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the weathering and transport of uranium through various environmental pathways and compartments by which human exposure may occur. This more detailed analysis should be structured to evaluate the speciation and bioavailability of uranium under the prevailing local environmental conditions. It is well established that the total metal concentration in an environmental medium is an unreliable guide to hazard quantification, as different forms of a metal can have substantially different bioavailabilities (Thornton, 1996; Plant et al., 1996; Elless et al, 1997).

It is noted that regional or local exposure scenarios are often structured to estimate the risk of two different types of health detriment:

(i) population detriment.

(ii) maximum individual detriment.

Population detriment is a traditional public health measure that estimates the number of cases of a particular outcome or disease in an exposed population attributable to a specific source of contamination. The maximum individual detriment relates to the individual who suffers the largest incremental risk due to a particular scenario. The relative importance of different sources and pathways is likely to differ depending on whether population detriment or maximum individual detriment is being calculated. In the case of population detriment it is particularly important that not only is the average exposure estimated, but also that its spatial distribution, and the relative importance of various exposure routes amongst the local population are defined.

Children are not small adults and their exposure may differ from an adult in many ways. Unfortunately, despite their obvious importance little definitive data exists concerning how their uranium exposure differs from that of adults (ATSDR, 1999).

Examples that follow in this chapter illustrate the relative importance of various exposure routes when assessing exposure within the context of population and maximum individual detriment and suggests factors that need to be considered when undertaking more site-specific studies. Such treatment is important in understanding the relative proportion of total exposure that may be allocated to a specific pathway during the assessment of human health risks (WHO, 1994), particularly where substance exposure pathways may exist.

The potential relationships between exposure to uranium and DU and specific forms of health detriment are discussed in Chapters 8 and 9.

5.2 Exposure via inhalation

The pyrophoric nature of uranium is considered to be of special relevance to the assessment of human exposure due to the production of dust containing mixed oxides of uranium. This scenario is especially likely to occur immediately following the use of DU munitions or where DU may be accidentally or deliberately heated (e.g. in the welding of reclaimed battlefield scrap). Its relevance to aviation accidents remains a subject of debate.

The oxides considered to be of principal concern are uranium dioxide (UO_2), uranium trioxide (UO_3) and triuranium octaoxide (U_3O_8) (Harley et al., 1999b; CHPPM, 2000). The size distribution, morphology and exact chemical composition of each particle released during the use of penetrators and armour is highly variable (e.g. Patrick and

Because of its rapid and substantial urinary excretion the concentration of uranium in urine can form the basis of assessing intake (e.g. Hooper et al., 1999; ICRP-78, 1997). Once measurements in urine have been made, biokinetic models may then be used to calculate intake. However, for inhalation, lack of information on the temporal pattern of exposure and chemical form and variation in natural excretion (e.g. Dang et al., 1992) reported urine concentrations of 0.0128 μg/l as an average for 'unexposed individuals' whereas Medley et al. (1994) observed values of 0.004 to 0.057 μg/l) can result in appreciable errors in such estimates (e.g. Stradling et al., 1998). For the specific case of DU, it may be possible to utilize differences in isotopic ratio to evaluate the upper limit of intake that corresponds to doses at the mSv level (Roth et al., 2001). Similar considerations should also apply for assessing the upper limits of DU in other tissues. These issues are discussed further in Chapters 10, 11 and 12.

For military veterans containing embedded DU, urine excretion levels of between 10 and 20 μg/l have been reported (Hooper et al. 1999). Negative finding regarding renal injury have been reported amongst such individuals (McDiarmid et al, 2000). This issue is discussed later in the following chapter. Gulf war veterans exposed to DU from inhalation, ingestion and wounds, showed average urinary excretion, 7 years post exposure, of 0.08 μg U/g creatinine, with the highest rates around 30 μg U/g (McDiarmid et al., 2000). Normal excretion of creatinine is considered to be 1.7 g/day (Jackson, 1966).

The occupational exposure decision level used for uranium workers at one facility in the United States is 0.8 μg/l of uranium in urine (FEMP, 1997). This value assumes an acute inhalation intake of moderately soluble uranium and a 60-day urine sampling frequency. For investigational purposes a value of 4 μg/l of urine is used for UK workers (information from Dr M Bailey, UK NRPB).

