postnatal day (PND) 20 were unremarkable and no gross abnormalities were observed in F1 offspring. No uranium was detected in whole-body homogenates of PND 4 or PND 20 pups. Necropsy findings of F1 PND 20 pups were negative and no instances of ribcage malformation were observed in F1 PND 20 pups. Body weight and body weight gain of F1 rats through PND 120 were similar across treatment groups. Eight of 414 F1 animals observed from PND 20 to 120 died of unknown causes; 7 were from litters of DU-implanted F0 mating pairs. F1 mating success at 10 wk of age was an overall 70% compared with 91% for F0 mating pairs. Mating success was similar between F1 animals derived from DU-implanted F0 adults and those derived from F0 implant control adults suggesting that the comparatively low mating success was not due to F1 DU exposure. The gestational index of F1 animals derived from mid-dose F0 mating pairs was found to be lower compared with F1 controls. The average gestation duration of F1 animals derived from high-dose F0 mating pairs was found to be significantly longer than F1 controls. F1 sperm motility analyses did not differ among experimental groups and no gross abnormalities were identified at necropsy among surviving F1 animals at PND 120. Histopathology of kidneys, spleen, thymus, bone marrow, ovaries, and testes of F1 high-dose animals did not differ from F1 controls. F1 high-dose females had significantly higher mean relative liver and heart weights compared with F1 controls; the biological relevance of this finding could not be determined. For the F2 generation, measures of F2 development through PND 20 were unremarkable and no gross abnormalities were observed in F2 offspring. Necropsy findings of F2 PND 20 pups were negative and no instances of ribcage malformation were observed in F2 PND 20 pups. Body weight and body weight gain of F2 rats through PND 90 were similar across treatment groups. Mean relative heart weights of males derived from high-dose F0 parents were significantly lower compared with F2 controls. Sperm motility and concentration analysis of F2 males at PND 90 were similar across F2 groups. Overall, the consistent absence of positive findings in this study seems to suggest that DU is not a significant reproductive or developmental hazard, particularly when one considers that mid- and high-dose rats were implanted with the equivalent of 0.3 and 0.5 lb of DU in a 70-kg human, respectively. However, the findings that seven of eight F1 adults that died postweaning were from DU-implanted F0 mating pairs, and that mean relative heart weights were elevated in high-dose F1 and F2 pups, suggest conservatism is warranted in characterizing the reproductive and teratogenic hazards of embedded DU until further studies are completed.

Uranium in drinking water: effects on mouse oocyte quality.
Kundt M. S., Martinez-Taibo C., Muhlmann M. C. and Furnari J. C.
Health Phys. 2009;96(5):568-74.

The aim of this work was to evaluate the reproductive toxicological effects of uranium (U) at 2.5, 5, and 10 mgU/kg/d chronically administered in drinking water for 40 d. Swiss female control mice (n = 28) and mice chronically contaminated with uranyl nitrate in drinking water (n = 36) were tested. The number and quality of ovulated oocytes, chromatin organization, and nuclear integrity were evaluated. No significant differences were obtained in the numbers of ovulated oocytes between the different groups. Nevertheless, in 1,520 of the oocytes examined, dysmorphism increased from 11.99% in the control group to 27.99%, 27.19%, and 27.43% in each of the contaminated groups, respectively, in a dose-independent manner. On the other hand, morphological chromatin organization from 880 oocytes examined showed an increase in metaphase plate abnormalities from 37.20% (+/-7.21) in the control group to 55.13% (+/-21.36), 58.29% (+/-21.72), and 64.10% (+/-12.62) in each of the contaminated groups, respectively. Cumulus cell (CC) micronucleation, a parameter of nuclear integrity, increased from 0.21% (+/-0.31) in the control group to 1.92 (+/-0.95), 2.98 (+/-0.97), and 3.2 (+/-0.98), respectively. Both metaphase plate abnormalities and CC micronucleation showed an increase in a dose-dependent manner ($r = 0.9$; $p < 0.001$). The oocyte and its microenvironment showed high sensitivity to uranium contamination by drinking water. The lowest observed adverse effect level for this system is estimated at a level below 2.5 mgU/kg/d for female mice.

Natural uranium disturbs mouse folliculogenesis in vivo and oocyte meiosis in vitro.
Arnault E., Doussau M., Pesty A., Gouget B., Van der Meeren A., Fouchet P. and Lefevre B.
Toxicology. 2008;247(2-3):80-7.

