

Reproductive and developmental toxicity of natural and depleted uranium: a review

NIRS/PC Prefiled Exhibit 108□
Docketed 09/23/05

Jose L. Domingo*

Laboratory of Toxicology and Environmental Health, School of Medicine, "Rovira i Virgili" University, Reus 43201, Spain

Abstract

Although the biokinetics, metabolism, and chemical toxicity of uranium are well known, until recently little attention was paid to the potential toxic effects of uranium on reproduction and development in mammals. In recent years, it has been shown that uranium is a developmental toxicant when given orally or subcutaneously (SC) to mice. Decreased fertility, embryo/fetal toxicity including teratogenicity, and reduced growth of the offspring have been observed following uranium exposure at different gestation periods. The reproductive toxicity, maternal toxicity, embryo/fetal toxicity, and postnatal effects of uranium, as well as the prevention by chelating agents of uranium-induced maternal and developmental toxicity are reviewed here. Data on the toxic effects of depleted uranium on reproduction and development are also reviewed. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Uranium; Depleted uranium; Reproductive toxicity; Maternal toxicity; Developmental toxicity; Chelating agents

1. Introduction

1.1. Uranium toxicity

Uranium (U) is a naturally occurring element the best known use of which in the last 55 years has been as fuel in nuclear power reactors and nuclear weapons. During uranium processing, workers may inhale or ingest some uranium giving rise to internal contamination, which could result in radiation doses to the body. In addition, if uranium exposure were large enough, chemical toxicity could also occur. Under some circumstances, the chemical toxicity of soluble uranium compounds can even surpass the potential radiotoxic effects. The general population may be exposed to low levels of uranium by inhalation or through the diet. Uranium may be also introduced into drinking water supplies through the mining and milling of uranium ore [1,2].

In the early days of the Manhattan Project, a very extensive toxicology program on uranium was carried out [3,4]. The principal objectives included the establishment of exposure limits for airborne uranium in the workplace based upon uranium's known chemical renal damage. Although the biokinetics, metabolism, and chemical toxicity of ura-

nium, including the toxic effects of this metal on kidney function, are well established [5,6], until recently there was a lack of published observations regarding uranium-induced reproductive and developmental toxic effects [7]. In 1987, a program directed at filling the gaps regarding uranium reproductive and developmental toxicity in mammals as well as concerning possible prevention/amelioration by chelating agents was started in our laboratory. Although uranium can exist in oxidation states +3, +4, +5, or +6, in solution the uranyl ion (UO_2^{2+}) is the most stable species and the form in which this element is present in the mammalian body [1,7,8]. Taking this fact into account, in our studies uranium was administered as uranyl acetate. The results of those studies, together with some additional data reported by other investigators, are summarized in the present review (Table 1).

1.2. Depleted uranium toxicity

Depleted uranium (DU) is a low-level radioactive waste product of the enrichment of natural uranium with U-235 for reactor fuels or nuclear weapons. Natural uranium is approximately 99.3% composed of the U-238 isotope (by weight), and 0.7% of the U-235 isotope, with a negligible amount (about 0.005%) of U-234. All three of these uranium isotopes are primarily alpha particle emitters. The particles have a long penetrating ability and they are haz-

* Corresponding author. Tel.: +34-977-759380; fax: +34-977-759322.

E-mail address: jlldr@fmc.s.urv.es (J.L. Domingo).

Table 1

Chemical toxic effects of uranium on reproduction and development in mammals: a summary of studies

Uranium compound	Species	Doses (mg/kg/d)	Dosing period	Route	Toxic effects	NOAEL for reproductive or developmental toxicity (mg/kg/d)	Reference
Uranyl acetate dihydrate	Male mice	10, 20, 40, and 80	64 d before mating	Drinking water	Interstitial alterations at 80 mg/kg/d. Reduction in pregnancy rate at all doses	<10 mg/kg/d	Llobet et al. (23)
Uranyl nitrate hexahydrate	Male rats	Not reported	12 months	Diet	Severe degeneration in the testes, depletion of germ cells	Not available	Maynard et al. (26)
Uranyl nitrate hexahydrate	Male rats	0.07	16 weeks	Diet	Decreased testes weight, testicular lesions, necrosis of spermatocytes, spermatogonia	Not available	Malenchenko et al. (27)
Uranyl acetate dihydrate	Mice	5, 10, 25 and 50	d 6-15 of gestation	PO	Maternal toxicity, fetotoxicity including teratogenicity	<5	Domingo et al. (32)
Uranyl acetate dihydrate	Mice	0.05, 0.5, 5 and 50	d 13-18 of gestation and d 1-21 of lactation	PO	Decreases in viability and lactation indices	5	Domingo et al. (53)
Uranyl acetate dihydrate	Mice	5, 10, and 25	Males, 60 d and females 14 d before mating	PO	Lower viability indices and reduced growth of the offspring	5	Paternain et al. (24)
Uranyl acetate dihydrate	Mice	0.5, 1, and 2	d 6-15 of gestation	SC	Maternal deaths and reduction in body weight. Embryo/fetal toxicity including teratogenicity	< 0.5	Bosque et al. (34)
Uranyl acetate dihydrate	Mice	4	one of d 9-12 of gestation	SC	Embryo/fetal toxicity. Most sensitive effects: d 10		Bosque et al. (36)
Uranyl acetate dihydrate (+ Tiron)	Mice	4 + (500, 1000 and 1500 Tiron)	gestation d 10, Tiron d 10-13	SC (Tiron, IP)	Maternal and developmental toxicity in Tiron-untreated group. Tiron ameliorated the general condition of the dams.		Bosque et al. (49)

