DEVELOPMENT OF AN IMPROVED INTERNAL DOSE ASSESSMENT METHODOLOGY FOR PLUTONIUM

by

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ABSTRACT

Plutonium is carcinogenic when it is taken into the body because it is an alpha particle emitter. There is limited direct epidemiological evidence of the scale of specific risks from plutonium intake. Assessing doses arising from plutonium exposure is an onerous task. Doses have to be assessed from urine samples and mathematical models which describe the passage of plutonium through the body. Information on plutonium absorption, distribution, metabolism and excretion is very limited. Models of plutonium transport within the body continue to evolve. Different assessment methodologies have been employed to assess plutonium doses for worker cohorts.

A review of existing methodologies for producing plutonium doses has been conducted. A strategy for setting research priorities based on their potential impact on estimates of risk is discussed. Ways of improving plutonium dose reconstruction, including the production of reliability/uncertainty estimates are investigated. Efforts to harmonize approaches to the production of doses for the major plutonium worker cohorts are discussed. Recommendations are made for methodological approaches to plutonium dosimetry to meet current epidemiological research needs. The way in which the recommended methodological approach has been implemented for one major plutonium worker cohort is described. Some potential future research priorities are suggested.

To

Deb and Aidan

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Acronyms and Abbreviations

ADME	Absorption, Distribution, Metabolism and Excretion
ADS	Approved Dosimetry Service
α-RISK	ALPHA-RISK project (FP6 project)
Am	Americium
AMAD	Activity Median Aerodynamic Diameter
BNFL	British Nuclear Fuels Ltd.
Bq	Becquerel
DTPA	Diethylene-Triamine-Pentaacetic-Acid
eV	electronvolt
FP	European Framework Programme for research
GI	Gastro-Intestinal
GSD	Geometric Standard Deviation
Gy	Gray
HATM	Human Alimentary Tract Model
HPA	Health Protection Agency
HRTM	ICRP Publication 66 Human Respiratory Tract Model
ICRP	International Commission on Radiological Protection
JEM	Job Exposure Matrix
LET	Linear Energy Transfer
LOD	Limit Of Detection
Mayak PA	Mayak Production Association
MCMC	Markov Chain Monte Carlo
ML	Maximum Likelihood
NRPB	National Radiological Protection Board
Pu	Plutonium
SOLO	Southern Urals Low dose project (FP7 project)
SOUL	Southern Urals Radiation Risk Research (FP6 project)
SUBI	Southern Urals Biophysics Institute
Sv	Sievert
U	Uranium
UK	United Kingdom
USA	United States of America
USTUR	United States Transuranium and Uranium Registries
WBM	Whole Body Monitor
WeLMoS	Weighted Likelihood Monte-Carlo Sampling
WRI	Westlakes Research Institute

1 INTRODUCTION

The health risks of occupational exposure to ionizing radiation are still not fully understood. This is particularly true for exposures to alpha particle emitters, such as plutonium, which pose a significant risk if they become internally deposited in the body through inhalation, ingestion or puncture wounds. There have only been a limited number of epidemiological research studies of the health risks of exposure to plutonium to date. One of the reasons for the paucity of research in this area is that epidemiological studies require accurate, reliable and unbiased, dosimetry information for the population under study and, as plutonium dose assessment is in itself an incomplete science at present, this is particularly problematic for plutonium exposures. Previous research has shown that predictions of plutonium content in the liver and skeleton (the main sites of plutonium retention in the body) using current assessment methodology tend to substantially overestimate the actual measured content at autopsy, when such measurements are available for comparison. All other things being equal, the accuracy and reliability of the risk estimates produced by any epidemiological research into the health effects of plutonium exposures is directly correlated to that of the dosimetry data. Furthermore, the ability of an epidemiological study to resolve any adverse health effects is directly related to the size of the study population and, for plutonium exposures, this raises two further dosimetry related issues: Firstly, to increase the size of the study population it may be desirable to conduct meta-analyses involving workers from more than one facility, where differing methodology has been used to calculate plutonium doses: However, because of the direct relationship between dose and estimates of risk, it is not possible to combine the information from different facilities in any meaningful way unless doses have been reconstructed on the same basis. Secondly, the task of actually producing the dose assessments required for large cohort studies can be daunting, particularly as it may well

prove impractical to apply the procedures previously used for smaller case control epidemiological studies.

1.1 Primary Aim of this Research

The primary purpose of this research is to develop improved plutonium dose assessment methodology and the means to effectively implement it, so as to enable the production of the most accurate and unbiased dose estimates it is currently possible to produce, specifically for use in epidemiological research. This research will also help inform the dosimetry committees for the two major epidemiological studies of plutonium workers, ALPHA-RISK (http://www.alpha-risk.org) and SOUL (http://www.gsf.de/soul/index_new.htm), conducted, under the auspices of the European Union Sixth Framework Programme for Research (FP6), and to harmonise their approaches to plutonium dosimetry, with the consequent benefits that this will bring.

2 BACKGROUND

Plutonium is a radioactive, very dense, rare earth, metal, of the actinide series, predominantly it is a man-made element, and was first discovered by synthesis, but some primordial plutonium was produced in natural fission reaction related processes, such as that which occurred in uranium ore at the Oklo site, in Gabon (Neuilly et al., 1972). Plutonium is known to be toxic, when it is taken into the body, but while it is a heavy metal, this toxicity is primarily due to its carcinogenicity as an alpha particle emitter.

2.1 Plutonium Production

The original need to produce plutonium and much of the consequent exposure of individuals to it, are inextricably linked to the development of nuclear weapons.

2.1.1 Nuclear Weapons

Experimental evidence of, what became known as, nuclear fission was first recognised by Hahn and Strassmann (1939), at the Kaiser Wilhelm Institute for Chemistry, in Berlin, in December 1938, the possible mechanics of, and energy released in, this process were subsequently postulated by Meitner and Frisch (1939).

Following the discovery of nuclear fission, it was speculated that the energy released might be used to produce bombs with a destructive capacity orders of magnitude greater than previous weapons and several countries initiated nuclear weapons related research but it was in the United States of America (USA) that this idea was most vigorously pursued. Initial work focused on the use of uranium-235 as the fissile component of a weapon, this was partly as a

result of a memorandum describing a potential "Super Bomb" and the utility of this isotope in its production, which was written, in March 1940, by Frisch and Peierls, then researchers at the University of Birmingham. However, it soon became apparent that separating, or "enriching", uranium-235 from natural uranium would not be a trivial task: Being chemically identical, isotopes cannot be separated by chemical means and because uranium-235's physical characteristics are little different from uranium-238, which is much more prevalent (>99% by mass) in natural uranium, physical separation techniques proved to be expensive and difficult. However another potential route of producing fissile material had become apparent: It had been theorised that isotopes of elements with a higher atomic number than uranium (Transuranium), that had yet to be discovered, would also be fissile, that these elements could be produced by nuclear bombardment of uranium and, because they would be chemically distinct from it, they would be easier to isolate.

2.1.2 Element 94

In 1939 McMillan and Abelson used the 60 inch cyclotron in the Radiation Laboratory at the University of California, Berkley, to generate neutrons with which to bombard uranium-238, in 1940 they used chemical means to confirm that this reaction produced a previously unknown element with atomic number 93. The new isotope that had been produced was radioactive and it was speculated that the product of this decay might be another new element, with atomic number 94, but this could not be proved before McMillan left Berkley in November 1940. McMillan passed on his Transuranium element research to colleagues at Berkley, during the Winter of 1940 and Spring of 1941, Seaborg, Kennedy and Wahl, attempted to synthesise element 94 and finally confirmed its discovery on the 24th of February 1941. Because of their potential use as strategic materials the discovery of elements 93 and

94 was not made public and they were initially referred to only by their atomic number or by code names. Experiments conducted at Berkley on the 28th March and 18th of May 1941, determined that the isotope of element 94 with an atomic mass of 239 was, as theory had predicted, fissionable and had a larger (by a factor of ~1.7) fission cross section than uranium-235.

The initial code name "copper", that had been assigned to element 94 inevitably resulted in some confusion, in a March 1942 report, Seaborg suggested the formal name plutonium after the (now dwarf) planet Pluto for element 94 and, somewhat mischievously, the elemental symbol Pu (Seaborg). However, the name plutonium was to remain classified until the end of the Second World War and because of the secrecy surrounding nuclear weapons various code names (e.g. "copper", "49", "tube alloy") would continue to be used for plutonium, both within the USA and elsewhere, for many years.

2.1.3 The Metallurgy Project

Although, the micro-gram amounts of plutonium that could be produced in the Berkley cyclotron were sufficient to conduct experiments to determine its fundamental properties, it was apparent that this would not be a practical technique for producing the large quantities of plutonium needed for nuclear weapons development. Initial estimates of the amount of fissile material required to produce a nuclear weapon indicated that kilogram quantities would be required and calculations showed that production of this amount of plutonium using cyclotrons could take thousands of years. However, it had been theorised that if controlled self-sustaining nuclear fission, could be established in natural uranium, capture of fission neutrons by uranium-238, and subsequent radioactive decay processes, would produce

plutonium-239: Neutron capture in uranium-238, produces uranium-239, which beta decays, with a half-life of 23 minutes, to neptunium-239 which in turn beta decays, with a half life of 2.3 days to plutonium-239.

On the 6th of December 1941, the United States Office of Scientific Research and Development gave Compton the remit of investigating methods for the large scale production of plutonium. In January 1942, Compton initiated the "Metallurgy Project", a name used to obfuscate its role in researching methods of plutonium production, and this work was to be centred on the Metallurgical Laboratory ("Met Lab"), at the University of Chicago. Compton brought Fermi and others, to Chicago to build an experimental "Pile" (i.e. nuclear reactor), to be housed below the disused West stands of the University football ground, Stagg field, with the objective of demonstrating the feasibility of establishing controlled self-sustaining fission in uranium.

It should also be noted that the need to protect those working on the Metallurgy Project from the effects of radiation exposure were recognised at an early stage and a "Health Division" was established for this purpose (see below).

2.1.4 The Manhattan Engineer District

By the summer 1942 it had become apparent that, to meet the future needs of nuclear weapons research, much larger industrial scale facilities would be required. The United States Army Corps of Engineers assumed overall responsibility for all work relating to the development and production of nuclear weapons and they established the Manhattan Engineer District, again a name chosen to obfuscate its actual remit for national security reasons, for this

purpose on the 18th of August. The Metallurgy Project, along with its Health Division, now became part of this newly concerted effort, which subsequently became known as the "Manhattan Project".

On the 2nd of December 1942, under the direction of Fermi, the Chicago Pile (CP-1) achieved controlled self-sustained nuclear fission for the first time. The CP-1 pile was subsequently dismantled and was used to construct the CP-2 pile, in February 1943, at the new Argonne Laboratory in the Palos Hills Forest Preserve, irradiated uranium fuel from this pile underwent chemical separation and yielded the first plutonium, produced using this method, on the 12th of October 1943. This separation (now generally called reprocessing) was achieved using a technique whereby irradiated fuel from the pile was dissolved in nitric acid, which liberated the plutonium it contained as aqueous plutonium nitrate, and this was then chemically isolated. This work established the template for the production of plutonium as a strategic material. A much larger pilot facility was constructed at the Clinton Engineer Works (now called Oak Ridge), in Tennessee, in 1943 and this was the model used for the full-scale plutonium production facility built at the Hanford Engineer Works, in Washington State. Hanford became operational in September 1944 and began shipping plutonium to the Los Alamos nuclear weapons development site, in New Mexico, in February 1945.

2.1.5 Proliferation

The enormous efforts by those involved in the Manhattan project only yielded enough plutonium to build two nuclear bombs by the end of the Second World War, the "Trinity" test device ("The Gadget") detonated on July 16, 1945, at the Alamagordo bombing range in New Mexico and the weapon ("Fat Man") dropped on Nagasaki on the 9th of August 1945.

However, the Manhattan project had also demonstrated the enormous destructive power of nuclear weapons and the technological means for producing them, much of which was extensively documented in the Smyth report (Smyth, 1945) published in 1945. The USA continued to increase its plutonium production capability, and other nations strove to develop their own capabilities, after the Second World War. The facilities needed for plutonium production, as described in the Smyth report, were reproduced by the Soviet Union, who had also learned much about them through espionage, and the United Kingdom (UK), who also had extensive knowledge of them from scientists it had seconded to the Manhattan project. Historically, it has been at these, nuclear weapons related, plutonium production facilities e.g. Hanford, Mayak (Russia, then part of the Soviet Union) and Sellafield (UK), where the largest, in terms of both number and magnitude, plutonium exposures have tended to occur, particularly in their earliest years of operation.

2.1.5.1 Sellafield

Construction of nuclear facilities at the former Royal Ordnance Factory at Sellafield, in North West England, began in September 1947, the site was initially renamed Windscale and then Windscale and Calder works, following the construction of the Calder Hall nuclear power station on adjacent land, before later reverting back to Sellafield. The initial purpose of this facility was, primarily, the production of weapons grade plutonium for the British nuclear weapons programme, the first separation plant started operations in 1952, reprocessing of spent nuclear fuel from civil nuclear reactors began in 1964 and this subsequently became the major focus of operations at the site.

2.1.5.2 Mayak

The Mayak Production Association (PA), also previously known by various code names e.g. “Base 10”, “Kasli”, “Chelyabinsk-40” and “Chelyabinsk-65”, is located in the South Urals in the central region of the Russian Federation, construction of the site began in the Summer of 1946. Even thought construction of the Mayak facility only commenced, approximately, a year in advance of that at Sellafield, political pressure to develop nuclear weapons drove much more rapid progress, with the first separation plant becoming operational in 1948, this rapid progress was associated with much larger plutonium exposures than at Sellafield or Hanford. Like Sellafield, operations at the Mayak PA were initially focused on the production of weapons grade plutonium, for the Soviet Union’s nuclear weapons programme, but from 1977 onwards evolved into the reprocessing of civilian nuclear fuel.

2.1.6 Global Plutonium Inventory

As of 2003, the global inventory of separated plutonium was estimated at 495.5 tonnes (some 3 to 4 times this quantity is though to remain in irradiated nuclear fuel), approximately 257.5 tonnes of this was weapons grade (see below) plutonium, with most of this, 244.5 tonnes, being held by the United States, 99.5 tonnes, and the Russian Federation, 145 tonnes. The United Kingdom only held around 7.6 tonnes of weapons grade plutonium but held approximately 70.2 tonnes of the world’s separated civilian plutonium stocks, which is more than the United States (none) and the Russian Federation (38.2 tonnes) combined. It can be seen that the separated plutonium held by the United States, the Russian Federation and the United Kingdom accounts for the vast majority, 360.5 tonnes, of the current global inventory (ISIS, 2005).

2.2 Plutonium Isotopes

All known plutonium isotopes, which range in mass from 228 to 247, are radioactive. Because of the way in which the majority of plutonium has been produced, in nuclear piles/reactors (see above), the most commonly occurring isotopes are Pu-239, Pu-240 and, as fuel utilisation ("Burnup") has increased, in civil reactors, Pu-238, Pu-241, Pu-242. Because Pu-240 can decay by spontaneous fission, producing neutrons that might then initiate fission in surrounding Pu-239, it is an obstacle to the design of nuclear weapons: Hence, so called, "Weapons grade" plutonium comes from low burnup nuclear fuel which contains no more than 7% Pu-240 by mass. The way in which the isotopic composition of plutonium changes with fuel burnup is illustrated in Table 1 below.

Table 1. Plutonium Isotopic Composition as a Function of Fuel Burnup

Type of Pu	Burnup (MWd/t)	Pu Isotopic Composition (% by mass)					Specific Pu Alpha Activity (GBq/g)
		238	239	240	241	242	
Weapons Grade	<1000	-	93.0	7.0	-	-	2.72
Magnox*	3000	0.1	80.0	16.9	2.7	0.3	3.89
AGR*[1]	18000	0.6	53.7	30.8	9.9	5.0	7.63
PWR*[2]	53000	2.7	50.4	24.1	15.2	7.1	20.3

Notes: * Plutonium produced in civil reactor programmes
[1] Advanced Gas-cooled Reactor
[2] Pressurised Water Reactor

Pu-238, Pu-239, Pu-240 and Pu-242, are primarily alpha particle emitters. Pu-241 is primarily

a beta particle emitter but it decays, with a half life of 14.4 years, to Americium-241, this is an alpha particle emitter and can make a significant contribution to the overall dose from plutonium intakes. The half-lives, primary decay modes and energies, for these isotopes are given in Table 2 below.

Table 2. Isotope Characteristics

Isotope	Decay Mode	Half-Life (Years)	Energy (MeV)
Pu-238	Alpha	87.7	5.5
Pu-239	Alpha	24,065	5.1
Pu-240	Alpha	6,537	5.2
Pu-241	Beta	14.4	0.02
Am-241	Alpha	432	5.5
Pu-242	Alpha	376,300	4.9

2.3 Radiation and Health

One of the reasons that exposures tended to be larger in the early years of plutonium production is that the potential health hazards of exposure were largely unknown and overall knowledge of the cancer risks of radiation exposures, particularly from internally deposited radionuclides, was very limited at this time.

2.3.1 Radiation Health Effects

Within a year of the discovery X-rays, by Wilhelm Röntgen, in 1895, the first suspicions that ionising radiation exposure could lead to adverse health outcomes were voiced (Edison, 1896). The initial health effects observed related to direct cellular damage, resulting in erythema (i.e. visible reddening of the skin) and ultimately radiation burns (Thomson, 1896) and the severity of these effects were seen to be directly proportional to the level of individual exposure (i.e. they were deterministic). Consequently, by 1900 it was recognised that steps should be taken to avoid over exposure to X-rays to prevent such effects occurring.

2.3.2 International Commission on Radiological Protection

For many years radiation protection efforts simply consisted of a variety of, largely empirical, local and/or national recommendations based on the practical experience of those working with radiation. It was not until the mid-1920s that there was a more concerted international approach to radiation protection. At the second International Congress of Radiology, in Stockholm, in 1928, the International X-ray and Radium Protection Committee was formed, this subsequently became the International Commission on Radiological Protection (ICRP), in 1950, which is still extant as the recognised international advisory body on radiological protection.

2.3.3 Tolerance and Dose

In these early years of radiation protection, the effects of radiation exposure were seen as analogous to those of chemical toxins, which did not produce any toxic effects until they reached sufficient concentration in the body, such concentrations being described in terms of "Dose"' (i.e. mass of toxin per unit body mass). It is perhaps unsurprising that the toxic effect

of radiation in a body would also come to be described in terms of "Dose". Conventional toxicology uses the term "Tolerance" to describe a dose which is below the threshold for observable ill effects and which is thought to constitute a safe dose limit for those exposed to a toxin and it was believed that there was a similar tolerance for radiation exposure. Initial efforts to define tolerance dose for radiation in the mid to late 1920s were based on some fraction of the exposure known to produce erythema. These early attempts at radiological protection were successful in that they greatly reduced the incidence of effects such as skin burns and hair loss, which were fundamentally deterministic in nature, i.e. the severity of the outcome increase proportionally with exposure.

2.3.4 Deterministic and Stochastic Effects

While it had not taken long to identify, and start to control, the obvious deterministic effects of radiation exposure, it was some time before another significant health hazard, increased risk of contracting a cancer, was fully recognised. X-ray induced skin cancer had been observed only seven years after their discovery (Frieben, 1902) but early attempts to control the, at that time, frequent and alarming deterministic effects of radiation exposure also helped to ensure that such rapid onset cancers became less common. As cancer induction appeared to be much less frequent than deterministic effects and with similar "Spontaneous", cancers also observed in individuals who had not been anthropogenically exposed, this was thought at the time to be a lesser hazard of radiation exposure. Consequently, it was believed (because of the concept of a tolerance dose that had been inherited from conventional toxicology) that if deterministic effects could be avoided, this would also eliminate any risk of cancer induction. However, unlike radiation burns, or the other deterministic (or non-stochastic) effects of radiation exposure, it is now known that cancer induction is a stochastic effect of

exposure (i.e. the probability of contracting cancer, rather than the severity of the cancer, increases with exposure to radiation).

Because of the stochastic nature of the effect, the background rate of spontaneous cancers and the long latency periods normally associated with carcinogenesis, it is perhaps unsurprising that it took a lot longer to identify increased risk of contracting cancer as a significant hazard of radiation exposure. It would be exposure to alpha radiation that would provide some of the first evidence that carcinogenicity was a serious hazard of radiation exposure.

2.3.5 Alpha Radiation

Alpha radiation was discovered shortly after the discovery of X-rays (Rutherford, 1899) but the health hazards of exposure to alpha particle emitters were not immediately apparent. Alpha particles rapidly loose energy and acquire electrons from the surrounding environment, to become inert Helium-4 (their typical lifetime is a few pico-seconds), they also exhibit very low penetration (~ 50 μm in body tissues) and are unable to penetrate the outer dead layer of the epidermis (ICRP reference skin thickness for radiological protection purposes is 70 μm). Consequently, it was soon widely acknowledged that alpha particles did not present any significant hazard when their source is external to the body ("External dose") but it would take many years for it to be recognized that this did not mean that they presented no significant hazard to health. This was because alpha emitters only prove to be a major health hazard when their source is located within body tissues ("Internal dose") and it took some years before sufficient exposures of this type occurred, and also because the primary health effects of alpha radiation exposure are stochastic in nature.