We investigated whether uranium intoxication affects female fertility by assessing its effects on ovarian function and on the oocyte. We treated two groups of female mice for 15 weeks with 5, 50 or 400 mg/L of uranyl nitrate in drinking water. In the first group, mice were euthanized immediately after intoxication. Mice of the second group were paired after intoxication with untreated males. Dams and their female pups were euthanized 3 months after the end of intoxication. We assayed the kidneys, femurs and one ovary per female for U content and collected the other ovary for histology. The number and size of all the ovarian follicles were analyzed. Mice from the first group and female pups had significantly fewer large antral follicles (Ø > 200 microm) than the untreated mice. By contrast, dams in the second group had more secondary and early preantral follicles (Ø 70-110 microm) than untreated mice. However, U had no effect on follicle atresia. We then analyzed the in vitro effects of U on oocyte maturation and fragmentation. GV-oocytes were cultured in the presence of 1mM uranyl acetate and observed for 72 h. Oocyte maturation was slowed down by U during resumption of meiosis and at metaphase II. However, the rhythm and rate of oocyte fragmentation

were similar to those of control mice. Our findings demonstrate that U induces changes in folliculogenesis and oocyte maturation in mice and could consequently represent a risk for women who are chronically exposed.

Alteration of mouse oocyte quality after a subchronic exposure to depleted Uranium.
Feugier A., Frelon S., Gourmelon P. and Claraz M.
Reprod Toxicol. 2008;26(3-4):273-7.

Gametes and embryo tissues are known to represent a sensitive target to environmental toxicants exposure. Oocyte quality can impact subsequent developmental competence, pregnancy course and even adult health. The major health concern from depleted uranium (DU) is mainly centred on its chemotoxic properties as a heavy metal. Little attention was paid to the impact of uranium on female gamete quality. The aim of this research was to evaluate the effect of DU on mouse oocyte quality after 49 days of subchronic contamination in drinking water and to correlate the observed effects with the amount of DU accumulated in organs. Four different DU concentrations were investigated: 0 (control), 10 (DU10), 20 (DU20) and 40 mg L(-1) (DU40). DU did not influence the intensity of ovulation but affected oocyte quality. The proportion of healthy oocytes was reduced by half ($P < 0.001$) from 20 mg L(-1) compared with control group (0.537; 0.497; 0.282 and 0.239 in control, DU10, DU20 and DU40 groups respectively) whereas no accumulation of DU was recorded in the ovaries whatever the dose tested. Abnormal perivitelline space ($P < 0.001$) or absence of the 1st polar body ($P < 0.001$) was identified as the main characteristic of DU impact. In the context of this study, the NOAEL for oocyte quality was determined at 10 mg L(-1) in drinking water (1.9 mg kg(-1)day(-1)). An increase in the dose of contamination over 20 mg L(-1) did not amplify the proportion of oocytes contracting a specific alteration but conducted to a diversification in oocytes abnormalities. Further investigations are necessary to correlate morphologic assessment of female gamete with its developmental competence.

The effects of uranium on reproduction, gestation, and postnatal survival in mice.
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iii. Male reproductive toxicity

a. <u>Studies identified in the open literature search</u>

Preconceptional paternal exposure to depleted uranium: transmission of genetic damage to offspring.
Miller A. C., Stewart M. and Rivas R.
Health Phys. 2010;99(3):371-9.

Depleted uranium (DU) is an alpha particle emitter and radioactive heavy metal used in military applications. Due to internalization of DU during military operations and the ensuing chronic internal exposure to DU, there are concerns regarding its potential health effects. Preconceptional paternal irradiation has been implicated as a causal factor in childhood cancer and it has been suggested that this paternal exposure to radiation may play a role in the occurrence of leukemia and other cancers to offspring. Similarly, in vivo heavy metal studies have demonstrated that carcinogenic effects can occur in unexposed offspring. Using a transgenic mouse system employing a lambda shuttle vector allowing mutations (in the lacI gene) to be analyzed in vitro, we have investigated the possibility that chronic preconceptional paternal DU exposure can lead to transgenerational transmission of genomic instability. The mutation frequencies in vector recovered from the bone marrow cells of the F1 offspring of male parents exposed to low, medium, and high doses of internalized DU for 7 mo were evaluated and compared to control, tantalum, nickel, and gamma radiation F1 samples. Results demonstrate that as paternal DU-dose increased there was a trend towards higher mutation frequency in vector recovered from the DNA obtained from bone marrow of F1 progeny; medium and high dose DU exposure to P1 fathers resulted in a significant increase in mutation frequency in F1 offspring (3.57 +or - 0.37 and 4.81 + or - 0.43 x 10; $p < 0.001$) in comparison to control (2.28 + or - 0.31 x 10). The mutation frequencies from F1 offspring of low dose DU, Ta- or Ni-implanted fathers (2. 71 + or - 0.35, 2.38 + or - 0.35, and 2.93 + or - 0.39 x 10, respectively) were not significantly different than control levels (2.28 + or - 0.31 x 10). Offspring from Co (4 Gy) irradiated fathers did demonstrate an increased lacI mutation frequency (4.69 + or - 0.48 x 10) as had been shown previously. To evaluate the role of radiation involved in the observed DU effects, males were exposed to equal concentrations (50 mg U L) of either enriched uranium or DU in their drinking water for 2 mo prior to breeding. A comparison of these offspring indicated that there was a specific-activity dependent increase in offspring bone marrow mutation frequency. Taken together these uranyl nitrate data support earlier results in