ardous only if uranium is ingested or inhaled [9]. In DU, most of the U-235 and U-234 isotopes have been selectively removed through industrial processes, meaning that the radiologic hazard of DU is less than that from natural or enriched uranium [9,10]. However, DU is also a heavy metal with toxicity being a function of route of exposure, particle solubility, contact time, and route of elimination [11]. Consequently, although DU exposure can result in both chemical toxicity and toxicity from radioactivity, the chemical toxic effects (mainly on the kidney) occur in general at lower exposure levels than the radiologic toxic effects [12]. One exception is inhalation exposure to insoluble uranium compounds, about which the main concern is increased cancer risk from the internal exposure to radioactivity. In contrast, insoluble compounds are poorly absorbed from the gastrointestinal tract, and generally have low toxicity [11].

Since the end of the Persian Gulf War, a number of soldiers who participated in that war have claimed to be suffering a new chronic illness generally known as Gulf War Syndrome (GWS), a poorly understood disease with multiple symptoms and with diversified theories about etiology and pathogenesis [13-15]. Among the potential dam-

aging risk factors in the genesis of the GWS, DU has been considered as a possible causative agent. Moreover, as a consequence of that war, a cohort of US soldiers wounded while on or in vehicles struck by DU penetrators was also identified [16,17]. The clinical health effects of DU exposure in these veterans were recently evaluated compared with nonexposed Gulf War veterans. More than 7 years after the first exposure, DU-exposed individuals with retained metal fragments continue excreting elevated concentrations of urinary uranium. Although mean values for physical characteristics of semen examined by the low and high urinary uranium groups did not show significant differences, it was stated that the results might have been biased by some differences in the processes for collecting semen [17]. At present, the reproductive health evaluation continues being explored [18]. The report on GWS of the US Presidential advisory panel in 1996 stated that there was no evidence of a connection between DU and Gulf war illnesses [10].

DU has been also used as armor-penetrating ammunition in the Balkans. It has been suggested that DU could be also related to a new illness, the Balkan syndrome, which is currently under investigation [15]. In 1992, a large cargo

Table 2
Chemical toxic effects of depleted uranium (DU) on reproduction and development in mammals: a summary of studies

Uranium	Species	Doses	Dosing period	Route	Toxic effects	NOAEL for reproductive or developmental toxicity	Reference
DU pellets	Male rats	3 dose levels	18 months	Implanted in muscle	Accumulation in testicles suggesting possible physiological consequences	Not available	Pellmar et al. (28)
DU pellets	Female rats	Not reported	Gestation	Implanted in muscle	Correlation between-uranium levels in maternal kidney, placenta, and whole fetus with increasing levels of maternal DU	Not available	Benson and McBride (39)

plane crashed into an apartment building in a quarter of Amsterdam (The Netherlands). In the years following the accident, an increasing number of people reported health complaints, which they attributed to exposure to dangerous substances after the crash. Since the aircraft had been carrying DU as a counterbalance weight, a risk analysis was performed in order to assess the possible relationship between DU exposure and the health complaints. The conclusion was that it was improbable that DU was responsible for the complaints [19].

In a recent article on the toxicity of depleted uranium in humans, Priest [20] concluded that at any conceivable level of uptake, DU would have no appreciable radiologic or chemical carcinogenic potential. Even if cancers were to be produced, they should occur many years after exposure taking into account the long period between damage to sensitive cells and the appearance of recognizable tumors. In humans, these latency periods typically lie in the range of 10 years to several decades. Consequently, tumors in individuals exposed for shorter periods (e.g. subjects exposed to DU in the former Yugoslavia within the past decade) cannot be attributed to radiation from DU, while the only chemical toxic effect expected would be reversible damage to the kidney [20]. Similar conclusions were also reached by McDiarmid [10].

The very few data on the effects of DU on reproduction that are available in the literature are also reviewed here (Table 2).