2.3.6 Internal Dose

Internal dose results from exposure to sources of ionising radiation that have been taken into the body by inhalation, ingestion, absorption or through a puncture wound, it should be noted that, by definition, the source of the radiation needs to be freely available to systemic/metabolic processes (i.e. swallowing an encapsulated radiation source does not constitute internal dose)

In direct contrast to the position with external dose, alpha particle emitters present the greatest radiological hazard, when compared to X, gamma and beta emitters, for internal exposures. It is now know that this is because alpha particles cause proportionally more damage, per unit energy, than penetrating radiations do, when they interact directly with living tissues, because they are highly ionising and deliver all of their energy within a small volume i.e. they exhibit high Linear Energy Transfer (LET): For example, typical gamma/X-ray LET is about 3 keV/μm while that for Alpha particles is around 100-200 keV/μm. However, it was empirical evidence following exposures to radium which played a key role in the initial identification of the potential health effects from internal radiation exposure to alpha particle emitters.

2.3.7 Radium Dial Painters

Radium was discovered in 1898 (Curie, Curie and Bemont, 1898), it was the third alpha particle emitter to be identified, after uranium and polonium. The practice of painting clock dials and other items, with radium based paint to make them luminous was introduced just prior to the first world war. The production and application of luminous paint became a major industry, particularly in the USA. Because of the precision required in applying these radium based paints “Dial painters”, or “Luminisers”, (as they were commonly known), frequently

"Tipped" their brushes (i.e. brought the bristles to a point) using their mouths and as a result would ingest some of the paint and the radium it contained. Between 1922 and 1924 suspicions began to develop about the cause of the lesions commonly being found on dial painter's jaws and the first description of jaw necrosis in a dial painter was published (Blum, 1924). While it was understood that these adverse health effects were the result of radium exposure, at first, it was thought that they were caused by simple chemical toxicity, "Radium poisoning", as it was then known. However, in 1929, unusually high incidence of osteosarcomas within employees at a radium painting factory was first noted and this was linked to their occupational exposure to radium and, importantly, the radiation it emitted (Martland, 1929 & 1931).

It was as a result of this experience with the radium dial painters that the need to control internal exposures to alpha particle emitters was initially recognised. In 1941 the USA's National Bureau of Standards (NBS) established the first limit on internal exposure with the publication of a handbook "Safe Handling of Radioactive Luminous Compound" (NBS, 1941) which contained a recommended residual body content "Tolerance level", for radium of 0.1 μCi (3.7 kBq).

2.3.8 Health Division of the Manhattan Project

As noted above, in view of the potential radiological hazards involved, the Metallurgy Project had created a Health Division, which, along with the Metallurgy project itself, was later subsumed into the Manhattan project. Health Division was formed to provide equipment, services, and advice, on radiological protection and to conduct research to enable it to deliver these objectives.

Because plutonium is an alpha particle emitter, like radium, it was recognised at an early stage that the plutonium being produced to manufacture nuclear weapons could pose a health risk to those involved. In 1945 the first leader of Health Division, Stone, stated: "When the scientists of America became reasonably certain that they could produce a nuclear chain reacting pile, they were brought face to face with the hazards of such an undertaking. It was realized before any pile was in operation that the amounts of radioactive material produced by the fission of uranium in a relatively small system would be equivalent to hundreds or even thousands of grams of radium".

As almost all of the existing knowledge of the risks from internal exposure came from experience with radium, the first tolerance limit, 0.3 μCi (11.1 kBq), set for plutonium exposure in 1944 was estimated by calculating the amount of plutonium that would radiate energy at a similar rate to the established tolerance limit for radium, 0.1 μCi (3.7 kBq). However, Health Division also identified that a particular problem with controlling the risks from plutonium exposure lay in being able to quantify the body content of any individual. Plutonium, like radium, emits alpha particles that, while being relatively, energetic, exhibit high linear energy transfer and low penetration, typically 50μm in body tissues. Hence, once plutonium is taken into the body it is extremely difficult to measure using direct measurement techniques employing external detectors. Even today, when far superior detectors are available, the threshold of detection for direct measurement of plutonium *in vivo* ("Whole Body Monitoring") is relatively high and equates to a dose that would be several times greater than recommended annual dose limits. With radium methods had been developed to estimate body content through direct measurement of the gamma radiation that was emitted by radium-226 and/or by measuring radon gas, its radioactive daughter, in exhaled breath, this

was not possible for plutonium. The Manhattan project health physics group realised that that the only way to effectively measure body content would be indirectly from biological samples, taken from exposed individuals, as these would contain a proportion of any plutonium to which they had been exposed. The plutonium content of these biological samples could be assayed directly, to relatively low levels, and could be used to infer the amount of plutonium remaining in the individual's body, providing this relationship was sufficiently understood and quantifiable to the extent that it could be described mathematically. Because urine is easy to collect in sufficiently large volumes this was considered to be the best practical choice for routine bioassay measurements. A programme to develop techniques to measure relatively low levels of plutonium in excreta and to produce a mathematical description of the urinary excretion of plutonium, over time following an exposure, was made a research priority. By the winter of 1944 a technique for measuring plutonium in urine had been developed by the Los Alamos Health Group and this was used to monitor accidental exposures to workers at the site in early 1945.

2.3.8.1 The Langham Plutonium Excretion Function

Initial knowledge of the relationship between levels of plutonium in urine and total body content were derived from animal experiments conducted in 1944 but there was considerable debate as to the relevance of such information to plutonium metabolism in humans. To resolve these uncertainties, with respect to plutonium metabolism, in August of 1944 an urgent programme of research was proposed by scientists working on the Manhattan project, among other things this proposal suggested the possibility of conducting experiments involving human test subjects. This proposal to conduct human experiments was endorsed by the Manhattan project leaders at a meeting in March 1945. During the period April 1945 to

July 1947, eighteen, purportedly terminally ill, test subjects were injected with known quantities of plutonium citrate, following injection urine was collected and analysed on a systematic basis for up to 200 days (Langham, 1950). Following these experiments the first mathematical description of plutonium excretion was developed, the "Langham function", this was named after the scientist in charge of this experimental programme Wright Langham. The Langham function was the basis of the description of plutonium excretion presented in ICRP publication 10 (ICRP, 1968). The purpose of the Langham function was to describe the excretion of plutonium immediately following a large single exposure with prompt uptake of plutonium to blood, which is representative of accidental exposure scenarios. The manner in which Wright Langham, and his colleagues, conducted these experiments is now considered ethically dubious and they could not be repeated in their original form. Consequently, this dataset, including the additional data that was collected on three of these test subjects by Rundo et al. (1973), is still one of the key information resources on plutonium excretion.

2.3.9 Evolution of Dose Quantities and Units

At the 7th International Congress of Radiology in Copenhagen on 1953, the International Commission on Radiological Units (ICRU) formalised the concept of *absorbed dose* by assigning the special unit "rad" being that quantity of any type of ionizing radiation which produced in an increment in energy density of 100 ergs per gramme (0.01 J kg^{-1}) of target material. Under the Systeme International (SI) the rad has been replaced by the gray (Gy) which has dimensions, in SI base units, of one joule per kilogramme (ICRP, 1991).

2.3.9.1 Plutonium Dose

In 1959 ICRP issued publication 2 (ICRP, 1959) which established the first system for controlling plutonium, and other internal, exposure risks on the basis of radiation dose. Another key change introduced by ICRP2 was the concept of a "critical organ", this recognised the fact that internally deposited radionuclides such as plutonium do not deliver the same dose to all organs and tissues, because of the way they are metabolised and their short-range emissions, unlike exposure to highly penetrating external radiation sources.

2.3.9.2 Equivalent and Effective Dose

The ICRP have defined two weighted dose quantities to be used for radiological protection purposes, "Equivalent Dose" and "Effective Dose" (ICRP, 1991), like the gray both of the quantities have the dimensions Joules per kilogramme but have a special unit name, the sievert (Sv).

Equivalent dose includes a radiation weighting factor (W_R), which is dimensionless, that seeks to adjust for the observed differences in biological effects in living tissues, for radiation of different types, at the same level of absorbed dose. The W_R for alpha radiation is 20, this is based on knowledge gained from laboratory radiobiology experiments and reflects the observed relative increase in various biological endpoints as a result of exposure to alpha radiation rather than to x and gamma radiation. Obviously not all these different biological end-points show the same level of enhancement, as a result of alpha radiation exposure, and the W_R value of 20 chosen is thought to represent the cautious upper limit for enhancement of effects suitable for use in radiological protection (i.e. cancer induction in man at low doses and low dose rates).

Effective dose is the weighted sum of the equivalent doses to specific organs and tissues of the body, using the tissue weighting factors (W_T), which are dimensionless, specified by the ICRP. The values of W_T used are intended to permit the normalisation of the risks of non-uniform irradiation of the body, of the type which occurs with internal exposures, to those of uniform whole body irradiation, typical of external exposures, and have, in part, been derived from epidemiological research of externally exposed populations. It should also be noted that for radiological protection purposes all risks are considered and the W_T used for the gonads reflects potential hereditary risks to offspring more than any somatic risk to the individual. Since W_T represents the organ risk as a proportion of the risk from a whole body exposure $\Sigma W_T = 1$.

However, one of the objectives of epidemiological analyses involving alpha emitters should be to investigate the effects of different types of radiation and non-uniform irradiation, *in vivo*. Consequently, epidemiological analyses should use absorbed dose (Gy) so that any difference in effect between radiation of different types is immediately apparent. This has been recognised by the ICRP which has stated that: "The ICRP protection quantities are not intended for detailed assessments of dose and risk to individuals. They should not be used in epidemiological analyses or …" (Harrison and Streffer, 2007).

2.3.9.3 Committed Dose

For internal exposures, doses calculated for radiological protection purposes are often integrated, with respect to time, over the fifty year period following exposure, this being known as the "Committed Dose" (e.g. the committed effective dose) and its intention is to provide operational control of the lifetime risk to an individual from such exposures. Again,

such doses should not be used for epidemiological research as the dose required is the absorbed dose, to a specific organ or tissue, during the period(s) of interest. When possible causative relationships are being explored, the period of interest for any outcome is always prior to its onset and will often include a latency period. The latency periods used will be based on the latest estimates of the time between a causative event and the onset of physical symptoms for a specified outcome (e.g. a minimum of 2 years for Leukaemia or 10 years for lung cancer, but usually multiple periods will be tried). For epidemiological analyses the doses incurred during the latent period are ignored. Because various latency periods and outcomes may be considered in an epidemiological analysis, the dose data sets produced for these analyses often take the form of annual absorbed doses across the entire study period which can then be summed to provide the dose to individuals in the specific period(s) of interest for any outcome or latency period.

2.4 Radiation Epidemiology

One of the aims of dosimetry is not just to measure radiation exposure but to provide some mechanism for controlling it and hence to control risks to those exposed (i.e. in effect dose becomes an analogue for risk). As stated previously, this was relatively easy to do in relation to rapid onset deterministic effects but to understand the stochastic risks from exposure to ionising radiation in logical and quantitative way, epidemiological analyses are required. It was only after the Second World War that the stochastic risks from radiation exposure started to be given serious consideration and epidemiological analyses were conducted on exposed populations such as the survivors of the atomic bombings in Japan. The United States National Academy of Sciences created the Atomic Bomb Casualty Commission in 1947, which subsequently became the Radiation Effects Research Foundation (RERF) in 1975, to

study the health of the Atomic Bomb Survivor (ABS) cohort in Japan. RERF still conducts research on this important cohort, however, the vast majority of the exposure to the ABS cohort was from external radiation as has also been the case with the majority of radiation epidemiology studies conducted to date.

2.4.1 Dosimetry and Epidemiology

The statistical power of an epidemiological study to detect any association between an exposure and an adverse health outcome is largely dependent on three factors the size of the cohort, the magnitude of exposures within the cohort and the dose response relationship for the health outcome being investigated. For any given dose response relationship, as the magnitude of exposures for a cohort decreases, the size of the cohort needed to detect this effect increases. Although, the plutonium intakes in some facilities have been substantial, particularly in the earliest years of their operation, the resulting doses are generally considerably lower than for the ABS and tend to be protracted in nature rather than the single exposure suffered by the ABS cohort. Consequently in order to detect health effects in occupationally exposed cohorts these cohorts need to be as large as possible in order to have sufficient statistical power. One of the reasons that there has been little epidemiological research into the health effects of internal alpha emitters such as plutonium is that producing the dose information required for such research is a far from trivial exercise.

2.4.2 Previous Plutonium Worker Epidemiological Studies

As outlined above, work related to the Manhattan project in the USA resulted in the earliest occupational exposures to plutonium and the subsequent nuclear weapons build up during the cold war military programme meant that many thousands of workers have potentially been

exposed to plutonium there. However, the way in which weapon development had been organised in the USA, with many contracting agencies being involved, means that assembling large cohorts of plutonium workers for epidemiological study is relatively difficult. Consequently there have only been a limited number of studies of separate relatively small groups of plutonium workers at facilities e.g. Rocky Flats (Wilkinson et al., 1987; Brown et al., 2004), Los Alamos National Laboratory (Wiggs et al., 1994; Voelz et al., 1997), Hanford (Wing et al., 2004) and Rocketdyne (Boice et al., 2006) in the USA. It is also noteworthy that only two of these studies, Brown et al. (2004) and Boice et al. (2006), actually used estimates of plutonium organ doses in the epidemiological analysis. Furthermore, Wing et al. (2004) observed "The majority of workers in the Hanford cohort had no bioassay monitoring in most years of employment".

In the, former, Soviet Union and in the United Kingdom nuclear weapons research, development and production activities were conducted by groups of individuals who were employed by a relatively small number of government agencies. Hence, it is much easier to gather the information required to conduct large scale epidemiological analyses of plutonium workers in the Russian Federation and the United Kingdom. Two worker cohorts in particular, those of the Mayak Production Association in the Southern Urals, and the Sellafield site in North West England, each having more than ten thousand plutonium workers are considered to be potentially the most informative from an epidemiological perspective.

2.4.2.1 Sellafield Cohort

While analyses of the health of radiation workers at the Sellafield plant had been conducted for some time, it was not until 1999 that the first full cohort study that included plutonium

dose estimates was published (Omar et al., 1999) this had been undertaken by researchers at the London School of Hygiene and Tropical Medicine (LSHTM). A detailed description of the dosimetry used for this study was published in a paper by (Riddell et al., 2000), although it should be noted that the dose assessments had been passed to the epidemiologists in the early 1990s and consequently the methodology used had been superseded by the time their analysis was completed.

2.4.2.2 Mayak Cohort

Because of the importance of the Mayak worker cohort to plutonium related epidemiological research it is a focus of international research efforts and has been subject to several studies (e.g. Koshurnikova et al. 1994, 1999, 2000, 2002, Gilbert et al., 2000; Kreisheimer et al., 2003; Gilbert et al., 2004). However, these studies have often been conducted using different dosimetry and study populations, depending on the investigators involved in a particular analysis, and this has produced varied estimates of risk.

2.4.3 Current Plutonium Worker Epidemiological Studies

The two largest epidemiological projects requiring plutonium dose estimates ongoing at the commencement of this research were commissioned under the European Union's Sixth Framework Programme for research (FP6), ALPHA-RISK and SOUL. The ALPHA-RISK project includes the Sellafield worker cohort and the SOUL project encompasses analyses of the Mayak worker cohort.

2.4.3.1 ALPHA-RISK Project

Alpha-Risk is a multi-national study of the risks associated with occupational exposure to alpha particle emitters involving eighteen partners from nine countries within the European Union. This is a large project and it contains two Work Packages (WP) that relate to plutonium exposures, including those at the Sellafield site as part of the (former) British Nuclear Fuels Ltd cohort.

WP3 is a nested case control study of lung cancer and leukaemia in plutonium and uranium workers, this type of study only requires doses for a sub-set, the cases and matched controls, from the overall worker population:

- Belgium – Studiecentrum voor Kernenergie - Centre d'Etude de l'énergie Nucléaire (SCK.CEN)
- France – Commissariat à l'Energie Atomique and Compagnie de Gestion des Matière Nucléaires (CEA-COGEMA)
- UK – Atomic Energy Authority (UKAEA)
- UK – Atomic Weapons Establishment (AWE)
- UK – British Nuclear Fuels Ltd (BNFL)

WP4 is a feasibility study looking at the possibility of conducting an epidemiological study involving the entire worker cohorts from facilities in the United Kingdom (BNFL) and France (CEA-COGEMA), two specific aims of this research is to assess the feasibility of generating the required dosimetry data for such a study and the production of a dosimetry protocol describing how this would be done.

2.4.3.2 SOUL Project

One of the main goals of the Southern Urals Radiation Risk Research (SOUL) project is the exploration and quantification of health risks due to chronic exposures to plutonium in individuals who have been occupationally exposed through their work at the Mayak facility.

3 MATERIAL AND METHODS

3.1 Outline Of Plutonium Dose Assessment Methodology

As previously indicated, internal doses, i.e. from radionuclides that have been taken into the body by inhalation, ingestion, absorption or puncture wound, are difficult to measure directly when the radionuclide is primarily an alpha particle emitter, such as plutonium. Hence, routine occupational doses are "Assessed", indirectly using biological samples (normally urine, as this is relatively easy to collect in the required volumes) and mathematical models that describe radionuclide Adsorption, Distribution, Metabolism and Excretion (ADME).

The process used to calculate organ, and tissue, doses from plutonium using urine monitoring data is outlined below:

- The base data used are urine sample results which provide information on the daily rate of urinary excretion of plutonium, by an individual, at the time of sample collection.

- A mathematical excretion model, or function, that describes daily urinary excretion of plutonium over time following uptake to blood, is used to estimate the plutonium uptake to blood from the urine sample results. (N.B. As urinary excretion is a function of metabolism, the excretion model/function used should logically be derived from the biokinetic model, see below, but in some assessment systems this is not the case.)

- Using the estimate of plutonium uptake to blood and a "Biokinetic" model, a mathematical model that describes the distribution and retention of plutonium in the

systemic organs/tissues, the amount of plutonium activity within the systemic organs/tissues over time can be derived. The dose (i.e. energy deposited per unit mass) to the systemic organs/tissues of interest (e.g. Liver, Bone Surfaces, Red Bone Marrow) can then be calculated using the number of disintegrations occurring within the relevant organ/tissue along with reference values for the organ/tissue mass and the energy of the alpha radiation (known as the "dose" model).

- A "Lung" model, that mathematically describes the deposition, retention and transfer to blood, of inhaled material is used, in conjunction with the biokinetic model, to calculate plutonium intake, and dose, to the lung (in a similar manner to the systemic organs/tissues above) when an exposure has occurred through inhalation of plutonium bearing aerosols (this being by far the most common route of occupational exposure).

- When a material has been inhaled a proportion of it is mechanically cleared by the lung into the gastrointestinal tract, a "Gut" model that describes the transit of this material through the gastrointestinal tract is used to calculate doses to the different regions of the tract (e.g. stomach) from this material (again in a similar manner to the systemic organs/tissues above). Note: This model can also be used, in conjunction with faecal samples, to assess intake of plutonium, particularly shortly after an intake has occurred or when material has been ingested (although it should be noted that ingestion of material is not a common occurrence in an occupational exposure context and faecal sampling is generally found to be an unpopular form of monitoring among workers, so it tends to be used only when large abnormal intakes are suspected).

A diagrammatic representation of the above process is presented in Figure 1 below.

