Summary Report of a Peer Involvement Workshop on the Development of an Exposure Factors Handbook for the Aging

February 14-15, 2007
Arlington, VA

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC 20460

DISCLAIMER

This document was prepared initially by Versar, Inc., an EPA contractor (Contract No. GS-00F-0007L, Purchase Order No. EP06C000358), as a summary of the discussion held at the Peer Involvement Workshop on the Development of an Exposure Factors Handbook for the Aging (February 14-15, 2007). This report captures the main points and highlights of the meeting. It is not a complete record of all detailed discussion, nor does it embellish, interpret, or enlarge upon matters that were incomplete or unclear. Statements represent the individual views of each participant.

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PREFACE

Exposure factors define the rate of contaminant intake (e.g., food consumption, breathing rate), the frequency of contact with different media, and other physiological parameters for estimating dose (e.g., body weight). The Exposure Factors Program of the National Center for Environmental Assessment (NCEA) of the U.S. Environmental Protection Agency's (EPA's) Office of Research and Development (ORD) has three main goals: (1) provide updates to the *Exposure Factors Handbook* and the *Child-Specific Exposure Factors Handbook*; (2) identify exposure factors data gaps and needs in consultation with clients; and (3) develop companion documents to assist clients in the use of exposure factors data. The activities under each goal are supported by and respond to the needs of the various program offices.

The growing proportion of older adults has increased the need to understand how age-related changes in physiology, behavior, disease status or other health conditions may impact exposure and toxic response to environmental agents. Information is needed to better characterize differential exposures of the older adult population to environmental agents. To that end, NCEA convened a panel of experts in the fields of gerontology, physiology, exposure assessment, risk assessment, and behavioral science. This panel of experts discussed existing data, data gaps, and current relevant research on the behavior and physiology of older adults, as well as practical considerations of the utility of an *Exposure Factors Handbook for the Aging* in conducting exposure assessments. This report summarizes the discussions held during the workshop, highlights several sources of existing data, and provides recommendations for additional research.

AUTHORS AND REVIEWERS

The National Center for Environmental Assessment-Washington Division (NCEA-W) of the U.S. Environmental Protection Agency's Office of Research and Development was responsible for the preparation of this document. Preliminary and revised drafts were prepared by Versar, Inc. under an EPA contract (Contract No. GS-00F-0007L, Purchase Order No. EP06C000358). The initial summary report draft was reviewed by members of the workshop expert panel, and the final document was reviewed and revised by the EPA Technical Project Officer.

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Members of the workshop expert panel (Appendix A) were given the opportunity to review the initial draft of the summary report. The comments received from these participants have been addressed and incorporated into the final report.

EXECUTIVE SUMMARY

On February 14-15, 2007, the U.S Environmental Protection Agency sponsored a workshop to discuss issues related to the development of an Exposure Factors Handbook for the aging population. The colloquium was sponsored by the Office of Research and Development, National Center for Environmental Assessment (NCEA) and co-sponsored by the U.S. EPA Office of Children's Health Protection (OCHP). This workshop served as an opportunity to brainstorm ideas associated with the need for a new Exposure Factors Handbook for the Aging (EFHA). The workshop expert panel consisted of 20 experts in exposure, risk assessment, behavior, physiology, toxicology and geriatrics from universities, Federal and State governments, industry, and medical centers.

The first day of the workshop provided for presentations on the workshop's purpose, background on the potential need for a handbook for the aging, the EPA aging initiative currently in place, and the history and use of EPA's current Exposure Factors Handbook (EFH) and the Child-Specific Exposure Factors Handbook (CS-EFH). In addition, the expert panel began its discussion of the charge questions that were developed by the EPA to set the tone for the workshop. These questions had been provided to the expert panel members prior to the workshop. Following two days of presentations and discussion of the charge questions, the workshop participants made the following key conclusions and recommendations:

