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Letter Report

URANIUM HEXAFLUORIDE PUBLIC RISK

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Report Submitted: August 1, 1994

Project JCN Number: W6068

NRC Project Manager: Charles W. Nilsen

MASTER

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SUMMARY

The limiting value for uranium toxicity in a human being should be based on the concentration of uranium (U) in the kidneys. The threshold for nephrotoxicity appears to lie very near 3 μg U per gram kidney tissue. There does not appear to be strong scientific support for any other improved estimate, either higher or lower than this, of the threshold for uranium nephrotoxicity in a human being. The value 3 μg U per gram kidney is the concentration that results from a single intake of about 30 mg soluble uranium by inhalation (assuming the metabolism of a standard person).

The concentration of uranium continues to increase in the kidneys after long-term, continuous (or chronic) exposure. After chronic intakes of soluble uranium by workers at the rate of 10 mg U per week, the concentration of uranium in the kidneys approaches and may even exceed the nephrotoxic limit of 3 μg U per gram kidney tissue. Precise values of the kidney concentration depend on the biokinetic model and model parameters assumed for such a calculation.

Since it is possible for the concentration of uranium in the kidneys to exceed 3 μg per gram tissue at an intake rate of 10 mg U per week over long periods of time, we believe that the kidneys are protected from injury when intakes of soluble uranium at the rate of 10 mg U per week do not continue for more than two consecutive weeks. For long-term, continuous occupational exposure to low-level, soluble uranium, we recommend a reduced weekly intake limit of 5 mg uranium to prevent nephrotoxicity in workers. Our analysis shows that the nephrotoxic limit of 3 μg U per gram kidney tissues is not exceeded after long-term, continuous uranium intake at the intake rate of 5 mg soluble uranium per week.

PURPOSE

The purpose of this study was to evaluate the potential health risks to members of the general public from accidental exposures to uranium in the forms used at gaseous diffusion plants. The validity and adequacy of the current occupational limit for uranium intakes in 10 CFR 20.1201(e), which is 10 mg per week, was also evaluated. Scientific knowledge on the toxicity of

uranium was reviewed to determine whether new information is available on the health hazards associated with human exposure to uranium, uranium hexafluoride, or its hydrolysis products. In that regard, we conducted a thorough literature search of scientific information on the toxic effects of uranium in humans, the current status of uranium exposure standards, and the appropriateness of limits for uranium exposure for members of the general population.

INTRODUCTION AND BACKGROUND

The primary health and safety hazard for consideration at gaseous diffusion plants is public exposure to uranium hexafluoride (UF_6) and its hydrolysis products: uranyl fluoride (UO_2F_2), hydrogen fluoride (HF), the uranyl ion (UO_2^{++}), and the fluoride ion (F^-).

Volatile UF_6 hydrolyzes rapidly on contact with water vapor in air to produce HF and UO_2F_2. The analysis of health risk from exposure to UF_6 must therefore include analysis of health effects and risks of exposure to several components including the following:

- chemical toxicity of uranium in the kidneys from UO_2^{++}
- chemical toxicity of HF, which is of concern for inhalation and skin burns, has the potential for creation of large airborne clouds, and has unique toxicological properties compared with many other inorganic acids and other hydrogen halides
- chemical toxicity of the fluoride ion (F^-) from dissolution of UO_2F_2 in body fluids, and
- radiation exposure from emissions by the uranium isotopes ^{238}U, ^{234}U, and ^{235}U, with bone surfaces and the lungs being the principal biological targets of concern.

The published scientific literature contains a large amount of information on the toxicology of UF_6 and its hydrolysis products in human beings and animals. A wide range of toxicity values are quoted for uranium compounds. Of the four modes of toxicity listed above, current scientific consensus is that *the chemical toxicity of inhaled or ingested soluble uranium is greater than its radiotoxicity, and that chemical nephrotoxicity is the principal health hazard of concern.* Specifically, the chemical toxicity of soluble uranium is more limiting than its radiological toxicity for ^{235}U enrichments of less than

about 80%. The acute effects of fluoride ion toxicity are not significant compared to those of U and HF.

The International Commission on Radiological Protection (ICRP) provides guidance for limiting internal exposures to uranium. The most recent limits in ICRP Publication 60 (ICRP 1991) are based solely on the effective dose equivalent, considering only radiological toxicity. However, the ICRP recognizes that the chemical toxicity of uranium will usually be more limiting than its radiological toxicity for both inhaled and ingested soluble uranium.

A previous U.S. Nuclear Regulatory Commission (NRC) report entitled *Chemical Toxicity of Uranium Hexafluoride Compared to Acute Effects of Radiation* (NUREG-1391, McGuire 1991) found a reasonable comparison between the health effect severity of exposure to: (a) 25 rems of ionizing radiation to the whole body or (b) 300 rems of ionizing radiation to the thyroid, and an intake of about 10 mg of uranium in soluble form (or an exposure to hydrogen fluoride at a concentration of 25 mg per m^3 air for 30 min). Risks from radioactive emissions from uranium were considered; however, the conclusion reached was that the chemical toxicity of UF_6 and hydrolysis reaction products presented a greater potential hazard to human health than any radiation component of the uranium or its associated decay products. A review of the equivalence of the radiological and chemotoxicological effects of uranium was also prepared by Ringot and Hamard (1988). Ringot and Hamard concurred that the principal health hazard of concern was the chemical toxicity of uranium, rather than radiological toxicity.

