DEVELOPMENT OF KINETIC AND ANATOMICAL MODELS FOR BRAIN DOSIMETRY FOR INTERNALLY DEPOSITED RADIONUCLIDES

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Preface

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President (2012 – 2018)  President (2019 –)
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1. Executive Summary

This Commentary examines ways to improve current biokinetic and dosimetric modeling of the brain that may result in improved dose estimates for brain tissue from internally deposited radionuclides, with emphasis on alpha emitters. In addition to exploring improvements in brain dosimetry relevant to radiation protection, better estimates of brain radiation doses from alpha emitters will be applicable to ongoing epidemiologic research aimed at evaluating dementia, Alzheimer’s, Parkinson’s, motor neuron diseases and cognitive impairment as possible adverse effects of radionuclide depositions in the brain (Boice 2017, 2019; NCRP 2019).

The blood-brain barrier is composed of the blood vessels of the brain and the surrounding milieu and regulates the transport of essential substances between the blood and brain to achieve proper neuronal function while shielding the brain from foreign substances. Human and animal studies have shown, however, that radioisotopes of nonessential as well as essential elements can accumulate in the brain, in some cases in concentrations approaching or exceeding those in other tissues. Published studies indicate various routes by which radionuclides may enter the brain. While the available information is often not definitive, it appears that a particularly important mode of entry may be via specialized blood-brain barrier transport systems that cannot fully discriminate between the required elements and close chemical and physical analogues of those elements.

Element- or compound-specific biokinetic models are used to derive dose coefficients for radionuclides or reconstruct doses to tissues from internal emitters. Generally, a systemic model for an element explicitly depicts only the element’s dominant repositories. Remaining tissues are aggregated into a source region called Other in which the element is assumed to be uniformly distributed. In systemic models used in radiation protection, the brain usually is addressed as an implicit mass fraction of Other rather than an explicitly depicted repository.

Case studies were performed for selected radioisotopes of 10 elements (manganese, cesium, mercury, bismuth, lead, polonium, radium, uranium, plutonium, americium) to investigate the extent to which dose estimates for brain tissue might be improved for internal emitters by
explicitly modeling brain kinetics rather than treating the brain as a mass fraction of Other. In all, 17 radionuclides were addressed. The case studies include radionuclides frequently encountered in the Million Person Study (MPS) (e.g., $^{239}$Pu and $^{210}$Po) and radioisotopes of elements known to have relatively high accumulation in the brain (e.g., $^{54}$Mn and $^{210}$Pb). Injection dose coefficients were calculated for each radionuclide using two versions of the International Commission on Radiological Protection’s (ICRP) current systemic biokinetic model for that element: the original version and a modified version differing only in the treatment of brain. An injection dose coefficient for a given radionuclide and tissue is defined here as the 50-y committed equivalent dose to the tissue following input of 1 Bq of the radionuclide into blood at time zero. If the ICRP model for the element contained an explicit brain region, the modified version of that model depicted brain instead as a mass fraction of Other. If the ICRP model included brain in Other, the modified version included an explicit brain region with kinetics based on best available brain-specific data. The comparison of dose coefficients for a given radionuclide was expressed as a ratio A:B, where A and B are the dose coefficients based on the versions of the model with and without an explicit brain region, respectively.

For the 17 radionuclides addressed in this study, the ratio A:B was <0.2 in two cases, in the range 0.5-2.0 in 12 cases, and in the range 3-5 in three cases. The results indicate that addition of an explicitly identified brain can sometimes result in a substantial (factor of 3 or more) difference in the dose coefficient for the brain compared with use of an implicit brain model. In such cases it is important to incorporate an explicit brain region into the systemic model used for dose reconstruction, if feasible in view of the quality and quantity of available biokinetic data for the element of interest.

Ideally, only data for human subjects would be used in the development of a biokinetic model for humans. However, data on the accumulation of an element in the brain at early times after intake generally are available only from animal studies. Best available data for the human brain generally come from postmortem measurements of stable elements or radionuclides in tissues of occupationally or environmentally exposed subjects. Such autopsy data were found for all 10 of the elements addressed here but were suspected of not being representative in one case.
(polonium) and were of doubtful relevance in another case (bismuth) due to limitations in the data.

An important finding from these case studies and additional reviews of the literature is that the brain typically has a much lower rate of uptake per gram of tissue but a longer residence time than do most other studied soft tissues. Thus, an initially low uptake of a radionuclide by brain should not be interpreted as indicating that the dose to brain is substantially lower than that to most other tissues.

Dosimetry systems used in radiation protection generally have not included sophisticated or detailed dosimetric models of the brain. Rather, the brain generally has been treated as a single compartment. One exception is a model introduced by the Committee on Medical Internal Radiation Dosimetry (MIRD) in 1999. That model is built on a stylized dosimetric phantom and depicts eight separate regions of the brain. Applications of the MIRD model to selected radiopharmaceuticals with reasonably well-known distribution in the brain indicate that the doses to brain tissues from radionuclides within the brain can be highly nonuniform.

In recent years there has been a considerable expansion of information on the anatomy and functions of the brain. The recent advances in MRI technology have enabled measurements of brain function linked to brain structure. It may now be feasible to refine ICRP’s current dosimetric methodology for the brain to produce a relatively detailed brain model analogous to the 1999 MIRD model but having a more realistic spatial configuration.
2. Introduction

Scientific Committee 6-12 was charged with preparing a commentary that describes new approaches for estimating radiation dose to the brain from high-LET alpha particle-emitting radionuclides. Few biokinetic models used in radiation protection include an explicit model of the brain, and the Committee was to develop and contrast different treatments of the brain in biokinetic models used to estimate radiation dose following intakes of radionuclides (Leggett et al. 2018). In addition to potential improvements in brain dosimetry relevant to radiation protection, a better understanding of biokinetic models and dosimetry parallels the increasing medical application of alpha-particle emitters in neuroimaging and radiopharmaceutical therapy (Poty et al. 2018a, 2018b; Sgouros et al. 2020). Further, better estimates of brain radiation doses from alpha emitters will be applicable to ongoing epidemiologic research aimed at evaluating dementia, Alzheimer’s, Parkinson’s, motor neuron diseases and cognitive impairment as possible adverse effects of radionuclide depositions in the brain (Boice 2017, 2019; NCRP 2019).

Element-specific biokinetic models are used to reconstruct doses to systemic tissues from internal emitters. Typically, a systemic model for a radionuclide explicitly depicts only its dominant repositories. Remaining tissues and fluids are aggregated into a source region called \textit{Other} in which the radionuclide is assumed to be uniformly distributed. In the systemic biokinetic models used in radiation protection, the brain usually is addressed as an implicit mass fraction of \textit{Other} rather than an explicitly depicted repository. Due to increasing interest in radiation effects on the brain, efforts are underway to improve brain dosimetry for internal radiation sources (Leggett et al. 2018, 2019).

2.1 Background

NCRP recommended that studies of workers with intakes of alpha-particle emitters be initiated to evaluate possible late CNS effects (NCRP 2019). The recommendation was to:

“Initiate studies of workers exposed to polonium, radium, plutonium, uranium and americium. Workers with intakes of radionuclides that expose brain tissue to
high-LET alpha particles (helium nuclei) could be studied for late CNS effects (i.e., cognitive function and dementia).”

Scientific Committee 6-12 was convened to improve estimates of radiation dose to brain tissue from the intake of radionuclides that emit alpha particles, specifically to investigate potential improvements in brain dose estimates for internal emitters resulting from explicit rather than implicit biokinetic treatment of brain (and improved dosimetric treatment). As described in Appendix A, the improved estimates of brain dose will be used in ongoing epidemiologic studies of Department of Energy workers with known intakes of radionuclides and may be relevant to NASA’s interest in evaluating the possible adverse effects of space radiation and especially Galactic Cosmic Rays (GCR) on cognitive function and CNS conditions such as dementia and Alzheimer’s disease in human populations exposed to high-LET radiations (Boice 2017, 2019; Boice et al. 2019; NCRP 2019).

2.2 Scope and Approach

Scientific Committee 6-12 has developed and described methodological approaches and biokinetic models for brain dosimetry for internally deposited radionuclides. It was concluded that inclusion of an explicit model of the brain in the biokinetic model describing the systemic behavior of an element is preferred over reliance on an implicit brain model if data are sufficient to develop a reasonably well supported explicit brain model. This evaluation is developed in six Sections. Section 3 presents an overview of anatomy and physiology of brain that will provide a foundation for understanding the biokinetic models developed for estimating radiation brain dose following the intake of radionuclides that emit alpha particles. Section 4 discusses pathways by which internally deposited radionuclides are thought to be transported into the brain. Section 5 discusses current knowledge of the uptake and retention of each of the 10 selected elements by the brain. Section 6 addresses the importance of explicitly describing the brain in the biokinetic model for each of the 10 selected radionuclides. Section 7 explores potential improvements in dosimetric models of the brain for internal emitters. Section 8 provides conclusions and recommendations of the work completed by Scientific Committee 6-12. Appendix A discusses
the applicability of improved estimates of radiation dose to brain tissue following intakes of radionuclides for the purposes of radiation protection guidance and for epidemiologic research.
3. Anatomy of the Brain

The human brain controls thought, memory, speech, body movement, and the functions of many organs. The brain is complex not only in its neurological function but also in its anatomical structure. Fig. 3.1 shows major regions of the human brain.

The mass of the adult human brain ranges from 1.25 to 1.53 kg (Dekaban and Sadowsky 1978). The reference value for adult males is 1.45 kg. For adult females, the reference mass of the brain is 1.30 kg (ICRP 2002).

The brain is grossly subdivided into three distinct regions: the cerebrum, the brain stem, and the cerebellum. The masses and dimensions of the cerebrum and cerebellum are further subdivided into right and left regions are shown in Table 3.1, obtained from Henery and Mayhew (1989). The left and right regions are not differentiated in the table because no statistical differences were found in these quantities.

The brain stem mass is 1.9 to 2.3 % that of the whole brain (ICRP 1975). The hemispheres are connected via a bundle of fibers called the corpus callosum. A representation of brain anatomy with almost all the established functional structures has recently been developed. Names and volumes of these functional structures are listed in Table 3.2.

The water content of brain makes up approximately 77 % of the brain mass (ICRP 1975) while the blood percent mass is approximately 4.6 % (ICRP 2002). Although the brain blood volume is relatively low compared to other organs, it is one of the most highly perfused organs. The fraction of cardiac output received by brain volume is given by the cerebral blood flow divided by the cardiac output (denoted CCRI). ICRP Publication 89 (2002) gives a reference value for CCRI of 12 % for a resting adult human. A recent study by Xing et al. (2017) suggests a higher central value of CCRI, particularly in young adult females. Results of that study also indicate that CCRI declines with age during adulthood (Fig. 3.2) (Xing et al. 2017).
**Fig. 3.1.** Some major regions of the brain (mid-sagittal section) (McGraw-Hill).
Table 3.1— Masses (g) and linear dimensions (cm) of cerebral hemispheres and cerebral halves in adult humans. The listed values are means (with standard error of the group mean in parentheses) of 6 males aged 76-81 y mean age 79 y and 6 females aged 70-98 y mean age 79 y mean age 81 y

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerebrum</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass</td>
<td>428 (5.0)</td>
<td>383 (6.3)</td>
</tr>
<tr>
<td>Length</td>
<td>15.7 (0.15)</td>
<td>14.4 (0.08)</td>
</tr>
<tr>
<td>Width</td>
<td>6.0 (0.20)</td>
<td>4.1 (0.11)</td>
</tr>
<tr>
<td>Height</td>
<td>7.1 (0.14)</td>
<td>6.7 (0.15)</td>
</tr>
<tr>
<td><strong>Cerebellum</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass</td>
<td>51.4 (0.64)</td>
<td>48.2 (1.05)</td>
</tr>
<tr>
<td>Length</td>
<td>3.6 (0.02)</td>
<td>3.5 (0.02)</td>
</tr>
<tr>
<td>Width</td>
<td>3.2 (0.05)</td>
<td>3.0 (0.05)</td>
</tr>
<tr>
<td>Structure</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>---------</td>
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</tr>
<tr>
<td>Meninges</td>
<td>222.0</td>
<td>162.5</td>
</tr>
<tr>
<td>Parietal cortex (grey matter)</td>
<td>46.9</td>
<td>40.3</td>
</tr>
<tr>
<td>Parietal white matter</td>
<td>41.1</td>
<td>40.8</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>79.7</td>
<td>77.5</td>
</tr>
<tr>
<td>Frontal white matter</td>
<td>74.3</td>
<td>76.5</td>
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<td>Temporal cortex</td>
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<td>Temporal white matter</td>
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<td>30.5</td>
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<tr>
<td>Insular cortex</td>
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<tr>
<td>Insular white matter</td>
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<td>1.1</td>
</tr>
<tr>
<td>Occipital cortex</td>
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<tr>
<td>Occipital white matter</td>
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<tr>
<td>Cerebellum cortex</td>
<td>44.1</td>
<td>34.2</td>
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<tr>
<td>Cerebellum white matter</td>
<td>18.7</td>
<td>20.1</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>10.8</td>
<td>9.7</td>
</tr>
<tr>
<td>Lateral ventricle</td>
<td>15.8</td>
<td>13.9</td>
</tr>
<tr>
<td>Lateral ventricle wall</td>
<td>4.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Third ventricle</td>
<td>0.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Third ventricle wall</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Fourth ventricle</td>
<td>1.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Fourth ventricle wall</td>
<td>1.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Thalamus</td>
<td>12.1</td>
<td>12.8</td>
</tr>
<tr>
<td>Pituitary</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Pons</td>
<td>9.3</td>
<td>9.6</td>
</tr>
<tr>
<td>Medulla oblongata</td>
<td>3.0</td>
<td>3.2</td>
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<tr>
<td>Midbrain</td>
<td>7.7</td>
<td>6.3</td>
</tr>
<tr>
<td>Putamen</td>
<td>5.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>3.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>0.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Internal capsule</td>
<td>4.8</td>
<td>1.8</td>
</tr>
</tbody>
</table>

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Fig. 3.2. Age- and sex-related differences in CCRI: (cerebral blood flow)/(cardiac output) ratio index. (a) The regression equation was: CCRI = −0.127 % × age + 22.72 %, with a standard error of the slope equal to 0.035 % per year ($R^2 = 0.13$, $P < 0.001$). (b) Solid lines inside the box represent median values, the cross (+) represents the mean value; $P < 0.001$ for the age group; $P < 0.001$ for sex; and $P = 0.264$ for age and sex interaction. The differences in CCRI between men and women in each age group were as follows: Young (21 – 45 y), 21.3 ± 5.6 % vs. 14.8 ± 5.3 %, $P < 0.05$; Middle age (45 – 65 y), 16.4 ± 5.5 % vs. 13.0 ± 3.7 %, $P < 0.05$; Old (66 – 80 y), 14.8 ± 5.5 % vs. 11.7 ± 2.9 %, $P < 0.05$. From Xing et al. (2017).
3.1 Brain Structure

About 48% of the brain consists of gray matter, and white matter fills the remaining 52%. The neuron synapses of the brain are primarily within the gray matter. White matter consists of the axons connecting different parts of the gray matter. Neuron signals are processed within gray matter, and white matter provides the channels of communication of these signals. The cerebral cortex and cerebellum represent about 90% of the brain mass. The cerebellum, which acts to coordinate the body muscles, represents about 10% of the brain mass and contains about half the neurons of the brain. The hippocampus, with mass of about 3 g, is associated with memory formation. The thalamus and hypothalamus are two structures that serve to connect messages among the various regions of the brain. In addition, the hypothalamus controls the pituitary gland’s secretion of hormones, which in turn control various body functions. Questions regarding the potential impact of ionizing radiation on the brain’s function necessitate consideration of the dose to individual regions. The substructures of the brain identified above consist of gray matter with the bulk of the white matter being within the cerebral cortex. It is estimated that gray matter consumes the bulk (~94%) of the brain’s energy and presumably has a relatively high blood perfusion rate. It is not clear whether the absorbed dose within the gray matter or white matter is more limiting regarding impact of dose on neurological function. These considerations are most critical for internally deposited radionuclides that emit radiations of low penetrating range, particularly alpha particles.