- Aged individuals can be very different than younger adults in terms of exposure factors and thus do merit special attention in an Exposure Factors Handbook
- It is probably better to not present this material as a separate handbook but rather join the information on aged individuals into the current Exposure Factors Handbook to form an expanded handbook. This will enable ready comparison of parameter values across life stages.
- Geriatric populations can be binned based upon a wide variety of parameters; however, it may be most useful from an exposure assessment standpoint to group aged populations on the basis of functional categories according to the 3 groups described in Section 3.2.3. Chronological age can still be part of the grouping framework by developing age bins that are informed by the percentage of people that are within the full functioning, compromised functioning, or low functioning categories.
- Frailty, per se, should not be used as a discriminator for binning aged adults.
- Make as much of the individual study data and raw data available so that analysts can more fully examine variability and uncertainty and potentially develop other subgroups for specific risk assessment purposes.
- There are numerous pharmacokinetic factors that differ between aged individuals and younger adults that could affect internal dose and risk. The EFH should

include a qualitative discussion of these but then refer to another document (still needs to be developed) for more detailed information.

- There are numerous physiologic and behavioral factors that can affect susceptibility to toxicants (e.g., disease states, polypharmacy, ADRs); these are not exposure factors in the traditional sense (e.g., that would help quantitate exposure dose) and so should be described in a separate document on vulnerability factors in aged individuals.
- Confidence and uncertainties in the exposure parameters should be made explicit as provided in the EFH and CS-EFH.
- This handbook should focus on mobility as providing a key set of activity/functional parameters that distinguish elderly individuals from the remainder of the population. These mobility parameters include daily mobility (e.g., to and from work or recreation), long-term mobility (how long one resides in the same house) and physical mobility (capability to walk and perform activities).
- Physiological parameters for a truly random sample of the older population would be useful information to include in the EFH, rather than just the healthy older population.
- There are many complex vulnerability factors and they may not line up well with exposure factors in terms of age or other types of bins. Rather than complicate the exposure handbook with this information, it was agreed to recommend that vulnerability factors in aged individuals merit their own document.
- Finally, the workshop participants recommend that the handbook be as forward-thinking as possible. As risk assessment has changed greatly in the last few years, developing a forward-looking document that anticipates new developments may be worthwhile. Even if the document includes data that cannot be used now, the data may be usable in the future.

1. INTRODUCTION

1.1 Workshop Background and Purpose

The Peer Involvement Workshop on the Development of an Exposure Factors Handbook for the Aging, hosted by the US EPA, National Center for Environmental Assessment was held on February 14-15, 2007, in Arlington, VA. The workshop format was guided by charge questions developed by the EPA specifically for this effort. The charge questions had also been forwarded to the expert panel members to obtain written comments and suggestions prior to attending the workshop.

The proposed concept of an Exposure Factors Handbook for the subgroup of the population that is considered older or geriatric was the starting point for this workshop. The utility of the existing Exposure Factors Handbooks and the fact that they do not cover aged individuals in any great detail, leads to this proposal for a third Exposure Factors Handbook. Additional rationale comes from the increasing percentage of the population that is being constituted by aging individuals. As this trend continues, it becomes increasingly important for risk assessments to take stock of exposures and risks to this age group.

The existing Exposure Factors Handbook provides a summary of the available statistical data on various factors used in assessing human exposure and health risk. Originally published in 1989, this Handbook is addressed to exposure assessors, both inside and outside the EPA, who need to obtain data on standard factors to calculate human exposure to toxic chemicals. These factors include: drinking water consumption, soil ingestion, inhalation rates, dermal factors including skin surface area and soil adherence factors, consumption of fruits and vegetables, fish, meats, dairy products, homegrown foods, human activity factors, consumer product use, and residential characteristics. In 2002, the EPA released a Child-Specific Exposure Factors Handbook to account for differences in exposure between adults and children resulting from age-related changes in behavior and physiology. Similarly, older adults are also likely to be more susceptible to the adverse effects of environmental contaminants due to differences in exposures stemming from behavioral and physiological changes, as well as the body's decreased capacity to defend against toxic stressors.

The purpose of the workshop was first and foremost to answer the charge questions provided to the workshop participants in advance of the workshop. These questions centered around the feasibility of such a handbook (e.g., what data are available on the behavior and physiology of aged adults), what other types of data should be included (e.g., metabolism, clearance, disease states, drug-taking patterns), how should the data be organized (e.g., categories by age group, functional level, frailty), and ultimately who will use the document and how will it be used.

This report is framed around the charge questions and brings in related discussion on a number of other points that surfaced during the workshop. The main body of the report summarizes in-workshop discussions while the appendices provide the pre-workshop comments which contain more detailed responses and citations.

