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AGING AND TOXIC RESPONSE: ISSUES RELEVANT TO RISK ASSESSMENT

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PREFACE

In 2002, EPA launched the Aging Initiative to develop a National Agenda for the Environment and the Aging to help guide the Agency's efforts to protect the health of older persons. This document, *Aging and Toxic Response: Issues Relevant to Risk Assessment*, is intended to orient EPA scientists and risk assessors to physiological and biochemical factors in the elderly that may influence their responses to exposures from environmental chemicals. Although it is not a comprehensive review of literature, the document identifies several data gaps and research needs that may inform the Office of Research and Development's Research Initiative on Aging in conducting research for better characterize risk to the elderly population from exposure to environmental agents.

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EXECUTIVE SUMMARY

Aging and Toxic Response: Issues Relevant to Risk Assessment was prepared to provide a very broad overview of the functional, physiological, and biochemical changes that occur in elderly persons, and the major age-associated diseases and conditions in order to better understand the age-related toxicokinetic and toxicodynamic impacts of environmental agents.

Elderly people can be vulnerable to environmental challenges due to their age-altered physiological processes and exposure patterns. In addition, the presence of age-associated diseases or conditions may increase susceptibility to the harmful effects of specific agents. Therefore, special consideration of the elderly population is needed in assessing risk from exposure to environmental agents.

A few examples of biological responses to exposure to environmental agents in the elderly population are provided, along with a succinct discussion of various animal models used to study the aged response to environmental agents. There is also recognition of risk assessment issues and relevant research needs.

This document is not meant to be a comprehensive review of the literature for the topic areas discussed. Instead, it is intended to orient the reader to the general subject of aging and potential toxic responses, particularly the identified physiological factors likely to influence the risk of exposure to environmental agents in elderly populations.

1. INTRODUCTION

Americans aged 65 years and older are a growing segment of the U.S. population. Various federal government organizations, including the U.S. Environmental Protection Agency (EPA, or Agency), recognized the challenges confronting older Americans. Attention to the possible health effects on elderly Americans from environmental exposures began with the publication of *Aging in Today's Environment* (Committee on Chemical Toxicity and Aging, 1987) and *Principles of Evaluating Chemical Effect on the Aged Population* (WHO, 1993). In 2002, EPA launched the Aging Initiative to develop a National Agenda for the Environment and the Aging to help guide the Agency's efforts to protect the health of older persons. In response to these efforts, the National Academy of Sciences convened a workshop entitled *The Differential Susceptibility of Older Persons to Environmental Hazard*s in December 2002 (NAS, 2002).

During certain life stages, particularly in early development (U.S. EPA, 2005a) and later life, individuals can be differentially exposed to and affected by a variety of toxicants in their environment. In the aging population, exposures may be related to disease and nutritional status, occupation (NRC and IOM, 2004), and lifestyle choices (e.g., smoking, consumer product use, subsistence activities, hobbies) (Verbrugge et al., 1996), and the effects of these exposures may accumulate throughout an individual's life (U.S. EPA, 2003). In addition, early-life exposures may impact the occurrence of later health conditions (Barker, 1998). Due to the gradual decline in physiological processes, and the increase in age-associated diseases and conditions, the elderly have or may have increased susceptibility to health effects from exposure to environmental agents.

The growing proportion of Americans in the aged demographic group heightens the need to understand the potential impact of environmental influences on this sector of the population. In 2002, 35.6 million persons in the U.S. were aged 65 years and older, accounting for about 12% of the total population; by 2030, the older population will more than double to 71.5 million (U.S. AoA, 2004). Worldwide, the number of persons aged 60 years and older is estimated to be more than 600 million, and that number is projected to grow to almost 2 billion by 2050, when the population of older persons will be larger than the population of children (0–14 years) for the first time in human history (WHO, 2002).

Subpopulations within the elderly population can be delineated by gender or race/ethnicity and are important distinctions. Women make up 58% of the population aged 65 years and older and 69% of the population aged 85 years and older (FIFARS, 2004). The U.S. is becoming more racially and ethnically diverse; in 2003 non-Hispanic whites made up about 83% of the population aged 65 years and older, but this proportion is expected to decline to 61% by 2050 (FIFARS, 2004). In addition, genetic polymorphisms related to metabolic capacity within the aged population may influence the toxicity caused by exposure to a parent chemical or a reactive intermediate.

Chapter 2 of this document defines the terms and age groupings for aging research. Chapter 3 discusses the physiological changes that occur in the elderly and highlights age-related diseases and conditions in each system. Chapter 4 highlights the impact of pharmaceutical use on the response to environmental toxicants. Chapter 5 gives examples of environmental contaminants of concern to the elderly population. Chapter 6 succinctly discusses various animal methodologies and models used in aging research. Chapter 7 evaluates and identifies risk assessment issues for the aged population and future research needs.

2. DEFINING THE AGING POPULATION

When referring to older humans, the terms "aged," "elderly," "geriatric," and "senescing" are used interchangeably. In the U.S. and many other countries, the aged population is defined as those aged 65 years and older, based on the traditional age of retirement from the work force. However, there is no general agreement on the start of this stage of life. For example, the United Nations defines people aged 60 years and older as elderly (WHO, 1993).

One concern about grouping all the elderly into one broad category is that because physiological changes occur variably after 65 years of age. Therefore, the creation of subcategories of age groups has been proposed: 65–74 years, young-old; 75–84 years, old; 85–99 years, old-old; and over 100 years, oldest-old (Spirduso, 1995). Most gerontologists refer to persons in the last group as "centenarians," and this group has recently been the subject of much research in an attempt to discover the basis of their extreme longevity. This document, for the most part, addresses all elderly as one age category: 65 years and older.

Physiological deterioration does increase with age (Crome, 2003), with the percentage of persons requiring help from others for basic life activities increasing from about 9% in the 65–74 years age range to 20% in the 75–84 years age range and to 50% in those 85 years and older (Jette, 1995). However, these age-based subcategories do not account for the variability that occurs among individuals of the same age (U.S. EPA, 2002). To address this issue, the term "biological age" is used to describe the functional ability of one individual when compared with another individual of the same chronological age. "Usual aging" is said to occur in individuals who function well but who may exhibit modest deterioration of the physiological systems; "successful aging" occurs in those who will continue to live in a healthy manner (Rowe and Kahn, 1998). Finally, the descriptive terms "fit" and "frail" refer to the maintained levels of independence for daily living (Geller and Zenick, 2005).

Animal models employed for research on aging are discussed in Chapter 6. The terms "elderly," "aged," and "geriatric" are not usually used for animals and there are no generally agreed-upon criteria available for determining old age for animal species. Using life table characteristics as a guide, an animal is deemed "old" if its age is greater than the median length of life of the population, and it may be placed in the category of "oldest old" if it is older than the age of the 10^{th} percentile survivors.

3. PHYSIOLOGICAL CHANGES AND AGE-RELATED DISEASES AND CONDITIONS

The progressive modification of structure and function with age involves alterations not only at the genetic, molecular, and cellular levels, but also at the level of the tissues, organs, systems, and the entire organism. The processes of how a toxicant affects the body are known as toxicokinetics (TK) and toxicodynamics (TD). TK, also referred to as pharmacokinetics, is the determination and quantification of absorption, distribution, metabolism, and excretion of chemicals. TD, also referred to as pharmacodynamics, is the determination and quantification of the sequence of events at the cellular and molecular levels leading to a toxic response to environmental agents.

Age-related changes in TK (Calabrese, 1986; Hattis and Russ, 2003) and TD (Roberts et al., 1996) have been studied, but given the interindividual variation in physiological changes, the degree to which a given elderly individual will exhibit TK and TD changes cannot be predicted solely on the basis of chronological age. The natural physiological deterioration in organs and tissues of elderly individuals may lead to increased responses toward xenobiotics that may additionally be compounded by the preexisting conditions of the individual. Also, genetic polymorphisms affect individual responses to environmental chemicals, although the database for such variation within the elderly population is quite limited (Dybing and Soderlund, 1999).

In the following sections, each organ or system is discussed in reference to age-related changes in its structure or function, not only as an inherent part of aging, but in response to environmental agents. The focus throughout this document is on the normal processes of aging and how these may alter risk, with a few examples of disease states or conditions that can also alter risk. Although it is important to differentiate between age-related pathology and true physiological aging, this is often difficult because the majority of age-related changes increase the vulnerability of an aging organism to disease and, ultimately, death.

3.1. GENETIC AND CELLULAR STRUCTURE AND FUNCTION

In general, genetic damage increases with age, including the frequency of DNA adducts, point mutations, microsatellite expansions and contractions, amplifications and contractions of DNA sequences, gene rearrangements, and chromosomal aberrations (Burkle, 1996). Telomere

length appears to decrease with increasing age, although the functional consequences are not clear. The rate of cellular repair decreases with age, and the occurrence of incomplete or inaccurate repair increases with age; this results in an increase in structural changes in the DNA or associated proteins. Genetic transcription may increase, decrease, or remain unaffected with age. In addition, the rate of gene expression or protein synthesis generally declines with age (Van Remmen et al., 1995).

A number of changes occur at the cellular level, leading to changes in structure or function of various organ systems. Cellular signal transduction plays a key role in functional regulation (Lodish et al., 1995) and may be altered during aging (Yeo and Park, 2002). Alterations in apoptosis have been suggested to play a major role in aging (Holt, 1995; Warner, 1999).

The elderly may be more vulnerable to chemical exposure because of a decreased capacity to repair DNA damage caused by mutagens. Decreased immunologic defenses may also increase the vulnerability of the elderly to chemical carcinogens. Also, the elderly have a decreased ability to detoxify free radicals and other reactive metabolites that can initiate carcinogenesis, promote proliferation of initiated cells, and drive progression to the malignant phenotype (Balducci et al., 1986; Rikans and Hornbrook, 1997). On the other hand, other physiological changes in the elderly may reduce their vulnerability to certain chemical carcinogens, including decreased capacity for metabolic activation, increased capacity for deactivation, decreased enteric absorption, and reduced capacity for cellular proliferation (Balducci et al., 1986).

Cancer is characterized by abnormal cells with partial or complete lack of structural organization and functional coordination with normal cells and tissue that grow more rapidly than normal cells; it is predominantly a disease of the aged (Dix, 1989). The accumulating abnormal growth forms a distinct mass (tumor), which can be either benign or malignant. Benign tumors are noncancerous; malignant growths invade and destroy the tissue in which they originate and can metastasize to other sites in the body via the bloodstream and lymphatic system.

Fundamental aspects of cancer development in the elderly are not well understood (Lee and Wei, 1997). The increase of cancer incidence with age may be related to decreased immune function, a longer duration of exposure to carcinogens due to increased length of life, increased susceptibility of cells to carcinogens, and several other biological factors (Cohen, 1994).

Because cancerous growths can continue long after the initiating stimulus ceases and they typically occur over many years, latency is an important consideration.

Examples of cancers that occur at a higher frequency in the elderly include those of the lung (Connolly, 1998), pancreas (Braganza and Sharer, 1998), skin (Chuttani and Gilchrest, 1995), colon (Wald, 1998), prostate (George, 1998), breast (Mansel and Harland, 1998), and uterus, ovaries and cervix (Brown and Cooper, 1998). Both the incidence of and mortality from cancer are higher in the elderly population, potentially due simply to the increasing length of life expectancy. Also, research seems to indicate that environmental exposure early in life is a key risk factor for cancer diagnosis later in life (Perera, 1997, 1998). Because the role of environmental agents in cancer risk is complex, a detailed discussion of cancer is beyond the scope of this document.