other model systems showing that radiation can play a role in DU-induced biological effects in vitro. However, since the lacI mutation model measures point mutations and cannot measure large deletions that are characteristic of radiation damage, the role of DU chemical effects in the observed offspring mutation frequency increase may also be significant. Regardless of the question of DU-radiation vs. DU-chemical effects, the data indicate that there exists a route for transgenerational transmission of factor(s) leading to genomic instability in F1 progeny from DU-exposed fathers.

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Depleted uranium (DU) munitions and armor plating have been used in several conflicts over the last 17 yr, including the Persian Gulf War and the Iraq War. Because of its effectiveness and availability, DU will continue to be used in military applications into the foreseeable future. There is much controversy over the use of DU in weapons and equipment because of its potential radiological and toxic hazards, and there is concern over the chronic adverse health effects of embedded DU shrapnel in war veterans and bystanders. This study evaluated the effects of long-term implantation of DU on the reproductive success of F0 generation adults and development and survival of subsequent F1 and F2 generations in a two-generation reproductive toxicity study. F0 generation Sprague-Dawley rats, 8 wk of age, were surgically implanted with 0, 4, 8, 12, or 20 DU pellets (1 x 2 mm). Inert implant control animals were implanted with 12 or 20 tantallum (Ta) pellets. The F0 generation was then mated at 120 d post DU implantation. In the F0 generation, when measured on postimplantation d 27 and 117, uranium was present in the urine of DU-implanted animals in a dose-dependent manner. F0 reproductive success was similar across treatment groups and the maternal retrieval test revealed no changes in maternal behavior. DU implantation exerted no effect on the survival, health, or well-being of the F0 generation. Necropsy results of F0 animals were negative with the exception of a marked inflammatory response surrounding the implanted DU pellets. For the F1 generation, measures of F1 development through postnatal day (PND) 20 were unremarkable and no gross abnormalities were observed in F1 offspring. No uranium was detected in whole-body homogenates of PND 4 or PND 20 pups. Necropsy findings of F1 PND 20 pups were negative and no instances of ribcage malformation were observed in F1 PND 20 pups. Body weight and body weight gain of F1 rats through PND 120 were similar across treatment groups. Eight of 414 F1 animals observed from PND 20 to 120 died of unknown causes; 7 were from litters of DU-implanted F0 mating pairs. F1 mating success at 10 wk of age was an overall 70% compared with 91% for F0 mating pairs. Mating success was similar between F1 animals derived from DU-implanted F0 adults and those derived from F0 implant control adults suggesting that the comparatively low mating success was not due to F1 DU exposure. The gestational index of F1 animals derived from mid-dose F0 mating pairs was found to be lower compared with F1

controls. The average gestation duration of F1 animals derived from high-dose F0 mating pairs was found to be significantly longer than F1 controls. F1 sperm motility analyses did not differ among experimental groups and no gross abnormalities were identified at necropsy among surviving F1 animals at PND 120. Histopathology of kidneys, spleen, thymus, bone marrow, ovaries, and testes of F1 high-dose animals did not differ from F1 controls. F1 high-dose females had significantly higher mean relative liver and heart weights compared with F1 controls; the biological relevance of this finding could not be determined. For the F2 generation, measures of F2 development through PND 20 were unremarkable and no gross abnormalities were observed in F2 offspring. Necropsy findings of F2 PND 20 pups were negative and no instances of ribcage malformation were observed in F2 PND 20 pups. Body weight and body weight gain of F2 rats through PND 90 were similar across treatment groups. Mean relative heart weights of males derived from high-dose F0 parents were significantly lower compared with F2 controls. Sperm motility and concentration analysis of F2 males at PND 90 were similar across F2 groups. Overall, the consistent absence of positive findings in this study seems to suggest that DU is not a significant reproductive or developmental hazard, particularly when one considers that mid- and high-dose rats were implanted with the equivalent of 0.3 and 0.5 lb of DU in a 70-kg human, respectively. However, the findings that seven of eight F1 adults that died postweaning were from DU-implanted F0 mating pairs, and that mean relative heart weights were elevated in high-dose F1 and F2 pups, suggest conservatism is warranted in characterizing the reproductive and teratogenic hazards of embedded DU until further studies are completed.

Parental exposure to enriched uranium induced delayed hyperactivity in rat offspring.
Houpert P., Frelon S., Lestaevel P., Bussy C., Gourmelon P. and Paquet F. Neurotoxicology. 2007;28(1):108-13.