1.2 Workshop Participants

The workshop was attended by 30 individuals and included participants from EPA, academia, other Federal agencies, industry, and State government. There were 20 Expert Panel members and 10 observer/participants. The list of attendees is presented in Appendix A.

1.3 Charge to Panel

The charge to the Panelists is provided in Appendix B.

The objectives for this workshop were to determine:

- What is known about the aged population, in terms of behavior, physiology, activity;
- If the older population be defined by age groups, by functional ability, by physiologic parameters, or by other special conditions;
- What the final document should contain;
- How the final document would be used; and
- If a separate Exposure Factors Handbook for the older population is needed.

1.4 Agenda

The workshop agenda is presented in Appendix C. The meeting began with the welcome and opening remarks. This was followed by a series of presentations that included issues related to developing an EFHA, the EPA aging initiative and background, history of the Exposure Factors Handbooks and the Exposure Factors Program.

1.5 Workshop Summary

Section 2 summarizes all presentations made at the workshop. Each presentation is followed by "discussion" sections, which summarize both facts and opinions presented by the workgroup participants in response to those presentations. Section 3 provides a summary of the panel discussions for the specific charge questions. Facts, opinions, and concerns brought up by workgroup participants have been recorded. Section 4 provides data gaps and research needs. Section 5 provides consensus recommendations from the Workshop participants. The Appendices A thru F provide the following: attendees, Charge, agenda, presentation overheads, and pre-meeting comments by Charge question and expert panel member, respectively. Background information on exposure factors was briefly discussed.

2. SUMMARY OF OPENING REMARKS/PRESENTATIONS

2.1 Welcome and Introductions

Doug Johns, Health Scientist, NCEA – Washington, opened the workshop by welcoming the workshop participants and observers, noting that scientists were present with expertise in physiology, exposure assessment, and risk assessment. He also thanked them for participating. The workshop participants then introduced themselves to the group.

2.2 Issues Related to the Development of an Exposures Factors Handbook for the Aging

Bob Sonawane, Branch Chief, NCEA Effects Identification and Characterization Group, gave a presentation describing briefly the EPA/ORD/NCEA organization and the history of the Exposure Factors Handbooks and the susceptible populations (children, adults). He also provided insight on the potential need for an EFH specifically for older adults (Appendix D) and issues with its development.

NCEA provides guidance for risk assessors who perform health risk assessments to protect sensitive subpopulations. There exist currently an Exposure Factors Handbook (EFH) and a Child-Specific Exposure Factors Handbook (CS-EFH). Both handbooks provide exposure data, which can be used in risk assessments. However, no such data source is currently available for the older adult population. Such a data source would be useful because, by 2010 older adults will make up a larger fraction of the population, and because the aged population represents a potentially sensitive/susceptible subgroup. Age alters the body's ability to protect against toxic exposure. Bob Sonawane then introduced the workshop chair, Gary Ginsberg, Connecticut Department of Public Health.

2.3 Background and Objectives

2.3.1 Presentation

Gary Ginsberg welcomed the Expert Panel members and thanked them for their pre-workshop participation and for making special efforts to attend the workshop despite the inclement weather. He gave a brief presentation to provide background to panel members (Appendix D) and posed questions for further discussion as the workshop proceeded. He noted that the biggest question posed to the workshop participants is: is a 3rd Exposure Factors Handbook needed? Although senior citizens are an important group to consider, are they sufficiently different from the rest of the population to warrant special scrutiny? However, EFH and CS-EFH are important resources, and an Exposure Factors Handbook for older adults may prove equally useful. Older adults may present unique exposure and risk issues that merit creating a separate database. In the existing Handbooks, basic physiology and behaviors are covered. However, they do not cover clearance pathways, pharmacokinetic modeling parameters, disease states, drug intake, or type of housing; these issues may be worth discussing.

If the exposure to toxins is less for senior citizens than for younger adults (less food intake, soil ingestion, etc), perhaps risk assessments for younger adults will capture the risks for the older population, as well. However, the risk for older populations can be different because of different exposures and vulnerability. Currently, in the EFH, there is provided for every parameter, factors for older populations lumped together (+65 or +70 years of age). So is a new, separate document necessary? Does EPA need a "personal factors handbook", instead of an exposure factors handbook, something that would encompass exposure factors, toxicokinetics, and vulnerability?