3.2 Brain Function

Brain function is critically dependent on maintaining and tightly regulating glucose supply. As noted by Mergenthaler et al. (2013), the human brain is 2% of the whole-body mass, yet this organ consumes 20% of glucose-derived energy (~5.6 mg glucose per 100 g human brain tissue per minute). In the brain, glucose is used for cellular respiration and metabolism and as one of the main precursors for neurotransmitters – a critical set of amino acid-based molecules that are used to transfer electrical impulses from one nerve to another or to several others. This typically occurs by neurotransmitter release from the transmitting neuron and diffusion across a small gap (synapse) to the connecting neurons. A series of glucose transporter (GLUT) molecules are used
to maintain tight regulation of glucose availability for the different cell types making up the
brain. Fig. 3.1 depicts the different transporter molecules and the cells and functions with which
they are associated.

The monocarboxylate transporters (MCTs) are responsible for transport of what are largely
products of glucose metabolism. Both the number and location of the different transporters are
modulated based on nutrient demands of the different cell types. For example, GLUT1, the
primary and most ubiquitous glucose transporter, may be found on both the luminal and
abluminal sides of the endothelial cells making up the capillaries that feed the brain (depicted as
a micro-vessel in Fig. 3.3). Accordingly, the number of transporters on either side of the
endothelial cells can be modulated to control influx of glucose into the brain environment. The
same is true of GLUT3, the other primary glucose transporter (Simpson et al. 2007).

Measurements of human cerebral blood flow, perfusion, glucose and oxygen utilization
rates, neurotransmitter transport, binding and receptor number, and other metabolic and
physiological markers of brain function and activity are now possible using PET and MR
Imaging. Such studies are used to examine and understand human memory (Owen 1997),
cognition, behavior (Duncan and Owen 2000) and the pathologies associated with these
(Backman et al. 1997; Bozzali et al. 2006; Chetelat et al. 2003; DeCarli et al. 1995; Phelps and
Mazzotta 1985). PET imaging has recently been used to provide a map of synaptic density
(Finnema et al. 2016) and is perhaps most relevant to understanding if brain absorbed dose leads
to alterations in cognitive function. Conventional brain MRI studies in astronauts have identified
anatomical effects on brain structures and on the cerebrospinal fluid that are associated with
visual impairment and intracranial pressure arising from prolonged residence in a low gravity
environment (Roberts et al. 2017). MR studies involving radiation effects have been conducted
primarily in patients treated with external beam (low LET) radiation for brain malignancies
al. 2013a, Redmond et al. 2013b). In general, MR imaging and spectroscopy techniques can
assess many brain functions. Examples include activation as measured by functional MRI
(fMRI) (Ghosh et al. 2018), white matter connectivity (Lebel and Deoni 2019), nerve fiber
tracking (Mori and van Zijl 2002), microstructural intactness (Filippi and Agosta 2016), and
Fig. 3.3. A schematic representation of the cellular localization of glucose transporters (GLUTs) and monocarboxylate transporters. Figure and legend are adopted from Simpson et al. (2007).
the evaluation of metabolite levels (Vinogradov 2019). These and other techniques on the horizon (van Zijl and Knutsson 2019) may be deployed in the future to assess the effects of high LET radiation to the brain.

One may speculate that radiation-induced damage to brain regions with a high synaptic density are the most likely to be linked to cognitive impairment. In this regard, estimation of the absorbed dose to these microstructures and their related vasculature is likely to be particularly important, especially for high LET radiation, whether delivered by alpha-particle emitters through the vasculature or directly via neuronal fiber tracts or by highly energetic iron ions from space. Idealized representations of such substructures have been used in other contexts to obtain the absorbed dose to these potentially critical anatomical regions for alpha emitters (Hobbs 2012).
4. How Radionuclides Enter the Brain

This section examines the transport mechanisms by which elements may enter the brain. Information about the mode of entry for manganese, analogues of potassium, and mercury vapor is presented highlighting some of the different pathways relevant to internally deposited radionuclides.

4.1 Potential Mechanisms of Transport

Blood vessels supply oxygen and nutrients to tissues throughout the body. The blood vessels of the brain have unique properties, referred to as the blood-brain barrier, that serve to regulate transport of essential substances between the blood and brain to achieve proper neuronal function while protecting the brain from toxic substances. The blood-brain barrier consists of various physical, metabolic, and transport properties possessed by the endothelial cells forming the walls of the blood vessels. These properties are regulated by interactions with different vascular, immune, and neural cells (Daneman and Prat 2015).

Tight seals (junctions) between the endothelial cells greatly limit paracellular flux of solutes. Only lipophilic substances can diffuse across the cell membrane. The endothelial cells contain efflux transporters that are polarized to the luminal surface and serve to transport back to blood a variety of lipophilic molecules that could otherwise enter the brain. The endothelial cells contain highly specialized nutrient transporters that facilitate entry of nutrients or removal of waste products to blood. The low permeability of the endothelial cells and their tight paracellular junctions allow the specialized transporters to control the movement of substances in and out of the brain. The reader is referred to a review by Daneman and Prat (2015) for more detailed descriptions of these and other components of the blood-brain barrier that control brain homeostasis while protecting the brain from foreign substances.

Several elements (e.g., sulfur, potassium, calcium, zinc, iron, copper, selenium) are essential to brain function and readily cross the blood-brain barrier along specialized transport pathways. Presumably, the transporters would not distinguish between different isotopes of an element, so
that radioisotopes of these essential elements could readily enter or exit the brain via specialized pathways.

While some membrane transporters may be highly specialized to specific elements, they may not be able to discriminate perfectly between the substrate element and a close chemical or physiological element analogue. For example, potassium channels are specialized to allow potassium to cross cell membranes by either active or passive transport but typically allow substantial passage of its chemical analogues rubidium and cesium. Measurements of extraction of potassium, rubidium, and cesium from blood during passage through the brain indicate that the extraction fraction (the fraction of atoms extracted by a tissue in a single passage from arterial to venous plasma) for rubidium is roughly 0.7 times the value for potassium and for cesium is roughly 0.15 times the value for potassium (Leggett et al. 2003). Thallium also tends to follow potassium across cell membranes, presumably due to the same charge and virtually identical hydrated radii of thallium and potassium. Calcium transport channels tend to transfer other divalent cations such as strontium and barium (Hurwitz and Plavnik 1986). There is suggestive evidence that mechanisms to transport calcium across the blood-brain barrier also transport lead into the brain (Yokel 2006). There is also evidence that the iron transport protein transferrin can transport trivalent manganese across the blood-brain barrier, although at a slower rate than it carries iron (Gunter et al. 2013). Plutonium also competes with iron for a specific binding site on transferrin, apparently as a result of similar charge-to-radius ratios of plutonium and iron (Jensen et al. 2011). It is known that plutonium accumulates in the brain in plutonium workers (Avtandilashvili et al. 2018; Dumit et al. 2019; Filipy and Kathren 1996; McInroy et 1991). The transferrin transport system across the blood-brain barrier may be a mode of entry of plutonium into the brain.

The choroid plexus is a network of capillaries and specialized epithelial tissue and is found in the cerebral ventricles. The choroid plexus produces cerebrospinal fluid (CSF) and helps to provide a barrier that protects the brain and other central nervous system tissue from xenobiotics. Substances traversing the choroid plexus enter the CSF and may diffuse from the CSF into the central nervous system. The choroid plexus is known to sequester many xenobiotics, particularly
metals, thus reducing but perhaps not totally preventing their transport into the CSF (Yokel 2006).

There is evidence that nasal deposition and transport along olfactory neurons and bypassing the blood brain barrier represents another route by which substances can enter some regions of the brain (Hanson and Frey, 2008). It appears that this pathway applies both to soluble substances and relatively small particles, particularly nanoparticles. The olfactory pathway is described in NCRP Report No. 176 (NCRP 2017) regarding its importance for inhaled nanoparticles (NP): “A separate pathway of clearance of NP from the respiratory tract involves the movement of NP that have deposited in the olfactory mucosae along olfactory neurons to the olfactory bulb in the brain. This translocation pathway has been well established in inhalation routes of exposure in rodents and nonhuman primates. Moreover, NP translocation via sensory trigeminal neurons of the nasal cavity to the trigeminal ganglion at the base of the brain has been described (Hunter and Dey 1998). This neuronal translocation may be significant as it circumvents the tight blood-brain barrier (Oberdorster et al. 2009). Additionally, the penetration efficiencies may not be trivial, ranging from <1% to >10% of the deposited NP (e.g., Elder et al. 2006), depending on NP surface chemistry, mass of deposited material, particle size and exposure method (Oberdorster et al. 2009).”

4.2 Pathways of Entry of Specific Elements into the Brain

Pathways of entry to the brain for different elements are discussed as examples. As illustrated below, at least a portion of the modes of entry into the brain are reasonably well understood for several elements.

4.2.1 Manganese

The essential trace metal manganese appears to enter the brain via multiple pathways. These include transport across the blood-brain barrier and the blood-cerebrospinal fluid barrier and entry via the olfactory pathway (Aschner et al. 1994; Henriksson et al. 1999; Takeda 2003; Gunter et al. 2013). Some but apparently not all these pathways are regulated. The effect is that
the brain normally receives a functional supply of manganese but also can receive an excessive and toxic amount under some circumstances. There appears to be a saturable component of divalent manganese transport across the blood-brain barrier (Aschner and Gannon 1994). Trivalent manganese may be transported across the blood-brain barrier after binding with the iron-transport protein transferrin (Gunter et al. 2013).

Manganese chloride was injected into the right nostril of rats, and its accumulation in the central nervous system (CNS) was followed (Gianutsos et al. 1997). Elevated levels of manganese were detected in the right olfactory bulb and olfactory tubercle within 12 hours and remained elevated for at least 3 days. No accumulation of manganese was seen on the left side of the brain. The manganese content of the striatum was unchanged after acute administration but was elevated when two injections were made one week apart. The findings suggest that airborne manganese can be transported along olfactory neurons and can reach deeper brain structures.

Dorman et al. (2002) evaluated the olfactory uptake and direct brain delivery of inhaled $^{54}$Mn phosphate in rats. The nose, olfactory pathway, striatum, cerebellum, and remainder of the brain were examined immediately after exposure and at 1, 2, 4, 8, and 21 d, with gamma spectrometry and autoradiography. The results indicated that the olfactory route resulted in $^{54}$Mn delivery to the rat olfactory bulb and tubercle, but no significant accumulation of activity was apparent in the striatum.

Henriksson et al. (1999) studied the dose dependence of manganese from the olfactory epithelium via olfactory neurons into the brain. Rats were exposed by intranasal administration. Manganese transport into the olfactory epithelium and transfer to the olfactory bulb was found to be saturable. Transport to the rest of the brain was related to the amounts in the olfactory bulb and the olfactory cortex. The investigators concluded that the olfactory neurons provide a potentially important pathway of transport of manganese into the brain and proposed that the neurotoxicity of inhaled manganese is related to uptake via the olfactory route.

Rats were exposed by nose only to manganese dioxide ($\text{MnO}_2$) aerosols of 1.3 and 18 µm mass median aerodynamic diameter (MMAD), five times per week for 3 weeks (Fechter et al.
2002). In rats exposed to the smaller particle size, the manganese concentration was elevated in the olfactory bulb, presumably through uptake by the olfactory nerve. The level of accumulation was highly variable. There was no evidence of olfactory nerve uptake in rats receiving the larger particles.

4.2.2 Potassium Analogues

It is known that the alkali metals rubidium and cesium follow the movement of the alkali metal potassium in the body and, along with potassium, readily cross the blood-brain barrier. The relative rates of entry of potassium, rubidium, and cesium into the brain are reasonably well established (Leggett et al. 2003). Radioisotopes of rubidium have been used as tracers to study potassium permeability of the blood-brain barrier under different conditions (Brooks et al. 1984; Betz et al. 1994).

Kanayama et al. (2005a) observed direct olfactory transport of $^{86}$Rb and $^{201}$Tl into the brain following their intranasal administration to mice. The $^{86}$Rb and $^{201}$Tl activity that accumulated in the olfactory bulb was gradually transported to other brain regions of the olfactory system. The investigators concluded that the results provided clear evidence of axonal transport via the olfactory nerve pathway from the nasal cavity to the olfactory bulb and to the olfactory cortex through the synaptic junctions. The olfactory transport of these radionuclides was judged to represent the behavior of potassium in the olfactory system.

Kanayama et al. (2005b) used multitracer techniques to compare the behaviors of 16 radionuclides, including $^{83}$Rb, in mice, following administration by various routes: intravenous, intraperitoneal, intramuscular, subcutaneous, intracutaneous, intranasal, peroral, and percutaneous. The brain uptake rate of $^{83}$Rb following intranasal administration was about twice the rates obtained with the other routes of administration. The results indicated that rubidium was delivered to the brain by olfactory transport.
4.2.3 Mercury Vapor

Elemental mercury is a liquid at room temperature but can be released into air as a vapor with increasing temperature. Inhaled mercury vapor is readily absorbed to blood and rapidly diffuses into blood and from blood into tissues. Elemental mercury is in an uncharged monoatomic form that is highly diffusible and lipid soluble and can cross the blood-brain barrier. Although elemental mercury vapor generally is oxidized rapidly to ionic mercury, it remains as vapor in the blood long enough to allow penetration of the blood-brain barrier before it is oxidized. The oxidized form does not effectively cross the blood-brain barrier and is retained in the brain for an extended period (Friberg and Mottet 1989; Park and Zheng 2012).

Mercury vapor can also pass through the mucosa and connective tissue of the nasal cavity and from there can move to the brain via the olfactory pathway. It has been proposed that mercury from dental amalgam fillings may be transported to the brain via the olfactory pathway similarly to manganese particles (Henriksson et al. 1999; Park and Zheng 2012).
5. Illustrations of Available Biokinetic Data for Brain

This section examines the quality and quantity of biokinetic data for the brain that are available for selected elements. Much of the information summarized here is taken from a review and analysis by Leggett et al. (2018).

5.1 Examples of Biokinetic Data for the Brain

Ten elements are examined and the quality of available biokinetic data presented. In Section 6 this information is used to evaluate the effect of explicit biokinetic modeling of the brain on dose estimates for brain for the selected radioisotopes of the elements considered here.

5.1.1 Manganese

Manganese (Mn) is required for metabolism of amino acids, proteins, carbohydrates, and lipids in mammals. Ingested manganese is absorbed via the portal vein and removed by the liver as required to achieve homeostasis. Manganese entering blood by other routes such as absorption from the lungs bypasses the control processes in the liver and ultimately becomes largely bound to transferrin, which may be transferred to the brain or other tissues by transferrin receptors. Thus, intake of manganese by routes other than ingestion can affect its homeostatic balance and result in elevated accumulation in the brain. Inhalation of elevated levels of manganese can result in progressive neurodegenerative damage with an associated motor dysfunction syndrome similar to that seen in Parkinson’s disease. However, manganese may also have beneficial properties in antagonizing iron-induced Parkinson’s pathology and via its antioxidant role in superoxide dismutase reactions (Sziráki et al 1998). Reported cases of manganese intoxication are often linked to chronic occupational exposure to airborne manganese, especially among welders, smelters, manganese miners, and workers in dry cell battery factories (Leggett 2011).