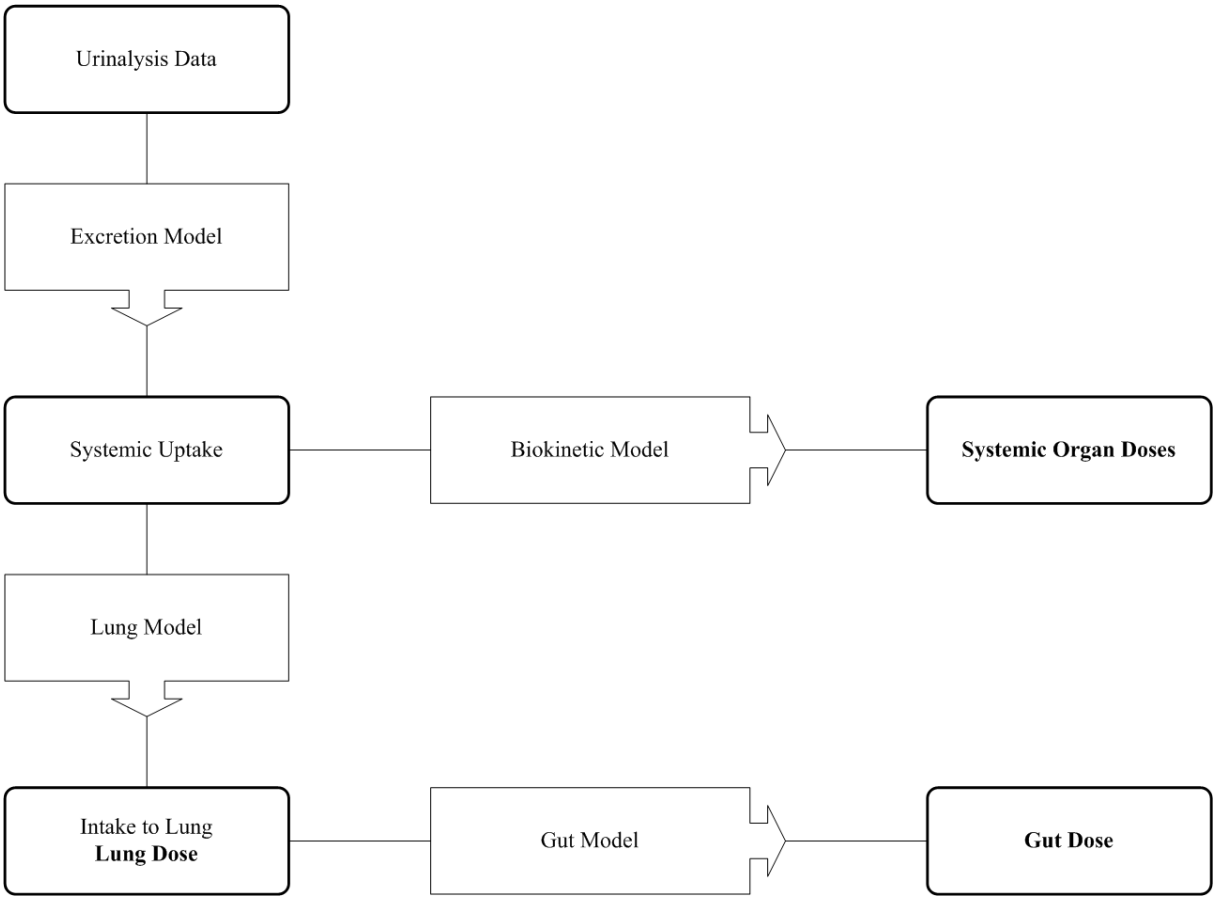

Figure 1. Generic Methodological Process for Assessment of Plutonium Doses

N.B. Both the Lung and Gut models only permit the calculation of doses to these organs from plutonium in transit through them. There is another component of the overall dose to these organs from plutonium within the tissues that constitute them, as a result of plutonium uptake to blood, this component is calculated using the biokinetic model.

3.1.1 Other Intake/Dose Assessment Considerations

In addition to the assessment methodology outlined above, there are various other issues that need to be considered when producing intake/dose assessments:

3.1.1.1 Pattern of Exposure

The most likely pattern of exposure for an individual needs to be determined, this pattern will be made up of one, or more, exposure event(s) of two basic types:

- Acute - Large single intake of material typically assumed to have occurred on a specific date following some sort of abnormal event e.g. a contaminated puncture wound.

- Chronic - Small regular daily intakes over a period of several days, weeks. months or years which is more typical of routine occupational exposures when an individual is working in an environment with low-level background contamination.

3.1.1.2 Mode of Exposure

As previously stated, inhalation is by far the most common mode of occupational exposure but accidents involving puncture wounds do occur, there are also rare cases of ingestion of material, in industrial environments and can lead to large intakes of plutonium (no common form of plutonium is known to be absorbed through the skin).

3.1.1.3 Nature of Exposure

The chemical form, or nature, of the exposure is important because while inhaled plutonium is believed to enter the blood in ionic form, the rate at which plutonium aerosols disassociate in the lung and are absorbed into blood is determined by their chemical form.

3.1.1.4 Use of Chelating Agents

Chelating agents, most commonly Diethylene Triamine Pentaacetic Acid (DTPA), have been used to enhance clearance of plutonium from the body, at times, knowledge of such use is important as it impacts on the applicability of standard excretion functions/models.

3.1.1.5 Implementation

Historically there has been no requirement to assess plutonium doses for all occupationally exposed individuals for operational protection purposes. Where plutonium doses have been assessed the methodology used might be outmoded (see Consistency/Harmonization section below), the individual may have been further exposed and/or subject to further monitoring, since the assessment was performed. Consequently, it is likely that the provision of doses for an epidemiological analysis is going to require a strategy for implementing the chosen methodological approach and delivering the required dose estimates.

Because of the complexity of the mathematical models describing plutonium ADME, the random variation and measurement error associated with urine samples and, for some individuals, potentially complex exposure patterns, computer software is required to make dose assessments practicable. Furthermore, because of the substantial numbers of dose assessments required for large-scale worker cohort studies some automation of the overall dose reconstruction process for the cohort is also required.

3.1.1.6 Consistency/Harmonization

Within large cohorts, dose reconstruction may have been ongoing over many years, or even decades, it is important to ensure that all the doses used for any epidemiological analysis have

been produced on a consistent basis, otherwise this may well bias the results. This means that any existing doses may need to be to re-assessed.

Similarly, for epidemiological research involving meta-analyses of two, or more, cohorts it is important to ensure that the basis of dose reconstruction is, as far as practically possible, the same. At the present time this usually requires agreement on harmonisation of approach and the recalculation of doses.

3.1.1.7 Reliability/Uncertainties

The importance of using knowledge of the reliability of dose estimates within epidemiological analyses is being increasingly recognised. This information can simply be a flag indicating an empirical estimate of the relative reliability of doses or, increasingly, an analytical estimate of the uncertainty associated with individual dose assessments.

3.2 Review of Current Plutonium Dose Assessment Methodology

A systematic review of existing plutonium dose assessment methodologies and processes has been conducted. This review placed particular emphasis on the methodology used for the Sellafield and Mayak cohorts as, they are the two largest plutonium worker cohorts currently subject to epidemiological research. They are also the two main sub-cohorts in the ALPHA-RISK and SOUL projects. Reference will also be made to the "IDEAS" project[1] (Doerful et al., 2007), "General guidelines for the estimation of committed effective dose from incorporation monitoring data", initiated under the European Fifth Framework Programme (FP5) for research, which aimed to produce guidance on best practice for internal dose

[1] Commenced in October 2001 and was completed in June 2005

assessments for radiological protection purposes. The section of the review considering the practical application of methodology for dose reconstruction has largely focussed on the Sellafield worker cohort as the doses used for epidemiological research involving this cohort will be produced using the process improvements that are one of the expected outcomes of this project.

3.2.1 Urinalysis Data

Urine is relatively easy to collect in sufficient volumes for analysis and because plutonium continues to be excreted in urine long after intake has ceased (unlike faeces where clearance by this route decreases rapidly following cessation of intake), urine monitoring forms the basis of most plutonium doses assessments.

3.2.1.1 Limits of Detection

The International Organization for Standardization (ISO) defines the Limit of Detection (LOD) as "The true net concentration (or quantity) of component in the material subject to analysis that will lead, with a probability $(1-\beta)^{1}$, to the conclusion that the concentration (or quantity) of component in the material analysed is greater than that of a blank sample" (ISO, 1997). Note: [1]The value of β recommended is 0.05 to give a 95% probability.

The LOD for plutonium urinalysis has steadily improved (i.e. decreased), reflecting improvements in measurement technology, over the decades since monitoring of workers first started, this is illustrated by reference to urine monitoring practices at Sellafield and Mayak.

3.2.1.1.1 Sellafield

At Sellafield urine monitoring was introduced on an experimental basis in 1951, comprehensive monitoring of all potentially exposed workers began when full-scale plutonium production commenced in 1952 and has continued to the present date.

Prior to 1961 a reporting level of 20 pg of plutonium (~ 46 mBq) per sample was used as an operational control measure (intakes resulting in excretion below this limit were considered "tolerable" at that time) and many results from this period are therefore simply recorded as being less than this value, even though the LOD for the analytical technique was 1 pg (~2.3 mBq). It should be noted that, where an individual's entire monitoring information entirely consists of below reporting level results, and there are ~600 such individuals within this cohort, this has been considered insufficient information to perform a reliable dose assessment (Riddell, 2000). It should also be noted that, these early plutonium results at Sellafield, and often elsewhere, were reported by mass not activity, this is not an issue when all the plutonium is produced from fuel with a similar burnup, but when this is not the case, plutonium's specific activity, and hence doses, can vary considerably. For example, given the current LOD of 0.5 mBq, this represents approximately 0.18 pg (i.e. 10^{-12}g) of weapons grade, or 0.13 pg of Magnox, or 0.02 pg of PWR, plutonium in a sample (the decreasing mass being the result of the increasing specific activity of the plutonium isotopic mix as fuel burnup increases - see Table 1 above), this also serves to illustrate the minuscule amounts of plutonium involved in such analyses. Because the energy of the alpha emissions for all the major plutonium isotopes are similar (~ 5 MeV, see Table 2 above) the resulting doses from them are also similar, so reporting plutonium content by activity, as is the case with later urinalysis results, avoids this potential issue. Over time, the limit of detection decreased from

~2.3 mBq prior to 1961, to 1.9 mBq (0.05 pCi in terms of contemporary units) from 1961 to 1985, to 0.5 mBq from 1985 onwards, per sample (nominally 1 litre) (Britcher et al., 1994).

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3.2.1.1.2 Mayak

Separated plutonium was first produced at Mayak in February 1949 but it was not until four years later, in May 1953, that a scientific/medical division was established and any urine monitoring was performed, and then only on a limited basis, by this time new improved plants based on early operating experience had also been introduced. Consequently there is no urine monitoring whatsoever covering the period when many of the largest intakes of plutonium are thought to have occurred (Khokhriakov et al., 2005).

The limit of detection for Mayak worker urine monitoring has also decreased over time, from ~1000 mBq in the period 1953 to 1960, to ~200mBq from 1961 to 1968, to ~80 mBq from 1969 to 1977, to ~30 mBq from 1978 to 1989, to ~10 mBq from 1990 to date, for alpha radiometry, and 1 mBq from 1998 to date, for alpha spectrometry (Khokhriakov et al., 2000; Krahenbuhl et al., 2005; Schadilov, personal communication).

3.2.1.2 Adventitious Contamination

Adventitious contamination is the transfer of plutonium, which has not been metabolised by the individual being monitored, directly into their urine sample, this will obviously result in an artificially inflated estimate of their plutonium intake. This contamination can occur in several ways but it is commonly the result of poor sampling procedures, e.g. individuals failing to ensure that there is no contamination on their hands prior to sample provision, specific examples are given below.

Sellafield urine samples were originally collected using glass reagent bottles, which were narrow necked, and funnels, to permit easy sample provision, that were washed and re-used, hence over time bottles and funnels could have been used by several individuals. An internal review conducted at Sellafield in the late 1960s concluded that significant adventitious contamination of samples was occurring. One mechanism for this, that was subsequently identified, was through the "plating out" of plutonium on the walls of the sample bottles and funnels, which was not removed by washing in water but which did re-dissolve in urine when these items were re-used. Following this review, sample collection procedures were changed and wide necked disposable plastic sample bottles were introduced, which did not require the use of a funnel for sample provision, these improvements were in place by the end of 1970. Hence, early urinalysis data for Sellafield workers collected prior to the introduction of these improved sampling procedures, i.e. before 1971, are considered to be much less reliable than later measurements. Consequently, where possible, plutonium dose assessments for Sellafield workers only use the more reliable post 1970 urinalysis data and any pre-1971 results are excluded. However, it should be noted that approximately 2000 members of this cohort only have pre-1971 data.

Since 1970 urine samples from Mayak workers have been collected off-site at the Southern Urals Biophysics Institute (SUBI), formerly Branch 1 of the First Institute of Biophysics (FIB-1), located in the Mayak PA dormitory town of Ozyersk. However, prior to 1970 samples were collected on the Mayak PA facility, they are known to have suffered from significant problems, including adventitious contamination, and are considered unusable for dose assessment purposes by SUBI (Romanov, personal communication).

3.2.1.3 Measurement Errors

The error distribution observed in urinalysis results is a composite of measurement error, which has Poisson distribution (which can be approximated by a normal distribution and is often censored by the LOD), and biological variation in excretion, which has a log-normal distribution (Miller, 2002), the apparent overall shape of this distribution being determined by which of the two major error components predominates. Many researchers have noted that biological variation is dominant and consider urinalysis results for an individual to be log-normally distributed (e.g. Beach and Dolphin, 1963), this is also the distribution recommended in the IDEAS guidelines (Doerfel, 2007). The typical range given by the IDEAS guidelines for the Geometric Standard Deviation (GSD) of this log-normal distribution is 1.3 to 2.0, a value of 1.8 has previously been used for Sellafield urinalysis results (Britcher et al., 1994).

3.2.1.4 Number of Samples

Obviously, at least one urine sample is required to perform a dose assessment but beyond that the relationship between the number of urine samples available for an individual and the accuracy and robustness of their dose assessment, "Sample size determination", is not an area that appears to have been widely explored.

For the LSHTM Sellafield plutonium worker epidemiology study (Omar et al., 1999) doses for all workers with one or more usable urinalysis result were supplied (Riddell et al., 2000). However, for subsequent analyses involving the Sellafield cohort (e.g. McGeoghegan, 2003) there was a change in policy (Riddell, 2002) so that dose assessments were only produced for

individuals with 5 or more usable samples. This policy change was introduced for the following reasons:

- One urine sample is extremely unlikely to give an unbiased estimate of true excretion and can provide no information on any change in excretion with respect to time.

- Given the relative complexity of the excretion functions/models used and the random variation in activity measurements, any assessment based on a statistical fit to small number of urinalysis results is unlikely to be robust.

- It is known that some Sellafield workers may have had urinalysis results attributed to them that they did not provide (see below), but in general this usually only involves a few sample results (only 30 out of 286 suspect data sets identified contained 5 or more samples). Other data quality issues are also known to have occurred but are thought to be limited to small numbers of samples. Consequently, restricting assessments to those with five or more urinalysis results should greatly reduce the scale of these potential issues.

- Since 1980 routine samples for Sellafield workers have been collected in sets of four and activity is usually determined using one "Bulk" sample containing an aliquot from each sample in the set. Using a minimum of five samples should ensure that at least two independent activity measurements have been made, which would give some indication if activity in urine is increasing, decreasing or constant, over time.

The IDEAS guidelines suggested a minimum of 3 samples, when expected doses are less than 6 mSv, and 5 samples, when expected doses are greater than 6 mSv, however it should be noted that this is based on the presumption of acute exposure.

The number of urine monitoring results actually available for dose assessments varies greatly within and between worker cohorts. Urinalysis monitoring coverage for the Mayak worker population is considerably less extensive than for the Sellafield worker population.

A database of more than 485,000 urinalysis results is available for, approximately 12,800, Sellafield plutonium workers, this gives an average of approximately 38 samples per worker, although some have considerably more with one individual having provided over 1000 samples. Only 2468 Sellafield workers have less than 5 urinalysis results and many of these are more recent employees subject to ongoing monitoring, very few plutonium workers have no monitoring information.

Although urine sample collection started at Mayak in the mid-1950's, with some 70,000 samples being collected on-site, these early results are not considered to be reliable, due to factors such as adventitious contamination. An off-site monitoring programme started in 1970. DTPA was used to enhance excretion prior to sample collection in the period 1961 to 1973. There are currently approximately 21,000 reliable urinalysis results on which to base dose assessments. These urine sample results are attributable to approximately 9,800 workers so less than 40% of those potentially exposed have any urine monitoring data. There is only an average of ~2 samples per worker for those who have been monitored. Consequently, dose assessments for the Mayak cohort are generated on the basis of an individual having one or

more reliable urinalysis results. Introducing a lower limit of 5 samples per assessment would exclude the vast majority of this cohort.

3.2.1.4.1 Other cohorts

Dose reconstruction for the ALPHA-RISK project commenced with a review of available monitoring information, this review concluded that for all the sub-cohorts, apart from the Sellafield worker cohort, within the UK, France and Belgium, an inclusion criteria of five or more urinalysis results would unacceptably limit the potential size of the study population.

3.2.1.5 Data Reliability

It should also be noted that the practicalities of bioassay monitoring can of themselves produce issues, in relation to the reliability of the resulting data. This is can be illustrated by reference to the large scale urinalysis monitoring programme at Sellafield and concerns the issue of tracking samples: Because hundred of individuals are subject to monitoring, and because it is a large site, there are multiple sample stations across the site, it is necessary to ensure that the information about the sample is accurately transcribed during the process of putting out the sample bottles, collecting them in again, transporting them to the laboratory for analysis and the results being returned. Since the early 1990s urine samples at Sellafield have been tracked using barcodes and all information relating to sample collection and analysis is transferred electronically thereby minimising the possibility of data errors. Prior to this tracking of samples relied on hand written labels, tracking sheets, paper records of analysis results and manual transcription of information and data entry onto database systems. With the large volume of monitoring information processed it is perhaps unsurprising that

there is evidence that some data transcription errors have occurred which affects the reliability of earlier urinalysis results.

3.2.2 Assessment Methodology

3.2.2.1 ICRP Methodology

The ICRP routinely publishes its recommendations for plutonium dose assessment methodology and when this research commenced this was as follows:

- Lung model: Publication 66 Human Respiratory Tract Model (HRTM) (ICRP, 1994)

- Biokinetic model: Publication 67 Plutonium metabolic model (ICRP, 1992), the structure of this model is shown in **Figure 2** below.

- Gut Model: Publication 30 (Part 1) Gut model (ICRP, 1972)

- Dose model: Publication 60 Dosimetric model (ICRP, 1991), using ICRP23 reference organ/tissue masses (ICRP, 1975) and radionuclide transformation data from ICRP38 (ICRP, 1983).

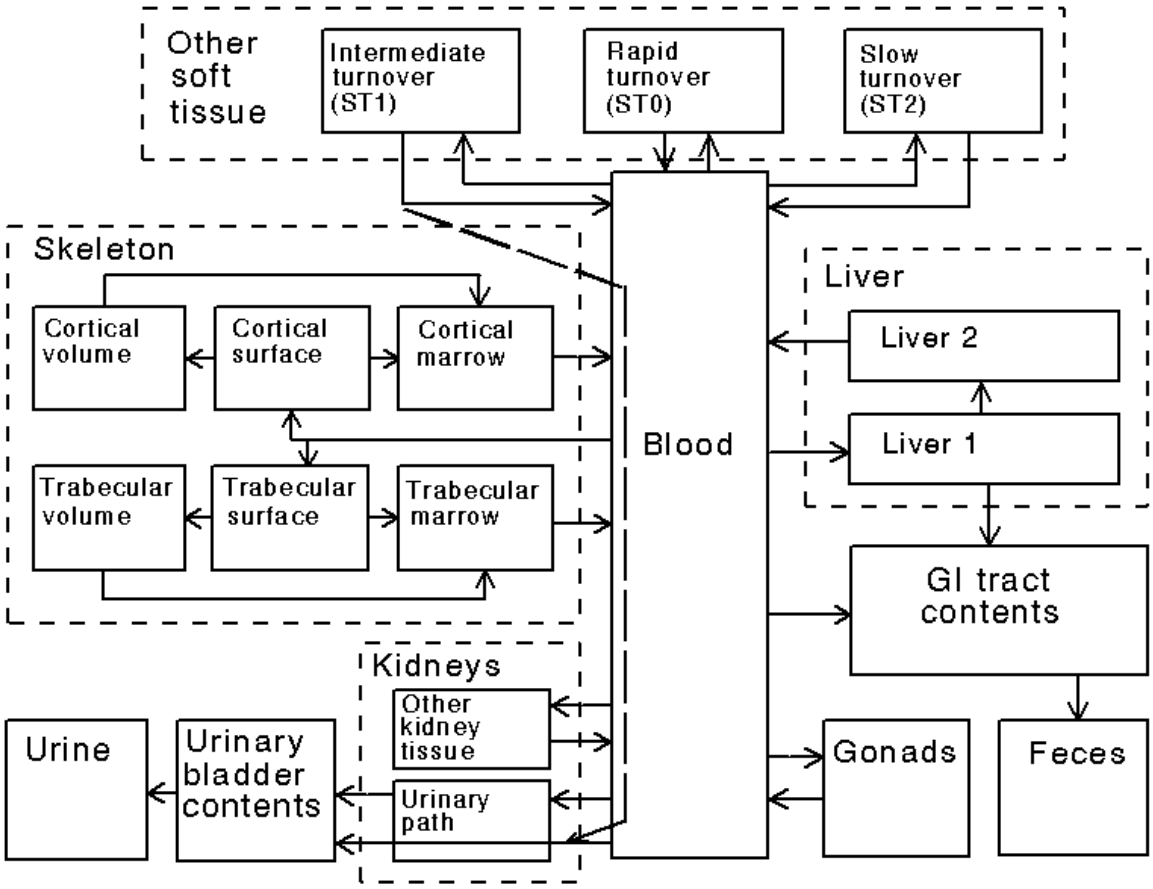

Figure 2. ICRP67 Plutonium Metabolic model (ICRP, 1993)

3.2.2.2 Alternative Methodology

When doses are calculated for epidemiological research those involved in their production may choose not to use, or rigorously adhere to, the recommended ICRP methodology, and use modified and/or alternative methodologies instead, with the aim of producing more accurate and unbiased estimates of dose for such research.