The following sections discuss more specifically the chemical toxicity of uranium in the kidneys, the comparative toxicity of hydrogen fluoride (HF) with that of uranium, limiting factors for consideration of UF_6 toxicity, special considerations involving exposure to the embryo/fetus, and an assessment of the acceptability of the NRC weekly intake limit of 10 mg U.

TOXICITY OF URANIUM

Uranium is one of the most thoroughly studied elements for chemical or radiological toxicity. Several major scientific reviews on the toxicology of uranium compounds have been published, including a summary on uranium metabolism and its acute and chronic toxicity (Durbin and Wrenn 1975), two books summarizing the animal and human studies on uranium (Hodge et al. 1973; Stannard 1988), a Canadian review (Stopps and Todd 1982), and a review of metabolic models for uranium (Durbin 1984). The behavior and chemical toxicity of uranium in kidney tissue was also extensively reviewed by Leggett

(1989). Wrenn et al. (1994) recently completed development of an updated compartment model based on review of experiments on injection and inhalation of uranium compounds in several animal species and human subjects.

The principal tissue of concern for chemical toxicity is the kidneys (Brickner 1988). Uranium poisoning leads to renal tubular damage, which may result in acute renal insufficiency and death after high exposure to soluble uranium. Because the kidneys have extra functional capacity, it is possible for adverse effects on renal function from uranium exposure to occur long before nephrotoxicity is evident (Moss 1989). Uranium damages the renal proximal tubules, inhibiting the transfer of nutrients across cell membranes. Tissue damage and loss of renal function are indicated by morphological changes, enzymuria, glucosuria, and increased excretion of amino acids and small proteins. Sever exposure may cause albuminuria and acute renal failure.

The principal scientific advances during recent years on the toxicology of uranium involve research to improve diagnostic tests for nephrotoxicity, particularly for detection of proximal tubular dysfunction. These tests make it possible to more accurately detect changes in kidney function after uranium exposure (Moss 1989). We were not able to identify any substantial new information on the renal toxicity of human kidney tissue to uranium.

Nephrotoxic Threshold

The best estimate of the toxicity threshold for uranium in human kidneys is 3 μg U per g of kidney tissue (National Council on Radiation Protection and Measurements, Scientific Committee 57-15, unpublished draft report on uranium toxicology). This threshold value was first proposed by Voegtlin and Hodge (1953) after extensive animal research at the University of Rochester during and after the Manhattan Project. This same value (3 μg U per g of kidney tissue) was reaffirmed by Spoor and Hursh (1973) as the threshold for nephrotoxicity. There does not appear to be any new toxicological information on uranium that supports a change in this estimate of the threshold for nephrotoxicity.

Typical indicators of uranium poisoning have been obtained with concentrations of 3 μg U (as the uranyl ion, UO_2^{++}) per g of kidney tissue in animals over extended periods of time (Morrow et al. 1982a, 1982b). The degree of tissue damage increases from minimal evidence of toxicity at 3 μg U per gram tissue to complete loss of functional capacity at much higher concentrations. The threshold for severe renal injury is estimated to be about 10 μg U per kg body weight for dogs, and about 100 μg U/kg body weight for rats (Morrow et al. 1982a, 1982b). The threshold level for severe injury in humans is thought to

be about 70 μg U/kg of body weight, between that for dogs and rats. This value corresponds to a renal injury threshold concentration of 16.3 μg U per g of human kidney tissue and is well above the 3 μg U per g level.

The NRC sponsored a study in 1987 on the nephrotoxicity of uranyl fluoride and the reversibility of renal injury in rats (Diamond et al. 1987). The objective was to examine the severity and duration of renal injury in rats from exposure to low levels of uranyl fluoride. Renal injury was characterized by cellular and tubular necrosis of the proximal tubule. Injury was apparent when concentrations of uranium in the kidneys ranged between 0.7 and 1.4 μg U per g of kidney tissue and was most severe when the renal uranium concentration was between 2.3 and 5.6 μg U per g of kidney tissue (Diamond et al. 1987). Numerous abnormalities in kidney function were associated with injury, including impaired tubular reabsorption, proteinuria, and enzymuria, which appeared to be related to the progression of renal injury over time and level of exposure. However, repair of minor tissue damage was rapid, with complete restoration within 35 days after the uranium exposure. This research showed that the concept of renal injury is difficult to define because damage to tissue at low uranium concentrations is transient and repairable.

Wrenn et al. (1985) reviewed the metabolism and kidney toxicity of ingested uranium in humans and concluded that, for chronic intakes, the chemical toxicity threshold for the kidney may lie between 1 and 3 μg U per g of kidney tissue. Kocher (1989) reviewed the implications of a 1 μg U per g of kidney tissue threshold for chemical toxicity with respect to regulatory limits and concluded that the chemical toxicity of uranium should be considered in developing protection standards for the public for ingested (and inhaled) natural or depleted uranium.

Studies at the Pacific Northwest Laboratory (PNL) on urine data obtained from Sequoyah Fuels Corporation workers after the 1986 UF_6 rupture accident showed that a maximum likely kidney tissue concentration of about 2.5 μg U per g of kidney tissue occurred in the highest-exposed workers. No long-term kidney tissue damage was observed at these concentrations, but there was some evidence of increased urinary protein in the highest-exposed workers (Fisher et al. 1990). The clinical laboratory evidence from this study suggested that uranium concentrations in kidneys of these workers may approached, but not exceed, the threshold for toxicity in humans. Results of this work supported the concept of a threshold concentration of 3 μg U per g of kidney tissue.