2. Reproductive toxicity of uranium

Information concerning the reproductive toxicity of uranium is scarce. Most reproductive effects of uranium are based on its chemical nature and properties rather than on its radioactive action. Zhu and associates [21] investigated in rats the reproductive toxicity induced by exposure (intratesticular injection) to enriched uranium ($^{235}\text{UO}_2\text{F}_2$) at different levels (not reported). It was found that the quantity of sperm DNA strand breakage increased with increasing doses of enriched uranium. In addition, it was noted that

$^{235}\text{UO}_2\text{F}_2$ caused skeletal abnormalities in fetal rats. In a previous study, the cytogenetic damage induced by a wide range of concentrations of uranyl fluoride injected into mouse testes had been also evaluated to determine the frequencies of chromosomal aberrations in spermatogonia and primary spermatocytes. It was observed that the damage depended on the administered dose of uranyl fluoride [22]. Both radiotoxicity and chemical toxicity of uranyl fluoride were considered to be responsible for the adverse effects.

The possibility that chronic uranium exposure of males might affect reproduction in mammals was investigated. In a study performed in our laboratory [23], male Swiss mice had as their water source for 64 days solutions of uranyl acetate dihydrate at concentrations of 0, 0.047, 0.091, 0.170, and 0.420 mg/mL, resulting in doses of 0, 10, 20, 40, and 80 mg/kg/day. In order to deliver the desired doses during the 64 days, solution concentrations were adjusted twice/week based on the measured daily fluid intake and body weight. To evaluate male fertility, animals were mated with untreated females for 4 days. There was a significant but non-dose-related decrease in the pregnancy rate of these animals (25-35% in uranium treated animals vs. 81% in the control group), while body weights were significantly reduced at 80 mg/kg/day (35.8 ± 2.04 g vs. 37.6 ± 2.53 g in the control group). Testicular function/spermatogenesis was not affected by uranium at any dose, as evidenced by normal testes and epididymis weights and normal spermatogenesis. Histopathologic examination of the testes in mice killed after 64 days of treatment did not reveal any significant difference between controls and uranium-exposed animals in tubule diameter, tubule alterations, and interstitial alterations (focal atrophy, binucleated cells), with the exception of an increase in Leydig cells vacuolization at 80 mg/kg/day. Although these changes might all have contributed to the reduction in pregnancy rate, it is also possible that uranyl acetate treatment for 64 days produced behavioral changes (including a decrease in the libido of those animals), which contributed in turn to this reduction [23]. However, in a previous study in which mature male mice were given by gavage 0, 5, 10, or 25 mg/kg/day uranyl acetate dihydrate for 60 days prior to mating with mature

virgin female mice exposed to the same uranium doses for 14 days prior to mating, no adverse effects of uranium on fertility were evident at any dose, while embryoletality was observed at 25 mg/kg/day [24].

According to the above results, the no observed adverse effect level (NOAEL) for reproductive toxicity of uranium is below 10 mg/kg/day, as at that dose the pregnancy rate was significantly diminished [23]. The oral LD₅₀ of uranyl acetate dihydrate in mice was previously found to be 242 mg/kg, with confidence limits between 155 and 327 mg/kg [25]. Therefore, 5, 10, and 25 mg/kg/day of uranyl acetate dihydrate corresponded approximately to 1/50, 1/25, and 1/10 of the acute oral LD₅₀ for this compound.

The above findings corroborated earlier studies suggesting the possibility that chronic uranium exposure in males might affect reproduction [26,27]. While a chronic diet of uranyl nitrate hexahydrate given to rats for 12 months caused severe degeneration in the testes and depletion of germ cells [26], 0.07 mg/kg/day uranyl nitrate hexahydrate added to the diet of rats for 16 weeks resulted in decreased testes weight, testicular lesions, and necrosis of spermatocytes and spermatogonia [27].

With respect to the reproductive effects of DU, Pellmar and coworkers [28] assessed in rats the potential health risks associated with chronic exposure to DU. Animals were surgically implanted with DU pellets in muscle at 3 dose levels (low-dose, 4 DU pellets; medium-dose, 10 DU pellets, and high-dose, 20 DU pellets) and uranium distribution was determined over the course of 18 months. These investigators found that although kidney and bone were the primary reservoirs for uranium redistributed from intramuscularly (IM) embedded fragments, accumulation in testicles, as well as in brain and lymph nodes, suggested the potential for unanticipated physiologic consequences of uranium exposure through this route.

In recent years, little attention has been paid to the possible effects of uranium (including DU) exposure on human reproduction. At the time of the original toxicology evaluations during the Second World War, two studies were performed, one of which featured exposure to high levels of the metal and the other of which involved only a brief 24-h exposure [29]. Although, in both studies statistically significant effects on reproduction were found (data not shown), the results were not repeated or extended by other investigators. In a study on the sex ratio of offspring of male uranium miners, more female offspring than predicted were noted, suggesting potential alterations in sperm [30]. Recently, unexpected rates of chromosomal instabilities and alterations of hormone levels were also found in uranium miners [31].