Several recent reports suggest that chronic exposure to uranium could induce behavioural effects in adult rats. As the immature brains are known to be more susceptible to toxic effects, rats were observed in an open field, in a Y-maze and in an elevated plus-maze at 2, 5 and 9 months old after exposure to enriched uranium (40 mg l-1) during gestation and lactation. The rats exposed to enriched uranium showed a significant decrease in alternation in the Y-maze at 2 months old which reflects a slight decrease in the spatial working memory capacities as previously described in adult rats. However, the main result was a delayed hyperactivity in the rats exposed to enriched uranium, which appeared to a slight extent at 5 months old and was more evident at 9 months old. Although this effect could not be directly explained by some uranium accumulation in the target organs, this experiment showed that early exposure to enriched uranium can induce a very late effect on the rat behaviour and that such studies should not be restricted to the effects observed on young rats.

Assessment of the pro-oxidant activity of uranium in kidney and testis of rats.
Linares V., Belles M., Albina M. L., Sirvent J. J., Sanchez D. J. and Domingo J. L.
Toxicol Lett. 2006;167(2):152-61.

The pro-oxidant activity of uranium (U) was assessed in kidney and testes of male rats, tissues in which toxic effects of this metal are well established. Eight groups of Sprague-Dawley rats received uranyl acetate dihydrate (UAD) in the drinking water at 0, 10, 20, and 40 mg/kgday for 3 months. Rats in four groups were concurrently subjected to restraint during 2 h/day throughout the study. Histopathological examination of the kidneys revealed an angiomatose transformation in U-treated animals. In kidney, thiobarbituric acid-reactive substances (TBARS) levels and oxidized glutathione (GSSG) activity were correlated with U exposure. The superoxide dismutase (SOD) activity was significantly enhanced in both kidney and testis. Oral UAD administration induced a decrease of glutathione reductase (GR) and reduced glutathione (GSH) in the male reproductive tract. The results of this study suggest that graded doses of U elicit depletion of the antioxidant defence system of the rat and induce oxidative stress in testes and kidneys. Although at the current U doses, restraint stress scarcely showed additional adverse effects, its potential influence should not be underrated.

Combined action of uranium and stress in the rat. II. Effects on male reproduction.
Linares V., Albina M. L., Belles M., Mayayo E., Sakharov D. G., Sanchez D. J. and Domingo J. L.
Toxicol Lett. 2005;158(3):186-95.

The effects of stress on the potential reproductive toxicity of long-term exposure to uranyl acetate dihydrate (UAD) were assessed in adult male rats. Six groups of animals were given UAD at 10, 20, and 40 mg/kg/day in the drinking water during 3 months. Animals in three of these groups were also subjected to restraint for 2 h/day during the same period. Control groups included restrained and unrestrained male rats not exposed to UAD. To evaluate the fertility, male rats were mated with untreated females for 2 weeks. Although body weight was not affected by uranium at any dose, there was a significant (not dose-related) decrease in the pregnancy rate. Moreover, spermatid number/testis was significantly decreased by uranium administration. Histopathological examination of the testes in rats killed after 3 months of treatment revealed few differences in the tubule and interstitial alterations (focal atrophy, binucleated cells) between control and uranium-exposed animals. The results of this investigation show that at the current UAD doses, restraint stress did not enhance the uranium-induced adverse effects on reproduction in male rats.

Influence of chronic exposure to uranium on male reproduction in mice.
Llobet J. M., Sirvent J. J., Ortega A. and Domingo J. L.
Fundam Appl Toxicol. 1991;16(4):821-9.

Relatively few data are available concerning the reproductive and developmental toxicity of uranium. The present study was designed to evaluate the reproductive effects of this metal in male Swiss mice. The animals were treated with uranyl acetate dihydrate at doses of 0, 10, 20, 40, and 80 mg/kg/day given in the drinking water for 64 days. To evaluate the fertility of the uranium-treated males, mice were mated with untreated females for 4 days. There was a significant but non-dose-related decrease in the pregnancy rate of these animals. Body weights were significantly depressed only in the 80 mg/kg/day group. Testicular function/spermatogenesis was not affected by uranium at any dose, as evidenced by normal testes and epididymis weights and normal spermatogenesis, whereas interstitial alterations and vacuolization of Leydig cells were seen at 80 mg/kg/day. The results of this investigation indicate that uranium does not cause any adverse effect on testicular function in mice at the concentrations usually ingested in the diet and drinking water, with a safety factor of more than 1000. However, although spermatogenesis was not affected by uranium administration, uranium produces a significant decrease in the pregnancy rate at 10, 20, 40, or 80 mg/kg/day.