Several authors have proposed a reduction in the estimate of a concentration threshold for nephrotoxicity, especially for conditions of chronic exposure (Morrow et al. 1982a, 1982b; Wrenn et al. 1985). The recommendation by Morrow

et al. (1982b) to reduce the threshold for human beings was based on the observed nephrotoxicity in dogs at a kidney concentration of 0.3 μg U per g of tissue. However, as indicated above, the Rochester studies also showed that the dog kidneys were more sensitive to uranium than human kidneys.

Uranium injection studies have been conducted in human beings, but the levels administered have exceeded the nephrotoxic limits and do not provide useful information on uranium nephrotoxicity threshold levels. Several cases have been documented in which adult humans experienced concentrations of uranium in kidney tissues that were estimated to have exceeded the value of 3 μg U per g kidney tissue, without demonstrating any long-term, adverse toxicity or functional impairment. There is anecdotal evidence of permanent kidney damage in workers exposed to high concentrations of uranium, but these have not been well documented in the scientific literature because quantitative measurements were lacking to establish intakes, body burdens, and urinary excretion rates over time.

ACGIH Threshold Limit Values for Uranium

The current threshold limit values (TLVs) recommended by the American Conference of Governmental Industrial Hygienists (ACGIH 1986, 1993) for occupational exposure to soluble and insoluble uranium, time-weighted average (TWA), is 0.2 mg U per m^3 of air. This value is based on an assumed nephrotoxic limit of 3 μg U per g of kidney tissue. The ACGIH TLV is equivalent to the Mine Safety and Health Administration time-weighted standard for exposure to airborne uranium. The ACGIH short-term exposure limit (STEL) is 0.6 mg U per m^3 of air. The Occupational Safety and Health Administration occupational permissible exposure limit (PEL) for an 8-hour exposure is 0.05 mg U per m^3 for soluble compounds and 0.25 mg U per m^3 for insoluble compounds (NIOSH/OSHA 1981).

Foreign Standards for Uranium

Foreign exposure standards for airborne uranium appear unchanged in recent years. Occupational exposure limits for Australia, Belgium, Denmark, England, Finland, The Netherlands, and Switzerland are the same as the U.S. ACGIH TLV limit of 0.2 mg U per m^3 of air for soluble and insoluble forms.

Germany has adopted an occupational limit of 0.25 mg U per m^3; the Philippines and Turkey have adopted a more restrictive limit of 0.05 mg U per m^3.

Russia and Poland have more stringent exposure limits (by a factor of about 3) for soluble airborne uranium than the United States and most other foreign

countries. The countries of Eastern Europe generally adhere to the exposure limit used by the former Soviet Union for soluble uranium of 15 μg U per m^3; however, there are no known, available, published documents providing the scientific basis for this limit.

The French occupational exposure limit for uranium is based on the recommendations of the ICRP (1991) for limiting radiation dose to workers, rather than limits based on chemical toxicity. Limits for the radionuclides ^{235}U and ^{238}U are 20 Bq m^{-3} (which translates to approximately 0.8 mg U (natural) per m^3.

TOXICITY OF AIRBORNE HYDROGEN FLUORIDE

Hydrogen fluoride is strongly acidic and irritating to tissues. It has a strong, distinctive and bitter odor, and can cause severe irritation at relatively low exposures. Inhalation exposure at 122 ppm (parts per million) for 1 min can cause severe irritation of the nose, throat, and respiratory tract. It reacts with water or steam, generating toxic and corrosive fumes. The corrosive effects of hydrofluoric acid are almost immediate, and the severity depends on the concentration of the acid. Hydrogen fluoride vapor has a density of 0.71 relative to air = 1.0.

The current TLVs recommended by the ACGIH (1986, 1993) for hydrogen fluoride are 3 ppm HF or 2.6 mg HF per m^3 as ceiling values. The current Occupational Safety and Health Administration (OSHA) PEL-TWA is 3 ppm (NIOSH/OSHA 1981).

For hydrogen fluoride, a threshold concentration limit (TCL) value for humans of 32 ppm (27 mg per m^3) is recommended (OHM/TADS 1990); this corresponds well with the 1985 National Institute for Occupational Safety and Health (NIOSH) "immediately dangerous to life or health (IDLH)" concentration of 30 ppm referenced in NUREG-1391 (McGuire 1991). Another recommended short-term inhalation limit is 50 ppm for 60 min (CHRIS Hazardous Chemical Data 1990). For comparison, the current French limit for public exposure to HF is 2.5 mg per m^3.

The Mine Safety and Health Administration standard for HF in air is 3 ppm, or 2 mg per m^3 (time-weighted average) (RTECS 1992). The NIOSH IDLH value is 30 ppm (as fluorine) (NIOSH 1990). Davis et al. (1987) endorsed an IDLH level for HF of 20 ppm. The HF odor threshold for human beings is 0.0333 to 0.1333 mg HF per m^3 (Ruth 1986) or 0.04 to 0.13 ppm.

Hydrogen fluoride has a National Fire Protection Association (NFPA) hazard rating of "health (blue): 4," indicating a material that, on very short exposure, could cause death or major residual injury (NFPA 1990).

According to the Emergency Response Planning Guidelines (ERPGs), developed under the auspices of the American Industrial Hygiene Association (AIHA), the maximum airborne concentration for HF (ERPG-1) at which individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly declined objectionable odor is 5 ppm, or 4.1 mg per m^3 (AIHA 1988).