3. Maternal and embryo/fetal toxicity of uranium

According to the online database MEDLINE (<http://www.ncbi.nlm.nih.gov>), only two references concerning

experimental studies on uranium-induced embryo/fetotoxicity or teratogenicity in mammals are available. Both studies were performed in our laboratory. A second electron search was carried out using the database DART/E (Developmental and Reproductive Toxicology; <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?DARTETIC.htm>), in which some additional references were found. However, none of them directly referred to experimental studies on maternal and/or developmental toxicity of uranium in mammals.

The maternal and developmental toxicity of uranyl acetate dihydrate given by gavage at doses of 0, 5, 10, 25, and 50 mg/kg/day was evaluated in pregnant Swiss mice on gestational days 6 through 15 [32]. Maternal toxicity was evidenced by decreased weight gain and food consumption, as well as elevated relative liver weight at all dose levels tested. Thus, the NOAEL for maternal toxicity was below 5 mg/kg/day. Although there was no evidence of embryoletality at maternally toxic levels, dose-related fetal toxicity consisting primarily of reduced fetal body weight and body length, and an increased incidence of developmental anomalies were observed. External malformations and variations included cleft palate and hematomas (dorsal and facial areas). In turn, bipartite sternbrae, reduced ossification of skull and caudal bones, and poor ossification of some hindlimb metatarsals and some proximal forelimb phalanges were the most notable skeletal variations (65-100% of affected litters in the uranium-treated groups vs. 22% in the control group). Although various anomalies could be caused by a number of maternal stressors, some of the fetal defects found in this study were also reported to occur independently on maternal toxicity [33]. Consequently, the NOAEL for fetotoxicity including teratogenicity was below 5 mg/kg/day, as some anomalies were observed at this level [32].

In order to examine whether the developmental toxicity of uranium depends on the route of exposure, the effects of multiple maternal SC injections of uranyl acetate dihydrate (0, 0.5, 1, and 2 mg/kg/day) given from day 6 through 15 of gestation were evaluated in mice [34]. The doses of 0.5, 1, and 2 mg/kg/day were approximately equal to 1/40, 1/20, and 1/10 of the acute SC LD₅₀ for uranyl acetate dihydrate [25]. Maternal toxicity occurred in all uranium-treated groups as evidenced primarily by some deaths (0, 1, 2, and 7 deaths at 0, 0.5, 1, and 2 mg/kg/day, respectively) and decreases in body weight gain and body weight at termination. Embryotoxicity was also noted in all uranium-exposed groups. Fetotoxicity was indicated by a significant reduction in fetal weight and significant increases in the incidence of several unossified districts or by decreased ossification at 1 and 2 mg/kg/day (50 and 100%, respectively, of affected litters vs. 9% in the control group). Cleft palate and bipartite sternbrae were the most notable malformations observed at these doses. According to the conclusions of a review on teratology studies conducted in mice [35], the embryotoxic effects detected in our study would be attributable to a direct consequence of uranium-induced maternal toxicity. How-

ever, malformations such as cleft palate or some developmental variations were not reported to be defects resulting from maternal toxicity [35]. Consequently, they probably would be primary effects of the developmental toxicity of uranium. On the basis of these data, the NOAELs for maternal toxicity and for embryotoxicity were below 0.5 mg/kg/day, whereas the NOAEL for teratogenicity was 0.5 mg/kg/day [34].

The influence of exposure day on the embryo/fetal toxicity of uranium was also examined in mice. Single SC injections of 4 mg/kg of uranyl acetate dihydrate were given to pregnant mice on one of days 9 through 12 of gestation. Dams were killed on day 18 of pregnancy and their uterine contents examined. Although the number of dead and resorbed fetuses as well as the percentage postimplantation loss were significantly increased on any of gestation day 9 through 12, the most sensitive time for the induction of uranium embryotoxicity was gestation day 10. Uranium exposure on day 9 through 12 of gestation also resulted in significant reductions in fetal body weight (0.84 to 0.94 g in the uranium treated groups vs. 1.32 g in the control group) and a high percentage of total skeletal defects. It was concluded that gestation day 10 was the most sensitive time for uranium-induced developmental toxicity in mice [36].