Results of animal studies indicate that absorbed or intravenously injected manganese leaves blood rapidly and initially concentrates mainly in organs rich in mitochondria, particularly the
liver, pancreas, and kidneys. Brain and bone gradually accumulate increasing portions of the retained activity due to slow removal of manganese from these organs. In rats, the time-dependent manganese concentration in most tissues roughly paralleled whole-body retention, but bone and brain had slower loss than other tissues. The adult human brain has been estimated to contain about 5% of total-body stable manganese (Leggett 2011).

Barbeau et al. (1976) studied the distribution of manganese in 14 regions of nine human brains. The lowest and highest mean concentrations based on dry weight were found in the medulla oblongata (1.33 µg g\(^{-1}\)) and pineal gland (8.79 µg g\(^{-1}\)), respectively.

Larsen et al. (1979) reported concentrations of manganese per gram wet weight in 24 areas of normal human brains from two women and three men. They found that the manganese concentration in white matter was on average about 44% higher than that in gray matter of the cerebral cortex.

Bonilla et al. (1982) determined the concentration of manganese per gram dry tissue in 39 areas of each of eight normal human brains. Manganese was unevenly distributed, with the lowest mean concentrations found in the white matter of the frontal and temporal lobes (0.72 and 0.74 µg g\(^{-1}\), respectively) and the highest mean concentrations found in the pineal gland (4.20 µg g\(^{-1}\)) and the olfactory bulb (3.36 µg g\(^{-1}\)). In contrast to findings of Larsen et al. (1979), the mean concentration was considerably higher in collective samples of gray matter (1.54 µg g\(^{-1}\)) than in collective samples of white matter (0.93 µg g\(^{-1}\)). The overall mean and median concentrations (calculated from the 39 mean concentrations found for the different areas) were 1.45 ± 0.65 (SD) and 1.35 µg g\(^{-1}\), respectively.

Yamada et al. (1986) determined the concentration per gram wet weight of manganese in 21 areas of the brain of a man who had suffered from chronic manganese poisoning and in brains of four normal control subjects. In the control subjects the lowest mean concentration (0.20 µg g\(^{-1}\)) was found in the gray matter of the parietal lobe, and the highest concentration (1.18 µg g\(^{-1}\)) was found in the pallidum. The average concentration in the gray matter of the frontal, parietal, temporal, and occipital lobes was on average about 75% higher than that in the white matter.
from these four lobes. The overall mean and median concentrations (calculated from the 21 mean concentrations found for the different areas) were 0.53 ± 0.24 (SD) and 0.47 µg g⁻¹, respectively.

5.1.2 Cesium

A strong physiological relationship of the alkali metals potassium (K), rubidium (Rb), and cesium (Cs) is well established. These elements compete for transport across cell membranes, with transport rates typically decreasing in the order K > Rb > Cs (Leggett et al. 2003).

The rate of transfer of potassium, rubidium, or cesium from plasma into a tissue can be estimated as the product of the blood flow rate to the tissue (plasma volumes per day) and the element- and tissue-specific extraction fraction, i.e., the fraction of atoms extracted by that tissue in a single passage from arterial to venous plasma. The rate of return of potassium, rubidium, or cesium from a tissue to plasma can be estimated from the relative contents of the element in plasma and the tissue at equilibrium, as estimated in autopsy studies of the distribution of the respective elements in the human body (Leggett et al. 2003).

For most tissues, experimentally determined tissue-specific extraction fractions generally are in the range 0.6 to 0.9 for potassium, 0.4 to 0.8 for rubidium, and 0.05 to 0.2 for cesium. Much lower extraction fractions, on the order of 0.015 for potassium, 0.01 for rubidium, and 0.002 for cesium, have been estimated for brain (Leggett et al. 2003). For an adult male, the transfer coefficient describing flow of cesium, for example, from plasma into brain is derived as 0.002 × 0.12 × 1766 d⁻¹ = 0.424 d⁻¹, where 0.002 is the estimated cesium extraction fraction for brain, 0.12 is the reference fraction of cardiac output received by brain, and 1766 l d⁻¹ is the reference cardiac output in terms of the volume of plasma pumped through the heart each day. The transfer coefficient describing total outflow of cesium from brain is estimated as 0.002 × 0.424 d⁻¹ / 0.01 = 0.0848 d⁻¹. This corresponds to a half-time of ~8 d, which is a relatively long half-time for escape of cesium from tissues. The values 0.002 and 0.01 used in this calculation are reference fractions of total-body cesium in plasma and brain, respectively, at equilibrium, as estimated from reported autopsy measurements of concentrations of cesium in tissues of the adult human body. Based on these concepts, potassium, rubidium, or cesium is estimated to be taken up much
more slowly by the brain than by other tissues but also to be retained much longer by the brain than by other tissues (Leggett et al. 2003).

### 5.1.3 Lead

Investigations of lead (Pb) kinetics in baboons (Cohen et al. 1970), dogs (Lloyd et al. 1975), and rodents (Keller and Doherty 1980) indicate that the brain has slow uptake but prolonged retention of Pb. Following intravenous administration of $^{210}$Pb to young adult female baboons, the brain contained about 0.04 % of the administered lead at 1 d but continued to accumulate activity released by other organs and contained about 0.07 % after 30 d and 0.08 % after 60 d (Cohen et al. 1970). Following intravenous administration of $^{210}$Pb to beagles, the brain contained ~0.04 % of injected $^{210}$Pb at 1 month and <0.003 % at 3 to 4 y (Lloyd et al. 1975).

The distribution of lead in the brain is non-uniform and varies with the level of exposure. For low-level exposures the distribution in the human brain appears to be associated with the potassium concentration, suggesting accumulation of lead in cell-rich parts of the brain such as the hippocampus (Grandjean 1978; Bryce-Smith and Stephens 1983; Petit et al. 1983). In individuals with high lead intake, lead may gain substantial access to brain tissue due to breakdown of the blood brain barrier (Petit et al. 1983).

### 5.1.4 Bismuth

Postmortem measurements on tissues of patients receiving intramuscular bismuth treatments indicate the following central bismuth concentrations in tissues normalized to 1.0 for kidneys: liver, 0.2; spleen, 0.048; colon, 0.039; lung, 0.027; brain, 0.018; blood, 0.015 (Sollmann et al. 1942; Sollmann 1957; Fowler and Vouk 1986). The times between treatment and death were not given, but the subjects apparently lived for extended periods following bismuth treatment.

Data on the systemic behavior of bismuth in rats indicate a low rate of uptake but a longer retention time for bismuth in brain than in other soft tissues. At early times post parenteral injection of bismuth compounds, the brain showed much lower uptake of bismuth than other
tissues (Gregus and Klaassen 1986; Zidenberg-Cherr et al. 1987). Following oral administration of bismuth for 4 mo, the bismuth concentration in brain was of the same order as that of most other studied tissues with the main exception of kidneys (Lee et al. 1980).

5.1.5 Polonium

Postmortem measurements of $^{210}$Po in tissues are available for uranium workers (Blanchard and Moore 1971), but the indicated systemic distributions of $^{210}$Po may be more indicative of the biokinetics of preceding members of the $^{238}$U chain than that of polonium. Polonium-210 was measured in tissues of an adult male who died 23 days after being poisoned with $^{210}$Po (Nathwani et al. 2016; Harrison et al. 2017). The highest activity concentration was found in the kidneys. The concentration in brain was approximately 10 % of that in kidneys, 20 % of that in liver, and 50 % of that in spleen. Findings for this subject could be misleading due to radiation damage to the blood brain barrier from the extremely high $^{210}$Po activity taken into the body.

Following intravenous administration of $^{210}$Po to baboons, the activity concentration was substantially lower in the brain than in other studied tissues over the first week. The brain content as a fraction of total-body content of $^{210}$Po increased monotonically over the three-month study period (Fig. 5.1). The data indicate that the residence time for polonium in the brain was substantially greater than in other tissues except pelt (Fig. 5.1 and Fig. 5.2).

5.1.6 Radium

Schlenker et al. (1982) tabulated postmortem measurements of the $^{226}$Ra content of soft tissues in 17 subjects who received relatively high levels of $^{226}$Ra by injection or ingestion from a few days to 53 y before death. The data set is too uneven to draw strong conclusions concerning a typical distribution of radium in soft tissues but suggest that inclusion of brain in tissues that make up Other in the ICRP’s biokinetic model for radium (ICRP 2017) could lead to a substantial underestimate of dose to brain from internally deposited $^{226}$Ra.
Fig. 5.1. Relative $^{210}$Po content in tissues of baboons as a function of time after intravenous injection (data from Cohen et al. 1989).
Fig. 5.2. Biological retention of $^{210}$Po in baboon tissues as a function of time after intravenous injection (data of Cohen et al. 1989).
Following intravenous administration of $^{224}$Ra chloride to dogs (Lloyd et al., 1982), biological retention (the percentage of injected $^{224}$Ra corrected for radioactive decay) in the brain remained nearly constant from a few hours to 7 d. Biological retention in other soft tissues combined declined by about a factor of 8 during the same period. When expressed as a percentage of activity in tissues that make up Other in the ICRP’s model for systemic radium (ICRP 2017) increased continually with time over the 7 d observation period: 0.07 % at 1 h, 0.13 % at 8 h, 0.28 % at 1 d, 0.61 % at 3 d, and 1.43 % at 7 d.

5.1.7 Uranium

The systemic distribution of uranium was studied at autopsy in subjects injected intravenously with uranium nitrate or chloride in the terminal phases of diseases of the central nervous system (Bernard and Struxness 1957). The concentration of uranium in brain was measured in four subjects who died 21-566 d post injection (and in two subjects dying at earlier times, but contamination of brain samples from these subjects is suspected). Uranium concentrations in the range 0.005-0.02% of injected uranium per kg were found in healthy brain tissue from the four subjects dying 3 wk or later post injection.

Since 1968, the United States Transuranium and Uranium Registries (USTUR) have studied the biokinetics and distribution of actinides in tissues of former nuclear workers with known history of exposure to these radioactive elements (Kathren and Tolmachev 2019). The distribution of uranium was determined in three USTUR tissue donors (Registrants) with only environmental exposure (Kathren and Tolmachev 2015) and two Registrants with occupational exposure to uranium (Russell and Kathren, 2004, Avtandilashvili et al. 2015). The uranium content of brain was 0.4 to 1.0 % of the total systemic content in the environmentally exposed individuals and 0.4 to 1.2 % in the occupationally exposed individuals. The arithmetic and geometric means for the five individuals were 0.7 ± 0.4 % (SD) and 0.6 %, respectively.
The concentration of uranium in brain was measured in rats following implant of depleted uranium pellets at low, medium, and high dose levels (Pellmar et al. 1999). Uranium was found to be unevenly distributed in the brain. The uranium concentration in brain was lower than in other measured soft tissues (kidneys, muscle, liver, and spleen) after 1 month, but by 6 months exceeded the concentration in liver at medium and high dose levels and in spleen at the high dose level. A meaningful comparison with the concentration in muscle at 6 months could not be made from a graphical presentation of the data.

Rats with repeated inhalation exposure to depleted uranium dioxide over 3 weeks showed uranium concentrations in brain statistically higher than control animals. At 1 d after the end of exposure the concentration in different regions of the brain decreased in the order: olfactory bulb > hippocampus > frontal cortex > cerebellum. The concentration in all regions decreased to control values over a few days (Monleau et al. 2005).

In dogs exposed to uranium oxide via inhalation, the average uranium concentration in bone, liver, kidneys, and spleen after 5 y was about 2200, 73, 45, and 35, respectively, times that in brain (Tikhaya et al. 1965).

5.1.8 Plutonium

Activity of $^{239}$Pu and $^{238}$Pu has been measured routinely in liver and bone of USTUR Registrants and in other systemic tissues including the brain in some cases (Tolmachev et al. 2011). Data for 38 plutonium workers indicate that, at 18 to 64 y after intake, the brain contains ~0.2 % (mean = 0.22 ± 0.13 (SD) %, median = 0.2 %, and geometric mean = 0.18 %) as much $^{239}$Pu as liver and skeleton combined (Fig. 5.3) (Tolmachev et al. 2019a). Data for 29 individuals indicate a similar distribution of $^{238}$Pu (mean = 0.25 ± 0.23 (SD) %, median = 0.19 %, and geometric mean = 0.17 %).\(^1\) For 12 Mayak Production Association workers, the fraction of the

Fig. 5.3. Probability distribution of $^{239}$Pu activity in brain relative to activity in liver and skeleton combined in former plutonium workers.
total plutonium body activity deposited in the brain ranged from 0.07 to 0.30 % (Suslova et al. 2017). Plutonium was found to be non-uniformly distributed in the brain. For six USTUR Registrants, $^{239}\text{Pu}$ concentrations in cerebellum were on average twofold higher than that measured in cerebral lobe (Boice et al. 2021).

In dogs, the ratio of activity in brain to that in the liver and skeleton combined varied from about 0.00004 to 0.0023 at 13 to 30 d after injection, with a mean of 0.0012 and a median of 0.0014 (Lloyd et al. 1976).

### 5.1.9 Americium

USTUR whole-body analyses include a subject thought to be exposed to pure $^{241}\text{Am}$ about 25 y before his death (Breitenstein and Newton 1985). The brain showed the lowest $^{241}\text{Am}$ concentration of all measured tissues (McInroy et al. 1985). The concentration in brain was about 9 % of the average concentration in soft tissues and 2 % of the average concentration in the body. The $^{241}\text{Am}$ content of the brain was ~0.037 % of the total systemic $^{241}\text{Am}$. This is near the lower end of the range of corresponding values for plutonium indicated in Fig. 5.3, assuming liver and skeleton contain at least 90 % of systemic plutonium at times well after exposure. Substantially higher fractions of systemic $^{241}\text{Am}$ were observed in brains from 28 former plutonium workers (Fig. 5.4) exposed to $^{241}\text{Am}$ as a decay product of $^{241}\text{Pu}$ (mean = 0.23 ± 0.18 (SD), median = 0.18 %, and geometric mean = 0.17 %). The relatively higher brain content of $^{241}\text{Am}$ indicated in Fig. 5.4 than in studies involving direct intake of pure $^{241}\text{Am}$ may represent some combination of: (1) $^{241}\text{Am}$ produced within the brain from decay of $^{241}\text{Pu}$ residing in the brain, (2) $^{241}\text{Am}$ entering brain after its production by decay of $^{241}\text{Pu}$ in tissues other than brain, and (3) $^{241}\text{Am}$ entering the brain after its direct entry into the body.

Filipy and Kathren (1996) compared the concentrations of $^{239+240}\text{Pu}$ and $^{241}\text{Am}$ in brain and liver in eight USTUR tissue donors 15 to 28 y after occupational exposure. A substantial portion of $^{241}\text{Am}$ measured in these subjects may have arisen from production of $^{241}\text{Am}$ in the body.
Fig. 5.4. Probability distribution of $^{241}$Am activity in brain relative to activity in liver and skeleton combined in former plutonium workers.
following intake of its parent $^{241}$Pu, which is usually found together with $^{239}$Pu and $^{240}$Pu. The concentration ratio $^{239+240}$Pu : $^{241}$Am in liver was in the range 1.7 to 21, with mean and median values of 10.6 ± 6.4 (SD) and 8.6, respectively. Mean and median concentration ratios of $^{239+240}$Pu in liver to that in brain were 173 ± 180 (SD) and 105, respectively. Mean and median concentration ratios of $^{241}$Am in liver to that in brain were 94 ± 104 (SD) and 55, respectively. The results suggest that the brain accumulates americium to a lesser extent than Pu, particularly in view of data indicating that the liver typically contains a much smaller portion of systemic americium than plutonium at times remote from exposure, either in plutonium workers or in subjects exposed directly to $^{241}$Am.