7.7 Accumulation

In autopsies of chronically exposed individuals, uranium has been observed in the skeleton, liver and kidneys in the average ratio of 63:2.8:1 (Kathren et al., 1989). Variations in this ratio are common and are dependent on the pattern and nature of exposure (Fisenne, 1993; ATSDR, 1999). The ratios are consistent with studies performed on mine workers and members of the public (Wrenn et al., 1985) and reflect the affinity of uranium for phosphate, which is abundant in bone. A similar distribution would be expected for DU and uranium provided the patterns of intake are comparable and the delay between cessation of exposure and autopsy are similar.

In the studies performed by Pellmar et al. (1999a) rats were surgically implanted with sterilized DU and/or tantalum pellets within the gastrocnemius muscle. As early as one month after pellet implantation and at subsequent sample times (six months), brain concentrations of uranium were statistically elevated in DU-implanted rats compared to controls implanted with tantalum (e.g. less than 2 to approximately 120 ng U/g tissue after six months implantation with 20 DU 1×2 mm pellets). The authors also observed that levels of uranium were statistically elevated in the testes of exposed animals when compared to those in the control group (e.g. less than 50 to approximately 600 ng U/g tissue after 18 months implantation with 20 DU 1×2 mm pellets). Levels of uranium in both testes and brain tissues were observed to be positively correlated with exposure (number of implanted pellets). Significant amounts of uranium were excreted in urine throughout the study (e.g. 1010 ± 87 ng uranium per ml urine in high-dose rats at 12-months exposure). The study suggests that in a rat model, uranium can accumulate

within the central nervous system and testicles. The accumulation of uranium in brain tissues has also been observed by Ozmen and Yurekli (1998).

No treatment-related effects (brain lesions) were identified during histopathological analysis of brains from animal studies performed by Gilman et al., (1998a, 1998b, 1998c).

7.8 Summary

Uranium may enter the body through the skin, lungs or gut. Once it has entered the systemic circulation it is distributed throughout the body, where it may become absorbed onto the surface of bone, accumulate or most likely be excreted through the kidneys.

Absorption via the inhalation route depends upon the size and chemical composition of the inhaled particulates and their biological solubility. While absorption through the gut and skin largely depend upon the bioavailability of the various DU compounds to which an individual has been exposed. Typical gut absorption factors for uranium in food and water are in the order of 2% for U(VI) compounds and less for the generally more insoluble compounds of U(IV). Soluble uranium and DU compounds may be absorbed through the skin.

A number of biokinetic models exist that describe and model the biokinetics of uranium and hence DU in the body. The most recent are the ICRP models for the lung, systemic circulation and gut (all summarized in Annex 4). Whilst these models describe the distribution of uranium amongst major organs, they tend to be orientated to radiological protection issues and have not addressed more recent data relating to the distribution of uranium into testes and brain.

Current gaps in knowledge include:

- Distribution (modelled and experimentally determined) of uranium at minor concentrations and in minor organs.
- Validation of animal data to man on biodistribution into brain, liver and gonads.
- Uranium distributions at a cellular level; bio-uptake of uranium derived from DU munitions throughout all exposure pathways in comparison with typical non-munition derived uranium and DU.

Table 8.1 Kidney and bone concentrations observed in experiments performed by Gilman et al., during the 1990s.

Study	SEX/Type	LOAEL mg U/kg body wt / day	Kidney µg/g	Bone µg/g
1	M Rat	0.060	<0.2	<1.78
	F Rat	0.090	<0.2	<1.78
2	M Rabbit	0.050	0.04 ± 0.03	0.09 ± 0.05
	F Rabbit	0.490	0.019 ± 0.01	0.053 ± 0.004
3	M Rabbit	<1.360	0.18 ± 0.13	0.20 ± 0.05
	F Rabbit	<1.360	0.18 ± 0.13	0.20 ± 0.05

1 Gilman et al. (1998a) 91 day experiment Sprague-Dawley Rat
2 Gilman et al. (1998b) 91 day experiment New Zealand White Rabbits (Specific Pathogen Free (SPF) derived)
3 Gilman et al. (1998c) 91 day experiment New Zealand White Rabbits (SPF)

The pathogenesis of the kidney damage in animals indicates that regeneration of tubular epithelium occurs in survivors upon discontinuation of exposure to uranium (Bentley et al., 1985; Dygert, 1949; Maynard and Hodge, 1949; Pozzani, 1949; Rothemel, 1949; Rothstein, 1949; Spiegel, 1949; Stokinger et al., 1953).