Gary Ginsberg concluded his presentation with a discussion of the objectives of the workshop, and posed the following items for thought:

- If the exposure to toxins is less for senior citizens than younger adults (less food intake, soil ingestion, etc), perhaps risk assessments for younger adults will capture the risks for the older population as well.
- The risk for older populations may be significantly different from younger adults because of different exposures and vulnerability.
- The current EFH already contains exposure factors for older populations, though the data for people of ages 65+ or 70+ are lumped together. Is a new, separate document necessary?
- Would a "personal factors handbook" be more useful than an exposure factors handbook—something that would encompass exposure factors, toxicokinetics, and vulnerability?

The charge questions (Appendix B) were then presented to the workshop participants. A discussion followed on the necessity of having a separate handbook for the aging. Highlights of the discussion are provided in Section 2.3.2.

2.3.2 Discussion

The necessity of a separate Exposure Factors Handbook for older adults was discussed by the expert panel. Points of discussion were as follows:

- For children, it's clear that there are very different potential exposure scenarios. From a toxicological standpoint, chronic exposure is more important for children. It's not clear that an older population has issues that stand out in such stark contrast to younger adults.
- Current literature shows that there are differences across life stages. Older adults take 4-5 drugs on average. It would be important to capture these differences.
- Although differences may be minor when comparing one younger adult against an older adult, comparing the populations as a whole may have the potential to show a much larger impact. The percent of older people in daycare and institutional

facilities may be comparable or even larger to the percent of children in institutional settings.

- Historically, children have been examined in risk assessments because they differ from adults. It may be that people have overlooked patterns in older adults because they are expected to die soon.
- The older population is the most plastic (most rapidly changing subpopulation). It is a population that is critical to the well-being of society: if healthy, they can be useful contributors to society, but if unhealthy, can be a burden.
- Older adults who live in institutional settings relinquish control over their environment. People living independently at home can control their environment much more easily than people in institutionalized settings.
- In the absence of knowledge of unique exposures associated with the aged population, risk assessors may wish to integrate the older population and their associated exposure factors as part of an overall assessment, rather than target the population specifically.

There was discussion regarding the need for a new Exposure Factors Handbook versus a "Personal Factors Handbook." Key points of discussion were:

- A risk assessment is generally composed of a dose/response assessment, in which the toxicity of a chemical is determined, and an exposure assessment, in which the quantity of chemical to which an individual is exposed is determined. The exposure factors handbooks have been geared towards helping assessors deal with the exposure assessment portion of the problem. A "Personal Factors Handbook" would include toxicokinetic factors and other information associated with the dose/response assessment.
- Although toxicokinetic factors are not included in the EFH or CS-EFH, it may still be worthwhile to include such information for the older population.
- It seems that risk assessment is moving towards looking at lifespan factors; therefore, having all information in a single volume may prove useful in the future.
- The separation of dose/response and exposure is artificial.

2.4 U.S. EPA Aging Initiative

2.4.1 Presentation

Kathy Sykes, Senior Advisor, Aging Initiative, EPA Office of Children's Health Protection gave a presentation describing the aging initiative undertaken by the Office of Children's Health Protection (Appendix D). The Aging Initiative is an initiative whose goals are to identify research gaps in environmental health, and translate the findings to public health prevention strategies. For the initiative, tools are desired that address the impact of a rapidly aging society. Half of the existing infrastructure in the United States will be rebuilt in the next 20 years. Older adults are a sensitive population, who undergo a decrease in organ function, the impaired ability for chemical clearance and detoxification, issues associated with being on medications, as well as a legacy of past occupational and environmental cumulative exposures to persistent agents. The number of deaths attributable to particulate matter (PM) in pollution is comparable to diabetes and renal disease deaths. Ozone and PM have the greatest potential to affect the health of older adults. The economic burden in 2002 was 250 billion dollars in direct medical costs and 9 billion in lost productivity for cardiovascular lung and blood diseases. The older population has greater prevalence of asthma. Chronic obstructive pulmonary disease (COPD) is the 4th leading cause of death in the United States. Older adults may also be more at risk of gastrointestinal illness (GI).