A recent publication (Alexeeff et al. 1993) proposes that a 1-hr reference exposure level to protect the public against respiratory irritation from a routine emission of hydrogen fluoride is 0.7 ppm HF (0.6 mg HF per m^3 of air), and that the level to protect against severe irritation from a once-in-a-lifetime release is 2 ppm HF (1.7 mg HF per m^3 of air). These 1-hr limits may be extrapolated to different exposure periods using a time-adjustment expression

$$c^n * t = k,$$

where c is the concentration, n is a chemical-specific parameter, t is the exposure time, and k is a constant. A suggested value for n is 2 (Alexeeff et al. 1993). Therefore, the corresponding HF exposure limits are 2.4 mg HF per m^3 for 30 min, and 3.4 mg HF per m^3 for 15 min.

The values proposed by Alexeeff et al. (1993) seem low when compared to the AIHA ERPG-1 level of 5 ppm (4.1 mg per m^3). The 2-ppm value was selected by Alexeeff et al. to protect essentially all of the population at a 95% confidence level, whereas the ERPG values were designed to protect most people and do not take into account the special response of more sensitive members of the population. The study by Alexeeff et al. was based on chemical-specific and species-specific data and incorporated concentration-response information rather than reliance on single-point estimates of lethal concentration levels, ten-fold uncertainty factors, or no-observed-adverse-effect levels.

Other guidance on occupational exposure to hydrogen fluoride was given by the National Institute for Occupational Safety and Health (NIOSH 1976, 1990) and by the Occupational Safety and Health Administration (NIOSH/OSHA 1981). As Alexeef et al. (1993) point out, there are no generally agreed-upon, acceptable acute exposure levels for HF. For the purpose of our analysis, we chose an HF exposure limit of 3.4 mg HF per m^3, or 4 ppm HF. The value of 3.4

mg HF per m^3 is much smaller than the 30-min IDLH level of 25 mg HF per m^3 cited in NUREG/CR-1391 (McGuire 1991).

LIMITING FACTORS FOR URANIUM HEXAFLUORIDE TOXICITY

The corresponding stoichiometric amount of uranium in a UF_6 release to produce 3.4 mg HF per m^3 is approximately 10 mg U per m^3 of air.

We compared the total uranium intake after 15 min at the 3.4 mg HF per m^3 standard with the 10 mg U weekly intake limit. The amount of uranium breathed in 15 min at the 10 mg U per m^3 level is

$$10\ mg\ U/m^3 * 1.2\ m^3/hr\ breathing\ rate * 1/4\ hr = 3\ mg\ U\ intake,$$

which is less than the weekly intake limit of 10 mg uranium. Thus, the HF concentration is limiting for short exposure times, and a weekly intake of 10 mg U is not exceeded during a 15-min exposure period to UF_6 with an HF concentration of 3.4 mg HF per m^3.

For times greater than about 50 min, the weekly intake limit of 10 mg U is the limiting value for human exposure to UF_6 and hydrolysis products.

TOXICITY TO THE EMBRYO/FETUS

Historical records show that the fetal toxicology of uranium was briefly studied during the Manhattan Project, but the data on biological effects of uranium exposure on the embryo/fetus were only obtained at exposure levels considered to be toxic to the mother.

The available literature and PNL experimental data in laboratory animals on the toxicology of uranium in the embryo/fetus were reviewed. No direct data were located relative to the toxicity of uranium hexafluoride to the developing embryo/fetus. However, the effects of exposures to other uranium salts, such as uranyl acetate, were studied.

In terms of chemical risks, detrimental effects on fertility were not seen in a study by Paternain et al. (1989), but Llobet et al. (1991) found decreased pregnancy rates at uranium intakes in excess of 10 mg per kg per day. Uranyl nitrate given intraperitoneally to male mice resulted in a decrease in seminiferous tubule diameter and impaired gametogenesis (Jadon and Mathur 1983). Continuous (or chronic) intakes of uranium at high levels during

pregnancy resulted in embryolethality, fetal growth impairment, and developmental effects including skeletal abnormalities and cleft palate (Domingo et al. 1989). However, these results were observed at levels that were also toxic to the mother, and it was not clear to what extent the developmental toxicity was attributable to the maternal effects or how much of the toxicity was a direct effect of uranium on the conceptus. Developmentally toxic effects occurred in the exposure range that was acutely maternally toxic, which would be far above the allowable exposure level, suggesting that maternal exposure limits would be adequate to protect against any detectable prenatal effects. Continuation of uranium treatment during pregnancy resulted in embryolethality, fetal growth impairment, and an increase in cleft palate and skeletal anomalies in the offspring (Paternain et al. 1989; Domingo et al. 1989). However, some of the embryotoxicity may have been associated with maternal toxicity rather than with a direct effect of the uranium compound on the embryo/fetus.

In summary, it appears that current limits on annual intakes (ALIs) for uranium isotopes in 10 CFR 20 (inhalation and ingestion of hexavalent uranium compounds) are adequate for protecting the embryo/fetus by limiting the radiation dose to less than 0.5 rem (5 mSv) from a single exposure during pregnancy (Sikov et al. 1992; Sikov and Hui 1993). In terms of radiological risks, therefore, it appears that the limits applicable to the pregnant woman also serve to provide adequate protection for the embryo/fetus.