3.2. NERVOUS SYSTEM

The central nervous system (CNS) may undergo progressive deterioration at all levels of organization: structural, biochemical, and functional. On the structural level, only a modest decrease in brain weight actually occurs with advancing age. However, the volume of the cerebrospinal fluid (CSF) does increase with age, with a concomitant decrease in brain volume (Stafford et al., 1988). Although generalized age-associated loss of neurons is small, the key issue is the decline in the number of synapses with advancing age (Masliah et al., 1993). Some localized brain regions suffer a more substantial loss of neurons than do others (Katzman, 1995); more specifically, motor neurons that supply skeletal muscle are lost with aging, although no available evidence suggests that this results in functional changes.

Aging alters the biochemistry of the neurotransmitter system in both the brain and the peripheral and autonomic nervous systems (Collins and Cowen, 1998; Cotman et al., 1995). For example, glutamate, N–methyl-D-aspartate, and kainic acid-binding receptor binding all change with age, as does the level of gamma amino butyric acid in the CSF. The elderly have higher blood levels of the sympathetic neurotransmitter norepinephrine than do younger people, probably due to an increased rate of release of norepinephrine by sympathetic nerve fibers, although a decreased clearance of norepinephrine from the circulating blood may also be involved. In addition, the response to the sympathetic neurotransmitter is impaired at advanced ages in a number of important target sites, e.g., the heart.

Carrier-based transport may be somewhat compromised (e.g., decreased transport of choline and glucose), and the blood-brain barrier may be more vulnerable to damage in elderly individuals. Most of the studies examining blood-brain barrier function and aging have failed to show any significant age-related alterations in permeability to lipophobic substances and high-molecular-weight solutes in the absence of neurological disease (Johnson and Finch, 1995; Mooradian, 1988). However, when exposure is concurrent with a chronic disease that may damage the integrity of the barrier (e.g., Alzheimer's disease, hypertension, diabetes, stroke), chemicals may more freely penetrate the blood-brain barrier in the elderly. Also, there is some evidence that exposure to these agents early in life may cause later neurological impairment (Barone et al., 2001; Landrigan et al., 2005; Logroscino, 2005).

3.2.1. Cognitive Function

Cognition refers to processes of the mind such as perceiving, remembering, thinking, learning, and creating. Aging impacts three aspects of cognition: attention, memory, and intellectual functions. Attention, the ability to focus on and perform a simple task without losing track of the task objective, does not undergo an appreciable age-associated change. Because this process involves the circuitry of the brain stem and the thalamus, it appears that these brain regions remain functionally intact in the elderly (Albert and Moss, 1995). However, other aspects of attention and response inhibition involving frontal lobe functioning and, presumably, dopamine modulation of frontal activity do appear to undergo an age-related decline (Volkow et al., 1998). Other aspects of intellectual function, such as executive function requiring abstraction and mental flexibility, can also be affected by aging and are associated with a subtle decline in dopaminergic modulation also in frontal cortical activity (Volkow et al., 1998).

Memory, on the other hand, progressively deteriorates in the elderly, with impairment evident in 15% of men and 11% of women aged 65 years and older and more than 33% of all elderly aged 85 years and older (FIFARS, 2004). However, many types of memory are not impaired in the healthy elderly, such as short-term memory (Smith and Earles, 1996) and the initial processing of sensory information.

In the absence of disease, intellectual functions can be rather well maintained in the elderly (Kausler, 1994). Although some kinds of learning become increasingly difficult with increasing age, e.g., learning tasks that require great perceptual speed and a high level of

physical coordination, some aspects of intellectual function may actually improve (e.g., creativity), although speed of performance may markedly deteriorate with advanced age. With respect to semantic knowledge (verbal ability in vocabulary, information, and comprehension), intellectual performance changes little during adult life. Procedural memory, which requires the use of both learned motor and cognitive skills (e.g., typing or riding a bicycle), does not deteriorate in the normal elderly, but the functional ability to perform them may be affected by aging.

Alzheimer's disease **(AD)** affected nearly 4.5 million Americans in 2000, and the affected population is expected to increase to 13.2 million by 2050 (Hebert et al., 2003). In 2002, AD was responsible for 3.2% of all deaths among the elderly (Anderson and Smith, 2005). AD typically involves the degeneration of neurons in the cerebral cortex and the hippocampus, and the morphologic hallmarks of the disease are senile plaques (containing the core protein beta-amyloid surrounded by swollen degenerating nerve terminals and glia cells) and neurofibrillary tangles (found inside the axons and dendrites of brain neurons). With further progression, deficits occur in the ability to communicate orally and in writing, recognize familiar objects by sight, and copy simple drawings. The individual often remains alert and cognizant until the terminal stages (Terry and Katzman, 1992).

A number of environmental exposures have been studied to examine the relationship with the development of AD (Brown et al., 2005), including aluminum and pesticides. A genetic predisposition for the development of AD also appears to exist; in particular, the epsilon-4 allele of the apolipoprotein E gene has been found to increase the risk of the disease at advanced ages. In addition, AD in women may be related to the loss of estrogen after menopause (Kawas et al., 1997).

Other dementias. Dementia is prevalent in the older population, with 15% of men and 11% of women experiencing moderate or severe memory impairment and the prevalence increases with age (FIFARS, 2004). However, although memory loss is the most common symptom of dementia, it does not necessarily indicate a diagnosis of dementia.

The most common disease that can cause dementia is AD, followed by vascular dementia (VaD). Other diseases that can cause dementia include Lewy body dementia, frontotemporal dementia, Huntington's disease, and Creutzfeldt-Jakob disease. VaD is related to a reduced blood flow to the brain (Hershey and Olszewski, 1994), and the subtype multi-infarct dementia is

caused by blood vessel obstructions, many too small to have produced a major clinical problem. A history of strokes or transient ischemic attacks may be present.

A number of environmental risk factors may be associated with cognitive decline, including polychlorinated byphenyls (PCBs) (Schantz et al., 2001), metals, pesticides, and solvents (Baker, 1994). For VaD, these include occupational exposure to pesticides, plastic, or rubber (Hébert et al., 2000; Lindsay et al., 1997).

3.2.2. Motor Function

The elderly have some loss in ability to precisely control skeletal muscle activity, resulting in a variety of deficits in motor performance ability. These deficits are due to age-associated deterioration of the central processing system, as well as to changes in sensory and muscle function.

Reaction time – the time from stimulus to initiation of a motor response, such as the contraction of a skeletal muscle – slows with advancing age (Spirduso, 1995). Although this is due in part to the slowing of both the muscle contraction and the peripheral nerve impulse conduction velocity, the slowing of central processing is the primary defect. Reaction time in the elderly is slowed even more when the individual is confronted with a choice of alternative responses or if the movement complexity increases. Reduced speed appears to enable the elderly to maintain accuracy of movement.

Mobility changes only moderately in the elderly who are free of discernible diseases. In particular, the speed of walking decreases with age; this occurs to a larger degree in women than in men (Fernandez et al., 1990). Although a slow gait is likely due to reduced muscle strength and joint deterioration as well as impairment of balance and posture (Walker and Howland, 1991; Woolacott et al., 1986), it may also enhance the ability of the elderly to monitor the environment, thus enabling them to avoid hazards. A number of environmental risk factors have been associated with a decline in motor function, including metals such as lead and manganese, pesticides, and solvents.

Parkinson's disease **(PD)** currently affects approximately 500,000 people in the U.S., and about 50,000 new cases are reported annually, with an average age of onset of 60 years. PD is a motor disorder with symptoms that include tremors at near rest, rigidity (resistance to passive movement of limbs), slowness in initiating movements, deterioration of postural reflexes, lack of

facial expression, and rapid, small steps with decreased associated movements such as arm swinging (Mutch and Inglis, 1998). This is a progressive disease, resulting in severe disability and ultimately death. The rate of progression varies among individuals, with death occurring within 5 years in 25% of the cases and within 10 years in 60% of the cases.

There is a clear association between the loss of dopamine receptors in the brain (nigrostriatal projection) and motor task performance as is seen in PD. Neurons in the substantia nigra that send axons to the striatum are lost, resulting in a decrease in the release of the neurotransmitter dopamine in this brain region (Volkow et al., 1998).

Although some genetic polymorphisms are linked to PD, the majority of PD cases are sporadic (Checkoway et al., 1998). Risk factors for PD include increasing age and environmental exposure (Ben-Sholom, 1997; Brown et al., 2005; Tanner and Goldman, 1996), including pesticides (Abbott et al., 2003), metals such as manganese, solvents, farm or rural residence, farming occupation (Petrovich et al., 2002), or drinking well water. In fact, only approximately 10% of PD cases are related to occupational exposures (Semchuk et al., 1992). Environmental toxicants may interact with genetic predispositions, e.g., pesticide exposure and glutathione-S-transferase polymorphism (Menegon et al., 1998). In addition, there is some evidence for early-life exposure to environmental agents and later development of PD (Logroscino, 2005).

Stroke refers to a sudden or relatively rapid occurrence of inadequate blood flow to the brain caused by the blockage or rupture of a brain blood vessel, resulting in brain cell death and neurological impairment (Ebrahim, 1998). Importantly, strokes can allow the blood-brain barrier to be breached, potentially leading to increased cerebral exposure to toxicants (Cipolla et al., 2004). Strokes may occur at any age, but are most common in the elderly. In the U.S., the incidence of stroke is about 700,000 per year, and more than 160,000 deaths annually are attributed to strokes. More than half the survivors have functional impairments, ranging from inability to function in the work force to loss of ability to carry out activities of daily living. Also, an estimated 20% of all dementia cases are thought to be due to stroke (Barba et al., 2002).

3.2.3. Sensory Function

Impairment of the sensory system occurs in almost all elderly people. Indeed, studies show that virtually all sensory modalities decline in acuity with age (Pathy, 1998). The sensory

system includes vision, hearing, touch, taste, and smell, and it can be affected by exposure to metals and solvents (Gobba, 2003).

Vision. Age-related sight impairment occurs in 16% of men and 19% of women (FIFARS, 2004). A number of changes occur in the visual system with age (Scialfa and Kline, 1996). Visual acuity, the ability to see objects in fine detail, decreases with increasing age and likely results from a decrease in the number of neurons making up the optic nerve. Loss of rods results in a reduced ability to adapt to low-intensity light. The reduced ability of the elderly to discriminate colors in the green-blue-violet region of the visible light spectrum does not appear to be due to a defect in the cones; rather it relates to a yellowing of the lens with increasing age (Hood et al., 1999), which also may underlie the increased susceptibility to glare. Those over age 50 years have some loss in depth perception, for reasons that remain to be identified.

Vision impairment can be caused by a decrease in resting pupil size, which reduces the illumination of the retina and the ability of the lens to become more spherical when the person is looking at near objects. This decrease is due to a change in the physical properties of the lens and in the function of the ciliary muscles, and it progresses with age. Several visual disorders occur much more commonly in the elderly than in the young, including cataracts (Young, 1991), glaucoma (Shiose, 1990), and age-related macular degeneration (Brodie, 1998). Visual function can be disturbed from exposure to metals, solvents, and pesticides (Gobba, 2003).