2.4.2 Discussion

- The aging population has decreased ability to cope with harmful agents (xenobiotics). Therefore, toxicodynamics is an important issue when considering the older population.
- Statistics may be underreported for the older population, as there is no-one acting as advocates for them the way parents do for children. Therefore, it may be worthwhile to explore how much confidence can be placed in data for the older population.
- There are medical issues that older people have that may not fall into a clinical category. These effects may not be captured in data.
- Mitigation of a risk to older people will yield quicker benefits to society than mitigation of a risk to children (who must grow up before becoming productive).

2.5 History and Use of the Current Exposure Factors Handbooks

2.5.1 Presentation

Jackie Moya, Environmental Engineer, NCEA-Washington, gave a presentation on the history of the existing exposure factors handbooks (Appendix D). The goal of the Exposure Factors Program (EFP) is to update CS-EFH and EFH by 2007 and 2008. CS-EFH should be complete by 2007. The Exposure Factors handbook is currently being revised. An internal review draft should be available March/April of this year, and a final draft later in the year. Both EFH and CS-EFH are used by many people, both inside and outside of EPA, so keeping them up-to-date is important. Companion documents describing how to use the data are planned for development, as are the establishment of consultation services to help clients use the data properly. The Exposure Factors handbook was published in 1989, updated in 1997, and a second update is planned for 2008.

Since 1995, regulations have been established with children in mind: the children's risk policy (1995), the Food Quality Protection Act (FQPA) (1996), which requires proof that

a tolerance is safe for children, and ORD's Children's Research Strategy (2000), which ensures that risks related to children are considered by the Agency. The CS-EFH was created in answer to these regulations.
To achieve the goals of the EFP, an Exposure Factors Advisory Group was established (2004) and charged to assist NCEA in identifying areas where research is necessary, and to assist in setting priorities for research. High-priority areas identified by the advisory group are: soil ingestion rates for adults and children, mouthing behavior, high-end exposure populations, which may include farmers, the subsistence population, and the older population.

Currently in the EFH, adults are generally lumped into age categories: 20-39, 40-69, and 70+, for example. When comparing exposure factors (inhalation rates, activity patterns) for these populations, there is not much variability. However, there appears to be variability in terms of what activity the older population is engaged in, dependant on each individual's health status.

2.5.2 Discussion

Workgroup participants again discussed if exposure factor data for all life stages should be integrated into one document. Highlights of the discussion were as follows:

- It is useful to have data for children and young adults, and the older population all in one place, as EFH is currently. If data are separated for the older population, one can lose the ability to compare older and younger populations, and it becomes harder to perform an integrated assessment across life stages.
- Ideally, a risk assessment should incorporate the overall variability in a population. Therefore, risk assessors often focus attention on the population with the greatest variability to exposure. However, as each risk assessment is unique, it will be up to each risk assessor to determine a population of interest. As such, risk assessors would probably want to see all data in one place, so that they can be compared.
- Physiological factors could be addressed in the EFH by referencing other work that has been done in this area. However, no chapter on physiological factors is planned by EPA at this time.

3. PANEL DISCUSSIONS OF SPECIFIC CHARGE QUESTIONS

This section presents the report of the Workshop Chair. Gary Ginsberg facilitated discussion of the specific charge questions that had been given prior to the workshop to the expert panel members. The information provided in this section is framed around the charge questions and brings in related discussion on a number of other points that surfaced during the workshop. Appendix E and Appendix F provide the pre-workshop comments for these questions by expert and contain more detailed responses and citations.

Summary of Key Findings

A key finding based on the discussions of the specific Charge Questions at the workshop is that aged individuals can be very different than younger adults in terms of exposure factors and thus do merit special attention in an exposure factors handbook. However, a separate handbook solely for people over a certain age or age group may not be needed. One issue with developing a separate handbook is how to define the aged, that is what age or physiological description is the point at which they are separated from the rest of the adult population? Since aging starts much earlier in life than 65 on the one hand, and healthy adults may not be considered old until age 75 on the other, the break point may be difficult to define. Another issue recognized by workshop participants is the value of having parameter values expressed in one place that encompasses a wide range of life stages. This would provide ready comparison of parameter values and see how they change over time. In addition, this can help focus a risk assessment on particular life stages for particular exposure pathways and chemicals. Separate Exposure Factors Handbooks would render such across-life stage comparisons more difficult.