The cytotoxic and genotoxic action of the uranyl ion was investigated in Chinese hamster ovary (CHO) cells. The toxic spectrum of uranyl at concentrations ranging from 0.01 to 0.3 M included decreased viability, depressed cell cycle kinetics, and increased frequencies of micronuclei, sister-chromatid exchanges, and chromosome aberrations [37], indicating that uranyl has the property of causing genotoxicity and cytotoxicity in CHO cells. The authors concluded that the cytogenetic toxicity of the uranyl ion could provide a biologic basis for the potential teratogenic effect of uranium on developing fetal mice [37]. The toxic effects of uranyl nitrate solutions (26, 52, 104, and 208 $\mu\text{g U/mL}$) in cultured preimplantation mouse embryos were recently investigated [38]. The percentage of embryos in the two-cell, morula, early blastocyst, expanded, blastocyst, and hatched blastocyst stages were recorded at 24, 72, 96, and 120 h of culture. The results showed that embryo development was delayed and cell number was lower than for controls throughout the culture period, suggesting that severe alterations might have occurred in DNA synthesis [38].

Only a short abstract regarding the maternal and/or developmental effects of DU could be found in the literature. Female rats were exposed at one of five doses (not reported) of DU via surgically implanted pellets and then bred with male rats. On gestation day 20, dams were euthanized and uranium levels in placenta, whole fetus, fetal liver, and maternal kidney were determined. Although an increasing trend of uranium levels in maternal kidney, placenta, and whole fetus with increasing levels of maternal DU implantation was noted, no maternal or fetal toxicity were evident. No adverse effects on maternal weight gain, food consumption, water intake, or histology of the kidney were observed,

and parameters such as litter size, pup weight, and sex ratio were also not affected by DU exposure [39].

In order to specifically address the association between birth defects, stillbirths, and other adverse outcomes of pregnancy and exposures to uranium from mining and milling operations, a study including 13,329 Navajos born at the Public Health Service/Indian Health Service Hospital (Shiprock NM) was conducted [40]. The only statistically significant association between uranium operations and unfavorable birth outcome was identified with the mother living near tailings or mine dumps. The associations between adverse pregnancy outcome and exposure to uranium were weak and attributed to radiation, not to the chemical toxicity of uranium.

4. Prevention by chelating agents of uranium-induced developmental toxicity

Chelation therapy has been the basis for the medical treatment of metal poisoning for the last five decades [41]. A number of experimental studies have shown that uranium intoxication can be alleviated by administration of chelating agents [42–47]. Tiron (sodium 4,5-dihydroxybenzene-1,3-disulfonate) and DTPA (diethylenetriaminepentaacetic acid) were found to be the most effective chelators in mobilizing uranium in rats and mice, with DTPA being less effective than Tiron [42–44,48].

In order to determine whether Tiron could ameliorate the developmentally toxic effects of uranium in mice [34], a series of four Tiron injections was administered IP to pregnant mice immediately after a single SC injection of 4 mg/kg uranyl acetate dihydrate given on day 10 of gestation, and at 24, 48, and 72 h thereafter [49]. Tiron effectiveness was assessed at 500, 1000, and 1500 mg/kg. In a previous study, the NOAEL for maternal and developmental toxicity of Tiron was found to be 1500 mg/kg/day [50]. Dam mortality (20%) was only observed in the group given uranium plus saline (positive control group). In addition, while at the end of the gestation period, maternal body weight in the positive control group was significantly lower than that in the uranium-untreated group (negative control), no significant differences between the groups given uranium plus Tiron and the negative control group were seen in maternal weight. It was concluded that treatment with Tiron ameliorated the general condition of the dams.

Although uranium-induced embryo/lethality was not significantly reduced at 500, 1000, or 1500 mg/kg/day Tiron [49], significant protective effects of Tiron against uranium-induced fetal growth retardation were noted at 1500 mg/kg/day. The protective effects of the drug were probably due to the fact that Tiron reduced the amount of uranium administered to pregnant mice to such low levels, which could partly obviate its developmental toxicity. However, the ability of Tiron to protect the developing mouse fetus against at least some harmful effects of uranium offered only modest

encouragement with regard to the possible therapeutic potential for pregnant women exposed to this metal. In contrast to these results, in a previous investigation Tiron caused a significant reduction of vanadate-induced embryo/fetal toxicity in mice [51,52].

5. Perinatal and postnatal effects of uranium

Only two reports were available from the literature concerning the perinatal and postnatal effects of uranium in mammals. These studies were also carried out in our laboratory. In the first investigation, male mice were given uranyl acetate dihydrate (0, 5, 10, and 25 mg/kg/day) by gavage for 60 days prior to mating with female mice treated orally (gavage) for 14 days prior to mating. Treatment of the females continued throughout mating, gestation, parturition, and nursing of the litters. Postnatal development was monitored after 0, 4, and 21 days of lactation. Significant increases in the number of dead young per litter were seen at birth (1.3 ± 2.4 vs. none in the control group) and at day 4 of lactation in the 25 mg/kg/day group (4.0 ± 3.1 vs. 0.4 ± 0.5 in the control group). The growth of the offspring was always significantly lower for the uranium-exposed animals [24].