3.2.2.2.1 Sellafield Worker Cohort

The first major study of the plutonium workers within this cohort was conducted by London School of Hygiene and Tropical Medicine (LSHTM) (Omar et al., 1999). The production of dose assessments for the LSHTM has been previously documented (Riddell et al., 2000).

Work on dose reconstruction for the LSHTM study began in the early 1990s and used the methodology recommended by the ICRP at that time which was mainly presented in publications 30 (ICRP, 1972) and 48 (ICRP, 1986). The main exception to the ICRP recommendations was the use of a separate plutonium excretion function, the "Jones function" (Jones, 1985), that had been developed at Sellafield, rather than using excretion as predicted by the ICRP48 plutonium biokinetic model. The Jones function, which was developed for operational protection purposes, was largely based on the Langham function but modified to better predict long term urinary excretion, with reference to worker data from the site. Doses provided for later studies of Sellafield plutonium workers had been updated and produced using the current ICRP recommended methodology (as above) but had continued to employ the Jones excretion function to predict excretion, rather than the ICRP67 biokinetic model. The methodology used to calculate organ, and tissue, doses is presented in Figure 3 below.

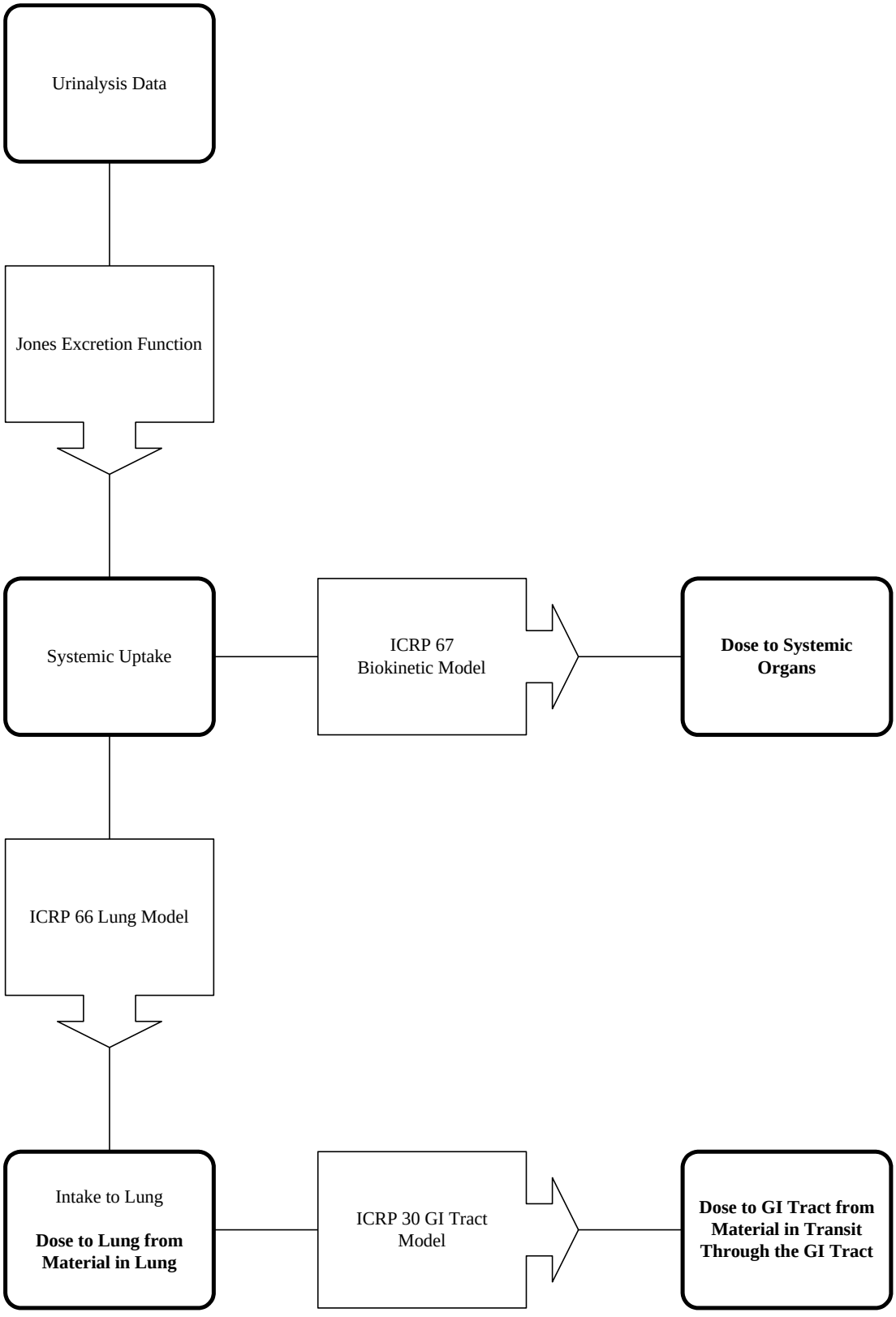

Figure 3. Previous Sellafield Dosimetry Methodology (McGeoghegan et al., 2003)

3.2.2.2.1.1 Calibration

A feature of the dosimetry methodology used for the LSHTM epidemiological analysis of the Sellafield worker cohort had been the calibration of this methodology against autopsy results. Previous experience had shown that the assessment process tends to systematically overestimate systemic plutonium burden in the liver and skeleton, by a factor of approximately 3 (Lawson et al., 1989), as compared to direct measurement of these quantities following autopsy analyses. This was consistent with ICRP's view, at that time, that as their recommendations are primarily for operational protection purposes "…it is appropriate to use models that are intended to give results that are not likely to underestimate the consequences of exposure…" (ICRP, 1991). However, when doses are used in epidemiological research they are the denominator in risk models and systematic bias toward overestimating doses will tend to systematically underestimates risks. Consequently, assessed values of plutonium intake for Sellafield workers were divided by a factor of three prior to the calculation of organ doses in an attempt to reduce or eliminate this bias (Riddell et al., 2000).

The ICRP has endeavoured to reduce the level of systematic bias in their recommended methodology by the introduction of new models, such as the ICRP 67 plutonium biokinetic model, and have indicated that they now consider them suitable for the production of doses for epidemiological analyses (ICRP 2007; Harrison and Day 2008). However, comparison of dose estimates for Sellafield workers produced for the LSHTM study with later estimates using current ICRP methodology, do not indicate than any tendency to overestimate doses has been significantly reduced but this could be because of the continued use of the Jones excretion function to assess intake.

It should also be noted that uptakes were divided by a further factor of three, i.e. by a total factor of nine, when assessments were based solely on less reliable pre-1971 urinalysis data (see above) as this was typical of the increase in assessed uptake observed during prior investigations of the effect of using such data (Riddell et al., 2000).

3.2.2.2.2 Mayak Worker Cohort

Historically, the methodology developed to assess doses to the Mayak PA workforce had been developed largely independently of that outside Russia and differed from the methodology used elsewhere in the world, this original dosimetry system was termed the "FIB-1 model" (Krahenbuhl et al., 2002). The FIB-1 model used a local adaptation of the Durbin excretion function (Durbin, 1972), which like the Jones function, is based on the work done by Langham and a modification of the ICRP 30 lung model (ICRP, 1972). In recent years collaborative research projects involving Russian scientists and scientists from the USA and Europe have lead to further developments in methodology and new dose estimates for this cohort. These revisions in the epidemiology dose database and associated dosimetry methodology for, the Mayak worker cohort are named after the year in which they were introduced, e.g. "Doses-1999" and "Doses-2000" (Khokhryakov et al., 2000). "Doses-2005" (Khokhryakov et al., 2007), which was the most recent dose data set being used for epidemiological analyses at the commencement of this research, was produced using two key methodological elements, a new/revised plutonium biokinetic model (Leggett et al., 2005), and a local adaptation of the ICRP 66 HRTM (Khokhryakov et al., 2005). This new plutonium biokinetic model is based on the ICRP 67 model and has been produced, utilising Mayak worker autopsy data, in collaboration with that model's primary author, the structure of this model is shown in **Figure 4** below.

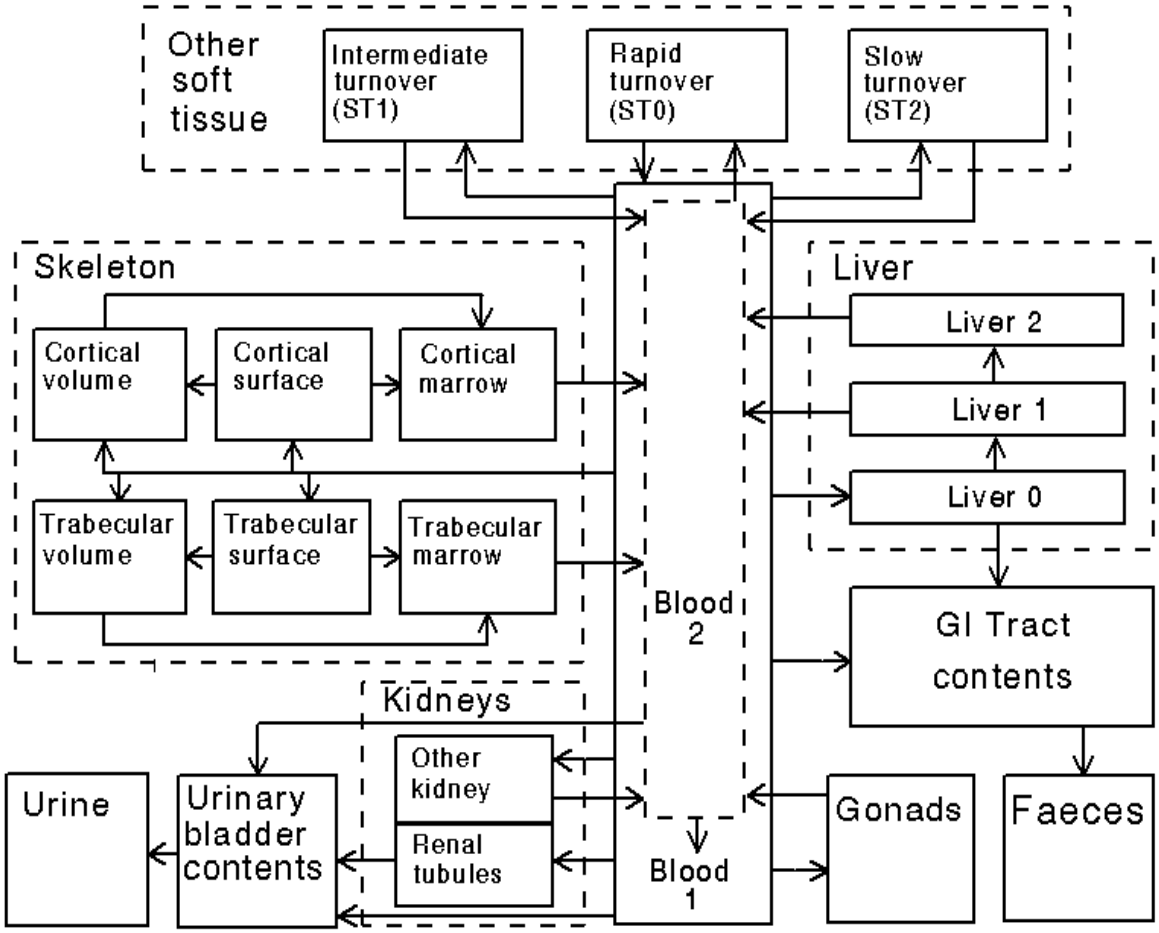

Figure 4. Leggett 2005 Plutonium Metabolic model (Leggett et al., 2005)

The adaptation of the HRTM used for Mayak worker assessments has been devised to make its predictions of the amount of plutonium long-term retained in the lung tally with observations of such material, as found during autopsy analyses. These autopsy analyses have shown that those exposed, even to more soluble forms of plutonium, can have significant amounts of plutonium retained in the deep lung, mainly in the parenchyma and scar tissue within it, decades after exposure (Hahn et al., 2004). The adaptation of the HRTM employed only extends to the treatment of absorption of inhaled material, the overall structure of the

model is unchanged, so this will be considered further in the sections dealing with the "Nature of Exposure", below.

With many Mayak workers having no urine monitoring information, the dose reconstruction system for this cohort also uses two other methods to assess doses, a Job Exposure Matrix (JEM) (Hoar, 1983-84) approach and autopsy analyses of organ/tissue plutonium content (Khokhryakov et al., 2007).

Analyses have been performed of the work histories of members of the Mayak worker cohort and a database describing the area(s) of the plant where an individual has worked and the period(s) in which they worked in these plants, has been assembled. Using this information and assessments of intakes for workers who have autopsy and/or urine monitoring information, a JEM has been devised to generate doses, termed "Surrogate doses", for the large number of individuals, within the cohort, with no monitoring information.

An extensive programme of autopsy analyses has been conducted, on over 1200, former Mayak workers. A database detailing the results of these analyses has been constructed and this information is used to assess intake and doses for these individuals (Khokhryakov et al., 2007). Autopsy analysis provides direct measurement of organ/tissue content of plutonium and gives a much more reliable means of assessing intake and doses than urine monitoring. However such assessments still rely upon the accuracy of other information e.g. the pattern, nature and type of exposure.

3.2.3 Pattern of Exposure

Plutonium exposure patterns can be separated into two basic distinct types acute and chronic.

3.2.3.1 Acute Exposure

Acute exposures are characterised by a single large intake generally resulting from an accident or other unusual event. Following an acute intake the concentration of plutonium in urine rapidly peaks during the hours following exposure and then constantly declines over time (see Figure 5, acute). True acute exposure events are comparatively rare as they usually involve some non-routine operational event, for example only ~450 acute exposures have been recorded for the Sellafield worker cohort and ~830 for the Mayak cohort.

3.2.3.2 Chronic Exposure

Chronic exposures are characterised by repeated and generally much smaller daily intakes which are the result of working in an environment with persistent low-level plutonium contamination. Chronic intake results in a period of increasing daily urinary plutonium content until an equilibrium level is approached, due to the rate in plutonium entering the body almost matching the rate at which it is cleared. This is followed by a period when daily urinary content is relatively constant until such time as the chronic exposure ceases (see Figure 5, chronic: 0 to 500 days). Following cessation of a period of chronic exposure urinary content declines in a similar manner to an acute intake (see Figure 5, chronic: 500 to 1000 days). Chronic intakes are mostly associated with inhalation as a mode of exposure.

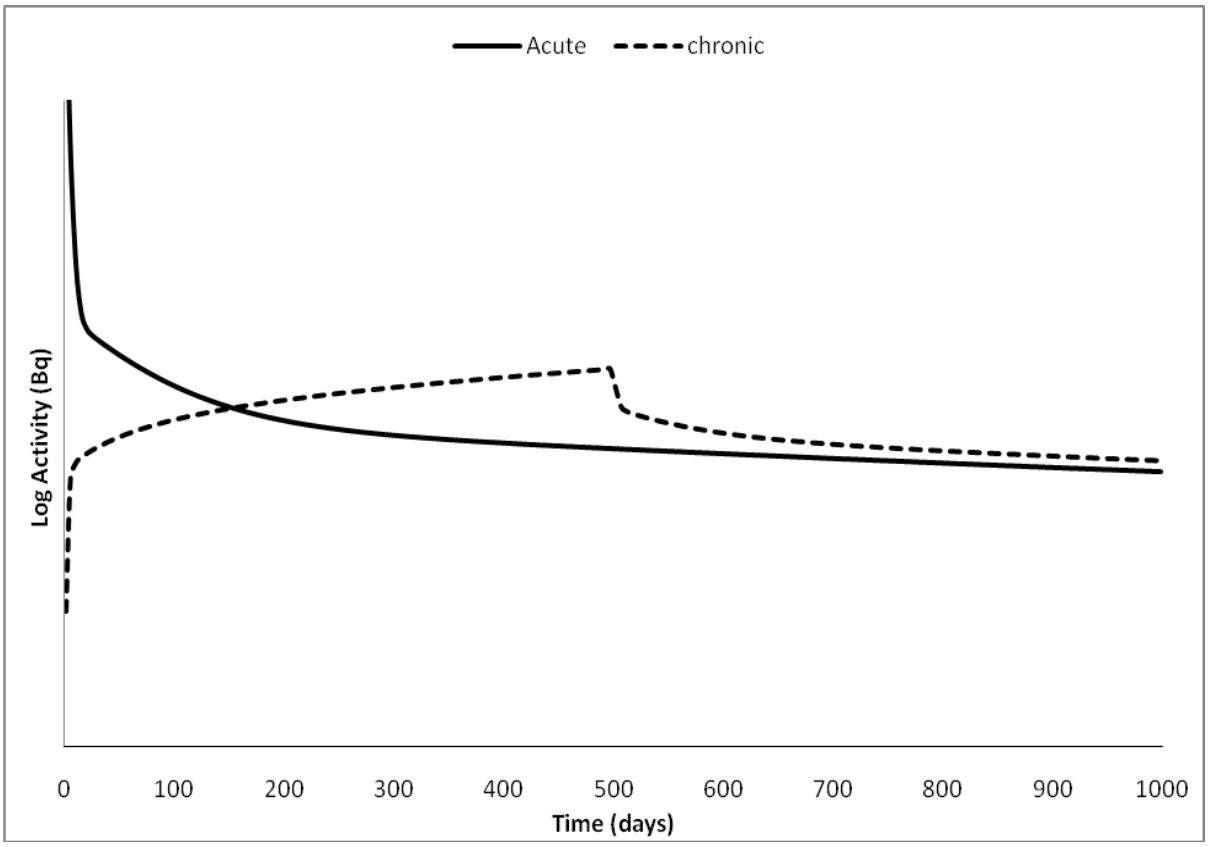

Figure 5. Urinary Excretion Profile Following Acute/Chronic Intake of Plutonium

Note: Chronic exposures usually involve much lower intakes than acute exposures but intakes have been matched here so that excretion profiles can easily be compared.

3.2.3.3 Unidentified Exposures

Figure 5 above shows that the fraction of activity excreted varies significantly over time, particularly in the time period following commencement or termination of exposure when the daily change in excreted activity is the greatest. It should also be noted that at times distant from the commencement or cessation of exposure excretion is relatively constant, hence it is important to make the correct assumption about exposure type because the available monitoring data may not be informative in this regard: If all sample results show similar activity, this could either be indicative of the period of maximal excretion from an ongoing chronic intake or minimal excretion following a much larger acute/chronic intake some time

ago. Furthermore, as plutonium is long-term retained in the body, excretion at any particular time is the product of all prior intakes. Hence it is evident that it is just as important to understand the relationship between the type and timing of any exposure events and urine monitoring, as it is to know the activity in the sample data in order to accurately estimate the intake of plutonium. Where specific information on an individual's exposure pattern is not available a default exposure pattern must be used and the choice of this pattern can have a significant impact on assessed doses.

3.2.3.4 Default Exposure Pattern

Both the IDEAS project and the ICRP recommend using a default acute exposure pattern with intake occurring at the mid-point of any period of possible exposure and it is suggested that this should be the mid-point between successive monitoring results. Whereas, the default exposure patterns used for Sellafield and Mayak workers are long term chronic exposures, with acute exposures only being used where there is specific evidence of such events.

3.2.3.5 Linked Chronic Exposures

The utility of using long term chronic exposure patterns to enable unreliable monitoring information to be excluded from the assessment process has been discussed above. However, for Sellafield dose assessments there are instances when it is desirable to use multiple shorter chronic exposure patterns and still only use later urinalysis results.

Individual review of the exposure history of some Sellafield workers has indicated that all of their potential exposure over a period of time results from them doing the same job and/or

working in the same building but this has been intermittent (e.g. interrupted by temporary secondment to another task, building or site where there is no possibility of plutonium exposure). If independent chronic exposure patterns are used to reflect these intermittent periods of exposure, urinalysis data quality can become an issue. Because data fitting is used (see below) with independent chronic regimes, changes in the reliability of measurements over time can produce substantially different estimates of daily intake rates within these periods when other indicators (e.g. air monitoring) would lead to the conclusion that they should be approximately the same. The solution to this problem has been to define "Linked chronic" exposures patterns whereby the data fitting routine is constrained to derive the same intake rate for chronic exposure patterns that are linked together in this manner. Such linked chronic exposure patterns permit unreliable monitoring information to be excluded, where possible, and prevents changes in the reliability and resolution of measurements over time from driving intake estimates.