Another key workshop finding is that there are numerous factors associated with aging that also can occur at younger ages and which are not traditionally incorporated into the Exposure Factors Handbook. These can be thought of as vulnerability factors which are unique or especially important in aged individuals and include: 1) onset of a variety of disease states (heart, respiratory and renal diseases, diabetes, cancer, neurological disorders, etc.); 2) consumption of numerous prescriptions and over-the-counter drugs, for example, polypharmacy, this can lead to morbidity, increased potential for drug-xenobiotic interactions on a PK or PD basis, and lowered host defense; 3) diminished hepatic and renal clearance both in normal aging and especially in those with renal or hepatic disorders; 4) altered hormone balance and body remodeling that comes with menopause; 5) diminished cellular defenses such as antioxidant factors and glutathione, there appears to be lowered reserve to quench or adapt to cellular oxidant or other types of stressors; 6) aging neurologic, immune and cardiovascular system may be more vulnerable to chemical stressors. Given that these vulnerability factors are not presented in the current handbooks, it raises the question of the merits of their inclusion in the current document.

These vulnerability factors could theoretically be combined with the exposure factors described throughout the rest of this workshop report to develop a comprehensive document on exposure and vulnerability factors in old age. However, there are many complex vulnerability factors and they may not line up well with exposure factors in terms of age or other types of bins. Rather than complicate the exposure handbook with this information, it was agreed to recommend that vulnerability factors in aged individuals merit their own document. However, there were several opinions to include toxicokinetic (TK) factors (ADME, clearance, size and composition of body compartments, blood flows, partition coefficients, protein binding) since these factors affect internal dose which is still an exposure factor. The existing Exposure Factors Handbooks do not include TK factors, but are presented in separate documents. EPA can consider inclusion of TK factors in the generation of aging parameters for the EFH or choose to compile them in a separate document.

Finally, the workshop recommends that the handbook be as forward-thinking as possible. As risk assessment has changed greatly in the last few years, developing a forward-looking document that anticipates new developments may be worthwhile. Even if the document includes data that cannot be used now, the data may be usable in the future.

CHARGE QUESTION NO. 1- Activity Patterns, Behavior, Physiology, Diet and Medication

3.1 *Age-related changes in activity patterns, behavior, and physiology may have a significant impact on exposures to environmental chemicals. In order to better characterize these changes, please discuss the following:*

3.1.1 *What information is available on activity patterns and behaviors in the aging? Specifically, what is known regarding: 1) where older adults spend their time, and 2) what activities older adults are engaged in? What research is currently being conducted in these areas? What are the data gaps and research needs?*

Response:
Workshop participants described from their general knowledge and experience as well as from selected citations (e.g., Baltimore Longitudinal Study as reported by Verbrugge, et al., 1996; the National Health Interview Survey; Leech et al., 2002), the evidence that there is a steady drop off in the percentage of people engaging in regular exercise, and that increasing amounts of time are spent indoors in passive leisure activities (e.g., watching television) and in conducting the activities of daily living (ADL). The most common physical activity in the aged is walking. Additionally, people are more likely to be retired from the workplace with advancing age which can mean less activity and more time spent at home. This leads to a greater opportunity for exposure from sources around the home or in the immediate neighborhood.

In summarizing activity data, it will be important to keep men and women separate and it may also be important to further subdivide on racial/ethnic grounds. There is evidence that men are more physically active than women in later life and that Caucasians are more active than minorities. This may be due to several factors including awareness level, health status (e.g., minorities may have higher rates of heart disease and diabetes which will diminish ability to be physically active), and location of residence (activity level is generally lower in areas where there is high traffic density or unclean or unsafe streets). Subdividing aging individuals by ethnic or income groups may add a degree of complexity to the handbook that would have to be carefully weighed in terms of the exposure information gained.

USEPA's Consolidated Human Activity Database (CHAD) is an excellent source of activity information (McCurdy et al., 2000). These records are compiled from data on individual subjects across a wide age range. Therefore, they can be probed to explore relationships between activity pattern and age, medical condition, location of residence, season, and other factors. CHAD does not exclude subjects on the basis of medical condition so it is fairly representative of those who live independently across a spectrum of functional states. There are over 2000 records for people over 65 years of age.