Hearing. Age-related hearing impairment (presbycusis) is found in nearly one-half of all elderly men and one-third of all elderly women (FIFARS, 2004). Many changes related to hearing loss occur in the structures of the inner ear (Willott, 1991). Cilia, which encode high-frequency sound, atrophy, auditory nerve cells are lost, blood supply to the cochlea is reduced, and the structure of the basilar membrane is altered. Age-related hearing loss due to changes in the external and middle ear appears to be of minor importance. In some individuals, altered functioning of the vestibular apparatus in the inner ear related to balance and sensory perception may be involved in the feeling of light-headedness and vertigo.

Many elderly people have difficulty in distinguishing spoken words, a problem magnified by background noise (Bergman et al., 1976). In addition, hearing loss is likely to contribute to an age-associated decline in cognitive ability in some individuals.

Although normal aging can cause hearing loss, exposure to toxicants such as solvents, gases such as carbon monoxide (CO), and metals such as lead and manganese (Gobba, 2003;

Johnson and Nylén, 1995; Rybak, 1992). In addition, chemicals (e.g., solvents) may interact with lifetime noise exposure and result in hearing loss (Cary et al., 1997).

Touch. Aging alters the cutaneous sensory system by decreasing the number of some sensory receptors (Pacinian and Meissner corpuscles) (Meisami, 1994). However, little change with age occurs in the number of other receptors (Merkel discs) and free nerve endings. Particularly in the hand region, sensitivity to touch decreases with age, as does the ability to distinguish between two spatially distinct points of contact. As an individual ages, decreased perception of ambient temperature is experienced. High-frequency vibration is sensed to a lesser degree with increasing age by the Pacinian corpuscles, particularly in the feet and legs. Although the ability to detect the onset of pain is not affected by age, whether the elderly are more or less tolerant of pain is debatable. The ability to sense limb movement and reproduce changes in limb position (proprioception) appears to deteriorate with advanced age (Skinner et al., 1988). Metals, solvents, and pesticides may impair the touch sensation (Gobba, 2003).

Taste and Smell. Because of methodological difficulties in testing, the effects of age on taste and smell are not well understood (Bartoshuk and Duffy, 1995). However, age seems to have a greater effect on the sense of smell than on taste (NIDCD, 2002a), with the sense of smell starting to decline around age 60 (NIDCD, 2002b). Loss of taste and smell can lead to inappropriate eating habits, malnutrition, weight loss or gain, weakened immunity, and increased exposure to toxicants (Santos et al., 2004). For instance, individuals who are not able to smell natural gas may have prolonged exposure and increased risk than those with the ability to smell. Some causes of taste and smell loss include medication, disease, infection, dental problems, head injury, smoking, and vitamin deficiencies, as well as metals (e.g., cadmium) and solvents (Gobba, 2003; NIDCD, 2002a, 2002b; Schwartz et al., 1990).

3.3. CARDIOVASCULAR SYSTEM

In healthy individuals, the heart increases modestly in size over time (Folkow and Svanborg, 1993), primarily due to an increase in the thickness of the wall of the left ventricle of the heart resulting from hypertrophy of the wall's cardiac muscle cells. The age-associated increase in heart mass is far greater in people who suffer from hypertension.

The conductile system of the heart also undergoes age-associated changes (Fleg et al., 1988). After age 60, the number of cells in the sino-atrial (SA) node progressively declines.

Some decrease in the resting heart rate with increasing adult age also occurs, and this appears to be due in part to a change in the SA node's pacemaker function. Some change with age also takes place in the atrio-ventricular node and its connection to the conductile system of the ventricles, causing a minor delay in the progression of action potentials from the atria to the ventricles. Increasingly common with aging are abnormal rhythms (arrhythmias) of the heart, such as a too rapid (tachycardia) or a too slow (bradycardia) heart rate, or the occurrence of pacemaker cells at sites other than the SA node. Sudden death due to an arrhythmia may be relatively common in the elderly (Cleland et al., 2002).

The pump function of the heart also changes with increasing age (Lakatta, 1995). The blood flow into the left ventricle during diastole becomes slower, but this is compensated for by the increased amount of blood pumped by the left atrial contraction in late left ventricular diastole. Thus, at rest, the total amount of blood entering the left ventricle during diastole is similar for old and young people of the same size and gender. The stroke volume in resting healthy people is similar for young and old of the same size and gender, as is the cardiac output. However, there is one difference between the healthy young and old in the pump function of the left ventricle: the contraction of the left ventricle is prolonged with increasing age, and this prolongation helps the healthy elderly maintain a stroke volume similar to that of the young. Although only small age-related changes in the functioning of the heart as a pump occur in healthy people at rest, substantial differences emerge when a person is challenged.

Arterial blood vessel structure changes with age (Kottke, 1985). With increasing age, the diameter of the lumen of the large arteries increases. The walls of these arteries increase in thickness and become stiffer. Although the lumen diameter of the smaller peripheral arteries shows less of an increase, wall thickness shows a greater increase. These age-related changes in arterial structure are due to several factors: a decrease in elastin relative to collagen in the arterial walls, an increased mineralization of the elastin with calcium and phosphorus, and an increase in sustained contractile activity of smooth muscle in the walls of the arteries. One of the hallmarks of aging of the cardiovascular system is the increased velocity of the pulse wave, which stems from the increased stiffness of the arterial walls. Arterial impedance does not increase through middle age because the increase in arterial wall stiffness is compensated for by the increase in the arterial lumen. However, at advanced ages, impedance increases because the effect of the increased stiffness prevails.

The influence of aging on capillaries is an understudied subject (Folkow and Svanborg, 1993). In some tissues, the number of capillaries decreases at advanced ages, but the limited information available indicates that no change occurs with age in either structure or function. In addition, an age-associated vein distensibility occurs; this interferes with the proper functioning of the valves and, as a result, fluid tends to collect in the legs. As peripheral vascular resistance increases with age, blood perfusion to the organs decreases (Lakatta, 1995).

The sympathetic nervous system plays an important role in the response of the cardiovascular system to challenges, and its influence is reduced with age (Lakatta, 1993). The intrinsic ability for muscle contraction or relaxation does not change, but alterations in the processes linking the receptor with the contractile or relaxation mechanisms do occur with age. These changes contribute to altered baroreflex responses that often impair the ability of elderly individuals to adapt to cardiovascular stressors. Because of the age-related decline in beta-adrenergic function, the maximal heart rate in response to exercise decreases with age.

Beta-adrenergic dilatation and alpha-adrenergic constriction of veins is decreased at advanced ages. A decline occurs in the beta-adrenergic receptor function (Tumer and Scarpace, 1996; Podrazik and Schwartz, 1999); this impaired stimulation of the heart is not due to a decrease in the number of receptors, but to an alteration in the cellular signal transduction response to receptor stimulation. Importantly, there are persistent effects after developmental exposure to nicotine (Navarro et al., 1990) and chlorpyrifos (Slotkin et al., 2002).

Release of norepinephrine from adrenergic nerve terminals within the cardiovascular system is the primary mechanism for increasing heart rate and blood pressure in order to increase organ perfusion. Systolic, diastolic, and mean blood pressure all increase with aging (Svanborg, 1989). The increase in mean and diastolic pressure is primarily due to increased resistance of the arterioles. The increase in systolic pressure stems from the increased stiffness of the walls of the arteries as well as to increased resistance of the arterioles. Although some studies have not seen an age-associated increase in blood pressure, body weight, physical exercise, smoking, and lead have been shown to increase blood pressure in the elderly (Svanborg, 1996).

In young adults, the need to increase the cardiac output during exercise is met by an increase in the activity of the sympathetic nerve fibers to the heart, which increases the heart rate and stroke volume, the latter because of the increased contractility of the ventricular cardiac muscle cells. In the healthy elderly, heart rate and ventricular contractility increase much less in response to exercise because of decreased effectiveness of the sympathetic nervous system. This

is compensated for by an increase in the blood volume in the chamber of the left ventricle at the end of diastole, causing an increase in the length of the left ventricular muscle cells. Within limits, an increase in the length of the cardiac muscle cells increases the force of contraction. Therefore, in the elderly, an increase in stroke volume during exercise is secondary to the increase in diastolic volume of the left ventricle. Thus, the healthy elderly can increase cardiac output in response to exercise, but by a different mechanism than that of the young. However, this compensatory ability is compromised in the elderly who suffer from age-associated cardiovascular disorders. A number of environmental factors can lead to cardiovascular conditions, including metals such as lead and air pollutants.

Heart failure involves a decline in the pump function of the heart, which can result in several systemic problems and potentially death. A person with heart failure may have inadequate oxygen delivery to the tissues, pulmonary congestion, systemic venous congestion, or all three life-threatening conditions (Lye, 1998). It is an age-associated syndrome in that 75% of the patients suffering from heart failure are over age 60 years. The two major causes of this syndrome are coronary heart disease and hypertension. Lesions in the heart valves, not an uncommon problem in the elderly, are also a potential cause.

Coronary heart disease and atherosclerosis are two major age-associated medical problems. Coronary heart disease is often caused by an inadequate supply of oxygen to the heart muscle (Shephard, 1997). The coronary arterial system can be subject to atherosclerosis, a progressive process involving plaques that narrow the lumen of the coronary arteries and can impede blood flow in the arteries in which they occur, particularly by serving as sites of clot formation (Crow et al., 1996). In addition, atherosclerotic plaques commonly occur in the internal carotid arteries near their origin in the neck, the middle cerebral arteries, the vertebral arteries, and the basilar arteries. As these plaques grow in size with increasing age, they often become sites for formation of blood clots that cut off the blood supply to regions of the brain.

If atherosclerosis is sufficiently great, the heart muscle suffers from ischemia, leading to the death of heart cells, referred to as myocardial infarction (MI). An MI can be sudden when, in addition to an atherosclerotic plaque, it involves a thrombus or an embolus. Both the incidence and the prevalence of coronary heart disease increase with increasing age. The prevalence is 50% in the age range from 65 to 75 years and 60% in those over 75 years of age. The major risk factors include elevated systolic blood pressure, high levels of low density lipoproteins, left ventricular hypertrophy, diabetes mellitus, elevated plasma glucose levels, smoking and air

pollution. Although in healthy people only modest changes in heart pump function occur with aging, coronary heart disease can cause serious deficits that range from difficulty in exercising to decreased function at rest. There is evidence that there may be fetal origins to both coronary heart disease (Barker, 1995) and atherosclerosis (Palinski and Napoli, 2002).

Hypertension and hypotension are blood pressure conditions common in the elderly (Scott, 1998). Hypertension – persistently elevated blood pressure – occurs in approximately 50% of the elderly (FIFARS, 2004). There are two basic forms of hypertension. One involves elevation of both the systolic and diastolic blood pressures (defined numerically as a systolic pressure above 140 mm Hg and a diastolic pressure above 90 mm Hg). The other form (isolated systolic hypertension) is systolic pressure above 160 mm Hg and diastolic pressure below 90 mm Hg. Both forms of hypertension increase the risk of stroke and heart attacks.