3.2.4 Mode of Exposure

As previously stated, inhalation is by far the most common mode of occupational exposure but accidents involving puncture wounds do occur and there are also rare cases of ingestion of material in industrial environments that can lead to large intakes of plutonium (no common industrial form of plutonium is known to be absorbed through the skin). Wound and ingestion events tend by their very nature to be acute exposures. Of the ~450 acute exposures at Sellafield only ~30 are related to wounds and to a much lesser extent ingestion, the remainder are all due to inhalation. However at Mayak of the 833 acute exposure events only 176 are the result of inhalation and the remainder are largely wound exposures of various types (Khokhryakov et al., 2007). Knowledge of these events is important to correctly estimate

doses, since if such an event is erroneously considered to have resulted from inhalation, very large lung doses can be calculated from excretion data (when in reality these would have been relatively small doses solely from plutonium within blood circulating in lung tissues).

3.2.5 Nature of Exposure

The chemical form or nature of any inhaled plutonium is important because this determines the rate(s) at which any inhaled material is cleared from the lung into the blood and this can have a significant impact on lung doses (Riddell, 2005).

Two alternative means of modelling the absorption of materials from the lung into the blood are given in the HRTM. The simplest and that most commonly used, is shown in Figure 6 (reproduced from ICRP66) below.

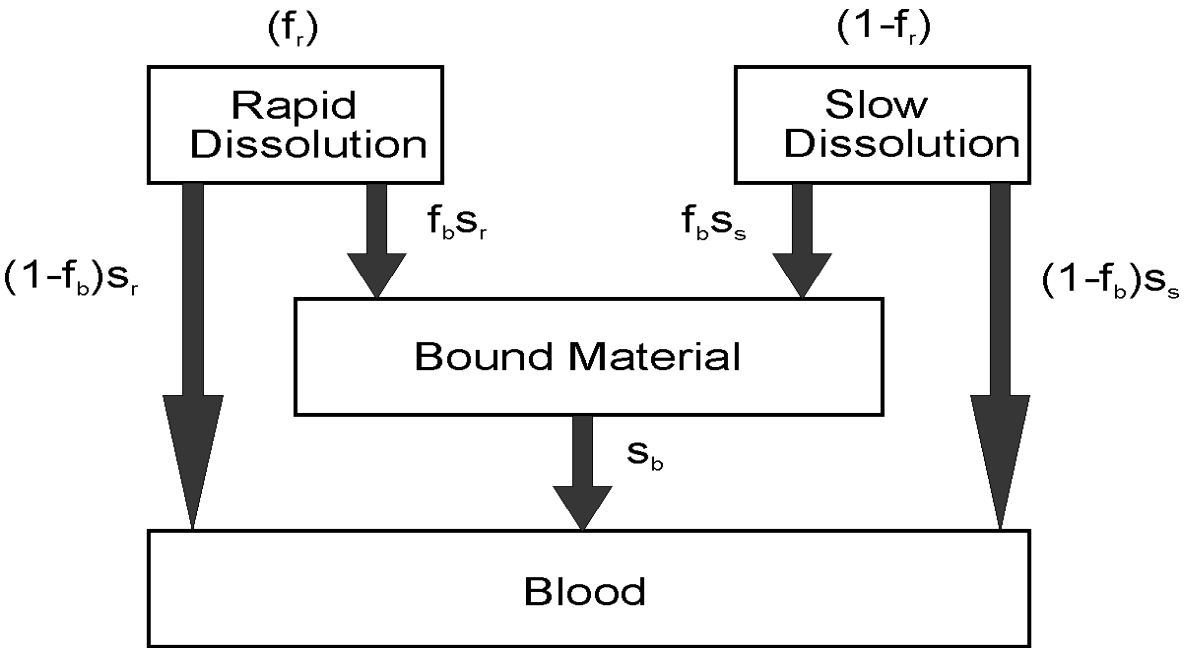

Figure 6. Compartmental model of absorption from lung to blood in the HRTM

In this model absorption from lung into the blood is a two stage process. The first stage of this process is the dissolution of inhaled plutonium bearing material to yield plutonium in its ionic form, the model permits dissolution to occur at two different rates, rapid and slow, with rate constants s_r and s_s, respectively, with a fraction $\mathbf{f_r}$ dissolving rapidly and the remainder (i.e. 1- $\mathbf{f_r}$) dissolving slowly. The second stage of this process is the transfer of ionic plutonium, across the lung blood barrier, into the blood this can either occur instantaneously or over time, due to chemical binding of the plutonium ions, with a fraction $\mathbf{f_b}$ being absorbed with a rate constant $\mathbf{s_b}$ (the subscript "b" indicating bound material). Because all dissolved plutonium is assumed to be in ionic form, this bound fraction and rate constant applies to both rapidly and slowly dissolved material equally. These rate constants and associated fractions are commonly referred to as the "Solubility parameters" for a material and are determined by its chemical form.

Plutonium chemistry is very complex It is highly reactive and can chemically interact with almost all other known elements (Clark, 2000). While many plutonium compounds have been created, the industrial processes used to separate plutonium on a large scale are fundamentally similar and most exposures are either to nitrate, $(PuNO_3)_4$, or oxide forms (PuO_2 - dioxide). Plutonium nitrate is a very common form of plutonium in reprocessing facilities as it is produced when irradiated fuel is dissolved in nitric acid during reprocessing. Plutonium dioxide is a common form of plutonium because, it is an important step in the process for the production of plutonium metal, as a chemically stable form it is used for long term storage of plutonium, it is produced by the rapid oxidation that occurs in finely divided plutonium metal (e.g. dust) and it is a component of mixed oxide ("MOX") reactor fuel.

The ICRP66 HRTM is supported by recommended solubility parameters for common compounds in the lung. Materials are assigned to one of three default solubility types, "F" for fast, "M" for medium and "S" for slow. The ICRP recommended default solubility for plutonium nitrate is Type M and for plutonium oxide it is Type S. Nevertheless, the ICRP also recommend that efforts should be made to try and determine specific solubility parameters for the materials to which individuals have been exposed. However, it is much more difficult to determine the solubility parameters for a material than it is to determine other parameters (e.g aerosol particle size) and only a limited number of studies have attempted to do this. Two issues that can arise when attempting to determine solubility parameters are illustrated by studies of Sellafield and Mayak PA plutonium nitrate solubility. Firstly, the same chemical form of a material can exhibit different solubility depending on its age and other environmental factors. This can be seen in Table 3 below which gives the solubility parameters for three Sellafield plutonium nitrate materials, labelled, in order of ascending age, "Material A", "Material B" and "Material C" (Moody et al., 1998). Secondly, different experimental methods and/or analyses can yield different solubility parameters for, ostensibly, the same material, this can be demonstrated by reference to the solubility parameters for Mayak plutonium nitrate derived from studies in 1998 (Khokhryakov et al.), 2003 (Romanov et al.) and 2005 (Khokhryakov et al.), shown in Table 3. For comparison purposes the HRTM default Type M solubility parameters which are recommended for plutonium nitrate and any intake where the chemical form is unknown (ICRP71), are also shown in Table 3. It can be seen from Table 3 that there is considerable variation in the estimates of the fractions of material which dissolve quickly or slowly, the fraction of dissolved material which is bound, and the slow dissolution and bound absorption rate factors, for plutonium nitrate. In particular it should be noted that, recent analyses for the Sellafield

worker cohort have used plutonium nitrate doses based on Sellafield Material A and analyses for Mayak workers have used doses based on the 2005 Khokhryakov et al. plutonium nitrate parameters, which are at the opposite ends of the solubility scale for nitrate materials. Information of plutonium oxide solubility is very limited and dose assessments for Sellafield worker studies have employed the recommended HRTM default Type S parameters. These, along with the oxide parameters used for Mayak dose assessments (Khokhryakov et al., 2005) are also shown in Table 3 below.

Table 3. ICRP66 HRTM Solubility Parameters for Plutonium Nitrate and Oxide

Material	f_r	s_r	s_s	f_b	s_b
Sellafield Material A	0.28	49.0	0.0058	0.57	0.214
Sellafield Material B	0.19	49.0	0.0015	0.57	0.214
HRTM Type M	0.1	100.0	0.005	0.0	N/A
Sellafield Material C	0.03	49.0	0.0011	0.57	0.214
Mayak 1998 Nitrate	0.1	100.0	0.005	0.035	0.0019
Mayak 2003 Nitrate	0.1	100.0	0.005	0.053	0.00013
Mayak 2005 Nitrate	0.03	100.0	0.00177	0.0226	0.0000001
HRTM Type S	0.001	100.0	0.0001	0.0	N/A
Mayak 2005 Oxide	0.003	100.0	0.000361	0.147	0.0000001

Notes: f_r = Rapid fraction, s_r = Solubility of the rapid fraction (Day^{-1}),
s_s = Solubility of the slow fraction (Day^{-1}),
f_b = Bound fraction, s_b = Solubility of the bound fraction (Day^{-1})
Materials are listed in order of decreasing overall solubility

N.B. The very small clearance rate (0.0000001 Day^{-1}) which equates to a clearance half time of approximately 19,000 years assigned to bound material (for both nitrate and oxide) in the

Mayak 2005 analysis (Khokhryakov et al., 2005), is intended to represent, effectively, infinite retention (i.e. in terms of a human lifespan): This artifice has been used in an attempt to make the HRTM better reflect the long term retention of plutonium in the deep lung as observed in Mayak worker autopsy analyses, as previously mentioned above.

3.2.6 Use of Chelating Agents

The use of chelating agents to enhance plutonium excretion began in the 1950s with Ethylene Diamine Tetraacetic Acid (EDTA) which had previously proved effective in the treatment of cases of heavy metal poisoning. However, since the 1960s, the most widely used plutonium chelating agent has been DTPA The efficacy of DPTA, and chelating agents in general, in actually reducing long-term doses has been the subject of some scientific debate (Menetrier et al., 2005: James et al., 2007). DTPA comes in two forms: calcium (Ca-DTPA) and zinc (Zn-DTPA). When given within the first day after internal contamination has occurred, Ca-DTPA is about 10 times more effective than Zn-DTPA at chelating plutonium. When administered at later times Ca-DTPA and Zn-DTPA appear to be equally effective. In general chelation therapy is only used to treat workers who have incurred a large acute exposure and this means that it has only seen very limited use in most worker cohorts (e.g. Sellafield) This was not, however, always the case at Mayak.

At Mayak, like most facilities, chelation therapy has only been used reactively in a relatively small number of acute exposure cases However, Ca-DTPA has also been used proactively to enhance urinary excretion to increase the possibility of finding detectable amounts of plutonium in urine for routine measurements during the period 1961 to 1974. Analysis of the effect of Ca-DTPA on excretion, in order to determine the level of enhancement in such

routine measurements, has derived a factor of 62.3 in the period immediately following administration. This factor subsequently decreased exponentially with a half- time of 3.7 days (Khokhryakov et al., 2007).

3.2.7 Implementation

When plutonium doses are assessed for operational purposes (e.g. radioprotection, statutory records, incident investigation) the process usually involves a comprehensive individual review performed by a trained internal dose assessor: For Sellafield workers this is known as a "Special" assessment and is conducted by Sellafield's Approved Dosimetry Service (ADS). An assessor undertaking a special assessment will consider the subject's work history, bioassay monitoring data and any other pertinent information (e.g. other monitoring), in order to construct possible exposure scenarios which are then evaluated using specially developed assessment software (see below), this is a time consuming process. Depending on their complexity the production of a special assessment for a Sellafield plutonium worker will take between a half and three person-days of effort, with the average special assessment requiring approximately one person-day. So while it may be practical to produce individual special assessments where epidemiological study populations are small, e.g. case-control studies, it can prove simply impractical to do this for large scale cohort studies that cover entire worker populations at major facilities like, for example, Sellafield. Another issue with these special assessments is that while the assessed plutonium intakes are useful to epidemiological research the doses produced tend to be Committed Effective Doses, which, as previously indicated above, are not. The solution to these problems is to seek to automate as much of the dose reconstruction process as possible, this can be illustrated by reference to the process used for the Sellafield cohort.

3.2.7.1 Automated Mass Assessment Process for the Sellafield Cohort

As stated above, the Sellafield ADS routinely conducts special assessments for operational protection, statutory and other purposes, e.g. they have produced special assessments for a number of small case-control epidemiological studies. However, to date, special assessments have only been produced for 2,362 of the ~12,800 Sellafield workers who had plutonium urinalysis results attributed to them, leaving ~8,848 individuals without a special assessment. Providing special assessments for all the remaining plutonium workers would be an enormous task (~8,848 person-days of effort) and, with only a limited number of trained assessors available, even if all this effort could be made available, this would take many years to complete. To deal with this issue an automated mass assessment system had been devised for the LSHTM Sellafield worker study. This strategy was successful and while the specifics of its implementation have changed considerably (see "Software" below), the same overall strategy has been used for the production of doses for all Sellafield cohort analyses conducted since the LSHTM study.

The results of Sellafield special assessments are held in a computer data file that records the following information for each individual:

- Identification number.
- Exposure pattern(s) (i.e. Start and end date of each exposure, exposures on a single day indicating an acute and multi-day exposures indicating chronic, exposure patterns).
- Assessed intake during each exposure.

- Lung solubility classification for each exposure. A dummy solubility classification is used as a flag to indicate exposures that involve direct uptake of plutonium to blood (e.g. wounds).
- Special assessment confidence category (see below).
- Date of assessment, and date assessment was last reviewed, this information is used to ensure that special assessments are up to date for workers still in employment and potentially exposed to plutonium.

It is known that, as a result of operational monitoring requirements, all plutonium workers with suspected acute exposures will have been individually reviewed and have special assessments. Therefore, the basic assessment strategy is to use software to extract the information in the special assessment file to produce the required (i.e. annual absorbed) doses for the individuals within it and to use simple rule based systems to generate exposure patterns from which to assess intakes and doses for all remaining members of the cohort through "Automated assessments". The rules used for automated assessments can be simple because it is logical to assume that individuals requiring automated assessment should only have had chronic exposures, otherwise they would have had a special assessment. A previous comparison of a sample of automated assessments with special assessments for the same individuals, produced independently by the Sellafield ADS for the purposes of this comparison, has indicated very good agreement, typically less than 10% difference, in the estimate of total plutonium intake. This level of agreement compares favourably with that found, in other intercomparison exercises, where different dose assessors have been asked to provide special assessments for the same individual (Doerful et al., 2003).

3.2.7.2 Data Fitting

Because of the need to determine plutonium intake(s) which may be from multiple exposures, of different patterns, modes and natures, using urinalysis results which are subject to random variation and censorship by a LOD which varies over time, data fitting is an integral part of internal dose assessment process. Two methods of data fitting are commonly used for plutonium dose assessment, "Maximum Likelihood" (ML) and "Bayesian", the ML method is recommended under the IDEAS guidelines (Doerful et al., 2007).

3.2.7.2.1 Maximum Likelihood

The ML technique was first used for plutonium dose assessment at the Sellafield site in the PLUTO program (Riddell and Britcher, 1994). It has since seen much wider use through the IMBA software project (see below).

The ML fitting technique utilises model generated predictions of excretion per unit intake (for acute exposures) or intake rate (for chronic exposures) at the time of the excretion measurements. Predictions from non-linked exposures are assumed to be entirely independent whereas those for linked chronic exposures are summed and treated as resulting from a single unit intake rate. Intake rates in each period are varied, using an optimisation algorithm (Powell, 1964), so as to arrive at a set of intakes estimates which maximises the probability of the observations being a result of such intakes on the basis of a supplied probability distribution of random variation in sample measurements (usually a log-normal distribution defined by its GSD). Two sets of probabilities are evaluated that for positive monitoring results and that for below LOD monitoring results. The overall probability is the product of these and this is the quantity maximised by the optimisation algorithm.

The advantages of the ML fitting technique are that it is computationally efficient (e.g. the PLUTO program can fit complex exposure patterns to large numbers, many hundreds, of urinalysis results in seconds) and it can handle urinalysis datasets with a high percentage of LOD data and still achieve a robust fit (Marsh et al., 2003). The only clear disadvantage to using the ML technique is that it cannot provide a fit when all of an individual's results are below the LOD. There are a considerable number of the Sellafield worker cohort who have urinalysis results that are all below the LOD: In order to provide dose assessments for these individuals their last result is assumed to be positive at the LOD and a chronic exposure pattern is fitted to all the data. The result is known as an "Upper limit assessment", as it provides a credible maximum upper bound on intake/dose (Riddell et al., 2000).

3.2.7.2.2 Bayesian

The use of Bayesian methodology, more specifically the application of Monte Carlo Markov Chain (MCMC) methods, for plutonium dose assessment, had been pioneered by the Los Alamos National Laboratory in the USA (Miller et al., 2002) but it has subsequently also been used for dose reconstruction for the Mayak worker cohort (Khokhryakov et al., 2007). The advantages of Bayesian techniques are that they can provide a fit to the data when all results are below the LOD without modifications to the data. They also provide the uncertainty associated with dose estimates through the posterior distribution (see below). The disadvantages of Bayesian techniques is that they are computationally much slower than the ML method, requiring either a supercomputer cluster or run times of many months (Miller et al., 2006) to perform, and the choice of prior distributions for the parameters of interest requires some care (see below).

3.2.7.3 Software

Because of the complexity of the plutonium dose assessment process all but the simplest calculations require the use of purpose designed computer software. The way in which such dose assessment software works is best illustrated by reference to the Integrated Modules for Bioassay Analysis (IMBA) project (Birchall et al., 1998), particularly as software based on the IMBA modules is used for dose reconstruction for many plutonium worker cohorts including Sellafield.

The five core IMBA software modules are as follows:

- **IMBA_DEP***

  Provides fractional deposition in the lung, based on the aerosol parameters supplied, using the methodology described in the ICRP66 Human Respiratory Tract Model, for inhalation intakes

- **IMBA_BIO***

  Calculates predicted bioassay quantities e.g. urine content, per unit intake, at the specified times of monitoring utilising the supplied biokinetic model, or excretion function, and other associated parameters e.g. intake characteristics, lung deposition fractions, e.g. from IMBA_DEP, for inhalation intakes

- **IMBA_DIS***

  Calculates the number of disintegrations, per unit intake, within the organs/tissues in the supplied biokinetic model during the specified period(s) of interest (for epidemiological purposes this is typically in each calendar year of the study period)

- **IMBA_FIT**

  From model predictions of bioassay quantities, which can be generated by IMBA_BIO, and the actual observed values of these quantities, e.g. urinalysis results, this module provides intake estimates for each period of exposure (maximum likelihood or least squares fitting is employed to do this)

- **IMBA_DOS**

  Using intake estimates calculated by IMBA_FIT and the number of disintegrations in organs/tissues per unit intake from IMBA_DIS this module calculates the dose to these organs/tissues in the periods specified

Note: * for multiple intakes these modules can be called multiple times

As originally conceived these IMBA modules were independent and relied on simple text files for data input and output, e.g. the input and output files for the IMBA_DEP module were IMBA_DEP.IN and IMBA_DEP.OUT respectively These text files could also be used to pass information between IMBA modules to perform a series of calculations. A particular feature of the design of the IMBA modules is that methodological changes can easily be implemented: For example, the description of the biokinetic model to be used is stored in a text file "IMBA.MOD", so using a different biokinetic model for a calculation is simply a matter of changing the model description in this file. The National Radiological Protection Board (NRPB), now incorporated into the Health Protection Agency (HPA) and British Nuclear Fuels Ltd. (BNFL), now Sellafield Ltd., in collaboration with Westlakes Research Institute (WRI), wrote two completely independent sets of computer code to implement each

IMBA module. An intercomparison and validation exercise was conducted between these two sets of IMBA modules to ensure that their functionality was identical and that they produced the same output with the same input (Marsh et al., 2003). The flexibility of the IMBA modules allowed each partner in their development to use them to produce computer software to meet their own requirements. Among other software, BNFL developed PLUTO2000 (Peace, 2003), the HPA IMBA Expert/Professional Plus (Birchall et al., 2005) and WRI, who were responsible for the production and management of dosimetry data for epidemiological research involving the BNFL worker cohort, which includes Sellafield plutonium workers, developed PUMASS.

3.2.7.3.1 PLUTO2000

The Sellafield ADS (i.e. BNFL) used IMBA modules to develop a replacement for the PLUTO program (Riddell and Britcher, 1994), PLUTO2000, which is optimised for rapid plutonium intake/dose assessments for individuals who can have large numbers of urinalysis results and complex exposure histories (including linked chronic exposure patterns). Particular features of PLUTO2000 are a facility to calculate Am-241 ingrowth and dose, based on a set of factors that give the ratio of Pu-241 in Sellafield plutonium on an annual basis, the capability to handle up to 2000 urinalysis results and a facility to deal with linked chronic exposure patterns. As indicated above, for many years, the results of individual Special assessments for Sellafield plutonium workers, produced using PLUTO and PLUTO2000, have been entered onto an electronic data file and this information is used by the PUMASS program (see below).

3.2.7.3.2 PUMASS

The main program used to generate plutonium intake and organ dose information for Sellafield worker epidemiological analyses is called PUMASS (PU Mass-ASSessment) and it is based on IMBA modules. Like the PLUTO/PLUTO2000 programs PUMASS can handle up to 2000 monitoring results for any specific individual, and also calculates Am-241 ingrowth and doses on the same basis. Given data files containing individual identifiers, work history information, urinalysis results and the results of special assessments, PUMASS provides a complete set of plutonium dose assessment data for analysis.