TOXICITY OF URANIUM IN CHILDREN

The importance of age of subjects exposed to uranium has been studied in laboratory animals (dogs and rats), but data are lacking on the toxicity of uranium in children or the relative differences, if any, in toxicity in children compared with toxicity in adults. Pelayo et al (1983) showed that young dogs (age 1-2 weeks) injected with soluble uranyl nitrate were more resistant to the effects of uranium than were somewhat older dogs (3-5 weeks). Voegtlin and Hodge (1953) found that the toxicity of ingested uranium in rats of different ages was highly variable (perhaps due to changing ability to absorb soluble uranium from the gastro-intestinal tract with age. The kidney tissue of children may be more sensitive than tissues of the adult. However, children breath less air than adults and intakes of uranium at a given concentration in air may be substantially less for children than for adults. The smaller intakes of uranium anticipated for children may likely offset their anticipated increased tissue sensitivity to uranium.

ASSESSMENT OF THE NRC'S WEEKLY INTAKE LIMIT OF 10 mg URANIUM

The NRC weekly limit of 10 mg U was based on the ACGIH threshold limit value of 0.2 mg per m^3, extended to a 40-h occupational week. For our analysis, we calculated the uranium concentration in kidneys after continuous intake at the NRC weekly intake rate of 10 mg U (1.43 mg U per day).

Assuming a continuous daily inhalation of soluble uranium, we obtained the following kidney burdens at times longer than 60 days of chronic intake (illustrated in Figure 1):

1.7 μg U per g kidney (Fisher/Wrenn recycling model, f_1 = 0.05, and $T_{1/2}$ biological from kidneys = 6 d)

and 2.4 μg U per g kidney (ICRP-30 model, f_1 = 0.05, $T_{1/2}$ biological from kidneys = 6 d)

Wrenn et al. (1985) suggest an f_1 value of 0.01 to 0.02, and a $T_{1/2}$ biological for kidneys of 15 d. Therefore, we also calculated the following kidney burdens:

2.4 μg U per g kidney (ICRP-30 model, f_1 = 0.02, $T_{1/2}$ biological from kidneys = 6 d)

and 4.2 μg U per g kidney (Wrenn/Lipsztein recycling model, f_1 = 0.05, and $T_{1/2}$ biological from kidneys = 15 d)

These calculations using CINDY version 3D internal dosimetry software (Canberra Industries, Meriden, Connecticut) showed that kidney concentrations of about 1.7 to 4.2 μg U per g of tissue were obtained after chronic intakes of uranium at the NRC weekly intake limit of 10 mg U. Depending on the method of calculation, the NRC weekly limit provides a reasonable measure of protection, perhaps by as much as a factor of 2 or 3, from the toxicity of uranium in the kidneys--depending on duration of exposure and assumptions used in the calculation. The f_1 value (or fractional uptake of uranium from the gastrointestinal tract) has negligible influence on the calculation of kidney concentration.

Figure 1 shows that the nephrotoxic limit could be exceeded if the behavior of uranium in the body followed the Wrenn-Lipsztein biokinetic model. Therefore, for long-term, continuous occupational exposure to low-level, soluble uranium, we recommend a reduced weekly intake limit of 5 mg U to prevent nephrotoxicity in workers. Our analysis showed that the nephrotoxic