Orthostatic or postural hypotension, a drop in systolic pressure of more than 20 mm Hg for at least 1 minute, occurs in about 60% of the population over age 65 (MacLennan et al., 1980). By decreasing blood flow to the head, hypotension is a contributor to falls among the elderly. Hypotension is caused by altered reflex responses to a falling blood pressure, the most important being the blunting of the arterial baroreceptor reflex, which readjusts the blood pressure by modifying both heart rate and resistance of the arterioles. The elderly are also prone to postprandial hypotension (a fall in blood pressure an hour or so after eating); this is due to an inability to compensate for a decrease in the resistance of the arterioles of the gastrointestinal (GI) tract by increasing the resistance of the arterioles of other regions (Lipsitz et al., 1983). There is some evidence that blood pressure in adults is linked to early growth factors (Lackland et al., 2003).

Anemia is commonly found in the elderly, although whether anemia occurs as a normal result of aging is debated. Anemia is a decrease in the normal concentration of red blood cells (erythrocytes), as measured by the hemoglobin count, that leads to the decrease of oxygen transported in the blood. This results in fatigue, weakness, and reduced mobility. It has been theorized that the disruption of proinflammatory cytokines response (e.g., interleukin [IL]-6) could be one explanation (Ershler, 2003). Causes include blood loss, nutritional deficiencies (iron, vitamin B_{12}, folate), chronic diseases such as chronic kidney disease, diabetes, cancer, cardiovascular disease (see above), rheumatoid arthritis, and gastrointestinal conditions, as well as medical treatments. In turn, anemia can increase the risk of cardiovascular disease (Pereira and Sarnak, 2003). Anemia in the presence of chronic kidney disease (McCullough and Lepor,

2005) may increase the risk of dementia (Atti et al., 2005). Those with anemia are at particular risk from exposure to CO.

3.4. GASTROINTESTINAL SYSTEM

The processing of food by the GI system involves the following activities: motor activity of the GI tract, glandular secretion, digestion, and absorption of substances from the lumen of the GI tract into the blood or lymph. Although the healthy elderly carry out these functions rather well, some age-associated changes in each of the functions do occur (Holt, 1995).

More than 25% of all U.S. adults aged 65 years and older have no natural teeth (FIFARS, 2004), and the skeletal muscles involved in mastication become weaker with aging, which can result in a reduced ability to chew and consequential malnutrition. Secretion of saliva may or may not decrease with age in the healthy elderly, but disease states or medications often alter salivary secretion.

Although the ability to digest carbohydrates, protein, and fat is not compromised at advanced ages (although people genetically susceptible to lactase deficiency have a progressively reduced ability to digest lactose with aging), the capacity to absorb these substances decreases with age. However, this poses little problem for the elderly because of increased gastric residence time (Evans et al., 1981; Horowitz et al., 1984), which generally increases the absorptive capacity to excess of what is needed. The slower transit time through the stomach and lower GI tract increases the time available for absorption and potentially increases the maximal plasma concentration and the length of time of maximal plasma concentration. In general, the extent to which chemical absorption is affected by age (Calabrese, 1986) depends on the nature of the foreign substance and the degree to which any elderly individual has compromised GI function. The absorption process may also be extended due to reduced gut motility.

Various xenobiotics may impair nutrient intake by altering GI acid and enzyme production, reducing appetite, slowing gut motility and gastric emptying, and reducing absorption (Iber et al., 1994). Reduced absorption of nutrients, in combination with reduced food intake, leads to decreased levels of vitamins in the body (Balducci et al., 1986; Schumann, 1999). Both vitamin and protein malnutrition in the elderly can have a severe impact on hepatic metabolism and clearance (Iber et al., 1994; Thomas, 1995).

Significant age-associated change in gastric emptying occurs only when a meal is very large, and constipation and diarrhea do not occur more frequently in the elderly unless related to a disease. However, the elderly are more prone to fecal incontinence because of both higher

rectal pressures when the rectum is distended by a fecal mass and reduced force of the anal sphincter.

Atrophic gastritis can reduce gastric secretion of hydrochloric acid, and the prevalence and severity do increase with age. This inflammatory disease, probably caused by an autoimmune mechanism, leads to destruction of the parietal cells, which secrete hydrochloric acid. These parietal cells also secrete intrinsic factor, and their loss can also result in pernicious anemia. Lower stomach pH and decreased active intestinal transport may reduce the absorption of both xenobiotics as well as essential vitamins such as A, B1, B12, folate and calcium (Saltzman and Russell, 1998). Additionally, gallstones, which are more prevalent at advanced ages, may prevent bile from reaching the lumen of the GI tract.

Dysphagia, or swallowing difficulties, are minor and do not cause significant functional difficulties in the healthy elderly. However, dysphagia can arise with age-associated diseases that adversely affect motor nerve control of the swallowing process (e.g., stroke, PD, amyotrophic lateral sclerosis). Reduced compliance of the upper esophageal sphincter, which interferes with the passage of the food bolus from the throat down into the esophagus, is somewhat common in the elderly. Another swallowing disorder, achalasia, relates to a reduced esophageal peristaltic wave production when swallowing and a failure of the lower esophageal sphincter to open; as a result, the food bolus tends to remain lodged in the esophagus. The prevalence of this disorder increases with age.

3.5. RESPIRATORY SYSTEM

Pulmonary function declines in the elderly due to loss of elastic recoil and weakness in diaphragmatic, chest wall, and abdominal muscles that result in decreased gas exchange (Tumer and Scarpace, 1996). The great reserve function of the lung permits reasonable physical capacity in healthy individuals despite these age-related changes, and training can improve aerobic capacity and endurance. However, when there is a need for increased breathing (e.g., exercise, high altitude), the lungs may not be able to keep up with the demand.

After about age 20, a healthy individual stops making new alveoli and the lungs begin a slow process of losing some of their tissue. Due to the loss of alveoli and lung capillaries over time, the amount of oxygen diffusing from the air sacs into the blood decreases. However, the transport of oxygen from the lungs to the tissues and of carbon dioxide from the tissues to the

lungs is not affected by aging. It is normal for healthy older people to have a reduced response to both decreased oxygen and increased carbon dioxide levels resulting in an increased rate and depth of breathing. In spite of age-related changes in the thorax-lung air pump, alveolar ventilation in the healthy elderly is not sufficiently altered so as to limit vigorous exercise. However, diffusion of oxygen may decline due to disruption of alveolar walls resulting from inflammatory insults or environmental pollutants. These changes are relatively minor, and sufficient lung surface area is available to allow gas exchange and the exposure to environmental agents. In those suffering from age-associated diseases, anemia can cause reduced gaseous transportation (Cohen and Crawford, 1992).

The volume of air exhaled progressively decreases (with residual air in the lungs increasing with age), and the rate of airflow slowly declines. This is due to the increased resistance to airflow in the bronchioles, the change in elastic properties of the lungs, and the decrease in the force generated by the respiratory muscles. The vital capacity – the volume exhaled following maximal inspiration and maximal expiration – decreases with age as the diaphragm and muscles between the ribs (intercostals) weaken. A change in lung capacity can also occur due to loss of bone mass of the ribs and vertebrae and mineral deposits in the rib cartilage. With aging, the airways tend to collapse more readily, particularly when an older person breathes shallowly or is in bed for a prolonged time (Rossi et al., 1996).

With aging, the body's defenses against lung infection may weaken and lead to an increased risk of lung infections. The cough reflex may not trigger as readily, and the cough may be less forceful. The cilia are less able to move mucus up and out of the airway. The nose and breathing passages secrete fewer antibodies that protect against viruses and are therefore less able to meet challenges to the system, such as pneumonia secondary to bacterial and viral infections. There is evidence that early developmental growth may have an adverse effect on lung development (Maritz et al., 2005). Environmental factors that can lead to lung disease include solvents (Jones and Brautbar, 1997), asbestos, and ambient air pollutants.

Asthma in the elderly is not uncommon, with 7% of men and 9% of women reporting symptoms (FIFARS, 2004). It is, however, often confused with chronic obstructive pulmonary disease (see below), possibly due to changes in the lung function as well as changes in the immune system (Vignola et al., 2003). For example, in older individuals there is a decrease in β-2 receptors in the smooth muscles lining the airways, with cholinergic receptors becoming the dominant smooth muscle receptors as aging progresses (Morris, 1994).

Chronic obstructive pulmonary disease (COPD) refers to the combined occurrence of chronic bronchitis and emphysema (Morris, 1994) and is the fourth leading cause of death in the U.S., with 119,000 dying from COPD in 2000 (NIHLB, 2003). Alone, chronic bronchitis occurs in 5–7% of all elderly adults, and emphysema (often associated with smoking) is diagnosed in 4–7% of all adults over age 65 years (FIFARS, 2004). In COPD, the bronchial lining undergoes progressive changes, including gradual loss of cilia and thickening of the epithelium by proliferation of mucosal cells. The emphysema component involves dilation and disruption of alveolar walls. Thus, unlike in most elderly, the deterioration of pulmonary function in those suffering from COPD markedly limits their functional abilities and can lead to cardiovascular disease (Curkendall et al., 2005), which can be exacerbated by exposure to ozone.

Pneumonia is the leading causes of death among the elderly, accounting for 3.2% of mortality in this age group (Anderson and Smith, 2005). Influenza, which can often be prevented by use of vaccines, often leads to pneumonia. Although bacteria, virus, or fungi often cause this condition, exposure to environmental etiologic pollutants including particulate matter (PM) $\leq$ 10 μm in diameter (PM_{10}) (Fischer et al., 2003; Zanobetti et al., 2000), nitrogen dioxide, and CO (Fischer et al., 2003), can increase risk of disease

3.6. HEPATIC SYSTEM

In healthy individuals, liver function appears to be relatively well preserved in aging. Hepatic blood flow decreases as a function of age by as much as 40% by age 70 (Marchesini et al., 1988; Wynne et al., 1988). Other morphological changes that can lead to reduced hepatic metabolism include a decrease in overall liver mass, number of hepatic cells (Lakatta, 1995; Wynne et al., 1988), and number of mitochondria, as seen by the gross appearance of atrophy. Although mitochondrial integrity and enzymatic activity appear to remain unchanged with aging (Ananthatraju et al., 2002), hepatic regeneration after injury is delayed in the elderly (Popper, 1986). In fact, livers from elderly individuals appear to regenerate much better when transplanted to a younger donor. No decline seems to occur in hepatic protein content, immunohistochemical content, or in vivo enzyme activity in the elderly.

After GI absorption, most xenobiotics pass through the liver, the central metabolic organ of the body, before entering the systemic circulation and reaching a site of action. Hepatic microsomal enzymes, particularly cytochrome P-450s, play a key role in xenobiotic metabolism. Phase I reactions (e.g., oxidation, hydrolysis, reduction), first-pass hepatic metabolism, and

serum albumin binding capacity (Tepper and Katz, 1998) are reduced with age, but a consistent decline in Phase II reactions (e.g., glucuronidation, sulfation) has not been observed. Subfamilies of cytochrome P-450 that may decline with age in humans (Lakatta, 1995) include CYP2A6, CYP3A, and CYP2C, (Knodell et al., 1988; Robertson et al., 1988; Sotaniemi et al., 1996), but possibly not CYP2D6 (Wood et al., 1979). These changes may contribute to the age-related hepatic clearance, although this decrease is primarily due to the losses in liver mass and hepatic blood flow (Wynne et al., 1988). Environmental contaminants such as solvents (Brautbar and Williams, 2002) can lead to liver toxicity.

Cirrhosis is a common liver disease caused by the replacement of normal hepatic tissue with fibrous tissue. It is the 12th leading cause of death, which occurs within a year of diagnosis for 60% of patients. Blockage of the bile duct can lead to primary biliary cirrhosis. Other major causes include alcoholism and hepatitis, along with autoimmune conditions, infectious agents, and xenobiotics (Kita et al., 2004).