Americium was non-uniformly distributed in the brain in the studied USTUR Registrants. For four Registrants, $^{241}$Am concentrations in the cerebellum were on average three times higher than that measured in the cerebral lobe.$^2$

Following intravenous administration of $^{241}$Am to baboons, the brain contained ~0.019 % of the administered amount at 1 to 86 d, 0.0081 % at 206 d, and 0.0024 % at 817 d (Guilmette et al. 1980). In dogs, the brain contained less than 0.001 % of intravenously administered $^{241}$Am at 1 to 22 d and 0.008 % at 401 to 4,448 d (Lloyd et al. 1970).

5.1.10 Mercury vapor

Inhaled mercury (Hg) vapor is transported in plasma to the brain, where it crosses the blood-brain barrier. Mercury vapor entering brain tissue is oxidized to the divalent form of mercury, which is trapped in the brain for an extended period due to limited transport across the blood-brain barrier. Data for mice, rats, rabbits, and monkeys indicate that uptake of mercury by the brain is an order of magnitude greater after inhalation of mercury vapor than after intravenous administration of mercury salts (Berlin et al. 1966, 1969).

In squirrel monkeys, rats, mice, rabbits, and guinea pigs exposed to mercury vapor via acute inhalation, the peak mercury content in the brain typically was 1 to 2 % of the initial body burden (Fig. 5.5). Retention of mercury by the brain was broadly consistent across species. The data indicate a biological half-time on the order of 10 d for the preponderance of inorganic mercury deposited in the brain. Estimates of the biological half-time of mercury in the brain in human subjects exposed to mercury vapor or divalent mercury are in the range 14 to 29 d (Hursh et al. 1976; Newton and Fry 1978). Longer retention of a small portion (at most 2 %) of mercury entering brain tissue is suggested by animal studies and autopsy data for human subjects occupationally exposed to mercury vapor.
Fig. 5.5. Observations of time-dependent content of mercury in the brain in laboratory animals after acute inhalation of mercury vapor. Data from Khayat and Dencker 1983, 1984; Magos 1967; Berlin et al. 1969; Nordberg and Serenius 1969; Hursh et al. 1976.
6. Case Studies of the Effect of Explicit Modeling of Brain Kinetics on Dose Estimates for Internal Emitters

Element-specific biokinetic models are used to reconstruct doses to tissues from internal emitters. These models generally depict explicitly only a few tissues that tend to dominate the systemic behavior of the element over time. The remaining tissues are aggregated into a source region called Other (sometimes called Other tissue, or Other soft tissue if applicable) in which activity is assumed to be uniformly distributed. The brain is included explicitly in systemic biokinetic models for a few elements but typically is addressed as an implicit mass fraction of Other.

This section assesses potential improvements in brain dosimetry for internal emitters from explicit modelling of brain kinetics rather than treating the brain as a mass fraction of Other. Comparisons are made of injection dose coefficients for selected radionuclides based on alternate versions of the systemic biokinetic model for each radionuclide, one with an explicitly depicted brain and the other with brain included implicitly in Other. (Recall that an injection dose coefficient for a given radionuclide and tissue is defined here as the 50-y committed equivalent dose to the tissue following input of 1 Bq of the radionuclide into blood at time zero.) The case studies summarized here are taken from a review and analysis by Leggett et al. (2018).

6.1 Methods

Most quantitative data on uptake and retention of elements by the brain come from studies on laboratory animals. Results of autopsy studies of element concentrations in human tissues based on modern measurement techniques also provide useful information on the long-term distribution of elements in the human body.

This section addresses 17 radionuclides for which informative element-specific data are available on relative levels of accumulation by the brain and other systemic repositories. Each radionuclide is an isotope of one of the 10 elements addressed in Section 5. Five of the radionuclides considered here are included because they are important internal emitters
encountered in epidemiological studies of potential health effects of occupational exposure to radionuclides: $^{210}$Po, $^{226}$Ra, $^{234}$U, $^{239}$Pu, and $^{241}$Am. Eight other radionuclides, $^{52}$Mn, $^{53}$Mn, $^{54}$Mn, $^{134}$Cs, $^{194}$Hg, $^{203}$Hg, and $^{210}$Pb, are included as convenient case studies because reasonably well-founded brain models already existed for these elements (i.e., manganese, cesium, mercury, and lead). Bismuth-207 is used to illustrate a situation that may often arise in efforts to build explicit brain models for individual elements, i.e., available data on brain kinetics are sparse or of questionable relevance for modeling biokinetics in humans. Three other radionuclides, $^{224}$Ra, $^{230}$U, and $^{237}$Pu, were added to demonstrate, along with examples involving multiple isotopes of manganese, mercury, and lead, that the inclusion of an explicit brain model may make considerable difference in brain dose estimates for some radioisotopes of an element and little difference for other isotopes of the same element. For example, the dosimetric effect may be much larger for a short-lived isotope than for a long-lived isotope (or vice versa). This is because the explicit and implicit brain models may initially predict much different concentrations of the radionuclide in brain but after some point may begin to predict broadly similar concentrations (or vice versa). Also, some isotopes of an element may have radioactive progeny that contribute considerably to the estimated brain dose, while other isotopes of that element may have no radioactive progeny or no dosimetrically important progeny.

Alternate dose coefficients for brain were compared for each of the radionuclides addressed here. One of the coefficients was based on ICRP’s current systemic model for the element. The other coefficient was based on a modification of that model with a different treatment of the brain as described below. Two different variations of the ICRP model were considered for $^{210}$Po. Each of the derived dose coefficients for brain was based on injection of the radionuclide into blood of a male worker. The ICRP’s updated dosimetry system for workers (ICRP 2016a) was applied.

If the brain is already considered explicitly in the ICRP model for the element, a modified version of the ICRP model was constructed by removing brain as an explicitly identified organ so that brain was included implicitly in Other. The deposition fractions (fractional outflows from a central blood compartment to specified destinations) for compartments of Other were increased proportionally so that the sum of the new deposition fractions for compartments of Other equaled
the sum of all deposition fractions for the brain and Other in the ICRP model. Suppose, for example, that in the ICRP model the deposition fraction for the brain is 0.006 and Other contains two compartments with deposition fractions 0.1 and 0.2. In the alternate model, the deposition fractions for the two compartments of Other would be increased to 0.1 + 0.002 = 0.102 and 0.2 + 0.004 = 0.204.

If the brain was implicitly contained in Other in the ICRP model for the element, then a modified version of the ICRP model was constructed by adding an explicitly identified brain that exchanged activity with blood and assigning transfer coefficients between brain and blood based on brain-specific biokinetic data. If needed, the deposition fractions for compartments of Other were decreased proportionally so that the sum of all deposition fractions for Other and the brain equaled the sum of the deposition fractions for compartments of Other in the ICRP model. Such an adjustment was not needed if the blood compartment feeding the added brain compartment(s) was not directly connected to Other.

6.2 Results

The results from evaluating the brain using the alternate versions of the ICRP biokinetic models are presented in Section 5 are presented in the following subsections.

6.2.1 Polonium-210

The ICRP’s current systemic model for occupational intake of polonium (Po) is described in ICRP Publication 137 (ICRP 2017). The structure of the ICRP’s model for systemic polonium is the portion of the model structure shown in Fig. 6.1 that does not involve the brain. The brain is not depicted explicitly in the ICRP model and hence is contained implicitly in the compartment named Other. ICRP’s transfer coefficients for polonium for a reference worker are listed in Table 6.1.

The ICRP’s model for polonium was based largely on data for human subjects exposed to $^{210}$Po. Data for laboratory animals, primarily baboons and dogs, were used to fill gaps in data for humans. Biokinetic data for baboons and dogs were given higher weight than other studied
Fig. 6.1. Model structure for systemic polonium. The unshaded boxes and associated arrows represent ICRP's current model for systemic polonium (ICRP 2017). The modified version of the ICRP model considered here adds the brain compartment and associated arrows. SI = small intestine, RC = right colon, LC = left colon, RS = rectosigmoid colon.
Table 6.1— Transfer coefficients in the ICRP’s model for systemic polonium (ICRP 2017).

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<th>Compartment</th>
<th>Transfer coefficient (d⁻¹)</th>
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<td>Plasma 1</td>
<td>Red Marrow</td>
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<tr>
<td>Bone Surface</td>
<td>Plasma 1</td>
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<td>Spleen</td>
<td>Plasma 1</td>
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<tr>
<td>Testes or Ovaries</td>
<td>Plasma 1</td>
</tr>
<tr>
<td>Other</td>
<td>Plasma 1</td>
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animals due to the relatively detailed information available for baboons and dogs; similarities in the distribution and retention of polonium in humans, baboons, and dogs; and the general consideration that primates and dogs have proven to be reasonably good laboratory models for human biokinetics of many elements (Leggett and Eckerman 2001). For the same reasons, data for baboons were used here to develop a modified version of the polonium model that contains an explicit brain model. The brain was not addressed in the dog studies considered in the development of the ICRP’s model for polonium.

A variation of the structure of the ICRP’s model for polonium was developed by addition of a compartment representing the brain (shaded box in Fig. 6.1) and deriving transfer coefficients describing exchange of polonium between blood and brain based on biokinetic data for $^{210}$Po in baboons. These transfer coefficients were set to approximate the time-dependent retention of $^{210}$Po in brain determined in the study on baboons (Fig. 6.2, solid curve) used in development of the ICRP model. A slow-release blood compartment (a compartment of the original model named Plasma 3 – Fig. 6.1) was used as the feed to brain because of the low rate of accumulation of $^{210}$Po into brain observed in baboons. The following transfer coefficients were added to those in Table 6.1:

$$\text{Plasma}_3 \text{ to Brain} = 0.0135 \text{ d}^{-1},$$
$$\text{Brain to Plasma}_1 = 0.0385 \text{ d}^{-1}.$$  

These transfer coefficients, which were derived from the fit to brain retention data for baboons, are referred to in Fig. 6.2 as Brain Model A.

A second variation of the ICRP’s polonium model was developed in view of the uncertain nature of interspecies extrapolation of biokinetic data and the absence of biokinetic data for polonium for the human brain other than the suspectedly non-representative data described in Section 5. The mass of the brain relative to total-body mass is about 70 % higher for adult humans than adult baboons, based on comparison of data of Cohen et al. (1989) for baboons with
Fig. 6.2. Predictions of the brain content of $^{210}$Po as a function of time after acute input of $^{210}$Po to blood based on three different models: ICRP’s current model for systemic polonium (ICRP 2017) in which the brain is implicitly contained in Other; and two variations of the ICRP’s model, both with an explicitly brain region but having different brain kinetics (Brain Model A and Brain Model B defined in text). Data for baboons from Cohen et al. 1989.
data of ICRP Publication 89 (ICRP 2002) for reference adult humans. The second variation of
the ICRP’s model for polonium addresses the difference in the mass of the human and baboon
brain as a fraction of total-body mass (in part to illustrate the uncertain nature of interspecies
extrapolation of biokinetic data). In this variation of ICRP’s model, fractional deposition in brain
is 1.7 times the deposition fraction in Brain Model A. The removal rate from brain to blood is
assumed to be the same as in Brain Model A. This second set of parameter values for brain is
referred to in Fig. 6.2 as Brain Model B:

\[
\text{Plasma}_3 \text{ to Brain} = 0.02295 \text{ d}^{-1}, \\
\text{Brain to Plasma}_1 = 0.0385 \text{ d}^{-1}.
\]

Dose coefficients for brain were derived for injection of $^{210}\text{Po}$ into blood of a male worker,
using the current ICRP model for polonium and each of the two modifications of the ICRP
model described above, i.e., using Brain Model A or Brain Model B. The dose coefficient for
brain based on the modification of the ICRP model using Brain Model A is 1.3 times the value
based on the ICRP model. The dose coefficient for brain based on the modification of the ICRP
model using Brain Model B is 2.0 times the value based on the ICRP model.

6.2.2 Bismuth-207

The ICRP’s current systemic model for bismuth (Bi) is described in ICRP Publication 137
(2017). The model structure is shown in Fig. 6.3. Parameter values for an adult worker are listed
in the section on bismuth in Publication 137. In the ICRP model the brain is implicitly contained
in Other, which consists of three compartments representing fast, medium, and slow phases of
removal of bismuth to blood.

A variation of the structure of the ICRP’s systemic model for bismuth in workers was
developed by addition of a compartment representing the brain that exchanges bismuth with
Fig. 6.3. Model structure for systemic bismuth. The unshaded boxes and associated arrows represent the ICRP’s current model for bismuth (ICRP 2017). The modified version of the ICRP model considered here adds the brain compartment and associated arrows. ST = soft tissue, SI = small intestine, RC = right colon, LC = left colon, RS = rectosigmoid colon.
blood plasma (Fig. 6.3). Parameter values for brain were set for reasonable consistency with the biokinetic data for bismuth described in Section 5, i.e., the semi-quantitative data on brain kinetics of bismuth in human subjects (the times between bismuth treatments and death were not found in reports of these studies) and the quantitative data for rats (which are not a preferred laboratory model for the human brain). The general pattern of accumulation of bismuth by the brain indicated by the available data was modeled by assuming that the brain receives 0.01 % of outflow from plasma and loses bismuth to plasma with a biological half-time of 100 d. The implied transfer coefficients describing exchange of bismuth between plasma and brain are

\[
\text{Plasma to Brain} = 0.04 \text{ d}^{-1}, \\
\text{Brain to Plasma} = 0.00693 \text{ d}^{-1}.
\]

The total outflow rate from plasma to all destinations combined was left unchanged by reducing the transfer coefficients from plasma to each of the compartments of Other proportionally to their values in the ICRP model.

Fig. 6.4 compares predictions of the time-dependent content of bismuth in brain following acute input of bismuth to blood based on alternate models: the ICRP’s current model, in which the brain is implicitly contained in Other (Fig. 6.3); and the modified ICRP model with an explicit brain region.

Alternate dose coefficients for brain were derived for the case of injection of the long-lived bismuth radioisotope $^{207}$Bi into blood of a male worker, using the current ICRP model for polonium and the modification of the ICRP model described above. The dose coefficient based on the modified ICRP model with an explicit brain compartment is 0.57 times the value for brain based on the ICRP model. It is not evident whether this is a meaningful finding in view of the limitations in the data sets on which the parameter values for the explicit brain model were based.
Fig. 6.4. Predictions of the brain content of bismuth as a function of time after acute input of bismuth to blood based on alternate models: the ICRP’s current model for systemic bismuth (ICRP 2017), in which the brain is implicitly contained in Other; and a variation of the ICRP’s model with an explicit brain region.
6.2.3  Lead-210 and lead-209

The ICRP’s current systemic model for lead (Pb) is described in Publication 137 (ICRP 2017). The model structure is shown in Fig. 6.5. In this model the brain is implicitly contained in Other, which consists of three soft-tissue compartments representing fast, medium, and slow phases of removal of lead to blood.

The lead model used in ICRP Publication 137 is a modified version of a model developed by Leggett (1993) for application to lead as a chemical hazard as well as a radiation source. The brain was addressed explicitly in the original model due to its sensitivity to lead as a chemical toxin. The brain was represented as a single compartment that exchanges lead slowly with a compartment representing diffusible lead in blood plasma. Parameter values describing the brain kinetics of lead were set for consistency of model predictions with data for laboratory animals including baboons and dogs (Cohen et al. 1970; Lloyd et al. 1975) and with postmortem measurements of lead in tissues of occupationally or environmentally exposed persons (Leggett 1993).