Leggett (1989) cites that tolerance may develop following repeated exposure to uranium, but this tolerance does not prevent chronic damage to the kidney, as the regenerated cells are quite different. Persistent changes in the proximal tubules of rabbits have been reported to be associated with the kidney's ability to store uranium (McDonald-Taylor et al., 1997). In another study Gilman et al. (1998c) describes a recovery study performed on New Zealand White Rabbits exposed to uranium nitrate (24 or 600 mg/l corresponding to 1.4 mg U/kg body wt/day and 41 mg U/kg body wt/day respectively) for 91 days. Renal tubular injury with degenerative nuclear changes, cytoplasmic vacuolation, and tubular dilation were seen in the high dose group without consistent resolution even after 91 days. Kidney concentrations observed in the high exposure group decreased from 3.48 ± 1.54 to 0.02 ± 0.01 µg/g over the 91 day recovery period in an exponential manner.

Reproductive and developmental toxicity In several studies with mice given soluble uranium compounds (uranyl nitrate hexahydrate, uranyl acetate dihydrate), the teratogenic, embryotoxic and reproductive effects of uranium have been studied (Domingo, 1989a,1989b). Exposure-related fetotoxicity, reduced fetal body weights, external and internal malformations, increased incidence of developmental variations, and decreased fertility were observed. In rats, unspecified degenerative changes in the testes have been reported following chronic administration of uranyl nitrate hexahydrate and uranyl fluoride in the diet (Maynard and Hodge, 1949; Maynard et al., 1953; Malenchenko et al., 1978).

Carcinogenicity Although bone cancer has been induced in experimental animals by injection or inhalation of soluble compounds of high-specific-activity uranium isotopes or mixtures of uranium isotopes, no carcinogenic effects have been reported in animals ingesting soluble or insoluble uranium compounds (Wrenn et al., 1985). However, given the nature of ionizing radiation damage to DNA, retention of any radioactive material in the body will have associated an increase in the probability of cancer; albeit small and depending on the radiation dose.

exposure levels will be well tolerated. However, quantitative information to assess, how much the long-term tolerable intake values may be temporarily exceeded without risk, is not available.

In the extrapolation from experimental animals to humans, comparative information on the toxico-dynamics is not available. Similarly, for inhalation exposure, reliable comparative information is not available on the toxico-kinetics. Thus for these parameters, default values for the extrapolation (10) have to be used. On the other hand, available information would tend to indicate that the oral absorption in humans is not greater than that in experimental animals and the default value for toxico-kinetics in this setting can be replaced by unity. Very limited information is available on the inter-individual variation in uranium toxicity within the human species, and thus the default uncertainty factor for the general population, 10, has to be applied.

8.6 Summary

The primary routes of exposure to uranium for humans are through ingestion or inhalation. The effects of embedded shell fragments containing depleted uranium (among other things) have also been studied (e.g. Fulco et al., 2000).

The target organ to be considered for uranium toxicity is the kidney (also considered to be the primary target organ for ingested uranium in WHO (1998b).

Uranium hexafluoride induces irritative effects at high doses; some uranium compounds may cause pulmonary effects at relatively high inhalation exposures. However, long-term exposure to lower concentrations (generally less than 10 mg/m^3) has usually not resulted in pulmonary toxicity. Carnotite mineral dust causes haemorrhages in dog lungs. Other factors such as diverse inorganic inhalable dust particles, radium, or radon progeny may contribute to these effects. No increase in malignant or nonmalignant respiratory disease mortality has been established in cohorts exposed to uranium in uranium processing. However, the available epidemiological data are generally limited by low statistical power, uncertainties in the assessment of uranium exposure, and/or the paucity of data on exposures to other agents.