Detection of DNA damage in spermiogenic stages of mice treated with enriched uranyl fluoride by alkaline elution.
Hu Q. Y. and Zhu S. P.
Radiat Environ Biophys. 1990;29(3):161-7.

DNA breakage in spermiogenic stages of mice treated with enriched uranyl fluoride (UO2F2) was studied using an alkaline elution technique. Mature spermatozoa were sampled from the animal's vas and eluted with a buffer (PH 12.2) at 3-day intervals over a 33-day period after i.p. injection of 2 mg UO2F2/kg and always at 36 days after thymidine labeling in the testes. Elution of sperm DNA from treated animals varied with spermiogenic stages. At 12 days after exposure the amount of the elution of sperm DNA was found highest and increased with the increasing UO2F2 dose up to 6 mg/kg.

Induction of chromosomal aberrations in male mouse germ cells by uranyl fluoride containing enriched uranium.
Hu Q. Y. and Zhu S. P.
Mutat Res. 1990;244(3):209-14.

Cytogenetic damage induced by a wide range of concentrations of uranyl fluoride injected into mouse testes was evaluated by determining the frequencies of chromosomal aberrations in spermatogonia and primary spermatocytes. Breaks, gaps and polyploids were observed in spermatogonia. The frequencies of the significant type of aberration, breaks, were induced according to the injected doses of uranyl fluoride. Primary spermatocytes were examined for fragments, univalents and multivalents. The

multivalents observed in this study resulted either from chromatid interchanges or from reciprocal translocations. The reciprocal translocations were induced in spermatogonia and recorded in primary spermatocytes. For primary spermatocytes the incidence of aberrant cells largely depended on the administered dose. Sampling time after treatment could affect the frequencies of chromosomal aberrations in male mouse germ cells.

The effects of uranium on reproduction, gestation, and postnatal survival in mice.
Paternain J. L., Domingo J. L., Ortega A. and Llobet J. M.
Ecotoxicol Environ Saf. 1989;17(3):291-6.

Uranyl acetate dihydrate was tested for its effects on reproduction, gestation, and postnatal survival in Swiss mice. Four groups of animals, each of which consisted of 25 males and 25 females, were administered 0, 5, 10, and 25 mg/kg/day of uranyl acetate dihydrate. Mature male mice were treated orally for 60 days prior to mating with mature virgin female mice treated orally for 14 days prior to mating. Treatment of the females continued throughout mating, gestation, parturition, and nursing of the litters. One-half of the dams in each group were sacrificed on Day 13 of gestation and the remaining dams were allowed to deliver and wean their offspring. Postnatal development was monitored after 0, 4, and 21 days of lactation. No adverse effects on fertility were evident at the doses employed in this study. Nevertheless, embryolethality could be observed in the 25 mg/kg/day group. Significant increases in the number of dead young per litter were seen at birth and at Day 4 of lactation in the 25 mg/kg/day group. The growth of the offspring was always significantly lower for the uranium-treated animals. However, the present results suggest that uranium does not cause any adverse effects on fertility, general reproductive parameters, or offspring survival at the concentrations usually ingested by man.

Gametogenic count and histopathological effect of thorium nitrate and uranyl nitrate on mice testes.
Jadon A. and Mathur R.
Andrologia. 1983;15(1):40-3.

Daily intraperitoneal administration of aqueous solution of 0.05 m mole/100 g b. wt. of uranyl nitrate and thorium nitrate has been observed for 7 days. Marked reduction in the seminiferous tubule diameter and gametogenic count was observed. Signs of testicular necrosis, exfoliation of germ cells, and karyolysis and karyorrhexis were seen in most of the tutubles. Mononucleate and polynucleate giant cells were also observed indicating prolonged pathological condition.

Effect of uranium on the induction and course of experimental autoimmune orchitis and thyroiditis.
Malenchenko A. F., Barkun N. A. and Guseva G. F.
J Hyg Epidemiol Microbiol Immunol. 1978;22(3):268-77.

The influence of acute and chronic uranium poisoning on the induction and course of experimental autoimmune thyroiditis and orchitis was studied. It has been demonstrated that the testes and thyroid gland are involved in the general pathological process in uranium poisoning. Autoantibodies to the testes and to the thyroid gland were found to circulate in the blood of the poisoned animals. Uranium poisoning caused destructive changes in the testes and in the thyroid, similar to the picture of an autoimmune process. No summation of the effect was observed in the synthesis of autoantibodies during the induction of experimental autoimmune thyroiditis and orchitis on the background of chronic uranium poisoning although the most conspicuous histological changes were found in these groups and were characteristic of a pronounced autoimmune process.

B. Studies reporting no developmental or reproductive toxicity

Evaluation of the effect of implanted depleted uranium on male reproductive success, sperm concentration, and sperm velocity.
Arfsten D. P., Schaeffer D. J., Johnson E. W., Robert Cunningham J., Still K. R. and Wilfong E. R.
Environ Res. 2006;100(2):205-15.