A modified version of the ICRP’s model for systemic lead was developed by adding a compartment representing brain and assigning flow rates between plasma and brain consistent with predictions of the more detailed model of Leggett (1993). The following transfer coefficients between plasma and brain were assigned:

\[
\text{Plasma to Brain} = 0.018 \text{ d}^{-1}, \\
\text{Brain to Plasma} = 0.00095 \text{ d}^{-1}.
\]

The outflow rate from plasma to all destinations combined in the ICRP model was left unchanged by reducing the transfer coefficients from plasma to each of the compartments of Other proportionally to their values in the ICRP model.
Fig. 6.4. Model structure for systemic lead. The unshaded boxes and associated arrows represent ICRP’s current model for lead (ICRP 2017). The modified version of the ICRP model considered here adds the brain compartment and associated arrows. ST = soft tissue, SI = small intestine, RC = right colon, LC = left colon, RS = rectosigmoid colon.
Fig. 6.6 compares predictions of the time-dependent content of lead in brain following acute input of stable lead to blood based on alternate models: the ICRP’s current model, in which the brain is implicitly contained in Other; and the modified ICRP model with an explicit brain region.

Dose coefficients were derived for brain for the case of injection of $^{210}\text{Pb}$ ($T_{1/2} = 22.2$ y) into blood of a worker, using: (1) the ICRP’s systemic model for lead together with the models for bismuth and polonium as progeny of lead given in ICRP Publication 137; and (2) the modified versions of the lead model and models for bismuth and polonium as progeny of lead, all including explicit brain compartments. As in the analysis for injection of $^{210}\text{Po}$ described earlier, two different brain models for polonium (Brain Models A and B defined in the earlier discussion of polonium) were considered when calculating dose coefficients for brain for $^{210}\text{Pb}$ based on the modified lead model. Thus, a total of three dose coefficients for brain were derived, one based on the ICRP’s current models for lead and progeny) and the other two based on the alternate models with explicit brain compartments including variations of the model for $^{210}\text{Po}$ as a progeny of $^{210}\text{Pb}$. The dose coefficient for brain for $^{210}\text{Pb}$ based on the modified models with an explicit brain compartment was found to be 3.0 times the value based on the ICRP models if Brain Model A is applied to the progeny $^{210}\text{Po}$, and 3.5 times the value based on the ICRP models if Brain Model B is applied to the progeny $^{210}\text{Po}$.

An analogous ratio of dose coefficients was calculated for the short-lived lead isotope $^{209}\text{Pb}$ ($T_{1/2} = 3.25$ h), which has no radioactive progeny. In this case the dose coefficient for brain based on the modified ICRP model with an explicit brain region is 0.65 times the dose coefficient based on the ICRP’s unmodified model.

6.2.4 Plutonium-239 and plutonium-237

The ICRP’s systemic model for plutonium (Pu) was updated in Publication 141 (ICRP 2019). As in previous ICRP models for plutonium, the brain is included implicitly in Other.
Fig. 6.5. Predictions of the brain content of lead as a function of time after acute input of stable lead to blood based on alternate models: the ICRP’s current model for systemic lead (ICRP 2017), in which the brain is implicitly contained in Other; and a variation of the ICRP’s model with an explicit brain region (Leggett, 1993).
An alternate version of the ICRP’s model for systemic plutonium was developed by adding a compartment representing brain and assigning flow rates between blood and brain consistent with observed accumulation of plutonium in the brain in plutonium workers and dogs (Section 5). The model structure is shown in Fig. 6.7. The following transfer coefficients were assigned:

Brain to Blood 2 = 0.0002 d\(^{-1}\).

Fig. 6.8 compares predictions of the time-dependent plutonium concentration ratio brain: (liver plus skeleton) after acute input of long-lived plutonium to blood based on alternate models: the ICRP’s current model, in which the brain is implicitly contained in \textit{Other}; and the modified ICRP model with an explicit brain region.

Injection dose coefficients were derived for brain, using the ICRP’s systemic model for plutonium and the modified version of that model with an explicit brain compartment. For \(^{239}\text{Pu}\) (\(T_{1/2} = 24,100\) y) the dose coefficient for brain based on the modified ICRP model with an explicit brain compartment is 0.96 times the value based on the ICRP model. The analogous ratio of dose coefficients for the relatively short-lived plutonium isotope \(^{237}\text{Pu}\) (\(T_{1/2} = 45.2\) d) is 0.66.

### 6.2.5 Americium-241

The ICRP’s systemic model for americium (Am) was updated in ICRP Publication 141 (2019). The main changes from the previous americium model for adults (ICRP 1993) are an added liver compartment and depiction of redeposition onto local cortical bone surface of a portion of the americium removed from cortical bone surface by bone restructuring processes. As in previous ICRP models for systemic Am, the brain is included implicitly in \textit{Other} in the updated model.
**Fig. 6.6.** Model structure for systemic plutonium. The unshaded boxes and associated arrows represent ICRP’s current model for plutonium (ICRP 2019). The modified version of the ICRP model considered here adds the brain compartment and associated arrows. ST = soft tissue, SI = small intestine, RC = right colon, LC = left colon, RS = rectosigmoid colon.
Fig. 6.7. Predictions of the plutonium concentration ratio brain: (liver + skeleton) as a function of time after acute input of long-lived plutonium to blood based on alternate models: ICRP’s current model for systemic plutonium (ICRP, 2019), in which the brain is implicitly contained in Other; and a variation of ICRP’s model with an explicit brain region.
Blood 1 to Brain = 0.0009 d$^{-1}$,

An alternate version of the ICRP’s current model for americium was developed by adding a compartment representing brain and assigning flow rates between blood and brain consistent with the observed accumulation of americium in the brain in human subjects and dogs (Section 4). The model structure is shown in Fig. 6.9. The following transfer coefficients were assigned:

Blood 1 to Brain = 0.0024 d$^{-1}$,
Brain to Blood 2 = 0.000077 d$^{-1}$.

Fig. 6.10 compares predictions of the time-dependent americium concentration ratio brain: (liver plus skeleton) after acute input of long-lived americium to blood based on alternate models: ICRP’s current model, in which the brain is implicitly contained in Other; and the modified ICRP model with an explicit brain region.

Injection dose coefficients for brain for $^{241}$Am ($T_{1/2} = 432.2$ y) were derived using ICRP’s systemic model for americium and the modified version of that model with an explicit brain compartment. The dose coefficient for brain based on the modified ICRP model with an explicitly identified brain is 0.13 times the value based on the ICRP model.

### 6.2.6 Cesium-134

An updated biokinetic model for cesium (Cs) is described in ICRP Publication 137 (ICRP 2017). The model structure is shown in Fig. 6.11. The model was based on blood perfusion rates of tissues, tissue-specific extraction fractions for cesium or its physiological analogues rubidium and potassium, and autopsy data on the distribution of cesium in adult humans. The model was originally constructed around a dynamic blood flow model (Leggett et al. 2003). The original model structure was later replaced by a conventional model structure depicting a central blood compartment (Leggett 2013). The latter structure was used in ICRP Publication 137. The version of the model applied in ICRP Publication 137 was designed to yield virtually the same tissue dose estimates for internally deposited radioisotopes of cesium as the original version.
Fig. 6.8. Model structure for systemic americium. The unshaded boxes and associated arrows represent the ICRP’s current model for americium (ICRP 2019). The modified version of the ICRP model considered here adds the brain compartment and associated arrows. ST = soft tissue, SI = small intestine, RC = right colon, LC = left colon, RS = rectosigmoid colon.
Fig. 6.9. Predictions of the americium concentration ratio brain: (liver + skeleton) as a function of time after acute input of long-lived americium to blood based on alternate models: ICRP’s current model for systemic americium (ICRP 2019), in which the brain is implicitly contained in Other; and a variation of ICRP’s model with an explicit brain region.
**Fig. 6.10.** Model structure for systemic cesium (ICRP 2017). St = stomach, SI = small intestine, RC = right colon, LC = left colon, RS = rectosigmoid colon.
The ICRP’s cesium model includes a compartment representing the brain. An alternate version of the ICRP model was developed by eliminating the brain compartment and increasing the deposition fractions in the compartments of Other so that deposition fractions for all repositories still add to 1.0.

Fig. 6.12 compares predictions of the time-dependent content of cesium in brain following acute input of stable cesium to blood based on alternate models: ICRP’s current model, which contains an explicit brain region; and the modified ICRP model in which the brain is implicitly contained in Other.

Alternate injection dose coefficients for brain for $^{134}$Cs were derived using the ICRP’s systemic model for cesium and the modified version of that model with brain implicitly contained in Other. The dose coefficient for brain based on the ICRP model with an explicit brain compartment is 1.5 times the value based on the modified model.

6.2.7 Manganese-54, manganese-53, and manganese-52

The ICRP’s current biokinetic model for manganese is described in ICRP Publication xx (ICRP 2021; Leggett 2011). The model structure is shown in Fig. 6.13. The model was developed from data on the time-dependent behavior of manganese in human subjects and laboratory animals, together with autopsy studies of the distribution of manganese in the human body and contains a compartment explicitly representing the brain. The brain is assumed to take up only 0.1% of the outflow of manganese from blood plasma following its inhalation and absorption to blood, but the assigned retention time is much longer in the brain than in other soft tissues, resulting in a gradual increase in the manganese concentration in brain relative to other soft tissues.
Fig. 6.11. Predictions of the brain content of cesium as a function of time after acute input of stable cesium to blood based on alternate models: ICRP’s current model for systemic cesium (ICRP, 2017), which contains an explicit brain region; and a variation of ICRP’s model in which the brain is implicitly contained in Other.
**Fig. 6.12.** Structure of ICRP’s biokinetic model for manganese. ST = soft tissue, SI = small intestine, RC = right colon, LC = left colon, RS = rectosigmoid colon.
An alternate version of the ICRP’s model for manganese was developed by eliminating the brain compartment and increasing the deposition fractions in the compartments of \textit{Other} so that deposition fractions for all tissues and excretion pathways still add to 1.

Fig. 6.14 compares predictions of the time-dependent content of manganese in brain following acute input of stable manganese to blood based on alternate models: ICRP’s current model, which contains an explicit brain region; and the modified ICRP model in which the brain is implicitly contained in \textit{Other}.

Alternate injection dose coefficients for brain for $^{54}\text{Mn}$ ($T_{1/2} = 312$ d) were derived using the ICRP’s systemic model for manganese and the modified version of that model with brain implicitly contained in \textit{Other}. The dose coefficient for brain based on the ICRP model with an explicitly identified brain is 1.7 times the value based on the modified model. The analogous ratio of dose coefficients for the shorter-lived isotope $^{52}\text{Mn}$ ($T_{1/2} = 5.59$ d) is 0.73 and for the longer-lived isotope $^{53}\text{Mn}$ ($T_{1/2} = 3.7 \times 106$ y) is 3.2.

6.2.8 Mercury-203 and mercury-194 (vapor)

ICRP’s biokinetic model for mercury vapor that enters the systemic circulation is described in ICRP’s series of reports on occupational intake of radionuclides (ICRP 2021). The model structure, which includes two compartments representing brain, is shown in Fig. 6.15.

An alternate version of ICRP’s biokinetic model for mercury vapor was developed by eliminating the two brain compartments and increasing the deposition fractions in the compartment of \textit{Other} named \textit{Other 1}, so that deposition fractions for all tissues and excretion pathways still add to 1.
Fig. 6.13. Predictions of the brain content of manganese as a function of time after acute input of stable manganese to blood based on alternate models: ICRP’s current model for systemic manganese (ICRP 2017) with an explicitly identified brain region, and a variation of ICRP’s model with the brain implicitly contained in Other.
Fig. 6.14. Structure of ICRP’s biokinetic model for mercury vapor (all compartments and paths) and inorganic divalent mercury (excludes Plasma 0 and associated paths).
Fig. 6.16 compares predictions of the time-dependent content of mercury in brain following acute input of stable mercury vapor to blood based on alternate models: ICRP’s model, which contains an explicit brain region; and the modified ICRP model with an implicit brain contained in Other.

Alternate injection dose coefficients for brain for $^{203}$Hg ($T_{1/2} = 46.6$ d) vapor were derived using the provisional ICRP model for mercury and the modified version of that model with brain implicitly contained in Other. The dose coefficient based on the ICRP model with an explicitly identified brain is 1.4 times the value based on the modified model. The analogous ratio of dose coefficients for the much longer-lived isotope $^{194}$Hg ($T_{1/2} = 440$ y) is 4.8.

6.2.9 Radium-226 and radium-224

The ICRP’s biokinetic model for systemic radium was updated in Publication 137 (ICRP 2017). The main changes from the previous model for radium (ICRP 1993) are an added liver compartment and compartments explicitly representing the kidneys. The brain is included implicitly in Other.

An alternate version of ICRP’s model for systemic radium was developed by adding a compartment representing brain and assigning transfer rates between blood and the brain compartment (Fig. 6.17) consistent with data on accumulation of radium in the brain in human subjects and laboratory animals (Section 5). The following transfer coefficients were assigned:

- Blood to Brain = 0.0035 d$^{-1}$,
- Brain to Blood = 0.00038 d$^{-1}$.

The transfer coefficient from brain to blood is the value applied to the slow turnover compartment of Other in the ICRP model. The total outflow rate from plasma to all destinations combined was left unchanged by reducing the transfer coefficient from the slow turnover compartment of Other by the transfer coefficient from blood to brain.
**Fig. 6.15.** Predictions of the brain content of mercury as a function of time after acute input of stable mercury vapor to blood based on alternate models: the ICRP’s current model for systemic mercury (ICRP 2021), which includes an explicitly identified brain region; and a variation of ICRP’s model with brain implicitly contained in *Other.*
Fig. 6.16. Model structure for systemic radium. The unshaded boxes and associated arrows represent ICRP’s current model for radium (ICRP 2017). The modified version of the ICRP model considered here adds two brain compartments and associated arrows. ST = soft tissue, SI = small intestine, RC = right colon, LC = left colon, RS = rectosigmoid colon.
Fig. 6.18 compares predictions of the time-dependent content of $^{226}$Ra in brain following acute input of long-lived radium to blood based on alternate models: ICRP’s current model, in which the brain is implicitly contained in Other; and the modified ICRP model with an explicit brain region.

Alternate dose injection coefficients for $^{226}$Ra ($T_{1/2} = 1600$ y) were derived for brain using ICRP’s systemic model for radium and the modified version of that model with an explicit brain compartment. For simplicity, attention was restricted to dose from the parent radionuclide $^{226}$Ra, as its progeny contribute a relatively small portion of dose to brain based on either the ICRP model or the alternate model. The dose coefficient for brain based on the modified ICRP model with an explicitly identified brain is 1.9 times the value based on the ICRP’s model. The analogous ratio of dose coefficients for the shorter-lived isotope $^{224}$Ra ($T_{1/2} = 3.66$ d), not including the contribution to dose from ingrowing radioactive progeny, is 0.16.

6.2.10 Uranium-234 and uranium-230

The ICRP’s systemic model for uranium is described in Publication 137 (ICRP 2017). In the ICRP model, the brain is included implicitly in Other.

An alternate version of the ICRP’s model for systemic uranium was developed by adding a compartment representing brain (Fig. 6.19) and assigning transfer coefficients between plasma and this compartment consistent with data on accumulation of uranium in the brain in human subjects and laboratory animals (Section 5). The following transfer coefficients between plasma and brain were assigned:

Plasma to Brain = 0.0015 d$^{-1}$,  
Brain to Plasma = 0.000019 d$^{-1}$.