In another study, mice were given uranyl acetate dihydrate at 0, 0.05, 0.5, 5, and 50 mg/kg/day by gavage from day 13 of gestation until weaning of the litters on day 21 postpartum. Postnatal development was monitored after 0, 4, and 21 days of lactation [53]. At doses of 0, 0.05, 0.5, and 5 mg/kg/day, treatment with uranyl acetate had no significant effects on sex ratio, mean litter size, pup body weight, and pup body length throughout lactation. However, significant decreases in the mean litter size on postnatal day 21 (5.5 ± 2.9 vs. 8.8 ± 3.7 in the control group), and in viability (0.53 ± 0.39 vs. 0.81 ± 0.38 in the control group) and lactation (0.76 ± 0.20 vs. 0.90 ± 0.30 in the control group) indices were observed at 50 mg/kg/day. The NOAEL for health hazards to the developing pup was established at 5 mg/kg/day [53].

To date, no data on the perinatal and postnatal effects of DU in mammals are available from the literature.

6. Assessment

The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) established that limits for natural uranium in drinking water should be based on its chemical toxicity for the kidney rather than on a hypothetical radiologic toxicity for skeletal tissue. A level of 100 μg U/liter of water was chosen as reasonable based on considerations of renal toxicity with the application of a safety factor of 50 to 150 [5]. Consequently, a 70-kg adult consuming 2 L/day water would not ingest more than 200 μg /day U. This amount would be equivalent to 0.005 mg/kg/day uranyl acetate dihydrate. Compared to the NOAEL

of uranyl acetate dihydrate for health hazards to the developing pup, 5 mg/kg/day [53], and the NOAEL for effects of this chemical on reproduction, gestation, and postnatal survival: 5 mg/kg/day [24], a margin of exposure (MOE) 1000 (MOE: 5 mg/kg/day [NOAEL]/0.005 mg/kg/day [human exposure]) is obtained for the intake of uranium from drinking water. With respect to the fetal toxicity of uranyl acetate dihydrate with a LOAEL of 5 mg/kg/day [32], a MOE of 100 (MOE: 0.5 mg/kg/day [LOAEL/10]/0.005 mg/kg/day [human exposure]) is estimated. Although these MOEs are relatively large, people living near uranium mines or mills may be exposed to higher quantities of the metal, and may require individual guidance.

Inasmuch as a significant decrease in the pregnancy rate in mice was noted at 10 mg/kg/day uranyl acetate dihydrate [23], investigations are still required to elucidate the mechanism of this effect and whether it may be totally or partially reversible. Studies on the developmental toxicity of DU are also clearly required. Moreover, taking into account that Tiron offered only modest protection against uranium-induced embryo/fetal toxicity in mice, the assessment of the protective activity of other uranium chelators, such as ethane-1-hydroxy-1,1-bisphosphonate (EHBP) [54], which in recent investigations was shown to be more effective than Tiron for the decorporation of uranium, would be of interest. Finally, it is important to note that, to date, most studies on uranium-induced developmental toxicity have been performed in mice. Consequently, developmental and reproductive investigations on the effects of uranium in other species of mammals would be also of interest.

References

- [1] Cothorn CR, Lappenbusch WL. Occurrence of uranium in drinking water in the US. *Health Phys* 1983;45:89-99.
- [2] Cothorn CR, Lappenbusch WL, Cotruvo JA. Health effects guidance for uranium in drinking water. *Health Phys* 1983;44(suppl 1):377-84.
- [3] Tannenbaum A. *Toxicology of uranium compounds*, New York: McGraw-Hill, 1951.
- [4] Voegtlin C, Hodge HC. *Pharmacology and toxicology of uranium*. New York: McGraw-Hill, 1953.
- [5] Wrenn ME, Durbin PW, Howard B, Lipsztein J, Rundo J, Still ET, Willis DL. Metabolism of ingested U and Ra. *Health Phys* 1985;48:601-33.
- [6] Taylor DM, Taylor SK. Environmental uranium and human health. *Rev Environ Health* 1997;12:147-57.
- [7] Domingo JL. Chemical toxicity of uranium. *Toxicol Ecotoxicol News* 1995;2:74-8.
- [8] La Touche YD, Willis DL, Dawydiak OI. Absorption and biokinetics of U in rats following an oral administration of uranyl nitrate solution. *Health Phys* 1987;53:143-62.
- [9] Hartmann HM, Monette FA, Avci HI. Overview of toxicity data and risk assessment methods for evaluating the chemical effects of depleted uranium compounds. *Human Ecol Risk Assess* 2000;6:851-74.
- [10] McDiarmid MA. Depleted uranium and public health. *BMJ* 2001; 322:123-4.
- [11] ATSDR (Agency for Toxic Substances and Diseases Registry). *Toxicological profile for uranium*. Washington, DC: US Public Health Services, 1999.