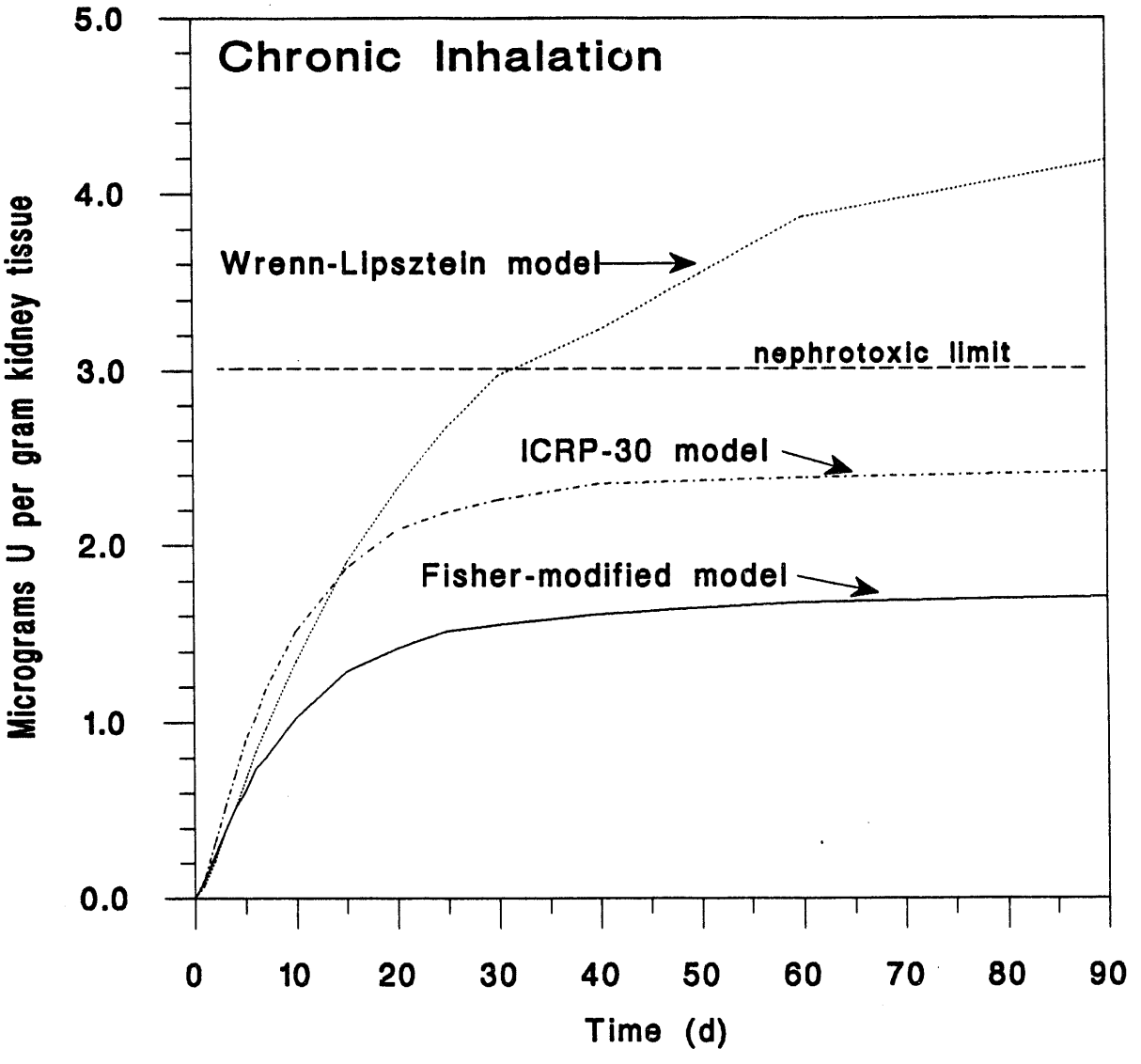

Figure 1. Uranium concentration in kidneys, calculated by different biokinetic models, for continuous daily intake of soluble uranium at the rate of 10 mg U per week. Concentrations in the kidneys with time are compared to the estimated threshold for toxicity.

limit is never exceeded after long-term, continuous uranium intake at the weekly intake rate of 5 mg uranium by inhalation.

CONCLUSIONS

A review of the literature on human exposures to uranium, including epidemiological studies, dosimetry studies, bioassay studies, and medical follow-ups failed to identify any conclusive information that there is an association between exposure to uranium above current occupational limits and an increase in nephrotoxicity or any other health impediment, including cancer, for kidneys, lungs, or the skeletal system in human beings. Although there have been several challenges to the postulated threshold limit on toxicity of 3 μg U per gram of kidney tissue, this review found no conclusive evidence that an alternative value would be better substantiated. The critical threshold level of 3 μg U per gram of kidney tissue appears to provide sufficient protection against uranium exposure in humans. This corresponds to an acute intake of 30 mg soluble U by inhalation, assuming the metabolism of the average man.

NUREG-1391 did not appraise the effect of uranium exposures of children or the embryo/fetus in expectant females. This may have been because very little data are available on the comparative toxicity of uranium in children and adults. The kidney tissue of children may be more sensitive than tissues of the adult. However, children breath less air than adults and the smaller intakes of uranium anticipated for children may likely offset their presumed greater tissue sensitivity to uranium. Concentrations of uranium in the embryo/fetus are much smaller than concentrations in the mother for any airborne exposure to soluble uranium. Thus, our review shows that age of subject exposed to uranium is not an important factor in assessing the consequences of airborne uranium. Children and the embryo/fetus in expectant females appear to be adequately protected by standards for adult members of the general public.

Exposure of the general public to hydrogen fluoride on the order of 3.4 mg HF per m^3 air for short time periods (15 min) should protect against serious irritation of lung tissue. The stoichiometric amount of uranium associated with 3.4 mg HF per m^3 after a release of UF_6 is about 10 mg U per m^3, which could result in an intake of 3 mg U in 15 min (standard breathing rates for periods of light work activity [ICRP 1975] were assumed).

The primary objective of establishing a limit on exposure to uranium should be to ensure that the uranium concentration in the exposed persons' kidneys does

not exceed the threshold for chemical toxicity, which is generally understood to be 3 μg U per g of kidney tissue. An acute intake of 10 mg soluble uranium may result in a short-term kidney concentration of about 1 μg U per g of kidney tissue, for a protection factor of about 3 below the threshold for nephrotoxicity. Thus, NRC's weekly occupational intake limit of 10 mg U in 10 CFR 20.1201(e) is appropriate for protecting workers from the chemical toxicity associated with acute or short-term (less than 2 weeks) exposure of uranium.

A special consideration involves chronic (continuous) occupational exposures to uranium as defined by 10 CFR 20. Uranium concentrations in the kidneys are expected to increase after chronic intakes of uranium over extended periods of time (and decrease with time after cessation of uranium intake). The precise concentration of uranium in the kidneys depends on many different factors. It can be argued under some assumptions that the NRC weekly intake limit of 10 mg U may not provide worker protection against the potential nephrotoxicity of uranium. It appears from model projections (Figure 1) that continuous exposure to uranium leading to intakes at the intake rate of 10 mg U per week could result in kidney concentrations in excess of 3 μg per g of tissue (Figure 1). For this reason, the NRC weekly intake limit of 10 mg U should not be considered a permissible amount for continuous exposure for more than two consecutive weeks. Again, the primary consideration is not uranium intake, but rather uranium concentration in kidney tissues. Consequently, we believe that 10 CFR 20 could be revised in either of two ways to reflect the results of this analysis. One change could be to simply lower the NRC's weekly occupational intake limit for continuous (chronic) exposure to 5 mg U, because our analysis showed that the nephrotoxic limit is never exceeded after long-term, continuous uranium intake at the weekly limit of 5 mg soluble U. Another possibility could be to retain the 10 mg U intake limit in 10 CFR 20 but define it as a limit for acute or short-term (not exceeding two weeks) exposures and redefine the chronic (longer than 2 weeks) intake limit as 5 mg U per week.