The outflow rates from Brain to plasma were assumed to be the same as the outflow rates from the medium and slow exchange compartments of Other in ICRP’s systemic model for
**Fig. 6.17.** Predictions of the brain content of radium as a function of time after acute input of long-lived radium to blood based on alternate models: ICRP’s current model for systemic radium (ICRP 2017), in which the brain is implicitly contained in *Other*; and a variation of ICRP’s model with an explicit brain region.
**Fig. 6.18.** Model structure for systemic uranium. The unshaded boxes and associated arrows represent the ICRP’s current model for uranium (ICRP 2017). The modified version of the ICRP model considered here adds a brain compartment with associated arrows. ST = soft tissue, SI = small intestine, RC = right colon, LC = left colon, RS = rectosigmoid colon.
uranium. The total outflow rate from plasma to all destinations was left unchanged by reducing the transfer coefficients from plasma to the slow exchange compartment of Other.

Fig. 6.18 compares predictions of the time-dependent content of uranium in brain following acute input of long-lived uranium, assuming no radioactive decay, to blood based on alternate models: ICRP’s current model, in which the brain is implicitly contained in Other; and a variation of ICRP’s model with an explicit brain region.

Alternate injection dose coefficients were derived for brain using ICRP’s systemic model for uranium and a modified version of that model with an explicit brain compartment. For $^{234}$U ($T_{1/2} = 2.46 \times 10^5$ y) the dose coefficient for brain based on the modified ICRP model with an explicitly identified brain is 0.81 times the value based on the ICRP model. For the relatively short-lived isotope $^{230}$U ($T_{1/2} = 20.8$ d) the analogous ratio is 0.78.

6.3 Summary and Discussion

The results of the 10 case studies are summarized in Table 6.2. The values in the right column of the table are ratios A:B, where A is the dose coefficient for brain based on the version of the model with an explicitly identified brain and B is the dose coefficient for brain based on the version of the model in which the brain is implicitly contained in Other. The dose coefficients are for acute injection of the radionuclide into blood of an adult male worker.

For the radionuclides addressed in this study, the ratio A:B was $<0.2$ in two cases, in the range 0.5 – 2.0 in 12 cases, and in the range 3 – 5 in three cases. The results indicate that addition of an explicitly identified brain can sometimes result in a substantial (factor of three or more) difference in the dose coefficient for the brain compared with use of an implicit brain model. In such cases it is important to incorporate an explicit brain region into the systemic model used for dose reconstruction, if feasible in view of the quality and quantity of available biokinetic data for the element of interest.
Table 6.2—Comparison of injection dose coefficients (Sv Bq⁻¹) for brain in a reference male worker, based on systemic biokinetic models with or without an explicitly modeled brain.

<table>
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<th>Radionuclide</th>
<th>Half-life</th>
<th>Biokinetic model with</th>
<th>Ratio A:B</th>
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<td>Explicit brain (A)</td>
<td>Implicit brain (B)</td>
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<td>Americium-241</td>
<td>432 y</td>
<td>3.62 × 10⁻⁶</td>
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<td>Cesium-134</td>
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<td>Lead-209</td>
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<td>Lead-210</td>
<td>22.2 y</td>
<td>4.50 × 10⁻⁷</td>
<td>1.37 × 10⁻⁷</td>
</tr>
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<td>Manganese-52</td>
<td>5.59 d</td>
<td>3.79 × 10⁻¹⁰</td>
<td>5.18 × 10⁻¹⁰</td>
</tr>
<tr>
<td>Manganese-53</td>
<td>3.7 × 10⁶ y</td>
<td>1.13 × 10⁻¹⁰</td>
<td>3.59 × 10⁻¹¹</td>
</tr>
<tr>
<td>Manganese-54</td>
<td>312 d</td>
<td>2.41 × 10⁻⁹</td>
<td>1.39 × 10⁻⁹</td>
</tr>
<tr>
<td>Mercury-194 (vapor)</td>
<td>440 y</td>
<td>3.55 × 10⁻¹⁰</td>
<td>7.36 × 10⁻¹¹</td>
</tr>
<tr>
<td>Mercury-203 (vapor)</td>
<td>46.6 d</td>
<td>7.32 × 10⁻¹⁰</td>
<td>5.25 × 10⁻¹⁰</td>
</tr>
<tr>
<td>Plutonium-237</td>
<td>45.2 d</td>
<td>9.98 × 10⁻¹¹</td>
<td>1.51 × 10⁻¹⁰</td>
</tr>
<tr>
<td>Plutonium-239</td>
<td>24,100 y</td>
<td>2.45 × 10⁻⁵</td>
<td>2.56 × 10⁻⁵</td>
</tr>
<tr>
<td>Polonium-210</td>
<td>138 d</td>
<td>5.30 × 10⁻⁷</td>
<td>3.12 × 10⁻⁷</td>
</tr>
<tr>
<td>Radium-224</td>
<td>3.66 d</td>
<td>1.04 × 10⁻⁹</td>
<td>6.53 × 10⁻⁹</td>
</tr>
<tr>
<td>Radium-226</td>
<td>1,600 y</td>
<td>3.62 × 10⁻⁷</td>
<td>1.87 × 10⁻⁷</td>
</tr>
<tr>
<td>Uranium-230</td>
<td>20.8 d</td>
<td>2.74 × 10⁻⁸</td>
<td>3.53 × 10⁻⁸</td>
</tr>
<tr>
<td>Uranium-234</td>
<td>2.5 × 10⁵ y</td>
<td>1.11 × 10⁻⁶</td>
<td>1.38 × 10⁻⁶</td>
</tr>
</tbody>
</table>

ᵃ Alternate brain models were considered for ²¹⁰Po as a parent or a progeny of ²¹⁰Pb. The listed value is the average of the two dose coefficients derived for brain for ²¹⁰Po or ²¹⁰Pb.

ᵇ Contribution of progeny to brain dose not addressed.
Ideally, only data for human subjects would be used in the development of a biokinetic model for humans. However, data on the time-dependent accumulation of element in the brain generally are available only for controlled studies involving laboratory animals. Best available data for the human brain generally come from postmortem measurements of stable elements or radionuclides in tissues of occupationally or environmentally exposed subjects. Such autopsy data were found for all 10 of the elements addressed here but were not used in one case (polonium) and were of doubtful relevance in another case (bismuth) due to limitations in the data.

An important finding from these case studies and additional reviews of the literature is that the brain typically has a much lower rate of uptake per gram of tissue but a longer residence time than do most other studied soft tissues. Thus, an initially low uptake of a radionuclide by brain should not be interpreted as indicating that the dose to brain is substantially lower than that to most other tissues.
7. Potential Improvements in Dosimetric Models of the Brain for Internal Emitters

The fundamental physical quantity of radiation protection is absorbed dose, which is a mass average of the energy deposited throughout a radiosensitive organ or tissue of the body. ICRP has identified radiosensitive cells within the skin, skeleton, respiratory tract, and alimentary tract. The absorbed dose within these cells is averaged over their mass (ICRP 2007). Without information on the specific cells at risk in the various tissues, including the brain, the absorbed dose is averaged over the total mass of the tissue.

The framework of a dosimetric model is an anatomical phantom representing the approximate masses, shapes, and spatial relationships of tissues of a reference person of a given sex and age. A dosimetric phantom is used together with nuclear decay data for radionuclides to predict the sites of deposition of energy in the body from radiations emitted from any site in the body.

The original dosimetric phantoms developed at Oak Ridge National Laboratory (ORNL) in the 1960s represented a reference adult hermaphrodite to allow calculation of doses to both male and female sex organs (Snyder et al. 1969). For computation convenience (e.g., for Monte Carlo calculations of cross-irradiation of tissues) the organs and tissues and external body surfaces of the ORNL phantom were represented by the union or intersection of regular geometric shapes such as ellipsoids, cylinders, spheres, and planes.

The ORNL phantom was adopted by the Medical Internal Radiation Dose (MIRD) Committee in the 1970s for applications in nuclear medicine and later by ICRP for use in reports that provided guidance on intake of radionuclides by workers. In the ORNL/MIRD/ICRP phantom, the brain was represented as a single ellipsoid of soft tissue. Eckerman et al. (1981) modified that model by differentiating the brain’s white and gray matter. With increasing interest in brain imaging agents, the MIRD committee revised their representation to depict several substructures of the brain, with each substructure represented as a simple geometrical shape (e.g., an ellipsoid or sphere) or an intersection of such shapes with one another or with planes (Bouchet et al. 1999).
In recent years the stylized models of the anatomy as represented by the original ORNL phantom have been replaced by voxel phantoms based on CT or MRI imaging. The ICRP has issued a set of reference voxel-based computational phantoms (ICRP 2009), but no substructure within the brain was identified.

This Section describes the ICRP’s current, relatively simple dosimetric treatment of the brain using modern dosimetric phantoms and summarizes the MIRD stylized model of the brain introduced in the late 1990s. The MIRD model is used to illustrate that a more detailed dosimetric treatment than currently used by the ICRP may provide improved dose estimates for substructures of the brain in cases where there is information on the actual or typical distribution of the radionuclide of interest in the brain.

### 7.1 Biokinetics Modeling of Brain Uptakes

The fate of a radionuclide following its uptake to blood from the respiratory or alimentary tract is described by systemic biokinetic models. These models detail the potential transfer of the radionuclide from the circulating blood to various organs and tissues of the body, its removal rates from the tissues, and its elimination from the body. Typically, a limited number of organs and tissues are identified explicitly in these models. Tissues not explicitly identified are collectively referred to as Other and denoted as $\text{Other}$. In the current set of models of the ICRP, the brain usually is not explicitly identified but is treated as a mass fraction of $\text{Other}$. The dosimetric calculations assume that the activity assigned either explicitly or implicitly to the brain is uniformly distributed within the brain.

### 7.2 Dosimetric Models

The ICRP computes the mean absorbed dose, $D_T$, in tissue $T$ of the body as:

$$D_T = \sum_{r_S} U_{r_S} S(T \leftarrow r_S)$$  \hspace{1cm} (7.1)
where $U_{rS}$ is the number of nuclear transformations of the radionuclide occurring in source region $r_S$ and $S(T \leftarrow r_S)$ is the absorbed dose in target region $T$ per nuclear transformation in source region $r_S$. The two quantities on the right-hand side of the equation are the essence of the dosimetry issue. That is, $U_{rS}$ embodies the assumed biokinetics of the radionuclide. The second term, $S(T \leftarrow r_S)$, embodies the energy and intensity of the radiations emitted in nuclear transformations of the radionuclide in source region $r_S$ and the fraction of emitted energy absorbed per mass in the target $T$. The fraction of energy absorbed depends on the spatial relationship of the source region $S$ and the target tissue $T$. Thus, the biokinetic and dosimetric aspects are represented separately in these two quantities. The mean absorbed dose to the brain, $T = \text{Brain}$, per Equation 7.1 can be rewritten as:

$$D_{\text{Brain}} = \sum_{r_S}^N U_{rS} S(\text{Brain} \leftarrow r_S) + U_{\text{Other}} S(\text{Brain} \leftarrow \text{Other})$$  \hspace{1cm} (7.2)

where $U_{rS}$ is the nuclear transformations occurring in the $N$ explicitly identified source regions and $U_{\text{Other}}$ is the nuclear transformations in Other as identified in the biokinetics. The quantity $S(\text{Brain} \leftarrow r_S)$ is calculated as:

$$S(\text{Brain} \leftarrow r_S) = \sum_{R} \sum_{i} E_{R,i} Y_{R,i} SAF(\text{Brain} \leftarrow r_S; E_{R,i})$$  \hspace{1cm} (7.3)

where $E_{R,i}$ is the energy of the $i^{th}$ radiation of type R emitted in nuclear transformations of the radionuclide, $Y_{R,i}$ is the yield of the $i^{th}$ radiation per nuclear transformation, and $SAF(\text{Brain} \leftarrow r_S; E_{R,i})$, the so-called specific absorbed fraction, is the fraction of energy $E_{R,i}$ emitted within source region $r_S$ that is absorbed per mass of the brain.

For a pure alpha emitter the estimated dose to brain is due entirely to alphas emitted within brain, so the first term on the right side of Equation 7.2 is zero for all source regions $r_S$ except $r_S$ being the brain if explicitly identified. The second term on the right side of Equation 7.2 plays no
role when the brain is explicitly identified in the biokinetics. In adult males, the absorbed dose to
the brain (1.45 kg tissue mass plus 0.07 kg blood content for a total mass of 1.52 kg) per nuclear
transformation (\( nt \)) within the brain of a radionuclide emitting a 6 MeV alpha particle would be:

\[
6.0 \frac{MeV}{nt} \times 1.602 \times 10^{-13} \frac{J}{MeV} \times \frac{1}{1.52 \, kg} = 6.32 \times 10^{-13} \frac{Gy}{nt}. \tag{7.4}
\]

With no further consideration it is assumed that all substructures of the brain would receive
this absorbed dose. If it is assumed that alpha emitter is distributed within the brain
proportionally to energy usage (94 % within gray matter representing 48 % of the brain mass),
then the absorbed dose within gray-matter substructures would be:

\[
0.94 \times 6.0 \frac{MeV}{nt} \times 1.602 \times 10^{-13} \frac{J}{MeV} \times \frac{1}{0.48 \times 1.52 \, kg} = 1.24 \times 10^{-12} \frac{Gy}{nt}. \tag{7.5}
\]

and within the white matter of the cerebral cortex would be:

\[
0.06 \times 6.0 \frac{MeV}{nt} \times 1.602 \times 10^{-13} \frac{J}{MeV} \times \frac{1}{0.52 \times 1.52 \, kg} = 7.30 \times 10^{-14} \frac{Gy}{nt}. \tag{7.6}
\]

This suggests that absorbed dose estimates to the brain subregions for a pure alpha emitter could
differ by orders of magnitude.

### 7.3 MIRD Stylized Model of Substructures of the Head and Brain

A variety of radiopharmaceuticals have been used in nuclear medicine for neuroimaging or
experimental therapy (Saha et al. 1994; Messa et al. 1995, Zalutsky et al. 2008). The spatial
resolutions of some current imaging systems allow quantification of the activity concentration
within different regions of the brain. In the late 1990s the Committee on Medical Internal
Radiation Dosimetry (MIRD) (Bouchet et al. 1999; Bouchet and Bolch 1999) introduced a
dosimetric model that allows separate dose estimates to different components of the head (e.g.,
eyes, skin, upper spinal cord) and brain (e.g., cerebellum, white matter, cerebral cortex). The
following summary of the MIRD model is taken from the description by Bouchet et al. (1999) of
the model for a reference adult.

The head, brain, and their individual features were constructed in the same manner as the
mathematical dosimetric phantoms originally developed at Oak Ridge National Laboratory
(ORNL). That is, the MIRD model of the head and brain consists of a set of mathematically
defined components such as portions of cylinders, ellipsoids, or spheres representing body
tissues and positioned to approximate the locations of the tissues in the human body. The model
of the adult head and brain is positioned atop a 70 cm tall trunk region serving as a source of
photon scatter but with no delineation of internal organs.

The components of the MIRD model of the head are shown in Fig. 7.1, which also shows a
portion of the model of the brain. The components of the model of the brain are shown in Fig.
7.2.