3.7. RENAL SYSTEM

Several structural and functional changes occur in the kidneys with increasing age (Epstein, 1996; Lindeman, 1995). The mass of the kidneys decreases progressively starting in young adulthood, primarily in the cortex, with little loss occurring in the medulla. Renal blood flow is reduced by 40–50% by age 60, mostly associated with the constriction of the kidney arterioles, which increases the resistance to blood flow through the kidneys. This reduction in renal blood flow results in a greatly reduced glomerular filtration rate (GFR), with the elderly having about 70% the rate of younger adults; however, this may not occur in all people (Lindeman et al., 1985). The number of functioning nephrons also declines with age (Papper, 1973; Lindeman, 1990).

Tubular secretion and reabsorption are also reduced with aging. Most of the renal transport systems involved in tubular reabsorption and secretion continue to function effectively in the healthy elderly. Hydrogen ion concentrations in the blood of healthy individuals increase by 6–7% in the elderly as a result of altered kidney function (Frassetto and Sebastian, 1996). In addition, the kidneys of the elderly excrete a large acid load much more slowly than do those of the young (Adler et al., 1968). The elderly are also less able than the young to cope with water deprivation, primarily due to a decrease in the ability of the kidney to generate urine that is

highly concentrated (high osmolality) because of decreased response of the kidneys to the hormone vasopressin (Kugler and Hustead, 2000).

Elderly individuals tend to excrete many xenobiotics and their metabolites at a reduced rate. Sixty-six percent of the healthy elderly have evidence of impaired renal function, resulting in a persistence of xenobiotics that are dependant on inactivation and excretion by the kidney (Dybing and Soderlund, 1999). In addition, exposure to solvents (Brautbar, 2004) or lead may result in renal interstitial fibrosis and nephrosclerosis and could accelerate the age-related decline in kidney function. Superimposing chronic diseases of the elderly, such as heart failure, may accelerate these changes in kidney function (Cody, 1993).

Hyponatraemia and ***hypernatraemia***, a deficiency or excess of sodium in the blood respectively, can result from changes in kidney function relative to water and electrolyte metabolism (Kugler and Hustead, 2000). One reason why the elderly are at higher risk of sodium imbalance is a reduced thirst sensation (Kenney and Chiu, 2001). The kidney does show a reduced ability to maintain sodium balance, independent of dietary sodium. The decreased ability to conserve sodium may be due in part to intrinsic changes in the kidney transport systems; however, much of the decrease appears to be the result of an age-related decline in the response of the renin-angiotensin-aldosterone system to low sodium levels. The decreased capacity for excreting sodium appears to arise from decreased renal blood flow and glomerular filtration rate with increasing age. This can result in CNS dysfunction due to the impact of an acute disease or the medications used to treat the disease (Miller, 1997).

Urinary incontinence occurs in an estimated 15–30% of community-dwelling elderly, and the prevalence is much higher in nursing home residents (Malone-Lee, 1998). Common causes are urinary infections, medications, psychological disorders, restricted mobility, endocrine disorders, and stool impaction. Enlargement of the prostate, which begins at about age 45, can often cause obstruction of urinary flow in elderly men (George, 1998). The ability to void may be lost, which can be fatally destructive to the kidneys unless appropriate medical intervention is employed immediately. In addition, diabetes is a common cause of long-term urinary incontinence.

Diabetes is increased in the elderly, with 14–18% affected (FIFARS, 2004). It is responsible for 3% of all deaths in this age group (Anderson and Smith, 2005). In particular, Type 2 diabetes (noninsulin-dependent diabetes mellitus) increases in prevalence with increasing age (Halter, 1995). In addition to a marked insulin resistance, the ability of the pancreas to

secrete insulin in those with Type 2 diabetes is also impaired. However, little insulin resistance is present in the elderly who are physically fit and relatively lean; the major causal factors appear to be the decrease in physical activity and the increase in body fat associated with aging. There is evidence that early fetal nutritional status may lead to diabetes in later life (Barker, 1999).

3.8. IMMUNE SYSTEM

The function of the immune system often diminishes with age (Hausman and Weksler, 1985; Miller, 1996; Vignola et al., 2003). Although the spleen and lymph nodes do not alter in size, the thymus continuously decreases in size, and the cellular elements of this gland are gradually replaced by adipose tissue. Altered immune response is due in part to altered intracellular signaling in macrophages and neutrophils, reduced apoptosis in neutrophils, and decreased stimulation of T and B cells by dendritic cells (Plackett et al., 2004) as well as alteration of IL-10, IL-12, and antigen presentation by dendritic cells (Uyemura et al., 2002). The ability to increase the number of T-lymphocytes that can respond to a particular antigen is impaired (Uyemura et al., 2002), and the amount of antibody secreted by a given number of B-lymphocytes decreases with age. Zinc, an essential compound for immune function, is reduced in the body with aging, although it can be restored by supplemental intake.

The deterioration of the immune system undoubtedly contributes to increasing susceptibility to infections and illnesses in the elderly. Importantly, the loss of immune functionality could be a factor in the increasing incidence of cancer with age. Specifically, the deterioration of immune surveillance may result in failure to effectively eliminate mutant cells, thereby increasing cancer risk; however, the validity of this scenario has yet to be established.

Autoimmune Diseases. The age-associated rise in autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and glomerulonephritis results from deterioration of the immune system, which also increases morbidity and mortality from such diseases. Environmental risk factors include mercury, pesticides (Holsapple, 2002), iodine, vinyl chloride, organic solvents, silica, particulates, ozone, and ultraviolet radiation (Powell et al., 1999).

3.9. SKIN

A number of naturally occurring age-related changes occur in the skin. The thickness of the flat keratinocytes at the surface of the skin does not change with age, but the rate of shedding and replacement of these cells decreases. Thus, in the elderly, these cells remain longer at the surface of the skin, which increases the likelihood of accumulating damage. The number of melanocytes decreases with increasing adult age by 10–20% each decade, increasing the damaging action of ultraviolet light. At advanced ages, the epidermis contains 20–50% fewer Langerhans cells than at young ages.

With increasing age, the structure of the basement membrane alters, decreasing the extent of interaction between the dermis and the epidermis and increasing the likelihood of injuries causing the two layers to separate. The thickness of the dermis is about 20% less in the elderly, and the dermis is stiffer and less malleable, making it more vulnerable to injury. Many of the changes in the dermis are due to alterations in the fibrous proteins (collagen and elastin) of the dermis' extracellular matrix; fine wrinkles are probably related to these alterations. The small blood vessels of the dermis change and the number of hair follicles declines.

Physiological functions of the skin are also altered during aging (Chuttani and Gilchrest, 1995). The barrier function is changed, and body water loss through the epidermis is decreased with increasing age. A 15% age-associated reduction occurs in both the number and the functional capacity of the sweat glands. In addition, with advancing age, subcutaneous fat increases in some regions of the body (the waist in men and the thighs in women) and decreases in others (face, hands, shins, and feet).

The inflammatory response of skin to harsh chemicals is less intense in the elderly. Also, vitamin D production declines with age, and decreased exposure to sunlight and reduced cutaneous synthesis may impair vitamin D status. Common risk factors associated with age-related skin conditions include smoking and exposure to sunlight (Kennedy et al., 2003).

Areas of the skin exposed to sunlight may deteriorate prematurely more than areas that are protected, a phenomenon called "photoaging" (Scharffetter-Kochanek et al., 2000), as opposed to "intrinsic aging" (Chuttani and Gilchrest, 1995). Chronic photo damage is estimated to cause more than 90% of cosmetic skin problems. It leads to coarseness of the skin, dilation of groups of small cutaneous blood vessels, irregular pigmentation, and deep wrinkles. It also causes a decrease in the number of epidermal Langerhans cells. Damage to the elastin and collagen in the dermal extracellular matrix probably underlies many of the cosmetic problems.

Pressure sores (i.e., decubitus ulcers or bedsores) are a major concern for the elderly (Bennett and Bliss, 1998), particularly for those with decreased mobility or diabetes. Additional risk factors are friction and moisture, particularly moisture due to fecal or urinary incontinence. The mildest form occurs as a redness of the skin area; if the lesion becomes more severe, it progresses to a loss of epidermal and dermal structures. Ultimately, full-thickness skin loss and tissue necrosis can occur, resulting in a severe lesion.

3.10. BODY MASS

Body mass, commonly referred to as body weight, consists of both lean and fat body mass (Forbes and Reina, 1970; Holloszy and Kohrt, 1995; Seidell and Visscher, 2000). During adult life, the lean body mass (which is greater in men than in women) declines by about 0.3% per year in men and 0.2% per year in women. Much of this decrease in lean body mass is due to the loss of muscle mass, but a loss of bone and other tissue is involved. Although individuals who continue to exercise have a greater lean body mass at any age than those of similar size who are sedentary, even athletes progressively lose lean body mass.

Although lean body mass is decreasing, percentage fat content of the body increases with age, and the distribution of body fat changes, with a preferential accumulation of fat in the abdominal region. However, many elderly individuals lose body weight, and this can potentially mobilize lipophylic substances back into the bloodstream. Also related to the reduction in lean body mass, is the decrease in total body water content in the elderly. The decrease in intracellular water causes polar compounds to be less well distributed but to be present at a higher concentration in the remaining body water (Greenblatt et al., 1982).

Drugs and environmental chemicals with hydrophilic properties would be expected to have a decrease in volume of distribution in the elderly. The distribution of lipophilic environmental chemicals such as dioxins, PCBs, and other halogenated substances depends on the adipose tissue content of the body. These changes mean that lipid-soluble compounds are better distributed and retained longer in the elderly (Wills, 1984). However, weight loss often seen in the elderly has the potential to mobilize stores of lipophilic toxicants.

Age-related changes in protein binding may be due to decreased liver production of serum proteins or changes in drug affinity for the proteins (Wallace and Verbeeck, 1984). Inadequate protein intake in the elderly may also contribute to decreased plasma protein

synthesis as well as malnutrition, which can result in anemia. Serum albumin may decrease by about 10–20% between ages 30 and 70 years, allowing for an increase in the amount of unbound free drug in the plasma. Increased free drug/environmental chemical or their reactive metabolite levels can enhance target organ responses and lead to adverse toxic reactions. The plasma albumin fraction is responsible for most toxicant binding in the plasma.

Dehydration is a common reason for hospital admittance among the elderly. The disturbance in fluid and electrolytes is due to already reduced water content in the body and renal changes. In addition, the elderly individual may have a reduced fluid intake due to cognitive or motor impairment, a desire to reduce incontinence, or a reduced thirst response (Kenney and Chiu, 2001).

Obesity increases with age, and by 65 years approximately one-third of all U.S. adults are considered obese (FIFARS, 2004). This may be somewhat due to the increase of sedentary lifestyle with age as well increased calorie intake. Obesity is associated with increased risk of heart disease, Type 2 diabetes, cancer, respiratory conditions, and osteoarthritis (FIFARS, 2004). There is evidence that early growth may have an influence on obesity in later life (Oken and Gillman, 2003).