An acceptable upper bound on occupational uranium intakes is one that does not result in uranium concentrations in the kidneys in excess of 3 μg U per g of tissue. An acute intake of about 30 mg uranium leads to the threshold concentration of 3 μg U per g of kidney tissue (Fisher 1991). Therefore, soluble uranium intakes in excess of 30 mg could result in short-term or permanent kidney damage and should be avoided. Other investigators have recommended a threshold concentration of 0.3 μg U per g of kidney tissue (lower by a factor of 10) for long-term, chronic exposures (Eckerman and Leggett 1994); however, we believe this value to be very conservative for human exposure and not justified by scientific evidence.

REFERENCES

Alexeeff, G. V., Lewis, D. C., and Ragle, N. L. 1993. "Estimation of Potential Health Effects from Acute Exposure to Hydrogen Fluoride Using a 'Benchmark Dose' Approach. *Risk Analysis* 13:63-69.

American Conference of Governmental Industrial Hygienists (ACGIH). 1986. *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 5th ed. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio.

American Conference of Governmental Industrial Hygienists (ACGIH). 1993. *1993-1994 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio.

American Industrial Hygiene Association (AIHA). 1988. *Emergency Response Planning Guidelines: Hydrogen Fluoride*. American Industrial Hygiene Association, Akron, Ohio.

Brickner, D. 1988. *Toxicology of Uranium Compounds: A Literature Survey*. Israel Atomic Energy Commission, Beersheba. Nuclear Research Center-Negev, Israel (in Hebrew).

CHRIS Hazardous Chemical Data. 1990. U.S. Department of Transportation, U.S. Coast Guard, Washington, DC. (CD-ROM Version) Micromedex, Inc., Denver, Colorado.

Davis, D. S., G. B. DeWolf, and J. D. Quass. 1987. Prevention Reference Manual: Chemical Specific. Volume 1. Control of Accidental Releases of Hydrogen Fluoride. South Coast Air Quality Management District (SCAQMD).

Diamond, G. L., R. M. Gelein, P. E. Morrow, B. J. Panner, and R. B. Baggs. 1987. *Nephrotoxicity of Uranyl Fluoride and Reversibility of Renal Injury in the Rat*. NUREG/CR-4951. Rochester University School of Medicine and Dentistry, Rochester, New York.

Domingo, J. L. *et al*. 1989. "The Developmental Toxicity of Uranium in Mice." *Toxicology* 55:143-152.

Durbin, P. W. and M. E. Wrenn. 1975. "Metabolism and Effects of Uranium in Animals." In *Conference on Occupational Health Experience with Uranium*,

pp. 68-139, ERDA-93, Energy Research and Development Administration, Washington, DC.

Durbin, P. W. 1984. "Metabolic Models for Uranium." In *Biokinetics and Analysis of Uranium in Man*, pp. F-1 to F-65. USUR-05-/HEHF-47, Hanford Environmental Health Foundation, Richland, Washington.

Eckerman, K. F. and R. W. Leggett. 1994. "Limits on Ingestion of U: An Update." *Health Phys.* (submitted).

Fisher, D. R., M. J. Swint, and R. L. Kathren. 1990. *Evaluation of Health Effects in Sequoyah Fuels Corporation Workers from Accidental Exposure to Uranium Hexafluoride*. NUREG/CR-5566, Pacific Northwest Laboratory, Richland, Washington.

Fisher, D. R., R. L. Kathren, and M. J. Swint. 1991. "Modified Biokinetic Model for Uranium from Analysis of Acute Exposure to UF_6." *Health Phys.* 60:335-342.

Hodge, H. C., J. N. Stannard, and J. B. Hursh, eds. 1973. *Uranium * Plutonium * Transplutonic Elements*. Springer-Verlag, New York.

International Commission on Radiological Protection (ICRP). 1975. *Report of the Task Group on Reference Man*. ICRP Publication 23. Pergamon Press, Oxford.

International Commission on Radiological Protection (ICRP). 1991. ICRP Publication 60, Pergamon Press, Oxford.

Jadon, A., and R. Mathur. 1983. "Gametogenic Count and Histopathological Effect of Thorium Nitrate and Uranyl Nitrate on Mice Testes." *Andrologia* 15:40-43.

Kocher, D. C. 1989. "Relationship Between Kidney Burden and Radiation Dose from Chronic Ingestion of U: Implications for Radiation Standards for the Public." *Health Phys.* 57:9-16.

Leggett, R. W. 1989. "The Behavior and chemical Toxicity of U in the Kidney: A Reassessment." *Health Phys.* 57:365-383.

Llobet, J. M., J. J. Sirvent, A. Ortega, and J. L. Domingo. 1991. "Influence of Chronic Exposure to Uranium on Male Reproduction in Mice." *Fund. Appl. Toxicol.* 16:821-829.

McGuire, S. A. 1991. *Chemical Toxicity of Uranium Hexafluoride Compared to Acute Effects of Radiation*. NUREG-1391. U.S. Nuclear Regulatory Commission, Washington, DC.

Morrow, P. E., L. J. Leach, F. A. Smith, R. M. Gelein, J. B. Scott, H. D. Beiter, F. J. Amato, J. J. Picano, C. L. Yuile, and T. G. Consler. 1982a. *Metabolic Fate and Evaluation of Injury in Rats and Dogs Following Exposure to the Hydrolysis Products of Uranium Hexafluoride*. NUREG/CR-2268. University of Rochester, Rochester, New York.