In the MIRD model, the brain is located within an idealized cranium represented as the
volume between two concentric ellipsoids. The reference volume of the adult brain is 1467.6
cm³. The brain contains eight regions: the cerebral cortex, the cerebellum, the thalami, the third
ventricle, the lateral ventricles, the caudate nuclei, the lentiform nuclei, and the white matter. The
cerebral cortex is described as two half ellipsoids, with the bottom ellipsoid cut by an inclined
plane and a vertical plane. The cerebellum is located on the back of the brain and is defined by
an ellipsoid cut by a vertical plane and a horizontal plane, where the two planes correspond to the
layers of the cerebral cortex covering the cerebellum. The thalami are represented by two
ellipsoids, one in each hemisphere. The third ventricle is located between the two thalami and is
represented by an elliptical cylinder. The lateral ventricles are modeled as two symmetrical
cylinders. The caudate nuclei are represented by two symmetrical cylinders, with each cylinder
capped on one end by a sphere representing the head of the caudate nucleus. The lentiform nuclei
**Fig. 7.1.** Features of the MIRD model of the head. The separated components of the model of the head indicated by the arrows, starting at the upper middle and moving counterclockwise, are an external view of the cranium, an interior view of the cranium excluding brain, upper facial region and eyes, teeth, mandible, thyroid, top of spine, and cerebral cortex (red) with cerebellum (blue). The geometric figures surrounded by the cerebral cortex and cerebellum are regions of the brain. Fig. 3.1 provides further identification of the components.
Fig. 7.2. Features of the MIRD brain model. The individual regions are the cerebral cortex (red), the cerebellum (dark blue), the thalami (light blue ellipsoids in the front) the ventricles (green cylinders and thin green slice below those cylinders), caudate nuclei (purple, beside the ventricles), the lentiform nuclei (yellow ellipsoids in the back), and the white matter (not shown, but assumed to occupy the space remaining within the cranium). Fig 3.1 provides further identification of the components.
are represented by two elliptical shapes representing the combination of the putamen and the
globus pallidus. The white matter is represented by the remaining space interior to the cranium,
\textit{i.e.}, the space within the brain that is not occupied by any of the other seven brain regions
depicted in the model. The reference volume of the white matter in the adult is 639.2 cm$^3$.

Bouchet et al. (1999) tabulated S values for photons and electrons (absorbed fractions of
energy deposited in target tissues by internally emitted radiations) for each combination of
source and target region of the MIRD model using Monte Carlo simulations. Twelve energies
between 10 keV and 4 MeV were simulated. Bouchet et al. (1999) demonstrated the usefulness
of the MIRD brain model for brain subregion dosimetry by deriving dose estimates for $^{123}$I-
labeled tropane. Tropane is an analogue of cocaine that crosses the blood-brain barrier and
selectively binds to the presynaptic dopamine transporter in the basal ganglia (Mozley et al.
1996). Data on the time-dependent distribution of activity in the total brain and six subregions of
the brain were available for a healthy human volunteer. SPECT (single photon emission
computed tomography) imaging indicated that the activity concentrations in the caudate and
lentiform nuclei were considerably greater than in the other brain structures in the first 500
minutes after administration. Residence times were calculated for the total brain and subregions
of the MIRD model, and dose estimates were developed for the total brain and its subregions.
The estimated absorbed doses to the caudate nuclei and lentiform nuclei were roughly fivefold
higher than the dose averaged across the brain.

7.4 Discussion

Nearly all dosimetry methodologies used in radiation protection over the years, including the
methodology currently applied by the ICRP, assume a uniform distribution of activity in the
brain. A notable exception is a model introduced in the late 1990s by the MIRD committee. The
model is built on a stylized dosimetric phantom. For most applications, stylized phantoms have
since been replaced with more sophisticated and anatomically realistic phantoms. Applications of
the MIRD model provide convincing evidence, however, that the doses to brain tissues from
radionuclides within the brain can be highly nonuniform. An example given in this Section
indicates that this is the case even for a radionuclide that emits penetrating radiations. Even more
nonuniform doses to brain tissues may be expected for alpha-emitting radionuclides. For sources within the vascular or neuronal network, elevated local absorbed doses to the vascular endothelial cells or to the neuronal synapses and the subsequent high-LET damage to these cells could impact nutrient and neurotransmitter transport. Interference with these key processes could result in cognitive changes. Development and implementation of improved dose estimation methodologies for such substructures of the brain is an important objective for future research.

In recent years there has been a considerable expansion of information on the anatomy and functions of the brain. Advances in MRI technology have enabled measurements of brain function linked to brain structure. It may now be feasible to refine the ICRP’s current dosimetric computational methodology for the brain based on these developments to construct a detailed brain model analogous to the 1999 MIRD model but constructed within a more realistic spatial configuration.
8. Summary and Conclusions

This Commentary examines ways to improve current biokinetic and dosimetric treatments of the brain that may result in improved dose estimates for brain tissue from internally deposited radionuclides. While the goal is to improve estimates of brain dose from all internal emitters, emphasis is on dose from alpha emitters as a surrogate for brain dose from high-energy radiations encountered on long space flights.

Human and animal studies show that nonessential as well as essential elements can accumulate in the brain, despite the presence of a blood-brain barrier that serves to shield the brain from foreign substances. Routes by which specific radionuclides may enter the brain include the following:

- Radioisotopes of elements essential to brain structure and function can cross the blood-brain barrier via the element-specific transport systems.
- Element-specific transport systems generally cannot discriminate infallibly between the target element and an element with similar chemical and physical features. For example, some elements including manganese and plutonium can replace iron in the iron transport protein transferrin and presumably can cross the blood-brain barrier via the transferrin transport system.
- Substances traversing the choroid plexus enter the spinal fluid and could diffuse from the spinal fluid into the central nervous system.
- Inhaled radionuclides deposited in the nasal region can be transported along olfactory neurons to the olfactory bulb in the brain. It is not evident, however, that this pathway can lead to significant access to a larger portion of the brain.

Typically, an element-specific systemic biokinetic model used to derive dose coefficients or reconstruct doses from intake of a radionuclide depicts explicitly only the dominant repositories of the element. Remaining tissues are aggregated into a source region called Other in which the element is assumed to be uniformly distributed. In the systemic biokinetic models currently used
in dose reconstructions for radiation workers, the brain usually is addressed as an implicit mass fraction of Other rather than as an explicitly depicted repository.

Seventeen case studies of selected radionuclides were performed to assess the quantity and quality of information available to add explicit brain models to best available element-specific biokinetic models and apparent improvements, if any, in resulting dose estimates for brain tissue. The radionuclides examined are isotopes of the 10 elements, manganese, cesium, mercury, lead, bismuth, polonium, radium, uranium, plutonium, and americium. One check regarding the potential importance of explicit modeling of brain biokinetics was derivation of the ratio A:B, where A is the injection dose coefficient (50 y integrated equivalent dose) if an explicit brain model is used and B is the corresponding coefficient if the brain is treated as an implicit component of Other. The findings indicate that:

- Most of the published data on brain kinetics of elements are for laboratory animals. The studied animal types usually included relatively large animals that have proven to be reasonably good laboratory models for humans such as dogs and baboons, in addition to the more commonly studied small animals such as rats and mice.

- Best available data for the human brain usually came from autopsy studies of occupationally or environmentally exposed subjects. The autopsy data usually provided some insight into the long-term concentration of the element in the brain compared to other tissues, which is useful information for modeling brain kinetics.

- Results of animal studies indicate that the brain typically has a lower rate of uptake per gram of tissue but a longer residence time than do most other studied soft tissues, which is also useful information for modeling brain kinetics.

- For each of the 10 elements listed above, an explicit brain model was constructed from best available data on accumulation of the element in the brain in laboratory animals and human subjects. From the standpoint of the quality of available data, the most problematic element considered was bismuth, for which the best data for brain consisted of data for rats and autopsy data for seriously ill patients who had received
bismuth treatments, both of which are regarded as relatively weak data sets for purposes of characterizing biokinetics in healthy human subjects.

For the 17 radionuclides addressed in this study, the ratio A:B was <0.2 in two cases, in the range 0.5-2.0 in 12 cases, and in the range 3-5 in three cases. The results indicate that addition of an explicitly identified brain can sometimes result in a substantial (factor of three or more) difference in the dose coefficient for the brain compared with use of an implicit brain model. In such cases it is important to incorporate an explicit brain region into the systemic model used for dose reconstruction, if feasible in view of the quality and quantity of available biokinetic data for the element of interest.

Dosimetry systems used in radiation protection generally have not included sophisticated or detailed dosimetric models of the brain. Rather, the brain generally has been treated as a single compartment. One exception is a model introduced by the MIRD Committee in 1999. That model is built on a stylized dosimetric phantom and depicts eight separate regions of the brain. Applications of the MIRD model to selected radiopharmaceuticals with reasonably well-known distribution in the brain indicate that the doses to brain tissues from radionuclides within the brain can be highly heterogeneous. Additional work to look at tissue and even cellular microdosimetry is needed since the distribution of radionuclides in various tissues is non-uniform. Such modeling is possible but has not been well-studied in radionuclide studies.

In recent years there has been a considerable expansion of information on the anatomy and functions of the brain. The recent advances in MRI technology have enabled measurements of brain function linked to brain structure. It may now be feasible to refine the ICRP’s current dosimetric computational methodology for the brain based on these developments to construct a detailed brain model analogous to the 1999 MIRD model but constructed within a more realistic spatial configuration.
Appendix A.

Supplemental Information on Brain Dose Assessment for Epidemiologic Studies

This appendix provides supplemental information on the relevance of radiation dosimetry for brain tissue to ongoing epidemiologic studies in the U.S. It also discusses the potential application of brain dosimetry analysis to judgements on radiological protection guidance for long-term space missions.

A.1 Rationale and Background

NCRP Report 183 entitled *Radiation Exposures in Space and the Potential for Central Nervous System Effects: Phase II*, recommended that studies of workers with intakes of alpha-particle emitters be initiated to evaluate possible late CNS effects such as dementia and cognitive impairment (NCRP 2019). Due to increasing interest in radiation effects on the brain, the expanding application of alpha particle emitters in medicine (Poty et al. 2018a, 2018b; Sgouros et al. 2020), and animal experiments showing that CNS effects can occur following galactic cosmic ray (GCR) simulated exposures (NCRP 2016, 2019), efforts were initiated to improve brain dosimetry for internal radiation sources (Leggett et al. 2018). These efforts were in addition to improving the biokinetic and dosimetric models from intakes of alpha-particle emitting radionuclides for radiation protection.

Epidemiologic studies of DOE workers with measured intakes of polonium, radium, plutonium, uranium, and americium are being conducted to evaluate possible CNS effects such as dementia, Alzheimer’s, Parkinson’s, motor neuron disease and cognitive function (Boice 2017, 2019). Recently, a dose response was reported for Parkinson’s disease among Mayak workers in Russia (Azizova et al. 2020) and among Los Alamos National Laboratory workers in the U.S. (Boice et al. 2021). The improved estimates of alpha dose to brain tissue will be relevant to radiation protection guidance and directly applicable to ongoing epidemiologic research. The possible applicability to radiation guidance for long-term missions in space is discussed below. Although alpha particle exposures to brain tissue are an imperfect analogue to GCR (HZE
particles), the epidemiologic studies are thought to provide another line of evidence that can be considered when making judgments for radiation protection guidance for flight crews on long missions in space.

A.2 CNS Effects, Space Radiation and the Need for Protection Guidance

Radiation-induced damage to the CNS has been recognized in patients treated with high-dose photon radiation therapy, but recent animal experiments have reported several early and delayed deleterious effects following exposures to high atomic number, high-energy particles (HZE particles) and at radiation levels lower than previously suspected as being damaging. Consequently, radiation exposures in space may result in acute functional and cognitive CNS effects that could impair missions, and in late occurring CNS effects that may result in serious cognitive and mental dysfunction in exposed crew members (NCRP 2016). National Aeronautics and Space Administration (NASA) has defined permissible exposure limits for cancer and certain noncancer effects, but guidance applicable to CNS and cognitive impairment remains to be developed.

Human data exist following radiation therapy for non-CNS conditions in childhood and in adulthood and subsequent early-onset dementia has been observed, but its relevance to space radiation is minimal at best. Further, risk-limitation strategies to reduce possible CNS effects may require a distinct strategy that differs from approaches used for cancer and noncancer effects (NCRP 2016). Other complicating factors include the dearth of human data on CNS or cognitive function following exposure to high-LET radiations, and much less for GCR (HZE particles); the absence of human data that such deleterious effects occur in adults following exposure to low level low-LET radiations; and the absence of human data on the effects of radiation exposure to brain tissue following low-level radiation exposure received continuously over a period of several years, as would be experienced in a mission to Mars. To provide human data on the effects of high-LET exposure to brain tissue over a period of years, epidemiologic studies of workers with intakes of alpha-particle emitting radionuclides were initiated.
NASA has programs in place to assess the radiation-related cancer risk to astronauts and flight crews (NRC 2012; NCRP 2014; Boice 2017). Animal experiments, however, have raised concern about potential behavioral and cognitive impairments from space radiation on the central nervous system, as well as the possibility that dementia and Alzheimer’s disease might develop later in life (Cherry et al. 2012; NCRP 2016, 2019). GCRs, the high-velocity heavy ions (e.g., $^{56}$Fe) [HZE particles] traveling through space, are of special interest (NCRP 2006, 2014, 2016, 2019; NAS/NRC 2012). Early and late neurological disorders from relatively brief exposures to these heavy ions are seen in animal studies. Yet there are no human populations with GCR exposures on earth that could be studied for CNS effects. The internally-deposited alpha emitters in radiation workers comprise a possible, though imperfect, human analogue for high-LET GCR exposure to brain tissue in space. For example, $^{226}$Ra has been detected in brain tissue of workers (Hursh and Lovaas 1963) and dial painters (Schlenker et al. 1982), as has $^{210}$Po (Nathwani et al. 2016), $^{241}$Am (McInroy et al. 1985; Filipy and Kathren 1996), plutonium (McInroy et al. 1991; Filipy and Kathren 1996; Suslova et al. 2017; Avtandilashvili et al. 2018; Dumit et al. 2019), and uranium (Russell and Kathren 2004; Avtandilashvili et al. 2015; Kathren and Tolmachev 2015).

**A.3 Human Research Involving High-LET Radiation Exposure to Brain Tissue**

In brief, ongoing research is addressing alpha particle dose to brain to U.S. Department of Energy (DOE) workers with intakes of radionuclides and subsequent risk of dementia, Alzheimer's, Parkinson’s, motor neuron disease and cognitive impairment. High-level cognitive performance is essential during space missions and can be influenced by environmental (e.g., radiation), physiological and psychological stressors (Basner et al. 2015; Moore et al. 2017). Studies of alpha particle exposure to brain tissue and cognitive impairment have begun (Boice et al. 2019), incorporating quantitative scores from neuropsychological testing available from Medicare and Medicaid files and from nursing home files (Rector et al. 2004; CMS 2018a, 2018b). The cohorts of DOE workers that are being evaluated for CNS effects and cognitive impairment include workers at Los Alamos National Laboratory, Mallinckrodt Chemical Works, Mound, Rocketdyne, Rocky Flats, Tennessee Eastman Corporation (TEC), Fernald, Middlesex, Portsmouth Gaseous Diffusion Plant, Paducah Gaseous Diffusion Plant, Oak Ridge National Laboratory (X-10), K-25, Y-12, Savannah River Site and Hanford.
Radionuclides that Expose Brain Tissue to Alpha Particles

Postmortem radiochemical analyses of human brain tissue have detected radionuclide deposition in brain tissue following intakes of radium (Schlenker et al. 1982), plutonium (James et al. 2003, 2007), americium (McInroy et al. 1985), uranium (Avtandilashvili et al. 2015; Kathren and Tolmachev 2015), and polonium (Nathwani et al. 2016). These radionuclides expose brain tissue at a low dose rate for years, concurrent with exposure to low-LET gamma radiation (Boice 2017; Ellis et al. 2018; Leggett et al. 2018; NCRP 2018).