3.11. MUSCULO-SKELETAL SYSTEM

By age 70, the height of men and women is 2.5–5% below its peak level (Spirduso, 1995), due primarily to the compression of the cartilaginous discs between the vertebrae and a loss in vertebral bone. Bone loss and joint deterioration commonly occur with increasing age. Bone loss is greater in women than in men, and the rate of loss accelerates after menopause; such acceleration has been found to be due to low postmenopausal levels of estrogen. In the young adult, remodeling of bone occurs by the process of bone resorption being balanced by bone reformation, so that remodeling causes no change in the amount of bone. With advancing adult age, the balance during remodeling shifts in favor of bone resorption (Kalu, 1995). Men start to lose bone at later ages than do women, and in general the amount of loss is less for men than for women.

A decrease in skeletal muscle mass (sarcopenia) occurs with increasing adult age (Lexell, 1995). A decrease in the number of muscle fibers is generally agreed to occur with increasing age in many, but not all, skeletal muscles. Associated with this decline in muscle mass is an

approximate 33% decrease in muscle strength (Hurley, 1995), along with a decrease in the speed of movement.

With increasing age, the strength and speed of smooth muscle function are reduced (Folkow and Svanborg, 1993). Some loss in the efficiency of sympathetic nervous system control of venous smooth muscle may also occur. The extent to which skeletal muscle disuse is responsible for the age-associated loss of skeletal muscle fibers is unknown, yet disuse will lead to a decrease in muscle fiber size as well as a change in functional characteristics. However, elderly persons who have been physically active or have undergone strength training can develop muscle force as great as that of sedentary young adults (Evans, 1995) because the development of increased muscle fiber size compensates for the reduced number of fibers. With increasing age, most people adopt a more sedentary lifestyle (Rowe and Kahn, 1998); thus, some of the changes in skeletal muscle function with advancing age are clearly due to lack of use.

Osteoporosis is characterized by low bone mass and increased susceptibility to bone fractures from minor trauma (Riggs and Melton, 1988), and its prevalence increases with advancing age. There are two major types of age-associated osteoporosis: Type I defined as an increase in the rate of remodeling of bone, with bone resorption outpacing bone formation, and Type II, defined as a decreased rate of bone formation. Type I is frequently associated with fractures of the vertebrae and wrists, whereas Type II results mostly in vertebral wedge fractures and hip fractures. Both are more common in women; the lower incidence in men is due to three factors: greater bone density upon reaching maturity, shorter life expectancy, and the lack of a rapid endocrine change equivalent to menopause.

Lifetime exercise and an adequate dietary intake of calcium minimize the occurrence of osteoporosis, whereas alcoholic beverages, smoking, and caffeine are risk factors for osteoporosis. The condition can lead to a release of toxins, such as lead, that are stored in the bone. In addition, there are links between bone growth in early life and later development of osteoporosis (Harvey and Cooper, 2004).

Osteoarthritis is the most common degenerative joint disease in the elderly (Felson, 1990; Radin and Martin, 1984) with approximately one-third of all elderly individuals experiencing some arthritic symptoms (FIFARS, 2004). In the healthy elderly, the synovial joints show deteriorative changes (Spirduso, 1995). Functionally, joint flexibility is lost, reducing the range of motion and increasing the possibility of damage to the joints and the muscles crossing the joints. In this disease, the cartilage of the joint changes in consistency,

cracks, and wears away, ultimately exposing the bone surface to another bone. With time, further changes in bone may occur, such as the development of bone spurs, abnormal thickness, and fluid-filled pockets. Periodic or chronic inflammation can occur, which is accompanied by pain. Although osteoarthritis can occur in any joint, it most commonly affects the joints of the fingers, knees, and hips.

Gout results in joint inflammation and involves the formation of uric acid crystals in the synovial fluid (Rubenoff, 1990). The joint in the big toe is the one most commonly involved, although any joint may be affected. Gout is more common and occurs earlier in men than in women, peaking in the fifth decade of life. Exacerbations and remissions characterize the course of the disease. The major causal factor of gout is an elevation in plasma uric acid concentration, which increases with age and in individuals who take diuretics thus probably accounting for the age-associated characteristic of this disease.

3.12. ENDOCRINE AND REPRODUCTIVE SYSTEMS

In the healthy elderly, the functioning of the pituitary-thyroid axis is not markedly different from that in the young (Mooradian, 1995). The concentration of serum thyroxine is not affected by aging. The concentrations of triiodotyrosine and thyroid-stimulating hormone and the rate of thyroid hormone production and degradation are either not affected or are modestly decreased by aging. The secretion of thyroid-stimulating hormone by the pituitary in response to the hypothalamic thyrotropin-releasing hormone is modestly decreased or unchanged by aging, as is the response of the thyroid gland to thyroid-stimulating hormone. The ability of thyroid hormone to suppress the pituitary secretion of thyroid-stimulating hormone is decreased at advanced ages, as is the response of the basal metabolic rate to thyroid hormone. The consequences to the healthy elderly, if any, of these modest age-related changes in the pituitary-thyroid axis have not been defined.

The pituitary-adrenal axis refers to the influence of pituitary adrenocorticotrophic hormone on the secretion of cortisol and dehydroepiandrosterone by the adrenal cortex. Little or no increase in the level of plasma cortisol occurs with advancing age in nonstressed healthy people, but under conditions of stress, plasma cortisol levels increase more in the elderly than in the young, and the increase is more prolonged (Masoro, 1995). Whether the increased cortisol response is beneficial or detrimental remains to be determined. The blood level of

dehydroepiandrosterone peaks at ages 25 to 30 years and decreases thereafter, so by age 80 the level is 10% of that at age 25 to 30 years (Yen and Laughlin, 1998). Low levels of blood dehydroepiandrosterone have been associated with age-associated disorders, such as some forms of cancer, dementia, cardiovascular disease, Type 2 diabetes, obesity, and osteoporosis.

Pituitary secretion of growth hormones decreases with increasing age, resulting in a progressive decrease in the plasma levels of growth hormone and in insulin-like growth factor I, the secretion of which is controlled by growth hormone (Bartke et al., 1998). Growth hormone promotes the use of fat as an energy source, thereby sparing the use of protein. Thus the decreasing level of growth hormone with increasing age may play a role in the age-associated increase in body fat and decrease in muscle mass.

Marked age-related changes occur in the reproductive function of elderly women (Sowers, 2000). Menopause is the natural permanent cessation of menstruation which occurs on average at about 50 years of age and is completed for most women by age 65. Menopause is believed to result primarily from the decreased ability of the ovaries to secrete estradiol. In the years following menopause, plasma estradiol levels drop, and follicle-stimulating hormone and luteinizing hormone levels are elevated. Also, pubic hair decreases, the vagina shortens and loses elasticity and is at increased risk of bacterial and yeast infections and mechanical damage, the oviducts shorten and their diameter decreases, breasts undergo atrophy of the glandular structure with replacement by adipose tissue, the uterus reduces in size, and the cervix atrophies.

Although men do not undergo an andropause that is comparable to menopause, the male reproductive system does undergo age-related changes (Plas et al., 2000). Atrophy of the seminiferous tubules occurs with advancing age. Semen volume and sperm motility are decreased, along with sperm concentration and count (Eskenazi et al., 2003). Plasma-free testosterone declines after the age of 40, but some older men have levels well within the range found in young men.

Hyperthyroidism and ***hypothyroidism*** are caused by excessive or decreased production of thyroid hormones, respectively. Hypothyroidism affects up to 17% of the elderly, with a higher incidence in women (Levy, 1991). Symptoms include decreased basal metabolism and skin conditions. The most common cause is autoimmune thyroid conditions. Hyperthyroidism affects up to 3% of the elderly (Levy, 1991). Symptoms of hyperthyroidism can include cardiovascular effects, psychological disorders, weight loss, muscular weakness, increased defecation, and visual effects and increased sensitivity to heat.

3.13. BASAL METABOLISM

Total daily energy expenditure (i.e., daily metabolic rate) decreases with increasing adult age (McCarter, 1995). However, if the basal metabolic rate is expressed per kilogram of lean body mass, little age-related decline can be seen. Thus, the major reason for the decreased basal metabolic rate is likely due to the change in body composition with age, namely the increasing fat mass and decreasing skeletal muscle mass.

Fat oxidation is decreased in the elderly at rest and during exercise (Calles-Escandon and Poehlman, 1997), likely due to the decrease of fat-free mass. With advancing age, the rate of protein synthesis and protein degradation (turnonver) decreases (Van Remmen et al., 1995). As they reside in the body, protein molecules are gradually damaged by oxidation, glycation, heat, and other factors. Thus, by increasing the average length of time a protein spends in the body, the age-associated decrease in the rate of protein turnover acts to increase the amount of damaged protein molecules. The age-associated decrease in muscle mass probably relates, at least in part, to the decrease in protein synthesis.

The use of energy may lead to the generation of reactive oxygen molecules (e.g., superoxide, hydrogen peroxide, and hydroxyl radicals), which cause damage to biological macromolecules such as mitochondrial DNA (Balin and Vilenchik, 1996) in conjunction with decreased protection from superoxide dismutase and glutathione (Bolzan et al., 1997), and such damage does accumulate with increasing age.

With increasing age, the ability of the body to regulate temperature deteriorates (Collins and Exton-Smith, 1983). The extent of this deterioration varies among individuals, depending on health, physical fitness, and lifestyle factors. In a hot environment, the elderly have a reduced ability to redistribute blood flow from the core of the body to the skin due to structural changes in the skin blood vessels and to a decreased capacity to constrict the vessels supplying the viscera, which also lead to a reduced sweating response. In a cold environment, the elderly show a decrease in constriction of the skin blood vessels and a reduced shivering ability.

Hyperthermia and ***hypothermia*** are much more likely to occur in elderly people than in young people. However, the main reason the elderly are more vulnerable to extremes in environmental temperature is the lowered perception of ambient temperature, resulting in fewer effective behavioral responses, such as seeking appropriate clothing or shelter.

4. POLYPHARMACY IN THE ELDERLY

The elderly may suffer from numerous degenerative diseases that require the chronic consumption of drugs intended to maintain organ function. Similar to toxicants, pharmaceuticals interact with the physiological states of the elderly. Multiple prescription drug use (polypharmacy) is high in the elderly; on average, a healthy individual filled 10 prescriptions in 2000, whereas those with comorbidities filled up to 57 prescriptions (FIFARS, 2004). Some medications may more profoundly impact the elderly than they do younger adults due to increased bioavailability, decreased metabolic ability, reduced volume of distribution due to reduced total body water, reduced clearance, or a combination of these factors.

Some medications may decrease in effectiveness in elderly individuals. For example, the elderly have lowered contractility and chronotropic responses in the heart to beta-adrenergic stimulus and experience a lower impact on peripheral vasodilation (Cody, 1993; Podrazik and Schwartz, 1999). The absorption of some prescription drugs used by the elderly may remain unchanged, but the half-life may be extended and the clearance slowed, resulting in an increased risk of associated adverse events. For example, angiotensin-converting enzyme (ACE) inhibitors used for the treatment of heart failure can enhance the risk of severe chronic renal insufficiency and renal failure due to decreased renal blood flow and tubular secretion in the kidneys. Calcium channel blockers used for heart conditions are cleared primarily via hepatic metabolism, which decreases with age, as does kidney function. Cipro, a treatment for bacterial infections (Lebel and Bergeron, 1987), has significantly reduced renal clearance in the elderly due to a reduction in the GFR and in tubular secretion, as well as reduced clearance through the hepatic, pulmonary, and intestinal systems.