In the kidney, proximal tubules are considered to be the main target (ATSDR, 1990, 1999). Currently, uranium is regarded as a less potent nephrotoxin than the classical nephrotoxic metals (cadmium, lead, mercury) (Goodman, 1985). No kidney toxicity related to urinary uranium concentrations was observed in people with embedded DU fragments.

Tolerable intakes for soluble (F and M type) and insoluble (S type) compounds can be derived for inhalation and ingestion. The TI for soluble uranium compounds is 0.5-µg/kg of bw/day and is 5.0 µg/kg of bw/day for insoluble compounds.

is a reasonable possibility of significant quantities of DU entering the ground water or food chain.

- Where possible, clean up operations in impact zones should be undertaken where there are substantial numbers of radioactive projectiles remaining and DU contamination levels are deemed unacceptable by qualified experts. If very high concentrations of DU dust or metal fragments are present, then areas may need to be cordoned off until removal can be accomplished.
- Guidance on the necessity for clean up of radioactive materials has been provided by the ICRP (1999b). Similar methodologies employed during the cleanup of land contaminated with heavy metals resulting from industrial activity are also appropriate, particularly as radiation dose levels of DU in conflict areas would not normally exceed those recommended for clean up by the ICRP.
- Young children could receive greater exposure to DU when playing in or near DU impact sites. Typical hand-to-mouth activity could lead to high DU ingestion from contaminated soil. Necessary preventative measures should be undertaken.
- General screening or monitoring for possible DU related health effects in populations living in conflict areas where DU was used is not recommended. Rather individuals who believe they have had excessive intakes of DU should consult their medical practitioner for an examination and treatment of any symptoms.
- Since DU is a radioactive metal, restrictions are needed on the disposal of DU. There is the possibility that DU scrap metal could be added to other scrap metals for use in refabricated products. DU is a pyrophoric metal that can produce oxides that can be inhaled when heated (welded). Disposal of DU should normally come under appropriate national or international (IAEA) recommendations for use of radioactive materials.

15.3 Research needs

Priorities for research that would significantly enhance knowledge and lead to better assessments of health risks from exposure to DU are given below.

- Studies are needed to clarify our understanding of the extent, reversibility and possible existence of thresholds for kidney damage in people exposed to DU. Important information could come from studies of populations exposed to naturally elevated concentrations of uranium in drinking water.
- WHO, through its International Agency for Research on Cancer (IARC), continues to study the effects of low-level exposure to ionizing radiation in order to improve the scientific base for health risk assessment and radiation protection. The utility and feasibility of studies to assess whether there has been an increased rate of cancer amongst military personnel who served in the Gulf or Balkans conflicts, and to evaluate the possible role of DU if an increase is found, should be investigated.
- Studies are needed that will allow better exposure assessments of children. This is particularly important given their unique exposure scenarios such as geophagia and hand-to-mouth activities.
- Studies are required to validate transfer coefficients for DU compounds entering the human food chain. For example, this is important given the amount of soil ingested by many livestock during browsing.
- There is a lack of information about the possible biological action of uranium or DU in the following areas:
  - Neurotoxicity: Other heavy metals, e.g. lead and mercury are known neurotoxins, but only a few inconsistent studies have been conducted on uranium. Focused studies are needed to determine if DU is neurotoxic.

- Reproductive and developmental effects have been reported in single animal studies but no studies have been conducted to determine if they can be confirmed or that they occur in humans.
- Haematological effects: Studies are needed to determine if uptake of DU into the bone has consequences for the bone marrow or blood forming cells.
- Genotoxicity: Some *in vitro* studies suggest genotoxic effects occur via the binding of uranium compounds to DNA. This and other mechanisms causing possible genotoxicity should be further investigated.

- Investigations are needed on the chemical and physical form, physiological behaviour, leaching and subsequent environmental cycling of specific forms of uranium from various industrial and military sources (e.g. depleted uranium alloys, phosphate by-products). Particular attention should be paid to where the bulk of DU finally goes.