Depleted uranium (DU) projectiles have been used in battle in Iraq and the Balkans and will continue to be a significant armor-penetrating munition for the US military. As demonstrated in the Persian Gulf War, battle injury from DU projectiles and shrapnel is a possibility, and removal of embedded DU fragments from the body is not always practical because of their location in the body or their small size. Previous studies in rodents have demonstrated that implanted DU mobilizes and translocates to the gonads, and natural uranium may be toxic to spermatazoa and the male reproductive tract. In this study, the effects of implanted DU pellets on sperm concentration, motility, and male reproductive success were evaluated in adult (P1) Sprague-Dawley rats implanted with 0, 12, or 20, DU pellets of 1x2 mm or 12 or 20 tantalum (Ta) steel pellets of 1x2 mm. Twenty DU pellets of 1x2 mm (760 mg) implanted in a 500-g rat are equal to approximately 0.2 pound of DU in a 154-lb (70-kg) person. Urinary analysis found that male rats implanted with DU were excreting uranium at postimplantation days 27 and 117 with the amount dependent on dose. No deaths or evidence of toxicity occurred in P1 males over the 150-day postimplantation study period. When assessed at postimplantation day 150, the concentration, motion, and velocity of sperm isolated from DU-implanted animals were not significantly different from those of sham surgery controls. Velocity and motion of sperm isolated from rats treated with the positive control compound alpha-chlorohydrin were significantly reduced compared with sham surgery controls. There was no evidence of a detrimental effect of DU implantation on mating

success at 30-45 days and 120-145 days postimplantation. The results of this study suggest that implantation of up to 20 DU pellets of 1x2 mm in rats for approximately 21% of their adult lifespan does not have an adverse impact on male reproductive success, sperm concentration, or sperm velocity.

Study of the reproductive effects in rats surgically implanted with depleted uranium for up to 90 days.
Arfsten D. P., Bekkedal M., Wilfong E. R., Rossi J., 3rd, Grasman K. A., Healey L. B., Rutkiewicz J. M., Johnson E. W., Thitoff A. R., Jung A. E., Lohrke S. R., Schaeffer D. J. and Still K. R.
J Toxicol Environ Health A. 2005;68(11-12):967-97.

In 2001, the Naval Health Research Center Toxicology Detachment was funded by the U.S. Army Medical Research Acquisition Activity (USAMRAA) to conduct a study of the effects of surgically implanted depleted uranium (DU) pellets on adult rat reproductive success and development across two successive generations. This article presents some of the findings for the group of offspring from adult rats mated at 30 d post surgical implantation of DU pellets. Adult male and female Sprague-Dawley rats (P1 generation) were surgically implanted with 0, 4, 8, or 12 DU pellets (1 x 2 mm). The P1 generation was then cross-mated at 30 d post surgical implantation. Urine collected from P1 animals at 27 d post surgical implantation showed that DU was excreted in the urine of DU-implanted animals in a dose-dependent manner. DU surgical implantation did not have a negative impact on P1 reproductive success, survival, or body weight gain through post surgical implantation d 90. There were no statistically significant differences in F1 birth weight, survival, and litter size at postnatal day (PND) 0, 5, and 20. No gross physical abnormalities identified in the offspring were attributable to neonatal DU exposure. A series of neurodevelopment and immune function assessments were also conducted on F1 offspring. No group differences were observed that were related to parental DU exposure. Studies are ongoing on the impact of leaving DU embedded in soft tissue for 120 d on rat reproduction and subsequent offspring survival and development.

II. Epidemiologic Developmental and Reproductive Toxicity Studies

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

i. Developmental toxicity

Navajo birth outcomes in the Shiprock uranium mining area.
Shields L. M., Wiese W. H., Skipper B. J., Charley B. and Benally L.
Health Phys. 1992;63(5):542-51.

The role of environmental radiation in the etiology of birth defects, stillbirths, and other adverse outcomes of pregnancy was evaluated for 13,329 Navajos born at the Public Health Service/Indian Health Service Hospital in the Shiprock, NM, uranium mining area

(1964-1981). More than 320 kinds of defective congenital conditions were abstracted from hospital records. Using a nested case-control design, families of 266 pairs of index and control births were interviewed. The only statistically significant association between uranium operations and unfavorable birth outcome was identified with the mother living near tailings or mine dumps. Among the fathers who worked in the mines, those of the index cases had histories of more years of work exposure but not necessarily greater gonadal dosage of radiation. Also, birth defects increased significantly when either parent worked in the Shiprock electronics assembly plant. Overall, the associations between adverse pregnancy outcome and exposure to radiation were weak and must be interpreted with caution with respect to implying a biogenetic basis.

ii. Female reproductive toxicity

There were no reports identified for this category.

iii. Male reproductive toxicity

Unexpected rates of chromosomal instabilities and alterations of hormone levels in Namibian uranium miners.
Zaire R., Notter M., Riedel W. and Thiel E.
Radiat Res. 1997;147(5):579-84.