The activities of seniors and other population subgroups are tracked by industries that market products and services to these age groups. Time spent in leisure activities such as golf or gardening and the purchasing patterns of consumer products and over-the-counter medications are areas which there are likely to be market survey information for aged individuals. This survey information may be expensive to obtain since it represents private marketing research. Also, users of the data would have to examine its representativeness: did the survey screen out individuals with particular infirmities or who are below certain income/savings levels. Other possible survey sources of information for gardening activities and pesticide use in aging individuals are the Gallup survey of gardening and lawn maintenance activities, the Residential Exposure Joint Venture (REJV), and National Home and Garden Pesticide Use Survey (NHGPUS). The availability and utility of these surveys would need further exploration (Whitmore, 1992).

An activity factor that can affect exposure dose is mobility; it is generally lower with advancing age in a number of respects:

- Aged individuals are less able to mobilize quickly to get out of harm's way during a chemical emergency (poorer hearing, slower reaction time, issues with cognition);
- They are less mobile in terms of daily activities due to retirement and less busy schedules and thus may not receive the array of exposures experienced by younger adults (e.g., roadway commuting exposures). Instead, they may spend more hours/day in a particular microenvironment – e.g., at home or in a rehabilitation or nursing home environment. The U.S. Bureau of Labor Statistics is a good source of information on age-related changes in time spent at work and commuting.
- Their residential location is more stable such that the number of years they live in one location may be greater than for younger adults. However, the distribution of residence time in one location will be truncated by mortality or morbidity-induced relocation (e.g., into a rehabilitation or nursing home) such that it is unlikely to be a large upper tail to the distribution. Workshop participants felt that the general population 90th percentile default of 30 year residence at one location is likely to be reasonably conservative for older

adults as well. However, this does not mean that risk assessments cannot be refined by more accurately depicting the true mobility of the population, particularly as these assessments move towards being able to display the full assessment of exposure, rather than just showing bounding scenarios.

Several concerns with activity pattern studies were raised during the workshop as follows:

- While a variety of studies and databases report activities engaged in by aging individuals, these studies often do not provide a comparison to younger age groups. Such a within-study comparison of age groups is more useful than obtaining this information across studies, in which case differing methodologies may affect results. That being said, several studies provide longitudinal data in which an individual is followed over numerous years with repeat surveys to determine how activity has changed over time. This type of data is generally highly useful for across-age comparisons. These studies are usually not conducted over long enough periods of time to show contrasts between middle age and older adults, but do provide trends within the geriatric population.
- Activity patterns are informative for exposure assessment to a degree, but often need additional information to provide quantitative information. The level of physical exertion required for an activity is typically not measured so that one cannot tell how the energy expenditure compares between 10 minutes of "light" activity in an aged individual versus 20 minutes of "moderate" exercise in a young adult. It may be that certain activities of daily living that are not traditionally thought of as physical exercise may be so for aged individuals. The most useful studies are those which characterize activity by location, time spent, and level of exertion or energy utilization to perform the activity at that age.
- Activity pattern data generally comes from self-reported information which is very difficult to validate with objective measures. Over-reporting of physical activity is believed to be a general phenomenon across age groups in such surveys.
- Because the older population's functional level and activities have changed over time, activity data collected in the 1980s may not be an accurate representation for 2007. Older data should be examined with circumspection.

Data appear to be most abundant in the area of exercise and strength-building and how they can maintain functions and improve physical and mental well being. Data gaps especially pertinent to the development of an activity database for aged individuals are: 1) comparative activity data across younger and older adults and across sub-categories of older adults (ethnicities, living situation, functional category); 2) data on activities related to water exposure – frequency and time spent bathing, showering, washing clothing, dishes; 3) potential exposure to soil and house dust – hand-to-mouth frequency, time spent gardening, home cleaning practices; 4) types of products used around the home; 5) hobbies engaged in – how often and what products are used, with a focus on hobbies that may involve toxic chemicals, physical labor, or time spent in specific microenvironments (e.g., dark room, ceramics workshop); 6) time spent commuting on mass transit, personal cars, on busy roadways; 7) independent cross-check of survey-based activity data with devices (e.g., accelerometers, pedometers, heart rate monitors) or physical testing (e.g., Up-and-Go). Objective measures of physical activity are needed for use in validation of activity surveys.