The PUMASS program performs the following functions:

- Extracts assessment data from the Sellafield worker special assessment file (see above) i.e. exposure pattern(s), exposure type(s), lung solubility used for inhalation exposure(s), assessed intake(s), special assessment "confidence" category (see below).
- Performs automated intake assessments using IMBA modules for all individuals who do not have a special assessment and who have urinalysis data of sufficient quality, quantity (e.g. at least 5 samples) and reliability (e.g. fall within known periods of employment).
- Provides a "confidence" category for all individuals (see below).
- Calculates annual plutonium alpha and plutonium 241 intake figures for all individuals with assessments (in the same manner as the PLUTO/PLUTO2000 programs).
- Calculates annual absorbed doses to organs/tissues from plutonium and americium, based on the assessed intake(s), using IMBA modules.
- Provides the number of urine sample records for an individual, by year, and also indicates whether all results are below the LOD which identifies upper limit assessments.

3.2.7.3.3 IMBA Professional Plus

The HPA developed software with a Graphical User Interface, based on the IMBA modules, IMBA Professional Plus (PP), that allows a wide variety of calculations to be made for an extensive range of radionuclides. This software is commercially available and is now used extensively throughout the World. A copy of IMBA PP was available to all the partners in the ALPHA-RISK study for the purposes of dose reconstruction for that study. IMBA PP is limited to a maximum of 400 urinalysis results for any individual assessment and while it can calculate doses from an "Associated radionuclide", such as Am-241, this is on the basis of a single fixed ratio over the entire period of intake.

3.2.8 Consistency/Harmonisation

As indicated above dose information is the denominator in risk models and if dose estimates for a study cohort have not been produced on a consistent basis this clearly has the potential to introduce biases which will undermine analyses of any dose response relationship. For similar reasons, it should be obvious that, meaningful comparisons between, or meta-analyses of, risks for multiple worker cohorts will require dosimetry data that was constructed on a similar methodological basis. However, as can be seen above, the methodology used for dose reconstruction has varied considerably between plutonium worker cohorts in the past. One of the objectives of this project is to provide enhanced capabilities to implement new assessment methodology and rapidly recalculate doses for major cohorts, particularly the Sellafield cohort, to ensure that they are consistent. Another objective is to coordinate the approaches to dose reconstruction for the two major European Commission sponsored plutonium worker epidemiological studies currently ongoing, SOUL and Alpha Risk, so that, as far as is practically possible, they are harmonised.

3.2.9 Reliability/Uncertainty

Assessing the reliability of, or the uncertainty associated with, internal dose assessments is a difficult task and consequently most epidemiological analyses of plutonium worker populations, to date, have proceeded without such information being available. The LSHTM Sellafield worker epidemiological (Omar et al., 1999) study is believed to be the first major plutonium worker study where any attempt was made to supply such information and this was on the basis of largely empirical "Confidence categories" (Riddell et al., 2000).

3.2.9.1 Assessment Confidence Categories

For the LSHTM Sellafield worker study, a system was developed for assigning confidence categories to assessments that reflected the relative reliability of the doses obtained based on knowledge of the assessment process. This confidence category system has been revised and extended to accommodate changes made to assessment strategy since the LSHTM study, the logic flowcharts for the latest scheme, used to generate these categories for both automated (Figure 7) and special assessments (Figure 8), are presented below. A similar approach has now been adopted for the Mayak worker cohort with workers' plutonium dose assessments being assigned to one of five "Reliability", groups (Krahenbuhl et al., 2005). However, this treatment also extended to attempting to quantify the uncertainty associated with dose estimates for each reliability group using Bayesian methodology.

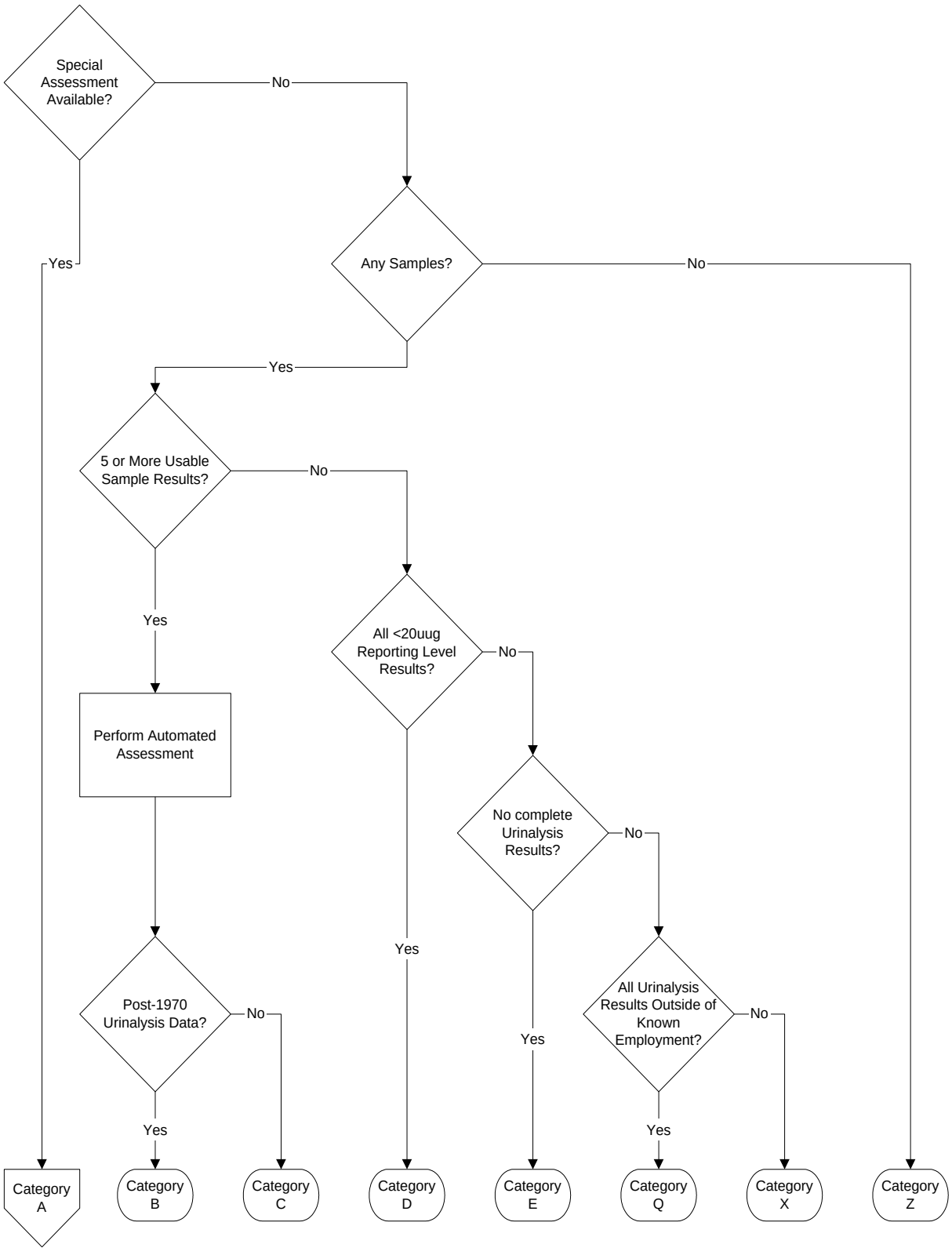

Figure 7. Sellafield Worker Cohort – Automated Assessment Confidence Categories

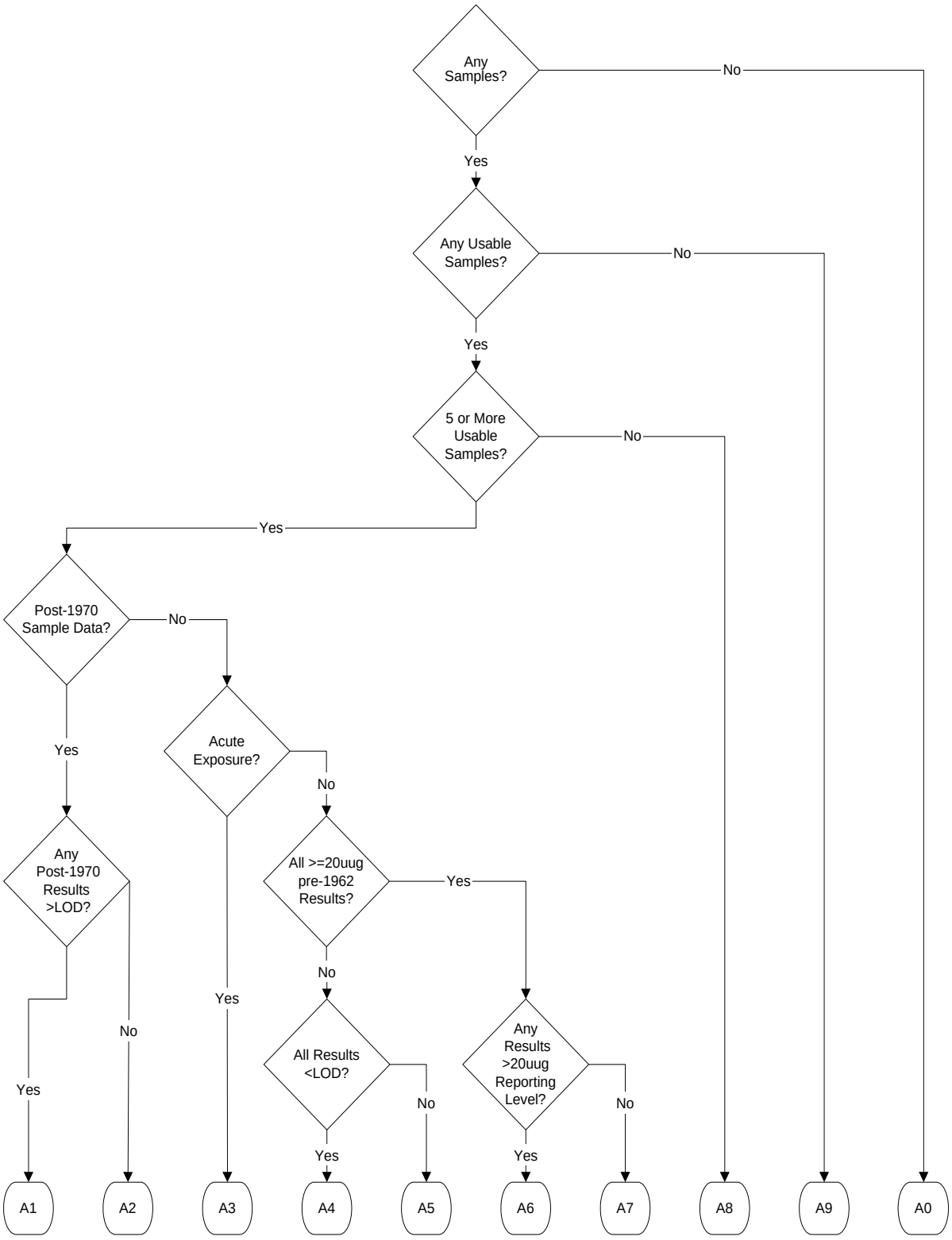

Figure 8. Sellafield Worker Cohort - Special Assessment Confidence Categories

4 DISCUSSION

It is clear from the review that has been conducted that there are a substantial number of areas to be addressed within the plutonium intake/dose assessment process and attempting to cover all of these, in depth, with the resources available to this project would simply be impractical. There was also an operational time constraint in that, as far as possible, any new methodological approaches developed would have to be implemented in time to deliver the dosimetry information required for the ALPHA-RISK project. A pragmatic view of what can be achieved in the time available and the impact that different avenues of research will have on the final outcome has been taken, a research strategy has been developed for this purpose.

4.1 Strategy

If improvement in assessment methodology, in the context of this research, is defined as "*those improvements which lead to dose estimates that will produce the greatest potential improvement in the accuracy and reliability of risk estimates*", this can be used to help prioritise current, and future, dosimetry research effort in this area. The "Bradford Hill Criteria" were viewed as appropriate framework within which to evaluate the potential impact that improved dosimetry could have on epidemiological research.

4.1.1 Bradford Hill Criteria

In 1965 the British Epidemiologist, and Statistician, Sir Austin Bradford Hill outlined nine criteria that would help to distinguish causation, from other explanations, between exposure to a potential hazard and effect, in relation to epidemiological analyses (Hill, 1965). These Bradford Hill Criteria, which have since become widely accepted, are as follows: "Strength"

(Strength of the association), “Consistency” (Consistency of the association across different studies), “Specificity” (specificity of effect), “Temporality” (putative cause proceeds the effect), “Biological gradient” (evidence of a dose response relationship between the putative cause and effect), “Plausibility” (causation of the effect is biologically plausible), “Coherence” (causation does not conflict with other biological knowledge of the effect), “Experiment” (experimental evidence of a detrimental relationship), Analogy (evidence of similar detrimental relationship). Obviously, not all these criteria are relevant to this research but assessed intakes and doses have an impact on:

- Strength – The strength of an association is dependent on how much more prevalent a health outcome is among those who are exposed in comparison to those who are not exposed and a basic prerequisite of dose assessment is to identify the exposed group and the extent of their exposure.

- Consistency – As previously noted, consistency of health outcomes across epidemiological analyses can only be demonstrated if the dosimetry used in all the analyses is produced on a consistent basis.

- Temporality – Assumptions made in relation to exposure scenarios for dose assessments affect the timing of the delivery of doses in relation to the health outcomes in an epidemiological analysis.

- Biological gradient – With dose being the denominator in any analysis of dose response relationships, assessed doses obviously have a fundamental impact on this criterion.

- Analogy – The dosimetry systems developed by the ICRP for use in radiological protection contain factors that attempt to relate the effect of one type of radiation with another and internal with external doses: The dosimetry used in epidemiological research can provide information on the validity of these factors and whether such exposures can be considered analogous.

4.1.2 Scale of Risks

Another consideration is that of the scale of potential risks, if the accuracy and reliability of risk estimates for the largest risks are improved, such improvements will also apply to estimates of overall somatic risk. The largest cancer risks from plutonium are likely to be to the lung, for inhalation exposures, liver and bone as these are the sites that receive the largest doses following intake. A summary analysis of mortality in the Mayak worker cohort, who have incurred the largest average plutonium exposures, tends to support this hypothesis, by the end of 2003, the principal solid cancer deaths in this cohort were for lung (681), liver (75) and bone (30) (Sokolnikov et al., 2008). Risks for non-cancer outcomes, particularly diseases of the circulatory system, are also beginning to attract greater attention and such an association has recently been identified within Sellafield workers (McGeoghegan et al., 2008) but the potential mechanism by which such outcomes might arise is unclear and, consequently, so is the organ or tissue dose of interest.

4.1.3 Research Strategy

The elements of the dose reconstruction process, and possible improvements to them, will be evaluated against their potential to provide better estimates of the greatest potential risks (i.e. lung, liver and bone cancers), as outlined above, and the practicalities of evaluating and implementing them with the resources and time available.

4.2 Urinalysis Data

As the base data for most dose assessments used for epidemiological research, the quality, in terms of resolution and freedom from adventitious contamination, quantity and reliability, of plutonium urinalysis data has a fundamental impact on the accuracy and reliability of dosimetry data and all resulting risk estimates.

4.2.1 Limit of Detection

All other things being equal the LOD for the analytical technique used, is directly correlated to the minimum plutonium intake/dose that can ultimately be produced by the assessment process. As indicated above there are ways of producing intake/dose assessments when all of an individual's results are below LOD but, by their very nature, such assessments must involve some measure of empiricism. Consequently the LOD on urinalysis effectively defines a boundary, "The minimum detectable dose" (Carbaugh, 2003), below which the true dose is censored and cannot be resolved by the normal assessment process and an upper bound for dose estimates based on all LOD data, which could in practise be anywhere between zero and this value. Obviously, the lower the minimum detectable dose is, so is the range of doses than can potentially be resolved. Such considerations clearly impact on the ability of an epidemiological analysis to determine dose response relationships. However,

because different plants have used different techniques at different times this means that there are variations in LOD, both within and between plants, this can be illustrated by comparing the changes in the LOD at the Sellafield and Mayak facilities over time, see Table 4 below.

Table 4. Urine Monitoring for the Mayak PA and Sellafield Worker Cohorts

Monitoring Period	**Detection Limit (mBq)**	
	Mayak PA	***Sellafield***
Early 1950s up to 1960	~1000	2.3 (46)[1]
1961 – 1968	~200	1.9
1969 – 1977	~80	1.9
1978 – 1984	~30	1.9
1985 – 1989	~30	0.5
1990 to date	~10[2]	0.5
1998 to date	~1[3]	0.5

Notes: [1] Records for some of these monitoring results only show them as being below the operational control limit, used at that time, of 46 mBq, [2] alpha radiometry technique, [3] alpha spectroscopy technique.

It should be noted that the detection limits are substantially different both between and within these cohorts over time and, all other things being equal, this means that the minimum detectable dose will also differ substantially. The very high detection limits for Mayak urinalysis results in the early years are particularly noteworthy. Indeed, it is not until the late 1990s that this drops to a level comparable with that for Sellafield results which had been in place in 1961. Two techniques are currently used for Mayak worker analyses, alpha radiometry, which was preferred because of its low cost, and alpha spectroscopy, which has better resolution. However, even the current alpha spectroscopy limit for Mayak urinalysis

results is double that for Sellafield results, which means that, all other things being equal, the minimum detectable dose for Mayak workers is also twice that for Sellafield workers, which is an obstacle to harmonisation of dosimetry between these cohorts. To address this issue, under the auspices of the SOUL project, provisions were made for analysts from SUBI, who conduct the urinalysis monitoring for Mayak workers, to receive training in the analysis and measurement techniques used for Sellafield workers, which are low cost and have good resolution. The expectation is that in the future the LOD for plutonium in urine monitoring for Mayak and Sellafield workers will be similar and hence so will the minimum detectable dose. However, the greatest potential benefit to epidemiological research comes from using modern analytical techniques on supplementary monitoring of surviving members of the early worker cohorts. Because plutonium is long term retained in the body later monitoring can still be used to substantially improve dose estimates through the reduction of the minimum detectable dose for earlier exposure(s). Early monitoring for both Mayak and Sellafield workers was subject to adventitious contamination and the analysis techniques used had considerably higher LODs. Hence, few useful contemporary urine monitoring results exist for many workers who have had potentially the largest exposures, during the early years of operations at both these facilities. This is not a major issue for the Sellafield cohort because most early workers have been subject to later monitoring that can be used to produce a dose assessment for them: Less than 5% of the cohort (~600) have entirely unusable monitoring results, while a further ~16% (~2000) only have pre-1971 results which are considered less reliable. However, ~60% of early Mayak workers have no reliable urine monitoring data on which to assess their exposures. It is believed that ~40% of these workers are still alive and many are still resident in the vicinity of the facility so there is still, currently, an opportunity to substantially improve the monitoring for this cohort in terms of both reliability and

resolution by collection of additional urine samples. The project plan for SOLO (http://solo-fp7.eu/), the successor project to SOUL under the Seventh European Framework for research (FP7), includes work to assess the feasibility of, and develop a proposal for, collecting and analysing further urine samples from former Mayak PA workers. This has the potential not only improve dose estimates for the individuals monitored but also improve surrogate dose estimates that are used for other member of the cohort for whom there is no monitoring information.

4.2.2 Adventitious Contamination

Dose assessments based on urinalysis data that has been affected by significant adventitious contamination will result in a systematic bias toward overestimating doses, if this information is then used in epidemiological analyses this will result in any risks being underestimated. There are two main ways of dealing with urinalysis data that has been affected by adventitious contamination: Firstly, to exclude data that has been affected from any dose assessment and only use data that is unaffected, secondly to use affected data and try and compensate for this in some manner. As previously stated, pre-1971 urinalysis data have, where possible, been excluded from Sellafield worker assessments. However, where pre-1971 urinalysis data is the only monitoring information it has been used and assessed intakes have been divided by a factor of 3 in an attempt to compensate for the affect of adventitious contamination. This factor of 3 was based on an analysis conducted at Sellafield (Riddell, 2000), that showed that this was the average level by which assessed estimates of intake increased when using only pre-1971 data, as opposed to only post 1970 data, for a group of individuals who had both, but this analysis also showed that the factor varied considerably, with a range of 1 to 20. This range of factors is unsurprising given that adventitious contamination is, by definition, a

stochastic process, so determining the effect that it will have on any specific individuals sample results, their dose assessment and any risk estimates based on their dose assessment is problematic. Those individuals who only have pre-1971 urinalysis results are likely to be influential in any epidemiological analysis as, because of their age, knowledge of the ultimate health outcomes for this sub-population is more complete. However, a recent analysis conducted by epidemiologists working on the Sellafield worker cohort has indicated, that the inclusion of this factor of 3 gives more robust estimates of dose response relationships for the main cancer outcomes but removing this sub-population from the analysis improves these estimates further (Gillies, personal communication). Clearly this is an issue which requires further investigation and various avenues of research could be pursued (e.g. additional monitoring, more sophisticated correction factors, the use of surrogate doses as with the Mayak cohort, use of individual dose uncertainty estimates). The resources and time needed to conduct a detailed analysis of this issue are beyond the scope of this project and the requirements of current epidemiological analyses, primarily for the ALPHA-RISK project, make such an analysis unnecessary. The ALPHA-RISK dosimetry committee agreed that for most of the cohorts involved in the project there is a date, designated as "t_1", prior to which urinalysis data is considered unreliable and should not be used to assess doses. It was concluded that the pragmatic solution to this issue for the Sellafield cohort was to declare t_1, for this cohort, to be the 1st January 1971.