A common problem in determining the health consequences of radiation exposure is factoring out other carcinogenic influences. The conditions in Namibia provide a test case for distinguishing the effects of long-term low-dose exposure to uranium from the other environmental factors because of good air quality and the lack of other industries with negative health effects. Present records indicate a much higher prevalence of cancer among male workers in the open-pit uranium mine in Namibia compared with the general population. The objective of the present study was to determine whether long-term exposure to low doses of uranium increases the risk of a biological radiation damage which would lead to malignant diseases and to derive a dose-response model for these miners. To investigate this risk, we measured uranium excretion in urine, neutrophil counts and the serum level of FSH, LH and testosterone and analyzed chromosome aberrations in whole blood cells using fluorescence in situ hybridization. A representative cohort of 75 non-smoking, HIV-negative miners was compared to a control group of 31 individuals with no occupational history in mining. A sixfold increase in uranium excretion among the miners compared to the controls was recorded ($P < 0.001$). Furthermore, we determined a significant reduction in testosterone levels ($P < 0.008$) and neutrophil count ($P < 0.004$) in miners compared to the unexposed controls. A threefold increase in chromosome aberrations in the miners compared to the nonexposed controls was recorded ($P < 0.0001$). Most remarkably, cells with multiple aberrations such as "rogue" cells were observed for the first time in miners; these cells had previously been found only after short-term high-dose radiation exposure, e.g. from the Hiroshima atomic bomb or the Chernobyl accident. We conclude that the miners

exposed to uranium are at an increased risk to acquire various degrees of genetic damage, and that the damage may be associated with an increased risk for malignant transformation. As expected, the chronic radiation injury of the hematopoietic system resulted in low neutrophil counts. Also, low hormone levels probably reflect damage to the gonadal endocrine system.

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

Incidence of major congenital malformations in a region of Bosnia and Herzegovina allegedly polluted with depleted uranium.
Sumanovi, Glamuzina D., Saraga K., Roncevi, Milanov A., Bozi and Borani
Croat Med J. 2003;44(5):579-84.

OBJECTIVES: To determine the prevalence of major congenital malformations in West Herzegovina, a part of Bosnia and Herzegovina, immediately and five years after 1991-1995 military activities, which allegedly included the use of weapons with depleted uranium. METHODS: The study included all live-born and stillborn neonates and excluded all aborted fetuses in two one-year cohorts (1995 and 2000) of neonates in the Maternity Ward of the Mostar University Hospital. Malformations were recorded according to the recommendations of the EUROCAT protocol. RESULTS: Major malformations were found in 40 (2.16%) out of 1,853 neonates in 1995 (95% confidence interval [CI], 1.49-2.82%) and in 33 (2.26%) out of 1,463 neonates five years later (95% CI, 1.50-3.01%), ie, at comparable prevalence. In both cohorts, anomalies of the musculoskeletal system were the most common, followed by anomalies of the digestive system (in 1995) and the cardiovascular system (in 2000). The prevalence of malformations and the organ systems involved were essentially comparable with those in other populations not affected by military activities. CONCLUSION: Despite alleged environmental pollution in some regions of the former Yugoslavia, which was attributed to military activities and the presence of depleted uranium (the ”Balkan syndrome”), there was no significant postwar increase in the prevalence of congenital malformations.

Analysis of the drinking water of mothers of neural tube defect infants and of normal infants for 14 selected trace elements by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS).
Longerich H. P., Friel J. K., Fraser C., Jackson S. E. and Fryer B. J.
Can J Appl Spectroscopy. 1991;36(1):15-21.

Fourteen trace elements (Mg, Cu, Zn, Sr, Y, Mo, Cd, Sn, Sb, I, Ba, Ce, Pb, and U) were determined using Inductively Coupled Plasma-Mass Spectrometry, a new and sensitive instrument for multielemental analysis. Using ICP-MS, the analysis of the drinking water of 28 women, who had given birth to an infant with a neural tube defect (NTD), along with 28 matched controls (C) is reported. For 13 of the 14 determined elements, the mean of the NTD group exceeded the mean of the C group. For most elements, there were more extremely high values in the NTD group than in the C group. For each

individual element, the difference in the results of the 2 groups, while not significantly different at the 95% confidence level, strongly suggest a relationship of trace elements in drinking water with NTD to the extent that further study is urgently suggested.

III. Other Relevant Information

A. Meeting abstracts

Effects of a low-dose-radiation on the reproductive endpoints - a 35-year analysis in a uranium mining area in saxony (germany).
Leichsenring G., Roesch C., Steinbicker V. and Arndt D. Reprod Toxicol. 2002;16(4):439-40.