Interaction between drugs and environmental contaminants is a major concern for the elderly, as are interactions between drugs (Cadieux, 1989; Lamy, 1990; Tumer et al., 1992). Both medications and environmental agents may alter the body's ability to process the other. Because a larger research base exists for pharmaceuticals than for environmental contaminants, much can be learned about TK changes due to exposure of xenobiotics from examining the literature on pharmaceuticals.

5. EXAMPLES OF ENVIRONMENTAL AGENTS AS RISK FACTORS FOR DISEASES IN THE ELDERLY

The following examples were selected to represent some of the environmental agents and environmental problems that are known to compromise the health status of the elderly population.

5.1. Metals

A number of metals are recognized as affecting the neurological system and have been suggested or implicated in having a role in the development of diseases of the elderly. In particular, aluminum and mercury have been debated as a causal factor in neurological diseases such as Alzheimer's disease, and mercury has been associated with heart attack risk in men (Guallar et al., 2002). Other metals not discussed here but studied intensely for adverse health effects include iron, zinc, copper, magnesium, and selenium.

Lead is a known toxicant that can be absorbed through the respiratory tract and the GI tract. Lead first distributes to the soft tissue and then redistributes to the bone. Absorbed lead is excreted predominantly through the urine; therefore, clearance in the elderly may be greatly reduced due to a decreased glomerular filtration rate (GFR), a typical consequence of aging.

Lead can cause effects in many physiological systems. In the nervous system, symptoms of lead exposure may be confused with effects of normal aging. Irritability, fatigue, decreased libido, anorexia, sleep disturbance, impaired visual-motor coordination, loss of hearing (Rybak, 1992), and slowed reaction time are conditions that occur with lead poisoning but also with advanced age. In the cardiovascular system lead exposure can increase blood pressure, and precipitate congestive heart failure (Balestra, 1991) and may cause anemia by interfering with heme synthesis, which can be exacerbated by poor nutritional intake. In the renal system, chronic high-dose lead exposure may result in renal interstitial fibrosis and nephrosclerosis, and such exposure has the potential to accelerate the age-related decline in kidney function.

The skeleton accumulates inorganic lead and holds 90% of the body's lead burden, given that the half-life in bone is in years or decades as compared with one to two months in soft tissues. Rapid release of this stored lead by skeletal disease could produce a considerable health risk (Berlin et al., 1995; Silbergeld et al., 1988). Lead may also aggravate osteoporosis by

inhibiting activation of vitamin D, uptake of dietary calcium, and aspects of bone cell function. Modeling of bone loss with aging also suggests that loss of bone in women after menopause could create a hazard related to release of lead into the blood (O'Flaherty, 2000).

Manganese (Mn) is essential to enzyme and membrane transport system function in all mammalian tissues. However, as with many other essential metals (e.g., copper and iron), both excess and deficiency in the body-burden of Mn, whether genetic or acquired, can seriously impair vital physiological and biochemical processes. Mn toxicity is not widespread, but excessive Mn exposure can occur, primarily from occupational exposure.

Mn exposure can occur via inhalation, oral ingestion, or intravenous administration. After absorption into the blood by these alternate routes, brain uptake of Mn occurs via transferrin receptors. Mn is apparently oxidized by ceruloplasmin, and the resulting trivalent Mn binds to iron carrying the protein transferrin; transferrin-bound trivalent Mn is not as readily removed by the liver as are protein complexes with divalent Mn, which is complexed with plasma proteins that are efficiently removed by the liver. Mn is a potent neurotoxicant (Cranmer, 1999) and clearly plays a role in the pathogenesis of neurodegenerative disorders resembling idiopathic Parkinson's disease). Other neurological effects such as loss of hearing (Rybak, 1992) are possible.

5.2. Pesticides

Pesticides are used to control various unwanted insects, rodents, plants, or molds. They can be either persistent or nonpersistent, meaning that they either remain in the environment – and therefore the body – for long periods of time or they are quickly metabolized. The use of persistent pesticides is declining, and the use of nonpersistent pesticides is increasing in use.

Exposure can occur from residential use (e.g., gardening, pest control), occupational use (e.g., farming, military), consumption of contaminated food or water, or from proximity to areas where application occurs. It is important to note that certain pesticides were used in higher frequency during the lives of those entering the elder years. For example, the application of DDT in the U.S. has ceased, although many individuals now aged 65 and older have a history of being directly exposed. Also, a number of Vietnam veterans were exposed to pesticides such as Agent Orange, and the latent effects of exposure may be substantial. This could have a large

impact on society since 9.5 million veterans were aged 65 years and older in 2000 (FIFARS, 2004).

Pesticides have been implicated as contributors to neurodegenerative diseases, including Alzheimer's and Parkinson's diseases. There is considerable evidence that many pesticides can cause a decline in cholinergic indices (choline acetyltransferase, acetylcholinesterase, and muscarinic acetylcholine receptors), as occurs naturally with aging, suggesting that aging humans may be more sensitive to organophosphate pesticides (Overstreet, 2000). There is also evidence documenting the decline in cognitive function attributed in part to the decline in cholinergic indices (Overstreet, 2000; Terry and Buccafusco, 2003), with studies reporting an improvement in cognitive functioning following pharmaceutical treatment with acetylcholinesterase inhibitors (Bullock and Dengiz, 2005; Ellis, 2005; Kaduszkiewicz et al., 2005).

5.3. Air Pollution

Elderly individuals are vulnerable to the health effects of air pollution (Fischer et al., 2003; Pope, 2000; Sandstrom et al., 2003) due to the reduced capacity of the respiratory and cardiovascular systems, which results in increased symptoms, exacerbations of disease, and mortality (Devlin et al., 2003). There is a large variation of exposure levels related to geographic location, seasonality, use of personal care products, cooking, cleaning, transportation use, housing (building materials, ventilation, heating, smoking, animals, pests), and recreational choices. Under the Clean Air Act, EPA sets National Ambient Air Quality Standards (NAAQS) for air pollutants deemed to be of particular concern to public health and the environment; these include ozone (O_3), PM, CO, sulfur dioxide (SO_2), nitrogen oxides (NOx), and lead.

Exposure to O_3 is a known risk factor for acute exacerbation of cardiopulmonary conditions in the aged population, leading to increased hospital admission (Delfino et al., 1998; Schwartz, 1994; Yang et al., 2003) or mortality (Izzotti et al., 2000) due to, for instance, COPD (Fischer et al., 2003). The O_3 8-hour standard was exceeded for 46% of elderly adults in 2002 and has been increasing since 2000 (FIFARS, 2004), although many of these responses to exposure are seen within NAAQS acceptable exposure range.

PM is a mixture of solid and liquid particles suspended in air that is emitted mostly from combustion products from sources such as transportation, manufacturing, and energy production.

PM standards were exceeded for 19% of elderly adults in 2002, although this number has actually been improving since 2000 (FIFARS, 2004). Although acute exposure to PM can lead to health effects (Hattis et al., 2001; Lippmann et al., 2003), both current and past exposures to sources of PM are important considerations. Several recent studies suggest that PM is associated with cardiovascular diseases (Anderson et al., 2003; Kunzli et al., 2005; Liao et al., 1999; Pope et al., 2004; Utell et al. 2002) and respiratory diseases (Anderson et al., 2003; de Hartog et al., 2003; Mann et al., 2002; Pope, 2000; Schwartz, 1994) in people age 65 and older.

Exposure to CO at all ages reduces the amount of oxygen in the blood, and it is a particular concern for the elderly due to the common condition of anemia. CO can cause a number of acute health effects, including fatigue, muscle weakness, shortness of breath, chest pain in individuals with chronic heart conditions, headaches, visual or hearing (Rybak, 1992) impairment, nausea, and dizziness. Behavioral effects include slowed reaction time, confusion, and disorientation. In severe exposure, CO can cause loss of consciousness and death. These effects can be exacerbated in elderly individuals due to their altered physiology and disease states.

SO_2 can have effects on the respiratory and cardiovascular systems (Venners et al., 2003), particularly in individuals with preexisting diseases (e.g., asthma, COPD). Similarly, NOx is associated with the exacerbation of respiratory (Simoni et al., 2003) and cardiovascular conditions (Maheswaran et al., 2005), and elderly individuals may be particularly susceptible to exposure.

6. ANIMAL MODELS FOR THE STUDY OF AGING

Animal models, and particularly rodent models, have been and continue to be extremely useful in defining and understanding the aging process and assessing the risk of environmental agent exposure in the elderly. These models may provide insight on the interaction between genetic, environmental, dietary, and disease factors and the normal aging process. Consideration of the evolutionary mechanisms by which senescence evolves suggests that researchers need to consider carefully the questions they wish to ask and choose their animal model accordingly (Phelan, 1992).

Just as there is variability among humans, there is variability among different experimental animal species as well as within a given species (e.g., strains). Therefore, it is essential to be careful how one extrapolates information from animals to humans. In particular, only a few experimental animal species (with the exception of nonhuman primates) live as long as humans. Also, the timing and route of exposure in an animal experiment versus a human scenario may be different, the TK and TD may be dissimilar, and the health outcomes may not occur consistently. Therefore, these models may not be generalizable to aging in humans, but they do allow basic theories of the molecular basis for aging to be tested.

In animal models, the role of restricting caloric intake is significant in the process of aging because such restriction may increase life span, delay physiological deterioration, delay the onset or slow the progression of most age-associated disease processes, and increase resistance to the damaging affects of acute stressors (Masoro, 2000). Also, dietary restriction can improve toxicant clearance, reduce the pathology associated with the toxicant, and even increase life span relative to that of controls. However, tissue antioxidant defense against free radical damage may be compromised under the nutritional deficiencies. In addition, there are relevant studies on interaction(s) of caloric restriction and environmental exposure in aged animals that show that the effect of some toxicants is reduced with caloric restriction (Apte et al., 2003; Maswood et al., 2004). It is important to note that some toxicants may lead to reduced caloric intake or a reduction in body weight.

6.1. IN VITRO MODELS

In vitro cell culture and ex vivo models offer defined cells and environments in which to explore specific genetic and cellular changes that occur during aging and study the mechanisms of toxicity. In vitro techniques have been used to identify toxic hazards and investigate mechanisms of toxicity (Cristofalo and Pignolo, 1995) in cells at various stages of proliferation and senescence. Studies can be performed in cell cultures derived from humans or animals of various ages in order to determine the vulnerability of these cells to free radical production initiated by drug or environmental chemical exposure, although the age of the donor providing the cells to be cultured can affect the success of the culture.

It is important to note that these systems supplement but do not replace experiments with whole animals, and that their use in hazard identification in human health risk assessment has not been widely accepted. This is due to the fact that a dose-response relationship obtained in vitro may not correspond with in vivo results. The entire TK process that determines xenobiotic concentration at the site of action in vivo cannot be accurately replicated in vitro, nor can in vitro models capture individual variability of TK response.

Two types of cell cultures are generally used in aging research: primary cell cultures and cell lines. Primary cell cultures are cells that are harvested directly from the organism's tissues, dissociated into single cells before seeding into the culture vessel, and maintained in vitro for periods beyond 24 hours. Cell lines are cultures that have been serially transplanted or subcultured through a number of generations and can be propagated for an extended period of time. In vitro systems often provide only partial answers to complex problems.