Radiochemical analyses of human brain tissue are made possible because of the generosity of radiation workers who donated their bodies for scientific research to the United States Transuranium and Uranium Registries (Kathren 1989; Filipy and Russell 2003; Tolmachev et al. 2011; Kathren and Tolmachev 2019; Tolmachev et al. 2019b). Brain dose from alpha particles has been determined for intakes of polonium (Boice et al. 2014; Boice 2017), radium (Anderson et al. 2012; Silver et al. 2013; Ellis et al. 2018), uranium (Boice et al. 2006, 2011), and plutonium (Boice 2019; Boice et al. 2019). Dosimetry efforts are planned for other DOE worker populations exposed to uranium and plutonium (Frome et al. 1997a, 1997b; Yiin et al. 2017; Boice 2019; Boice et al. 2019).

Previous Studies of Radiation-Exposed Populations and Late CNS Effects

Dementia is rarely considered in studies of radiation-exposed populations but will be in future investigations. Studies of dementia have been conducted in Japanese atomic-bomb survivors and in radiation workers who inhaled or ingested radioactive elements, such as polonium, that exposed brain tissues. The incidence of dementia was examined among 2,286 atomic-bomb survivors within the Adult Health Study Cohort (Yamada et al., 2009). Dementia, Alzheimer’s disease and vascular disease were diagnosed during biennial health examinations using standard testing instruments. Radiation exposure was not found to be associated with the development of dementia. Workers at the Mound Facility in Ohio during World War II were exposed to polonium in the production of the neutron triggers that were used for the first
plutonium bombs at the Trinity Site and at Nagasaki (Boice et al., 2014). Polonium is unique among alpha-particle emitters in that it goes to soft tissue, including the brain (Leggett and Eckerman, 2001). Mortality from dementia, Alzheimer’s disease, Parkinson’s disease, and motor neuron disease was evaluated in 4,977 workers exposed to radiation, including polonium, plutonium, tritium, and external gamma rays. Although mortality is a relatively weak indicator of behavioral issues, a dose response was suggested although not statistically sound (Boice 2017). A similar response was not seen for workers at Mallinckrodt with intakes of uranium and radium but at much lower dose levels (Ellis et al. 2018; Golden et al. 2019).

A.3.3 Ongoing Studies of Occupationally-Exposed Workers and Late CNS Effects

Ongoing and updated occupational studies using improved biokinetic and dosimetric models to compute dose to brain from internal intakes of radioactive elements include the workforce at Rocketdyne (Boice et al., 2011), Los Alamos National Laboratory (Wiggs et al. 1994), Rocky Flats (Brown et al. 2004), the Tennessee Eastman Corporation (Polednak and Frome 1981), Middlesex Sampling Plant, Fernald Feed Materials Production Center (Silver et al. 2013), three Gaseous Diffusion Plants (K-25, Portsmouth, Paducah), Savannah River Site (Cragle et al. 1988), Hanford (Gilbert et al. 1993), and Linde (Dupree et al. 1987; Boice et al. 2019).

A new follow-up of the 3,276 radium dial painters was recently initiated within the Million Person Study (MPS) (Rowland 1994; Fry 1998) in part to evaluate dementia and other possible indicators of cognitive impairment. The last follow-up was in 1980 and nearly 60% of the dial painters were alive at that time (Polednak et al. 1978; Stebbings et al. 1984). Intakes of radium were as early as 1913 among young women who painted dials, tipping brushes orally. Active research began in the 1910s and continued through the 1980s at Argonne National Laboratory (ANL). The USTUR received from ANL the detailed health and dosimetry records and biological tissues of radium dial painters, including brain tissue.

Information in this commentary is to provide guidance for these epidemiologic studies as to the optimum way to characterize brain tissue dose from alpha-particle emitting radionuclides in
relationship to the occurrence of dementia, Alzheimer’s, Parkinson’s, motor neuron diseases and cognitive impairment.

A.4 Other Populations that May Provide Useful Information on Possible CNS Effects from Space Radiation

The question is raised whether there are human populations other than the DOE worker populations and the radium dial painters discussed in section A.3 that could be studied effectively to assess high-LET exposure to brain tissue and CNS effects. The following sections identify some potential populations.

A.4.1 Patients Treated with Charged-Particles

NCRP in Commentary 25 (NCRP 2016) addressed the question “Are clinical studies with patients exposed to radiation (e.g., proton or carbon therapy; cranial irradiation for non-CNS disorders) of value in interpreting or modeling possible CNS effects from space radiation?” The answer at that time was that such studies are “very limited but may be useful for evaluating tests for CNS function”.

NCRP in Report 183 (NCRP 2019) provided a more comprehensive review. Although most literature on outcomes of medical radiation exposure involves examining survivors treated with photons, charged-particle irradiation (e.g., protons, carbon ions) is being administered more frequently today because these particles have Bragg peaks that permit better concentration of the radiation intensity at the tumor location, with improved sparing of healthy brain tissue. Further, the energy per nucleon of carbon ions used to treat glioblastomas and other brain diseases are of the order of several 100 MeV and much closer to GCR energies than the energy of a few MeV typical for alpha particle emitters.

At Berkeley, between 1954 and 1993 radiosurgical treatments of selected cranial targets with protons and helium ion beams were used to treat tumors that were encircling the brain stem or spinal cord, pituitary tumors, cranial tumors, and arterial venous malformations. The target absorbed doses at the tumor sites were comparatively large (> 40 Gy). “Nevertheless, the fact
that these absorbed doses were administered as daily fractions, and that, by nature of the particle beams, the neighboring cells in the brain could be exposed to low absorbed doses, the CNS findings from these patients are relevant to this study” (NCRP 2019).

Also, in the 1950s and 1960s heavy ion beams (protons only) were used clinically in Uppsala, Sweden, in Massachusetts at Harvard/MGH and in the former USSR. In 1975, the BEVALAC at Berkeley produced the first source of very heavy ions (helium to argon) to be used clinically (Skarsgard et al. 1980, Skarsgard 1998). “During the 1970s negative pi-meson (pion) beams for clinical use were developed in the US (LAMPF), Switzerland (SIN/PSI) and Canada (TRIUMF). … it was not until 1990 that the next clearly dedicated medical heavy ion facility went into operation: the 3-gantry proton synchrotron at Loma Linda” (Skarsgard et al. 1980, Skarsgard 1998).

NCRP (2019), however, concluded that “therapeutic radiation exposures differ dramatically from radiation exposure in space in terms of dose rate, duration, and mixture of radiation types. Consequently, it is unlikely that risks of adverse CNS effects due to space radiation can be inferred directly from the side effects of therapy”. Further, the interpretation of CNS effects, including cognitive impairment, would be problematic because of the underlying brain cancers or conditions being treated.

The growing clinical use of charged-particles to treat brain disorders, however, should not be discounted completely as there may be future value in interpreting or modeling possible CNS effects from space radiation. Accordingly, “harnessing the worldwide database of patients who have received charged-particle exposure to the brain will allow long-term tracking of endpoints related to short- and long-term behavioral and cognitive effects potentially associated with charged-particle exposures” (NCRP 2019).

A.4.2 Airline Crew Members

“Airline crew members are exposed to variable air quality, disrupted sleep and elevated radiation levels, primarily neutrons (Grajewski et al. 2002, 2003, 2018; Waters et al. 2009; Yong
et al. 2009; Anderson et al. 2011, 2014). Recent self-reported data indicate that crews might have higher prevalence of cancer (McNeely et al. 2018), but such increases are not consistent with more robust analytical studies (Schubauer-Berigan et al. 2015; Pinkerton et al. 2012, 2016a).

Aircrew may be at increased risk for cognitive impairment and brain white matter abnormalities (Reneman et al. 2016), and of dying from neurodegenerative disease amyotrophic lateral sclerosis (ALS) (Yong et al. 2014; Pinkerton et al. 2016b). Of particular interest are the possible interactions between “stressors” and radiation. Aircrew experience circadian disruption and sleep deprivation from traveling across multiple time zones and working at night (Grajewski et al. 2015; Pinkerton et al 2016a). Further they are exposed to poor quality air in the cabin (early aircrew worked during the days when cigarette smoking was allowed on airplanes), and there is a notable level of engine fuel leakage that contributes to a low level of air pollution throughout flights. Although this literature is too immature to make solid conclusions, enhanced research efforts could provide useful data that generalize to astronaut experiences” (NCRP 2019).

### A.4.3 Other Occupational Studies of Workers with Intakes of Radionuclides

There are international studies of workers exposed to radiation where intakes of radionuclides could be evaluated regarding brain dose and CNS effects (INWORKS, UK, Canada, Russia). Conceivably, such cohorts could be evaluated for CNS effects in relation to estimated alpha dose to the brain, and later combined with the US cohorts. It is of interest that the study of Mayak Production Association workers recently reported a statistically significant correlation between low-LET radiation and Parkinson’s disease (Azizova et al. 2020). However, similar associations are not seen in the large MPS cohorts.³ Workers at the Mayak facility, but in different processing departments apparently not evaluated in Azizova et al. (2020), had intakes of plutonium that were substantially higher than any other facility in the world, and could be similarly evaluated for dementia, Alzheimer’s, Parkinson’s and motor neuron disease.

³ Boice, JD. 2020. Personal communication.
A.5 Strengths and Weaknesses of Human Research on Protection Guidance for Long-Term Missions in Space

As a component of the MPS, NCRP and collaborators are evaluating DOE worker cohorts with intakes of radionuclides and will apply the improved estimates of radiation dose to brain tissue in risk evaluation for CNS effects. The relevance or strengths of the MPS investigations are that:

- the exposure is from high-LET radiation at a low dose rate (over years and not minutes or weeks as in the animal experiments);
- the exposure is to humans, and not rodents;
- the human exposure is to a mixed field of high-LET radiation and low-LET radiation (similar to exposures in space);
- the energy deposition is similar for a wide range of particle types and energies (cf, Brenner 1990; Zaider 1996; Hofmann et al. 2020); and
- human outcomes of interest can be directly evaluated, i.e., the occurrence of dementia and Alzheimer’s disease as well as quantitative measures of cognitive impairment.

While there are some similarities between high-LET alpha-particle exposure to brain tissue and high-LET GCR exposure, there are important dissimilarities (NCRP 2019). GCR and alpha particles emitted from radionuclides may share the same LET values, but their track structures and energies are quite distinct. The GCR energies can be of the order of several 100 MeV per nucleon which is much higher than the energy of a few MeV typical for alpha particles emitted from radionuclides. The range of alpha particles is about 20-35 microns in tissue while GCR ranges can be up to a meter. Alpha particles may expose single cells (delta electron ranges being negligible) while GCR tracks may simultaneous transverse over a million cells and their delta rays may extend out to 1 cm. Thus, alpha particles tracks are likely to expose single cells only while GCR tracks may simultaneously traverse $>10^6$ cells. For an individual cell, the effects may be similar, but at the tissue level there conceivably could be different outcomes when track and tissue structures are spatially correlated. Further, the distribution of dose from isotropic GCR exposures will not be subject to biokinetic modification but may show dose versus depth
dependence. The important weakness or limitations are that GCR (HZE particles) differ from alpha particles in the following ways:

- in track structure;
- in the range of energy deposition and particle traversal (from up to 1 cm versus 10s of microns); and
- in energies per nucleon (from up to 100s of MeV versus about 5 MeV).

It is unclear how these differences in track structure, energy deposition, and energies might affect the development of dementia, Alzheimer’s, Parkinson’s, motor neuron disease and cognitive function in humans since the possible mechanisms for such outcomes are not known. It is clear, however, that “the structure and function of the CNS results in damage mechanisms which are different from the mechanisms for cancer induction” (NCRP 2016). Comparisons are further complicated because CNS effects are seen only in rodents following GCR simulated exposures over a period of a few hours to perhaps a few weeks. “Although the CNS of mammals share the same basic biochemistry and physiology, they differ in details and degree of sophistication in function. These differences in details make it difficult to extrapolate from observed performance decrement in experimental animals to risk to a space exploration mission or to the mental health of individual crew members” (NCRP 2016). The overriding strength of the human studies is that they involve humans exposed to low dose rates (as opposed to rodents exposed to high dose rates). The overriding weakness is that alphas to the brain are imperfect analogues for GCRs (HZE particles).

The conundrum being faced by policy and decision makers with regard to protection guidance for space exploration is how to balance the CNS effects demonstrated in rodent experiments with the absence of any such effects in any human populations, except following high-dose radiotherapy circumstances. The MPS will evaluate worker populations with intakes of radionuclides and evaluate any associations between radiation dose to brain tissue and the occurrence of dementia, Alzheimer’s, Parkinson’s, motor neuron disease and cognitive impairment (Boice 2017, 2019). While alpha particles are an imperfect analogue for GCR (HZE
particles) the results in human populations can be used in conjunction with animal studies, radiation response and concept models, and the underlying assumptions related to human circumstances and space radiation (NCRP 2019). The complexity associated with judgments as to the potential risk for CNS disorders from space travel also includes addressing the background radiation of low-LET radiation, the exceptionally low dose rate received over a period of years, and the possible contribution of neutron exposures following GCR interactions with the space vehicle. The human data, then, should provide another line of evidence that can be considered when making judgments on radiation protection guidance for flight crews on long missions in space.

**A.6 Mechanisms for Radiation-Related CNS Effects**

This section discusses the imprecise understanding of the mechanisms by which radiation might cause CNS damage, and the uncertainties in extrapolating experimental animal findings to humans on a space exploration mission.

The mechanisms by which GCR (HZE particles) lead to CNS damage are not entirely clear but likely independent of the mechanisms leading to cancer, even though the initiating events may be the same (NCRP 2019). “The nature of CNS damage leading to functional and cognitive effects is significantly different from the cellular damage leading to cancer [cancer can be initiated through a wide range of mechanisms, often involving deoxyribonucleic acid (DNA) changes (mutagenesis), leading to uncontrolled clonal expansion] and therefore effects on the CNS may require a different approach to characterizing radiation exposure” (NCRP 2016).

The “established approach to characterizing radiation exposures was developed primarily to address the characteristics relevant to cancer biology. However, this perspective is not suitable for assessing GCR risks relevant to the CNS. The reasons for this incompatibility arise from the unique structure, organization and function of the brain relative to other organs and tissues elsewhere in the body. The fundamental cellular element of the brain is the nerve cell, or neuron. The adult human brain is comprised of \(~10^{11}\) neurons, including \(>10^{10}\) in the cerebral cortex, and a larger number of non-neuronal cells, including astrocytes, oligodendrocytes, and microglia.
(Azevedo et al., 2009; Herculano-Houzel, 2012). Other cell types form CNS-allied structures, including endothelial cells and pericytes at the blood-brain barrier, ependymal cells in the circumventricular organs, and neurosecretory cells in posterior hypothalamus (Peters et al., 1991)” (NCRP 2016).

“Although the CNS of mammals share the same basic biochemistry and physiology, they differ in details and degree of sophistication in function. These differences in details make it difficult to extrapolate from observed performance decrement in experimental animals to risk to a space exploration mission or to the mental health of individual crew members” (NCRP 2016).

Thus, the uncertainties to delineate possible mechanisms for radiation-related CNS effects following low level radiation exposures over a period of years and the dissimilarities between mouse and man regarding neurological functions make judgments as to mitigation and radiation protection matters challenging.
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