- [12] Cantaluppi C, Degetto S. Civilian and military uses of depleted uranium: environmental and health problems. *Ann Chim* 2000;90:665–76.
- [13] Jamal GA. Gulf War syndrome: a model for the complexity of biological and environmental interaction with human health. *Adverse Drug React Toxicol Rev* 1998;17:1–17.
- [14] Durakovic A. Medical effects of internal contamination with uranium. *Croat Med J* 1999;40:49–66.
- [15] Durakovic A. On depleted uranium: Gulf War and Balkan syndrome. *Croat Med J* 2001;42:130–4.
- [16] Hooper FJ, Squibb KS, Siegel EL, McPhaul K, Keogh JP. Elevated urine uranium excretion by soldiers with retained uranium shrapnel. *Health Phys* 1999;77:512–9.
- [17] McDiarmid MA, Keogh JP, Hooper FJ, McPhaul K, Squibb K, Kane R, DiPino R, Kabat M, Kaup B, Anderson L, Hoover D, Brown L, Hamilton M, Jacobson-Kram D, Burrows B, Walsh M. Health effects of depleted uranium on exposed Gulf War veterans. *Environ Res* 2000;82:168–80.
- [18] McDiarmid MA, Engelhardt SM, Oliver M. Urinary uranium concentrations in an enlarged Gulf War veteran cohort. *Health Phys* 2001;80:270–3.
- [19] Uijt de Haag PA, Smetsers RC, Witlox HW, Krus HW, Eisenga AH. Evaluating the risk from depleted uranium after the Boeing 747–258F crash in Amsterdam, 1992. *J Hazard Mater* 2000;76:39–58.
- [20] Priest ND. Toxicity of depleted uranium. *Lancet* 2001;357:244–6.
- [21] Zhu SP, Hu QY, Lun MY. Studies on reproductive toxicity induced by enriched uranium. *Zhonghua Yu Fang Yi Xue Za Zhi* 1994;28:219–22 [in Chinese].
- [22] Hu Q, Zhu S. Induction of chromosomal aberrations in male mouse germ cells by uranyl fluoride containing enriched uranium. *Mutat Res* 1990;244:209–14.
- [23] Llobet JM, Sirvent JJ, Ortega A, Domingo JL. Influence of chronic exposure to uranium on male reproduction in mice. *Fundam Appl Toxicol* 1991;16:821–9.
- [24] Paternain JL, Domingo JL, Ortega A, Llobet JM. The effects of uranium on reproduction, gestation, and postnatal survival in mice. *Ecotoxicol Environ Safety* 1989;17:291–6.
- [25] Domingo JL, Llobet JM, Tomas JM, Corbella J. Acute toxicity of uranium in rats and mice. *Bull Environ Contam Toxicol* 1987;39:168–74.
- [26] Maynard EA, Downs WL, Hodge HC. Oral toxicity of uranium compounds. In: Voegtlin C, Hodge HC, editors. *Pharmacology and Toxicology of uranium*. New York: McGraw-Hill; vol III, 1953:1221–1369.
- [27] Malenchenko AF, Barkun NA, Guseva GF. Effect of uranium on the induction and course of experimental autoimmune orchitis and thyroiditis. *J Hyg Epidemiol Microbiol Immunol* 1978;22:268–77.
- [28] Pellmar TC, Fuciarelli AF, Ejniak JW, Hamilton M, Hogan J, Strocko S, Emond C, Mottaz HM, Landauer MR. Distribution of uranium in rats implanted with depleted uranium pellets. *Toxicol Sci* 1999;49:29–39.
- [29] Stopps GJ, Todd M. The chemical toxicity of uranium with special reference to effects on the kidney and the use of urine for biological monitoring. Research Report, Atomic Energy Control Board, Ottawa, Canada 1982.
- [30] Muller C, Ruzicka L, Bakstein J. The sex ratio in the offspring of uranium miners. *Acta Univ Carol [Med] (Praha)* 1967;13:599–603.
- [31] Zaire R, Notter M, Riedel W, Thiel E. Unexpected rates of chromosomal instabilities and alterations of hormone levels in Namibian uranium miners. *Radiat Res* 1997;147:579–84.
- [32] Domingo JL, Paternain JL, Llobet JM, Corbella J. The developmental toxicity of uranium in mice. *Toxicology* 1989;55:143–52.
- [33] Khera KS. Maternal toxicity in humans and animals: effects on fetal development and criteria for detection. *Teratogen Carcinogen Mutagen* 1987;7:287–95.
- [34] Bosque MA, Domingo JL, Llobet JM, Corbella J. Embryotoxicity and teratogenicity of uranium in mice following SC administration of uranyl acetate. *Biol Trace Elem Res* 1993;36:109–18.