Morrow, P. E., R. Gelein, H. Beiter, J. Scott, J. Picano, and C. Yuile. 1982b. "Inhalation and Intravenous Studies of UF_6/UO_2F_2 in Dogs." *Health Phys*. 43:859-873.

Moss, M. A. 1989. *Study of the Effects of Uranium on Kidney Function*. Atomic Energy Control Board, Ottawa, Ontario.

National Fire Protection Association (NFPA). 1990. *Identification System for Fire Hazards of Materials, 1990*. NFPA 704. National Fire Protection Association, Quincy, Massachusetts.

National Institute for Occupational Safety and Health (NIOSH). 1976. *Criteria for a Recommended Standard, Occupational Exposure to Hydrogen Fluoride*. U.S. Department of Health, Education, and Welfare, HEW Publication No. (NIOSH) 76-143, GPO No. 017-033-00171-5, pp. 1, 9, 11, 13, 84, 87-88, 91-92, 126-128, 130, 156-161. U.S. Government Printing Office, Washington, D.C.

National Institute for Occupational Safety and Health (NIOSH). 1990. *Pocket Guide to Chemical Hazards*. National Institute for Occupational Safety and Health, Cincinnati, Ohio.

National Institute for Occupational Safety and Health/Occupational Safety and Health Administration (NIOSH/OSHA). 1981. *Occupational Health Guidelines for Chemical Hazards*, pp. 729-734, NTIS Publication No. PB83-154609. National Technical Information Service, Springfield, Virginia. See also: Occupational Safety and Health Administration (OSHA), Department of Labor, 1989, *Industrial Exposure and Control Technologies for OSHA Regulated Hazardous Substances*, Vol. I of II, pp. 1056-1059, NTIS Publication No. PB89-21019; Department of Labor, Occupational Safety and Health Administration, 29 CFR 1910.1200; Hazard Communication Standard; July, 1989; Department of Labor, Occupational Safety and Health Administration, 29 CFR 1910.134; Respiratory Protection, July, 1989; 29 CFR 1910.1000; *Air Contaminants; Final Rule*, July 1, 1991.

Oil and Hazardous Material Technical Assistance Data System (OHM/TADS). 1990. U.S. Environmental Protection Agency, Washington, DC; (CD-ROM Version), Micromedex, Inc., Denver, Colorado.

Paternain, J. L. et al. 1989. "The Effects of Uranium on Reproduction, Gestation, and Postnatal Survival in Mice." *Ecotoxicol. Environ. Safety* 17:291.

Pelayo, J. C., P. M. Andrews, A. K. Coffey, P. L. Calcagno, G. M. Eisner, and P. A. Jose. 1983. "The Influence of Age on Acute Renal Toxicity of Uranyl Nitrate in the Dog." *Pediatr. Res.* 17:985-992.

Registry of Toxic Effects of Chemical Substances (RTECS). 1992. National Institute for Occupational Safety and Health, Cincinnati, Ohio. (CD-ROM Version) Micromedex, Inc., Denver, Colorado.

Ringot, C., and J. Hamard. 1988. "Toxic and Radiological Risk Equivalence Approach in UF_6 Transport." *Proc. Uranium Hexafluoride--Safe Handling, Processing, and Transporting Conference*, Oak Ridge, Tennessee, May 24.

Ruth, J. H. 1986. *Am. Ind. Hyg. Assoc. J.* 47:A-142-51.

Sikov, M. R., R. J. Traub, T. E. Hui, H. K. Meznarich, and K. D. Thrall. 1992. *Contribution of Maternal Radionuclide Burdens to Prenatal Radiation Doses*. NUREG/CR-5631, Rev. 1, U.S. Nuclear Regulatory Commission, Washington, D.C.

Sikov, M. R., and T. E. Hui. 1993. *Contribution of Maternal Radionuclide Burdens to Prenatal Radiation Doses: Relationships Between Annual Limits on Intake and Prenatal Doses*. NUREG/CR-5631, Rev. 1, Addendum 1, U.S. Nuclear Regulatory Commission, Washington, D.C.

Spoor, N. L., and J. B. Hursh. 1973. "Protection Criteria,"pp. 241-270. In *Uranium, Plutonium, Transplutonic Elements*, volume 36. eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh. Springer-Verlag, New York.

Stannard, J. N. 1988. *Radioactivity and Health: A History*. DOE/RL/01830-T59, National Technical Information Service, Springfield, Virginia, and Battelle Press, Columbus, Ohio.

Stopps, G. J., and M. Todd. 1982. *The Chemical Toxicity of Uranium with Special Reference to Effects on the Kidney and the Use of Urine for Biological*

Monitoring. INFO-0074. University of Toronto, Faculty of Medicine, report to the Atomic Energy Control Board, Ontario, Canada.

Voegtlin, C. and H. C. Hodge, eds. 1953. *Pharmacology and Toxicology of Uranium Compounds*. National Nuclear Energy Series, Division VI - Volume I, Parts III and IV. McGraw-Hill, New York.

Wrenn, M. E., P. W. Durbin, B. Howard, J. Lipsztein, J. Rundo, E. T. Still, and D. L. Willis. 1985. "Metabolism of Ingested Uranium and Radium." *Health Phys*. 48:601-633.

Wrenn, M. E., L. Bertelli, P. W. Durbin, K. F. Eckerman, J. L. Lipsztein, and N. P. Singh. 1994. *A Biokinetic and Dosimetric Model for the Metabolism of Uranium*. Report prepared for Radiation Surveillance Associates, Inc., under contract to the Atomic Energy Control Board of Canada, March 14.

DATE FILMED

10/11/94

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