4.2.3 Measurement Errors

Efforts to better understand the structure of errors associated with urine monitoring and to quantify them do ultimately have the potential to improve dose and risk estimates, specifically through better data fitting, but are unlikely to have much impact at present. As noted above,

and explored further below, for many plutonium worker cohorts monitoring information is limited or even nonexistent. Improved knowledge of errors cannot improve the fit of the excretion model to the data unless there is sufficient data for statistical measures to apply, as per the "Central Limit Theorem". The ultimate solution to this problem is, again, to collect additional monitoring for key plutonium worker cohorts where such information is lacking (e.g. Mayak). Furthermore, where sufficient monitoring information does exist for an individual, it has been observed that using the ML fitting technique (unless there is a substantial percentage of below LOD results) the actual size of the error used in data fitting (in terms of the GSD) has little impact on the fit achieved (Marsh et al., 2003) and hence on intake/dose estimates. As most of the Sellafield cohort have substantial numbers of monitoring results and because the dosimetry for the ALPHA-RISK project for this cohort would only be based on more reliable post-1970 data, there appears to be little potential benefit in proceeding further with this issue within the current project.

4.2.4 Number of Urinalysis Results

One of the reasons why there has been so little investigation of this area is probably because urinalysis monitoring programmes, at times, seem to have occurred in an unplanned and unstructured fashion, so dose assessments have just had rely on any available results. Certainly, at present (because of the lack of urine samples for the Mayak worker cohort and most of the cohorts in the ALPHA-RISK study) it is not feasible to impose a lower limit on the number of urinalysis results required to perform a dose assessment, as any limit greater than 1 sample would make the potential study population too small for any meaningful epidemiological analysis.

The dosimetry committee for the ALPHA-RISK project decided to assess any individual with one, or more, sample(s) and for the purposes of harmonisation of approach this has also been used for the Sellafield worker assessments that have been used for that study. However, as noted above the ultimate solution to this problem is to have planned monitoring programmes for worker cohorts, even if these have to be implemented retrospectively. Where it proves impossible to assemble sufficient monitoring information for all members of a cohort in a particular time period it may be better to use a JEM approach to dose reconstruction, as has been the case with previous Mayak analyses and to use whatever reliable monitoring data that exists to provide assessments against which to calibrate the JEM.

It has been suggested that, to some extent this issue should also be ameliorated by the quantification of the uncertainties associated with individual dose estimates, as these should reflect the quality and quantity of urinalysis data on which they are based. This is the approach that has been taken for the ALPHA-RISK study and, if it proves successful, the intention is to use a similar approach for future analyses involving the Mayak worker cohort.

4.2.5 Data Reliability

Potentially one of the most serious dosimetry data error that can occur in relation to epidemiological analyses is the miss-assignment of samples. The fundamental level of stratification in any epidemiological analysis is between those who are exposed and those who are not. If a comparison between these two groups shows an increase in specific adverse health outcomes for the exposed group this provides some evidence of a toxic effect. In the worst case scenario, where the only monitoring information for one individual, who has been exposed, is miss-assigned to another individual, who has not been exposed, these two

individuals could then be incorrectly stratified on this fundamental measure of exposure. This will then reduce the ability of any epidemiological analysis to determine if there is a toxic effect. Other data miss-assignment permutations, while not as damaging, still reduce the ability of epidemiological analyses to discriminate any potential exposure effects.

When bioassay monitoring programmes are small it is less likely that data miss-assignment will occur. With very large monitoring programmes like that at Sellafield, even if the error rate is low, there is still potential for a significant number of errors to exist. In order to check for gross data miss-assignment the urine monitoring dates for Sellafield workers are now compared with known employment episodes, for the relevant individual, by the PUMASS program when it is run. PUMASS does not produce assessments for individuals for whom all sample data falls outside known employment but provides a data file listing such individuals and this information was used to identify the relevant urinalysis data (some 774 results, for the 292 individuals involved). WRI Data Management staff located on the Sellafield site, in collaboration with the Sellafield ADS, consulted original paper records of monitoring and have conclusively established that none of these monitoring results belonged to the individuals to whom they had been assigned. These data errors have now been corrected on the Sellafield urinalysis database and this will obviously improve future analyses for this cohort, following the success of this initiative further data quality checks are being considered.

4.3 Models and Functions

A particular difficulty with the models used for internal dose reconstruction is the relative scarcity of data on which to develop them. This leads to a situation where they are

constructed using all the available data. Any reasonable model should produce predictions that are in good agreement with the data that was used in its development. For this reason model building usually involves a process ("model validation") where the predictions of the model are compared with data that was not used to develop the model. Unfortunately, for many of the models used in internal dose reconstruction all available data is "Spent" in model development and there is none left for model validation. To address this issue and to determine the potential benefit of new models to the overall dose reconstruction process, Sellafield worker autopsy data was identified as a potentially invaluable resource as it had not been used to develop any of these new models.

4.3.1 Autopsy Data

When this research commenced it was with the intention of using the Sellafield plutonium worker autopsy data as a reference data set for quantifying the changes made by the proposed improvements in assessment methodology. Such analyses have been conducted in the past to calibrate previous methodology used for the Sellafield cohort. Permission to use this autopsy data had been obtained and a new computer program "Autopsy" was written. The Autopsy program uses IMBA modules to predict an individual's lung, liver and skeletal content of plutonium at the time of their death from their urinalysis measurements, so that these predictions could be compared with the actual observed organ content found by analysis of autopsy samples. Because, IMBA uses biokinetic model description files, rather than having these models "hard coded", it is relatively easy to test alternative models just by changing the model description file. Unfortunately, during the course of this research it became apparent that there were issues with regard to the legal and ethical provenance of the Sellafield autopsy

data and this has resulted in the establishment of a government inquiry ("The Redfern Inquiry") and a moratorium on the further use of this data pending its outcome.

4.3.2 Plutonium Biokinetic Models

Biokinetic models have a key role in determining plutonium intake from excretion and doses to systemic organs and tissues, while there is an ICRP recommended model, from ICRP 67, this is only partially used for Sellafield worker assessments and a later adaptation is used for the Mayak cohort.

The Jones function had been developed, and used, for Sellafield dose assessments specifically because it more accurately reflects observations of excretion in this worker population, in the longer term following exposure, than the older ICRP model recommended at that time. As previously indicated, the Jones function continued to be used for Sellafield workers even after the adoption of the ICRP 67 biokinetic model and comparisons with autopsy using that methodology still indicated that the content of liver and skeleton, on average, were still being over predicted by approximately a factor of 3. Preliminary calculations, completed before the use of autopsy data was embargoed, indicated that replacing the Jones function with the ICRP 67 model of urinary excretion would reduce the mean level of overestimation, of liver and skeleton content, to a factor of about 2. Three considerations prevented the immediate adoption of the full ICRP 67 plutonium model for Sellafield worker assessments: Firstly, the ICRP 67 model dates from 1993, using a structure previously developed by Leggett (1992), and, as indicated above, two suggested revisions to this model have been proposed. Secondly, one of these revised models, Leggett et al. (2005), was now being used for the Mayak worker cohort which raises an issue with regard to harmonisation of approach. Thirdly, the special

assessments for Sellafield workers had been calculated using the Jones function and the PUMASS program had no facility for recalculating intakes, only doses, for special assessments using another model or function, which leads to a problem with respect to implementation.

With respect to the evaluation of alternative biokinetic models, as indicated above, the intention had been to use Sellafield worker autopsy data to evaluate these models. With the use of autopsy data being embargoed it was concluded that a qualitative rather than quantitative review of these models would have to suffice for the present. One of the main criticisms of the ICRP 67 model is that it has a clearance route from "Other soft tissue", "Intermediate turnover (ST1)" compartment, direct to urinary excretion (see Figure 2 above), which conforms to no known physiological pathway. This deficiency was recognised by Luciani and Polig and this is one of the issues that they addressed in their revised plutonium metabolic model that was published in 2002, see Figure 9 below.

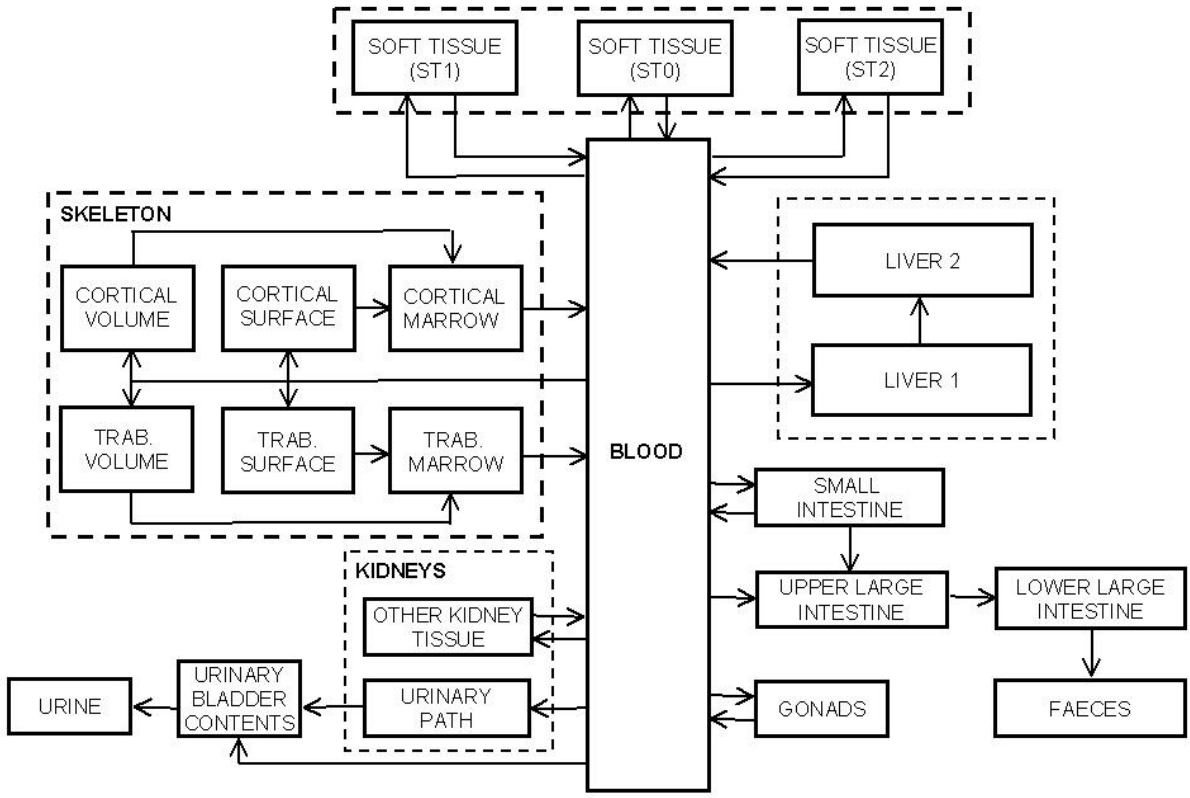

Figure 9. Luciani and Polig Plutonium Metabolic model (Luciani and Polig, 2000)

However, Leggett et al. have also removed this pathway from their model published in 2005 (see Figure 4 above). The Leggett 2005 also made use of information from Russian, i.e. Mayak, studies and human volunteer studies undertaken in the UK (Talbot, Newton and Warner, 1993; Ham and Harrison, 2000), using beta emitting plutonium isotopes (Pu-237 and Pu-244) which are radiologically innocuous, that were not available at the time that the Luciani and Polig model was developed. Leggett et al. have also noted that predicted excretion using their model only significantly differs from the ICRP 67 model at times shortly after uptake to blood and that both models accurately predict urinary content observed in the human volunteer studies, which in the case of Pu-244 measurements were up to 9 years after injection. It is clear that the biokinetic model proposed by Leggett et al. represents best

current knowledge. It has already been adopted for Mayak worker assessments and looks set to form the basis of the next ICRP model. Adopting this model for the Sellafield cohort and the other cohorts in the ALPHA-RISK study, would also have the advantage of further harmonisation of methodology with the Mayak cohort. Consequently, the Leggett et al. biokinetic model was selected for use in the ALPHA-RISK project and for use in any future research involving the Sellafield cohort. The adoption of this model for the Sellafield cohort raises issues with regard to implementation which will be dealt with below.

It should be noted that, another advantage potential advantage of the Leggett et al. 2005 model is that it has two blood compartments. These are used to distinguish between plutonium in different states of bioavailability in the blood. It has been indicated that, the ICRP 67 biokinetic model may still potentially over predict organ content, as compared to autopsy measurements, and with long-term excretion predictions from the Leggett et al. 2005 model being very similar, this is also likely to be the case with that model. One of the reasons for this could be that most occupational exposures are through inhalation whereas the data on which models are based tend to come from direct injection of plutonium to blood. Inhaled plutonium is thought to enter the blood in ionic form but experimental injections (e.g. Langham's experiments) have used plutonium citrate and it has been observed that plutonium is also excreted from the body in a citrate form (Beach and Dolphin, 1964). It could be that plutonium entering the blood from the lung is metabolised differently from that which has been directly injected and the results of the UK human volunteer experiments (Etherington et al., 2002, 2003), which used Pu-237/Pu-244 nitrate aerosols, offer some support for this theory. The two blood compartments within the Leggett et al. 2005 model could be used to investigate and perhaps more accurately model this effect if it does exist.

4.3.3 Lung Model

Inhalation is the primary route of intake for plutonium workers and it can be seen that the incidence of lung cancer greatly exceeds that for liver and bone cancer combined within the Mayak cohort. Clearly, lung dosimetry can potentially have a significant impact on analyses of risks for plutonium workers.

The HRTM is a fairly comprehensive model and no realistic alternative has been proposed since it was introduced. Recently some changes to the modelling of particle transport within the HRTM have been mooted (Bailey et al., 2007) but these proposals are yet to be finalised. Consequently, these proposed changes have not been incorporated into the standard assessment methodology here but in order to investigate their potential impact they have been included in the uncertainty analysis for the ALPHA-RISK study (see below).

The physical and chemical properties of the plutonium aerosol(s) to which individuals are exposed also have an impact on lung dose. It has previously been demonstrated (Riddell, 2005) that for the HRTM lung dose estimates are relatively insensitive to assumptions relating to aerosol particle size, within the 1 to 5 micron Activity Median Aerodynamic Diameter (AMAD) range typically found in industrial facilities like Sellafield (Kelso and Wraight, 1996). This analysis also showed that the assumptions made about the solubility of materials in the lung have the main impact on estimates of lung dose and this will be discussed further in the "Nature of Exposure" section below.

4.3.4 Gastro-Intestinal Tract Model

ICRP have recently produced a replacement for the ICRP30 Gastro-Intestinal (GI) tract model (ICRP, 1979). This is known as the Human Alimentary Tract Model (HATM) and was

published in ICRP100 (ICRP, 2007). A review of this model has been conducted for the Journal of Radiological protection (Riddell, 2007). The HATM is much more flexible than the ICRP 30 model in that it can, be used for children (as well as adults), take account of gender-related differences, calculate doses to all regions of the alimentary tract (including the oral cavity and oesophagus) and model absorption in regions of the GI tract other than the small intestine (the only possible site of absorption in the ICRP 30 model). It is clear that the HATM represents best current knowledge and has the flexibility to adapt to new information as it becomes available. However, direct ingestion is not a common route of occupational exposure and all exposures in this context are to adults. HATM recommended default absorption is still from the small intestine and the fractional absorption values for plutonium are unchanged from the ICRP 30 model. Given that GI tract related doses, from material in transit within the GI tract are normally a small component of GI tract and overall dose, replacing the ICRP 30 GI model with the HATM is unlikely to make a significant difference to the majority of workers dose assessments, so this is not considered a research priority.

4.4 Pattern of Exposure

The primary issue identified is in relation to the default to be used when there is no information available on the true exposure pattern for an individual.

4.4.1.1 Default Exposure Pattern

The ICRP (ICRP, 1997) and IDEAS project, both recommend using a default acute exposure pattern, with intake occurring at the mid-point of any period of possible exposure and, it is suggested, that this might be considered to be the mid-point between successive monitoring results. However, for the reasons given above, it should be noted that using this

recommended default exposure pattern will substantially overestimate intake and dose, when the true pattern is one of ongoing chronic exposure. For example, for an individual who has been exposed to plutonium nitrate bearing aerosols and has one urine sample containing 1 mBq of plutonium: Based on a typical six monthly (182 day) urine sampling interval, an acute exposure on day 91 (i.e. half the sampling interval) gives an assessed intake of 141 Bq of plutonium, whereas assuming chronic exposure over the entire monitoring period gives an assessed intake rate of 0.53 Bq per day and a total intake of 96.5 Bq. Obviously, the preceding is only an issue if acute exposure does not reflect actual exposure patterns but as stated above acute exposure events are relatively rare at both Sellafield and Mayak. Because acute exposures are associated with abnormal operational incidents (e.g. high airborne activity, wounds), they are usually subject to some further investigation and tend to be well documented.

Another disadvantage to the mid-point acute default exposure pattern is that the timing of the exposure is defined by the monitoring interval, as indicated above, in practice the monitoring of individuals is not always well correlated with their potential for exposure or the timing of such exposures. The chronic exposure patterns used for Sellafield and Mayak workers use exposure times that coincide with specific working practices and/or building occupancy, the long term chronic patterns used can run for many years, even decades, and can be largely independent of the vagaries of monitoring and monitoring intervals (e.g. missed samples). The assumption of long term chronic exposure patterns also opens up the possibility of using later, more reliable urinalysis results to assess intakes and to exclude earlier less reliable monitoring information where possible. Consequently, wherever possible, the default exposure patterns used for Sellafield and Mayak workers are long term chronic exposures

with acute exposures only being used where there is specific evidence of such events. The dosimetry committee for the ALPHA-RISK study were also convinced that a chronic exposure pattern should be the default for that study (Thierry-Chef et al., 2008).

4.5 Mode of Exposure

As previously stated, modes of exposure other than inhalation are relatively rare in an industrial context. So efforts to improve dose estimates for modes of exposure other than inhalation are unlikely to have a significant impact on the outcome of epidemiological analyses, unless the risks from them is disproportionate compared to other modes of exposure. Whether different modes of exposure do have a disproportionate effect on risks is a hypothesis that could be tested in a future epidemiological analysis but given the small numbers involved, the possibility of detecting such effects, if they exist, will be limited unless they are very large. Consequently, further investigation of methodology for dose reconstruction for modes of exposure other than inhalation, e.g. the NCRP wound model (NCRP, 2007), is not considered a priority for dosimetry relating to epidemiological research.

4.6 Nature of Exposure

As previously indicated, assumptions about the nature of the material that an individuals was exposed to and the HRTM solubility parameters for these materials have the single greatest impact on lung dose and risk estimates. The problems associated with identifying materials and determining their solubility in the lung have also been discussed, it should also be noted that for sites such as Sellafield and Mayak, exposure may have occurred decades ago in plants that no longer exist so determining such information retrospectively, by experiment, is often

not possible anyway. The potential scale of this problem can be illustrated by comparing the assessed intakes and doses produced by the different solubility parameters currently used for plutonium nitrate and oxide for Sellafield and Mayak, with those produced using the ICRP default parameters. Table 5 below shows assessed intake and lung dose (Committed Equivalent Dose has been calculated as this most simply demonstrates the overall effect) from one urine sample containing 1 mBq of plutonium at the end of a six month chronic exposure on the basis of the different material/solubility assumptions. Parameters for Sellafield Material A and Mayak 2005 Nitrate are compared against ICRP Type M, the recommended default for plutonium nitrate, Mayak 2005 Oxide is compared with ICRP Type S, the recommended default for plutonium oxide which is also used for Sellafield assessments.

Material	**Intake (Bq)**	**Lung Dose* (mSv)**
Sellafield Material A	60	1.27
HRTM Type M	96	1.99
Mayak 2005 Nitrate	263	34.9
HRTM Type S	4157	195
Mayak 2005 Oxide	1666	252

Table 5. Effect of Solubility Assumptions on Intake and Dose Estimates
Note: * Committed Equivalent Dose has been used for the purposes of illustration.

The differences in assessed intakes and dose in Table 5 are striking, particularly for plutonium nitrate. Further analysis shows that it is the assumptions regarding the binding of plutonium

to lung tissues (the bound-state in the HRTM) for Mayak assessments that are the main source of these differences.