- [35] Khera KS. Maternal toxicity. A possible factor in fetal malformations in mice. *Teratology* 1984;29:411–6.
- [36] Bosque MA, Domingo JL, Corbella J. Embryofetotoxicity of uranium in mice: Variability with the day of exposure. *Rev Toxicol* 1993;107–10 [in Spanish].
- [37] Lin RH, Wu LJ, Lee CH, Lin-Shiau SY. Cytogenetic toxicity of uranyl nitrate in Chinese hamster ovary cells. *Mutat Res* 1993;319:197–203.
- [38] Kundt M, Ubios AM, Cabrini RL. Effects of uranium poisoning on cultured preimplantation embryos. *Biol Trace Elem Res* 2000;75:235–44.
- [39] Benson KA, McBride SA. Uranium levels in the fetus and placenta of female rats implanted with depleted uranium pellets prior to breeding. *Toxicologist* 1997;36:258.
- [40] Shields LM, Wiese WH, Skipper BJ, Charley B, Benally L. Navajo birth outcomes in the Shiprock uranium mining area. *Health Phys* 1992;63:542–51.
- [41] Domingo JL. Prevention by chelating agents of metal-induced developmental toxicity. *Reprod Toxicol* 1995;9:105–13.
- [42] Domingo JL, Ortega A, Llobet JM, Paternain JL, Corbella J. The effects of repeated parenteral administration of chelating agents on the distribution and excretion of uranium. *Res Commun Chem Pathol Pharmacol* 1989;64:161–4.
- [43] Domingo JL, Ortega A, Llobet JM, Corbella J. Effectiveness of chelation therapy with time after acute uranium intoxication. *Fundam Appl Toxicol* 1990;14:88–95.
- [44] Domingo JL, Colomina MT, Llobet JM, Jones MM, Singh PK, Campbell RA. The action of chelating agents in experimental uranium intoxication in mice: variations with structure and time of administration. *Fundam Appl Toxicol* 1992;19:350–7.
- [45] Ortega A, Domingo JL, Gomez M, Corbella J. Treatment of experimental acute uranium poisoning by chelating agents. *Pharmacol Toxicol* 1989;64:247–51.
- [46] Ubios AM, Braun EM, Cabrini RL. Lethality due to uranium poisoning is prevented by ethane-1-hydroxy-1,1-bisphosphonate (EHBP). *Health Phys* 1994;66:540–4.
- [47] Henge-Napoli MH, Archimbaud M, Ansoborlo E, Metvier H, Gourmelon P. Efficacy of 3,4,3-LiHOPO for reducing the retention of uranium in rat after acute administration. *Int J Radiat Biol* 1995;68:389–93.
- [48] Domingo JL, De la Torre A, Bellés M, Mayayo E, Llobet JM, Corbella J. Comparative effects of the chelators sodium 4,5-dihydroxybenzene-1,3-disulfonate (Tiron) and diethylenetriaminepentaacetic acid (DTPA) on acute uranium nephrotoxicity in rats. *Toxicology* 1997;118:49–59.
- [49] Bosque MA, Domingo JL, Llobet JM, Corbella J. Effectiveness of sodium 4,5-dihydroxybenzene-1,3-disulfonate (Tiron) in protecting against uranium-induced developmental toxicity in mice. *Toxicology* 1993;79:149–56.
- [50] Ortega A, Sanchez DJ, Domingo JL, Llobet JM, Corbella J. Developmental toxicity evaluation of Tiron (sodium 4,5-dihydroxybenzene-1,3-disulfonate) in mice. *Res Commun Chem Pathol Pharmacol* 1991;73:97–106.
- [51] Domingo JL, Bosque MA, Luna M, Corbella J. Prevention by Tiron (sodium 4,5-dihydroxybenzene-1,3-disulfonate) of vanadate-induced developmental toxicity in mice. *Teratology* 1993;48:133–8.
- [52] Domingo JL. Vanadium: A review of the reproductive, and developmental toxicity. *Reprod Toxicol* 1996;10:175–82.
- [53] Domingo JL, Ortega A, Paternain JL, Corbella J. Evaluation of the perinatal and postnatal effects of uranium in mice upon oral administration. *Arch Environ Health* 1989;44:395–8.
- [54] Henge-Napoli MH, Ansoborlo E, Chazel V, Houpert P, Paquet F, Gourmelon P. Efficacy of ethane-1-hydroxy-1,1-bisphosphonate (EHBP) for the decorporation of uranium after IM contaminant rats. *Int J Radiat Biol* 1999;75:1473–7.