Stages in the cellular life cycle have been examined for possible mechanisms underlying cell senescence. These possible mechanisms include studies of DNA repair, errors of protein synthesis, and chromatin structure and function, as well as mechanisms modulating replicative life span. The stages of a cultured cell are (1) outgrowth and establishment in the culture; (2) vigorous proliferation that has a variable length, depending on the age of the tissue donor; (3) declining proliferative vigor that includes cell death; and (4) emergence of an apparently long-lived population that is unable to proliferate in response to mitogens.

Most cell types can be used in these models. Human diploid fibroblast cell models are often used to study the mechanisms that underlie cellular senescence (Cristofalo et al., 1998). In vitro studies of neurons are useful in controlling the response due to the fact that in vivo neuronal

response may be mediated by nonneuronal cells or systemic biological processes that produce toxic metabolites.

6.2. NONMAMMALIAN SPECIES

A number of nonmammalian species have been used to study the aging process. The most common are fruit flies (Drosophila melanogaster) (Arking and Woodruff, 1998), nematodes (Caenorhabditis elegans) (Reznick and Gershon, 1998), and zebrafish (Danio rerio) (Keller and Murtha, 2004). At the cellular level, many of the phenomena related to fundamental aging processes in mammals and nonmammals are similar, although the experimental results may be difficult to generalize to mammals due to the vast difference in life spans.

The primary advantage of using nonmammalian species for aging research is the rate at which genetic mechanisms can be studied (Liao and Freedman, 2002; Schwartz et al., 2004). Specific genes may be manipulated to extend or shorten the life span, or genes involved in the antioxidant defense systems can be tested to determine their effect on longevity and their vulnerability to toxic exposure. In addition, these species may provide a suitable model for examining the interaction between specific genes, environmental toxicants, and aging.

These species are particularly useful because (1) they have a short life cycle and life spans, allowing for inexpensive multigenerational studies; (2) they have a simple multicellular structure composed essentially of post-mitotic cells, which allows the examination of senescent processes uncomplicated by the effects of cell division and replacement; and (3) they are relatively easy to raise under well-defined and easily controlled nutritional conditions.

6.3. MAMMALIAN SPECIES

The aging animal as a model for the aging human may shed light on the aging process and the accompanying physiological changes. Rats and mice offer models to study complex changes in physiology and behavior and the indirect influences that organ systems have on each other during the aging process. Nonhuman primate models can be used to examine the effect of toxicant exposure on cognitive function in elderly animals. A main concern when using any animal model is that the shorter life span makes them potentially less generalizable to the human aging process.

The choice of test species for aging study research should be based on the similarity of TK or TD to humans, as well as the fact that not all species naturally demonstrate certain health outcomes. For example, in rodents without genetic modification, atherosclerosis and Alzheimer's-type brain lesions do not spontaneously occur. Therefore, the mammal species has to be selected carefully in order to observe the desired outcome.

Rodents, in particular rats and mice, are the most frequently used mammals for experimental models of aging (Masoro, 1998), primarily because of their size and relatively short life spans. Although a given phenotype may be similar among species, it is important to note that the underlying mechanism of the effect may not be the same. Similarities among rats, mice, and humans in aging phenotypic characteristics include

- Low mortality between puberty and midlife and high mortality thereafter,
- Marked increase in the prevalence of neoplasia after midlife,
- Decreased cognitive impairment and increased motor deficits after midlife,
- Total infertility of the female by about midlife and decreasing fertility of the male with advancing age,
- Increasing body fat mass through midlife and loss of body weight at advanced ages,
- Impaired response to cold environment at advanced ages.

In rodent assays, both the genetic and the environmental factors related to the aging process can be strictly controlled (van der Staay, 2002). Depending on the organ or system being examined for age-related changes, a number of rat strains are available, such as inbred strains, outbred strains, and natural populations that differ greatly in their genetic variability (Masoro, 1998). Heterozygous mice are more often being used in research (Lipman et al., 2004), with the advantage that any observed effects are likely to be more generalizable. As models of human aging, each strain possesses attributes that are suitable for particular lines of research but that limit the system's value for other lines of research. Transgenic and knockout models are also used (e.g., the long-lived $p66^{shc}$ knockout mice).

Rodent models have been used to support the connection between pesticide exposure and Parkinson's disease (Cory-Slechta et al., 2005; Sherer et al., 2003), and new mouse models have been established for human aging that express several aging phenotypes, such as atherosclerosis, osteoporosis, skin atrophy, and pulmonary emphysema (Utsugi et al., 2000). These mouse

models are expected to be important tools for aging research, particularly in studies that examine the effect of aging on the immune system.

In addition to rodents, dogs, cats, rabbits, and nonhuman primates are used in a variety of toxicological studies (Weindruch, 1995). Canines have moderate life spans, varying from about 12 to 20 years, depending on the breed (Cummings et al., 1996), and they are particularly used in biomedical research for cardiology, toxicity, and safety testing.

Several nonhuman primate species have been used in aging research, with rhesus monkeys being the best characterized and most extensively studied in biomedical gerontology (Gallagher and Rapp, 1997). However, relatively few aging studies using nonhuman primates have been performed because of the cost and limited availability of animals with known age and health status (Weindruch, 1995).

7. AGE-RELATED RISK ASSESSMENT ISSUES AND RESEARCH NEEDS

This document represents a broad overview of complex topics regarding the effect of normal aging on the action of xenobiotics. One goal of the Agency's Aging Initiative is to provide risk assessors with the tools needed to consider special sensitivities in order to conduct a life stage-specific risk assessment. As a significant and potentially vulnerable segment of the national population, the elderly represent a challenge in the measurement of exposure and the evaluation of the effects of environmental exposures for assessing risk.

Characterization of exposure consists of numerous considerations from source to internal dose, such as the pathway of exposure, including the description of the media (e.g., air, water, food), exposure route (e.g., ingestion, inhalation, dermal contact), and scenario. Other considerations for exposure include the frequency (e.g., intermittent, continuous) and length (e.g., acute or chronic) of exposure, as well as aggregate and cumulative exposures (U.S. EPA, 1997e). Other factors that may affect risk at all life stages include occupational status, socio-economic status, geographic location (e.g., climate), and individual behaviors and cultural practices (U.S. EPA, 1997b). Exposure assessment can be made through biomarker information achieved through biological monitoring (U.S. DHHS, 2005; McClearn, 1997; Pope et al., 2004). However, due to the financial costs and participant burden, the sample size in such studies is often very small. Some research needs related to exposure assessment include:

- Better characterization of factors that contribute to the exposure of elderly populations to environmental agents, such as activity patterns and microenvironments; and
- More research on biomarkers as a reliable measure of exposure.

Recognizing variability in TK and TD due to aging may help to explain interindividual differences in susceptibility among exposed populations. By studying the physiologic changes that occur during aging and the impact they have on TK and TD, this information can be used to predict the potential for greater or lesser vulnerability to any type of environmental stressor (Ginsberg et al., 2005). Table 1 summarizes the physiological changes seen in the elderly related to TK (adapted from Geller and Zenick, 2005). In general, aging reduces the reserve capacity that is available to adapt to environmental stressors.

Table 1. Physiological changes related to toxicokinetics (TK) in the elderly

TK process	Physiological changes in the elderly
Absorption	Increased gastric residence time; decline in gastric acid production Changes in dermal barrier function Decrease in lung volume and ventilation rate
Distribution	Decreased total body water (decreased volume of distribution; higher serum levels for polar compounds) Decreased muscle mass Increased adipose tissue (higher accumulation of lipophilic compounds; slower clearance rates) Changes in plasma protein binding (e.g., decrease in plasma albumin) Potential for increased permeability of blood-brain barrier with concurrent disease
Metabolism	Reduced liver volume and blood flow Minor effects on Phase I and II metabolism Decline in specific cytochrome P-450 activity Potential for interactions of environmental toxicants with pharmaceutical agents Significant effects in conjunction with age-associated disease.
Excretion	Reduced renal blood flow, glomerular filtration Reduced biliary excretion Reduced pulmonary excretion

Source: Adapted from: Geller and Zenick, 2005.

Superimposed on the normal physiological changes due to aging are changes in nutritional and disease status including: co-morbidity of diseases; the potential toxic effects of various prescription drugs, and the increased probability for adverse interactions between drugs or between drugs and environmental toxicants; and genetic polymorphisms. Any estimation of the potential effects of environmental toxicants on the elderly must take each of these circumstances into consideration.

Evidence that age-related changes in an environmental chemical's TK or TD can come from several types of investigations relevant to risk assessment. Most studies of the morphological and functional changes occurring with age are of a cross-sectional design, in which measurements are made on subjects of different ages at a given point in time. A disadvantage to cross-sectional studies is the lack of information on age-related changes in individuals (Crome, 2003) or within a cohort. A cohort effect is the mutual experience related to a particular situation, and a generational effect is related to the societal conditions of the time (e.g., diet, education). The observed differences between the young and the old could be the result of these experiences rather than of aging. For example, due to a longer life span, the current aged population has had greater exposure to certain compounds such as lead and banned pesticides such as DDT than those who will become aged in the future due to a cohort effect. Therefore, it is important to note that although the toxic effect of these environmental agents

remains the same, the exposure patterns may change over time. Another disadvantage to cross-sectional studies is selective mortality or survivor effect. With increasing age, the fraction of a cohort that is still alive decreases, which means that survivors at a given age may in many regards be different than those who have already died.

Longitudinal studies of individuals circumvent some of these problems, but they are costly and often have difficulty with retention of study participants over numerous years. Although there are on-going longitudinal studies of human aging, this line of research has primarily used, and will likely continue to use, the cross-sectional design. Similarly, biomarker information can be useful in ascertaining effect (as well as for exposure) (U.S. DHHS, 2005; McClearn, 1997; Pope et al., 2004), although the sample size for measures of effect may be very small. Making this scientifically more challenging, there is potential for long latency periods between exposures earlier in life and many health outcomes (U.S. EPA, 2005a, Figure 2.3), or the latency period may be longer than the expected remaining life span (Landrigan et al., 2005). In order to address these risk assessment concerns, some research needs include:

- A better understanding of the pathophysiological mechanisms of aging;
- Increased monitoring of the development and prevalence of chronic diseases, particularly through the use of longitudinal studies;
- More chemical-specific toxicity data in human epidemiological studies in the elderly population and in aged experimental animals;
- More dialogue between epidemiologists and mechanistic researchers of elderly individuals;
- Focused research on the interactions between drugs and environmental contaminants;
- Continued study of gene-environment interactions;
- More research on biomarkers as a reliable measure of biological age; and
- Improved understanding of latent effects from early life stage exposures.

The Agency recently explored age-related risk assessment concerns in the comprehensive document *A Framework for Assessing Health Risks of Environmental Exposures to Children* (U.S. EPA, 2005a). In addition, risk assessment guidance exists for carcinogens (U.S. EPA 2005b), neurotoxicity (U.S. EPA, 1998), reproductive toxicity (U.S. EPA, 1996), and environmental endocrine disruption (U.S. EPA, 1997a). However, specific guidance does not exist for assessing health risk to the elderly.

In order to improve our understanding of the interaction between biological aging and exposure to environmental agents, these broad set of research need to be addressed. It is evident that the aging population will require careful consideration regarding exposure, dose, and health effects through targeted research in the aforementioned areas to better characterize potential risks of environmental exposures and their interactions and relationships with genetic traits, nutrition, and disease factors. It is critical that we gain a better understanding of these issues in order to monitor and estimate differential exposures of the elderly population to environmental agents.

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