4.6.1 Effect of the bound state

As noted above, autopsies of Mayak workers have revealed that considerably more material has been retained in the deep lung than the ICRP 66 HRTM would predict. In order to model this deep lung retention the HRTM bound state has been used. The bound state allows the very slow lung clearance of some particularly insoluble materials to blood to be modelled within the HRTM. However, the retention of material in the deep lung for Mayak workers is largely associated with a phenomenon known as Parenchymal scarring. Parenchymal scarring occurs where plutonium particles become lodged within the Parenchymal folds of the deep lung and necrotise the surrounding tissue through the action of their alpha particle emission. This causes them to become effectively encapsulated and prevents their mechanical clearance or absorption to blood. Newman et al. (2005) have proposed that this effect may be common to all highly exposed plutonium workers and the intention had been to explore this hypothesis using Sellafield autopsy data but, for the reasons already given, this was not possible. While use of the bound state within the HRTM has improved the correlation between predicted activity in the deep lung and that observed in Mayak autopsy tissues it also predicts that there will be delayed clearance of material from the upper airways and this has not been observed at autopsy. This is an issue because material in the upper airways is usually rapidly cleared by mechanical transport (the mucociliary escalator) so preventing it delivering any significant dose. Use of the bound state within the HRTM increases the residency time of material within the upper airways and substantially increases predicted lung doses. If lung doses are systematically overestimated, estimates of lung cancer risk within any epidemiological

analyses using these doses will be proportionally underestimated. This is potentially a major issue and cannot be resolved without extensive further investigation of whether use of the bound state is appropriate (Romanov et al., 2007). Further research into this issue has been included in the work plan for the SOLO project. Plutonium worker autopsy tissue samples held in the United States Transuranium and Uranium Registries will be reviewed to evaluate the extent of any binding in the upper airways. Alternative methods of modelling the long-term retention of plutonium in the deep lung (i.e. without using the HRTM bound state) will also be considered.

4.7 Use of Chelating Agents

As previously identified, the use of chelating agents in most cohorts is comparatively rare and tends to be associated with well documented acute exposure events. Assessments for such acute exposures are usually performed using only that monitoring data which has not been affected by the use of chelation therapy. Once the use of chelation has ceased urinary excretion returns to normal after approximately a month and standard excretion models can again be used to interpret results. So the interpretation of urinalysis results affected by is only really an issue for the Mayak cohort where it was used routinely for a period. As discussed above, some excretion enhancement factors for use in Mayak worker assessments have already been produced. Consequently, further analysis of this issue is not seen as a priority at present.

4.8 Implementation

The utility of the modular approach used for the IMBA codes to facilitate methodological developments has been outlined above. An IMBA model file to implement the Leggett et al.

2005 plutonium biokinetic model was produced by the HPA. This was the only development work needed to allow IMBA PP to be used to assess doses for all the cases and controls within the ALPHA-RISK WP3 study with the exception of those from Sellafield. The number of Sellafield assessments required (424 out of a total ALPHA-RISK study population of ~950) meant that individual assessments were not feasible with the effort and time available. Furthermore, to demonstrate the feasibility of producing the dosimetry required for the putative multi-cohort study being investigated under ALPHA-RISK WP4, production of doses for the entire Sellafield cohort using the methodology developed for WP3 would be required. An additional consideration was that some of Sellafield assessments would involve individuals with more than the maximum number of bioassay results (400) permitted by the IMBA PP software. HPA indicated that the modification of IMBA PP to handle more than 400 bioassay results could not be completed before the deadline for delivery of doses for the ALPHA-RISK project. IMBA PP cannot, in any event, calculate Am-241 ingrowth in the manner required for the production of Sellafield dose assessments. It was obvious that production of doses for the Sellafield cohort would have to rely on a similar mass assessment strategy to that which had been used previously.

4.8.1 Revised Automated Mass Assessment Process for the Sellafield Cohort

In theory using Leggett et al. 2005 biokinetic model for the Sellafield cohort should be simple to implement as the IMBA model file required had been developed by the HPA. Because it uses the same file format, the PUMASS program can use this model file and a copy of it was obtained from the HPA. However, as this model was also going to be used to replace the Jones excretion function this introduced another issue with respect to the system that had been developed for the production of assessments. A long-standing assumption of the

automated assessment system was that there would be no requirement to reassess intake for those individuals with a special assessment. The data file containing the results of individual special assessments for Sellafield workers includes assessed intake(s) within each period of exposure. As these intakes had been calculated using the same excretion function (Jones) as used for the automated assessments, there was no need to reassess these intakes and doses could be calculated directly from them. The use of a new excretion model for the automated assessments would mean that intakes were calculated on a different basis to the special assessments and this could introduce a bias into the dosimetry and any future epidemiological analysis. Obviously, the solution to this issue is to recalculate the intake estimates for the special assessments on the same basis. However, for the reasons of economy of effort previously given, this would need to be done automatically by the mass assessment program. Recalculating intake(s) for the special assessments has required substantial modifications to the automated assessment software because of the greater complexity of some of the exposure patterns involved. Special assessments include individuals with acute and linked chronic exposure patterns (Because identification of acute and linked chronic exposure patterns requires detailed knowledge of an individual's work history and expert judgement, they are only found in special assessments). Identification of acute exposure patterns in the special assessment file was simply a matter of flagging those exposures that occur on a single day. However, identification of linked chronic patterns is more complex as it involves scanning all the exposure patterns for an individual and flagging all those chronic patterns which have the same intake rate (there can be more than 2 periods of exposure in a linked chronic pattern and an individual can have more than one linked chronic pattern). The preceding information can then be used to instruct the IMBA modules underlying the PUMASS program to reassess intakes (this will be discussed further in the "Software" section below).

4.8.2 Fitting Techniques

The ML fitting technique used for dose assessment for the Sellafield workforce remains very efficient and intakes and doses for the entire cohort can be recalculated in approximately 26 hours, even though this is one of the two largest plutonium worker cohorts and the associated urinalysis monitoring dataset is, by some considerable margin, the largest. While Bayesian methods offer some advantages, the computational overhead for MCMC techniques means that is currently impractical to consider using them for the assessment of doses for the entire Sellafield worker cohort. Even using the WeLMoS method (described below), which is a much more efficient Bayesian method than MCMC, it takes approximately 20 minutes on a high performance PC to perform one assessment. Obviously, multiple computers could be used for such calculations but for a large cohort like Sellafield (12,800 plutonium workers), a substantial amount of computational effort would be require to keep timescales for the production of assessments reasonable. It will be interesting to compare the intake/dose estimates produced by the ML and WeLMoS methods, and the risk estimates based on them, for the ALPHA-RISK study, particularly for individuals who only have below LOD monitoring results, to see if any potential benefits outweigh the computational cost.

4.8.3 Software

As indicated above, adoption of a new biokinetic model and resulting changes in the automated assessment strategy for the Sellafield cohort have meant that the PUMASS program has had to be modified. Further modifications were needed because of the dose uncertainty analysis required for the ALPHA-RISK study.

The PUMASS program was now required to re-calculate intakes for acute and linked chronic exposure patterns. Acute exposures are easily handled by the IMBA modules used by the PUMASS program as this is part of their core functionality. Assessments for linked chronic exposure patterns requires some manipulation of the IMBA modules' data input and output as assessment of such exposures is not part of their core functionality. Linked chronic exposures were handled by calculating predicted excretion, at the time of each observation, per unit intake for each period of exposure within the linked regime individually and then summing these results. These summed values of predicted excretion are then passed to the IMBA ML fitting routine as representing a single period of exposure. The resulting estimate of daily intake produced by the fitting routine for this period of exposure is then assigned to each of the component individual periods making up the linked chronic exposure pattern and this is then used for calculating doses. These modifications mean that the PUMASS program can now assess intakes from acute, chronic and linked chronic exposure patterns.

The dose uncertainty analysis for the ALPHA-RISK study was to be conducted using a Bayesian technique developed by the HPA (See below). The HPA developed software based on their IMBA PP code to implement this uncertainty analysis methodology called IMBA UA (i.e. Uncertainty Analyser). IMBA PP uses an overarching data input/output file called an "ix" file, as this is the suffix used to denote such files (e.g. "example.ix"). The ix file essentially contains all of the information relating to an assessment including that which was originally contained in the individual IMBA module input/output files. While the information is the same, the formats used in the ix file are different to those produced by the PUMASS program which conform to the original IMBA specification. The ix file format is also used by the IMBA UA software used for estimating the uncertainties on dose estimates.

Consequently, the PUMASS program has also been modified so that it can generate ix files either for use with IMBA PP or the IMBA UA software.

The FORTRAN source code for the PUMASS program was re-written to implement the above modifications. Test runs and checks were conducted using this modified PUMASS code to ensure that both new and existing functionality was working correctly. The PUMASS program was then used to generate the dosimetry data for the 424 ALPHA-RISK plutonium worker cases and controls from the Sellafield cohort and also to produce the ix files needed for the uncertainty analysis.

4.9 Consistency/Harmonization

The steps taken to standardize the implementation of the assessment process for Sellafield workers should provide increased confidence in the internal consistency of dose estimates used in epidemiological analyses for this cohort and any resulting risk estimates. The modifications to the PUMASS program outlined above mean that it is now possible to re-calculate plutonium intakes for all Sellafield workers including those who have special assessments. This also means that in the future new or alternative biokinetic models can be used for this cohort and all the resulting dose assessments will remain internally consistent. To demonstrate this capability and also the feasibility of dose reconstruction for the putative international cohort study which was the objective of ALPHA-RISK WP4 the doses for the entire Sellafield cohort were recalculated (Riddell, 2008) using the methodology endorsed for WP3 (See Figure 10 below).

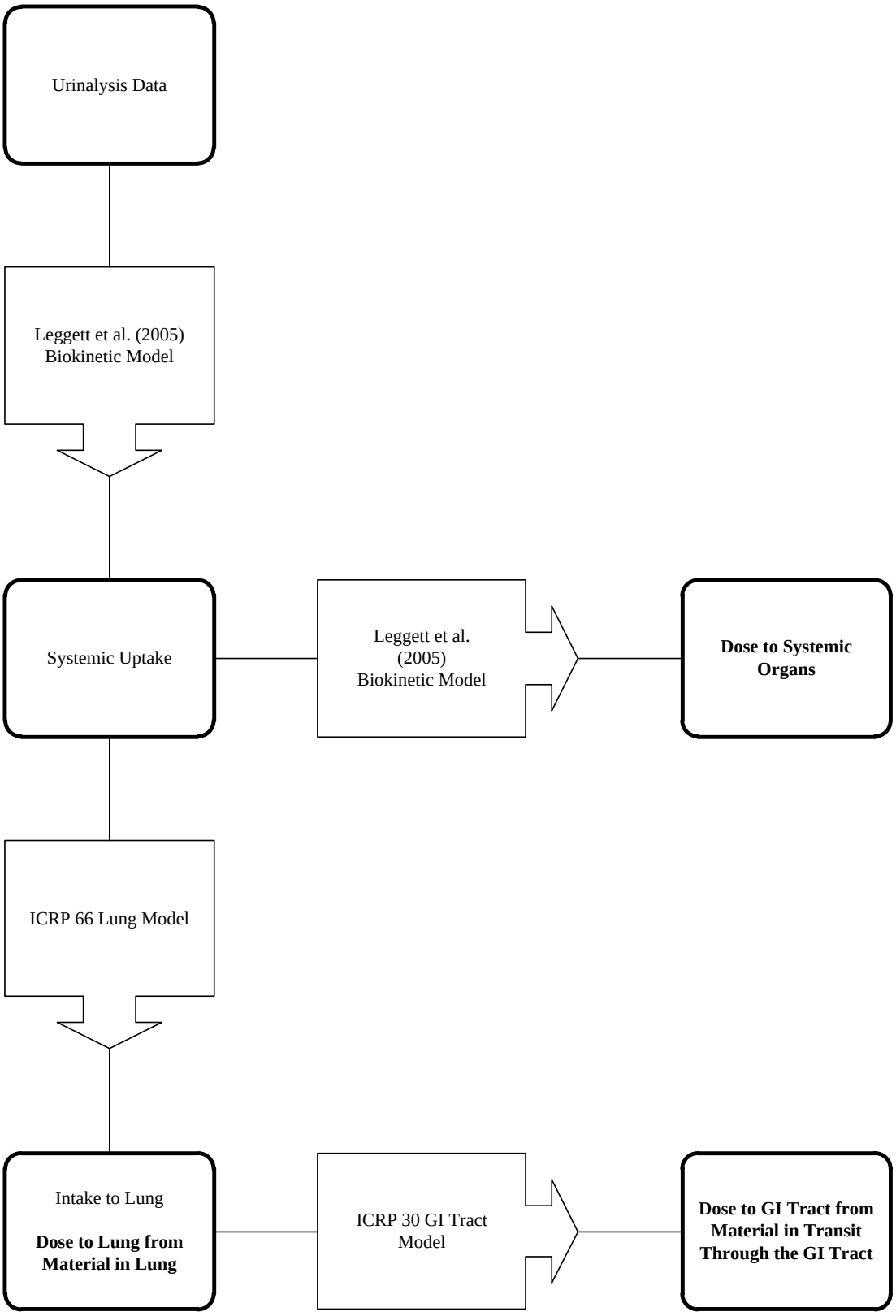

Figure 10. Final Dosimetry Methodology

Work with the dosimetry committees for the ALPHA-RISK and SOUL projects has helped to ensure that the key underlying methodology used for dose reconstruction for these projects has been harmonised as far as possible. As a result, for the first time the overall dosimetry methodology being used for Mayak and Sellafield (the two largest plutonium worker cohorts in the world) is the same (See Figure 10 above). This will permit more reliable conclusions to be drawn when comparing the outputs of these projects and opens up the prospect of further meta-analyses (e.g. the SOLO project) in the future to further improve risk estimates.

4.10 Reliability/Uncertainty

It is becoming increasingly evident that dose uncertainties can have a significant impact on the outcomes of epidemiological research (Schafer and Gilbert, 2006). Consequently, there is now a growing expectation that uncertainties for doses used in epidemiological research will be quantified if at all possible.

Bayesian methods for calculating uncertainties rely on prior knowledge (usually derived from expert judgement) of the potential uncertainty on key parameters in the dose reconstruction process. In this instance the parameters can be an individual rate constant in the HRTM or a complete alternative particle clearance model. The methodological approach, generally grouped under the term "Monte Carlo" methods, is to draw random samples from all the individual parameter distributions and calculate doses using these parameter values. By iteratively repeating this process, so as to effectively explore all the multi-dimensional parameter space, an estimate of the uncertainty distribution associated with assessed doses can be built up through the multiple realisations of each dose. However, these methods, such as Markov Chain Monte Carlo (MCMC), traditionally have a substantial computational

overhead for all but the simplest of analyses. Given the number of dose assessments required for the ALPHA-RISK study, the use of MCMC was considered impractical. To address this problem researchers at the Health Protection Agency have developed a more efficient algorithm, called the Weighted Likelihood Monte-Carlo Sampling method (WeLMoS) (Puncher M and Birchall A 2008) and this has been used for the ALPHA-RISK WP3 analysis.

4.10.1 WeLMoS and the IMBA Uncertainty Analyser

The primary advantage of the WeLMoS method is that it takes significantly fewer iterations and consequently less computer processing time than MCMC to explore the parameter space as it uses Latin Hypercube sampling. WeLMoS has proven to be approximately 30 times faster than using MCMC on the same problem.

The WeLMoS method is implemented through the IMBA Uncertainty Analyser (IMBA UA). IMBA UA is software package which iteratively calls IMBA PP to perform individual assessments using different modelling parameter assumptions and collates the results. As a starting point the uncertainty analyser uses the information about an assessment held in an IMBA ix file. As noted above, the PUMASS automated assessment program for Sellafield workers did not store information in this format and consequently it had to be modified to do so. However, it was recognised that certain information in the ix file was common to all assessments. The IMBA PP software was modified to allow information to be appended to a standard ix file. This meant that only such information which varied from assessment to assessment would have to be produced by the PUMASS program, which simplified this task.

The HPA with the assistance of the dosimetry committee for the ALPHA-RISK study generated prior probability distributions for assessment parameters. The ix files produced for the initial dose assessments were used by the IMBA UA software to generate 1000 realisations of each dose and the probability of each of these realisations. This information will allow the probability distribution of doses to be sample in order to investigate the effects of dose uncertainties. Although the WeLMoS method is much more efficient than MCMC methods, it still took approximately 5 days of computer time (on a high performance 3.4 GHz Intel I7 PC) to generate the uncertainty data for the 424 Sellafield dose assessments within the ALPHA-RISK study.

4.10.1.1 Potential issues with the uncertainty analysis

Bayes theorem P(H|D) = P(H) * P(D|H) / P(D), where H represents a hypothesis, D represents the data, P(H) represents the prior probability ("Prior") derived from expert input, P(D|H) represents the likelihood, P(H|D) represents the posterior probability ("Posterior") and P(D), the probability of the data, is usually ignored because it is always constant.

The Bayesian paradigm relies on information in the data set analysed to correct any misspecification of the prior in the posterior. However, if data sets are uninformative any misspecification in the prior is directly reflected in the posterior probability distribution. It should also be noted that the common assumption of an uninformative or "Flat", prior (where prior expert knowledge is lacking) will result in an equally uninformative posterior distribution in such circumstances.

An initial evaluation of the uncertainties for the ALPHA-RISK study has indicated that the central estimates of dose from the uncertainty analysis were almost an order of magnitude higher than the point estimates generated by the standard assessment process. This is almost certainly due to the specification of the priors used in the uncertainty analysis. Further analysis of these results points toward the need to use revised prior assumptions (e.g. an uninformative prior was initially used for the estimate of intake) and to repeat the uncertainty analysis.

5 CONCLUSIONS

A strategy of viewing dosimetry and epidemiological research holistically, so as to best identify ways of improving the accuracy and reliability of estimates of plutonium exposure risks, has been developed. This approach could prove useful in developing an overall strategy for future research in this area.

Production of more reliable risk estimates for plutonium exposure requires not only improved dosimetry methodology but a coordinated approach to the development and use of such methodology. Harmonisation of dose reconstruction methodology allows the results of epidemiological analyses to be directly compared or combined in meta-analyses which have the potential to increase study power and resolution.

The changes to the structural models used for plutonium dose assessment for epidemiological research as a result of this project have been limited to the adoption of the plutonium biokinetic model developed by Leggett et al. (2005), for use in dose reconstruction for the Sellafield worker cohort and all the cohorts involved in the ALPHA-RISK study. This relatively simple methodological change required considerable effort to implement within the automated assessment systems used for the Sellafield cohort. However, this change has brought the advantages of an improved biokinetic/excretion model, more flexible assessment systems and the complete harmonisation of overall methodological approach between the Sellafield and Mayak cohorts (The two largest and potentially the most informative plutonium worker cohorts in the world from an epidemiological perspective).

The importance of aspects of the dose reconstruction process other than the development of structural models of ADME has been highlighted:

- There are still important plutonium worker cohorts, like that at the Mayak PA, with limited (i.e. in terms of numbers, reliability and resolution) urinalysis data. Possibly the single greatest overall improvement to dosimetry for future epidemiological research for such cohorts would be achieved through collecting more urine samples (particularly from early workers, while this is still possible) and analysing them with modern reliable high resolution techniques.
- Investigation of anomalous sample results can substantially improve the overall quality of the dosimetry data for a cohort.
- The HRTM parameters used to describe the absorption of inhaled material from the lung into the blood have the greatest impact on lung doses. Specifically the slow absorption rate ($\mathbf{s_s}$), the fraction of bound material ($\mathbf{f_b}$) and the associated bound absorption rate ($\mathbf{s_b}$).
- Use of a default chronic exposure pattern is less likely to produce biased estimates of intakes, doses and risks than the mid-point acute pattern recommended for operational protection purposes.

Quantification of the uncertainties associated with plutonium dose estimates is still relatively novel. Analysis of the results of the uncertainty assessments for the ALPHA-RISK study should provide further insights into the production and use of such information.

The advantages of automated dose assessment systems and a modular approach to assessment software development has again been demonstrated.

5.1 Future Work

The Mayak cohort is internationally recognised as one of the most important for studying the effects of plutonium exposure. Further sample collection for Mayak workers, particularly for those who worked there in the earliest years must be considered a priority. There still appears to be the opportunity to do this, one which will soon be lost because of the age of these early workers and the passage of time[2].

Lung cancer appears to be the largest putative risk for plutonium workers. Consequently, efforts to better characterise the chemical nature of plutonium bearing aerosols and the mechanisms and rates governing their absorption from the lung into blood must also be considered a priority[2].

Further, identification and investigation of anomalous urinalysis results could substantially improve the dosimetry information used for epidemiological analyses, particularly for the Sellafield worker cohort.

The possibility that inhaled plutonium might have different biokinetics when it enters the blood, as compared to directly injected plutonium, needs further investigation.

Further work to quantify, understand, reduce and analyse the uncertainties associated with dose estimates is clearly required.

[2] Both of these research suggestions have now been incorporated into the work plan for the SOLO project.

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