Uranium levels in the fetus and placenta of female rats implanted with depleted uranium pellets prior to breeding.
Benson K. A. and McBride S. A. Toxicologist. 1997;36(1 Pt 2):258.

Amelioration by Tiron of uranium-induced embryofetotoxicity in mice.
Domingo J. L., Bosque M. A., Llobet J. M. and Corbella J. Toxicologist. 1993;13(1):299.

Developmental effects on mice after prenatal and postnatal exposure to uranium.
Domingo J. L., Ortega A., Paternain J. L., Llobet J. M. and Corbella J. Toxicologist. 1989;9(1):272.

Evaluation of the embryotoxicity of uranium in rats.
Sikov M. R. and Rommereim D. N. Teratology. 1986;33(3):41C.

B. Related articles

Effects of chronic uranium exposure on life history and physiology of Daphnia magna over three successive generations.
Massarin S., Alonzo F., Garcia-Sanchez L., Gilbin R., Garnier-Laplace J. and Poggiale J. C.. Aquat Toxicol 2010, 99(3):309-19.

Surveillance results of depleted uranium-exposed Gulf War I veterans: sixteen years of follow-up.
McDiarmid M. A., Engelhardt S. M., Dorsey C. D., Oliver M., Gucer P., Wilson P. D., Kane R., Cernich A., Kaup B., Anderson L., Hoover D., Brown L., Albertini R., Gudi R. and Squibb K. S. J Toxicol Environ Health A. 2009;72(1):14-29.

The effects of waterborne uranium on the hatching success, development, and survival of early life stages of zebrafish (Danio rerio).
Bourrachot S., Simon O. and Gilbin R. Aquat Toxicol 2008, Oct 20; 90(1):29-36.

Depleted uranium exposure and health effects in Gulf War veterans.
Squibb K. S. and McDiarmid M. A. Philos Trans R Soc Lond B Biol Sci. 2006;361(1468):639-48.

Failure to detect differences in the neurobehavioral development of rats following in utero and pre-weanling exposure to depleted uranium.
Rossi J. d., Bekkedal M. Y., McInturf S. M., McDougle F. J., Lenger A., Allen C. T. and Arfsten D. P. Neurotoxicology. 2004;25(4):718-9.

Effects of a low-dose-radiation on the reproductive endpoints - a 35-year analysis in a uranium mining area in Saxony (Germany).
Leichsenring G., Roesch C., Steinbicker V. and Arndt D. Reprod Toxicol. 2002;16(4):439-40.

Effects of uranium poisoning on cultured preimplantation embryos.
Kundt M., Ubios A. M. and Cabrini R. L. Biol Trace Elem Res. 2000;75(1-3):235-44.

[Corticosterone and testosterone in the blood of adult rats: the effects of low doses and the times of the action of ionizing radiation during intrauterine development].
Dygalo N. N., Sakharov D. G. and Shishkina G. T. (1997). Radiats Biol Radioecol. 1997 May-Jun; 37(3):377-81.

Unexpected rates of chromosomal instabilities and alterations of hormone levels in Namibian uranium miners.
Zaire R., Notter M., Riedel W. and Thiel E. Radiat Res. 1997;147(5):579-84.

[Studies on reproductive toxicity induced by enriched uranium]
Zhu S. P., Hu Q. Y. and Lun M. Y. (1994).. Zhonghua Yu Fang Yi Xue Za Zhi. 1994, Jul; 28(4):219-22.

Contribution of maternal radionuclide burdens to prenatal radiation doses: relationships between annual limits on intake and prenatal doses
Sikov M. R. and Hui T. E. NTIS Technical Report (NTIS/PB94-121787) 1993 Oct;:110 pp.

Survey of reproductive outcomes in uranium and potash mine workers: results of first analysis.
Wiese W. H. and Skipper B. J. Ann Am Conf Gov Ind Hyg. 1986;14:187-92.

C. Publications with a relevant title but no abstract

Effects of depleted uranium on development of the mouse.
Briner W. and Byrd K. Metal Ions in Biology and Medicine. 2000;6:459-61.

Evaluation of the health risks of embedded depleted uranium (DU) shrapnel on pregnancy and offspring development
Benson K. A. NTIS Technical Report (NTIS/AD-A356-238) 1998 Oct;:36 pp.

The sex ratio in the offsprings of uranium miners.
Muller C., Ruzicka L. and Bakstein J. Acta Univ Carol Med (Praha). 1967;13(7):599-603.

Oral toxicity of uranium compounds.
Maynard E., Downs W. and Hodge H. In: C. Voegtlin and H. Hodge, editors. Pharmacology and Toxicology of Uranium. New York: McGraw-Hill; 1953.