The following is a listing of additional resources for activity patterns information in aged populations identified the workshop participants. This listing complements the information and sources described above.

- Established Populations for Epidemiologic Studies of the Elderly (EPESE) have been performed for a number of geographic regions, providing information on activity patterns (National Institute of Aging (NIA), Bethesda, MD).
- The National Human Activity Pattern Survey (NHAPS) is a resource for assessing activities and behavior patterns that can affect the potential for exposure to environmental pollutants.
- The International Project for Attitude Change (IPAC) has a survey in which reported exercise levels are compared against VO_2 max. This may provide useful activity and survey reliability information. For example, IPAC reports little correlation in these two parameters.
- Medicare beneficiary studies may provide useful information on functional status in relation to living conditions (community dwelling, institutional, etc.).
- The National Gardening Survey contains soil contact data, regional information, and duration of time people spend gardening broken down by age groups.

3.1.2 *What information is available on age-related changes in physiological parameters such as inhalation rate, body composition, and body weight? What research is currently being conducted in these areas? What are the data gaps and research needs?*

There have been many studies of changing physiology with age. However, much of these data pertain to healthy adults and the influence of normal aging processes. “Normal” is understood as being in the absence of disease. However, disease is also a normal part of aging as there is a natural increase in the occurrence of aging-related conditions (e.g., heart disease, cancer, diabetes, neurologic diseases). The standard physiology tables in sources like The Handbook of Physiology (1995) and studies of healthy aging individuals miss the decrements in function due to disease processes and the variability that this introduces. Both types of information, normal aging-related physiological changes, and disease-related impairments in function, should be considered for inclusion in the EFH.

The physiological status of healthy older adults may be within the range of that seen in the general population since parameters such as height, weight, lean muscle mass, breathing volumes, energy utilization, and cardiac function decline gradually in the non-diseased individual. It is important to perform statistical tests to determine if there is a perceptible modality or breakpoint from the general population distribution at a certain age or other type of grouping. Workshop participants are of the opinion that the majority of healthy older adult are likely to be part of the general population distribution for most physiological parameters. This means that there may not be an obvious discrimination into a separate aged category on the basis of one or more physiological parameters for these healthy older adults. However, older individuals with disease or those so old as to have lost substantial function may be distinct from the general population distribution and thus represent a separate mode. This could be the basis for binning as described in Charge Question No. 2.

Many factors tend to decrease with age, ranging from height and weight (that is, beyond a certain age; weight and body fat tend to increase through much of adult life and then decreases in the older groups), lean muscle mass, ventilation rate and volume, energy expenditure (related to activity patterns and functional capability), and liver and renal clearance of xenobiotics. There are generally good statistical databases for these factors, often cross-sectional but in some cases longitudinal. Obesity appears to diminish in old age, but that may be more a function of selective survival due to early death of obese individuals rather than a physiologic/metabolic change in old age. Involuntary weight loss can be associated with various diseases such as cancer, depression, drug side effects, gastrointestinal conditions, etc. However, it can also occur as a natural stage of aging involving loss of physiological function and what has been termed frailty. Metabolic rate stemming both from basal metabolism and from activities also declines with normal aging. An excellent dataset reports results for a wide age range based upon doubly labeled water measurements (Brochu, et al. 2006). This information can be used to understand energy requirements and ventilation rate across life stages including the aged.

The workshop participants identified a number of factors about aging physiology that are relevant to changes in exposure that are of potential importance to an Exposure Factors Handbook.

- Acid secretion in the gastrointestinal tract is generally believed to be diminished, but this may be more a function of a disease/malfunction (atrophic gastritis) than a normal consequence of aging; nevertheless, it may affect GI uptake of nutrients, drugs and environmental chemicals.
- Respiratory physiology changes with age such that there is increased dead space (Zeleznik *Clin. Geriatr. Med.* 19: 1-18, 2003); however alveolar ventilation is primarily a function of metabolic rate and so aged individuals may increase minute ventilation to deliver sufficient air to the deep lungs. This may increase air flow in the upper respiratory tract and lead to greater deposition of reactive/water soluble gases and large particles. As age advances, chest wall compliance decreases and lung compliance tends to increase, with the net result being a decline in both forced expiratory volume in 1 second (FEV1) and forced

vital capacity (FVC). With advancing age, breaths/minute tend to increase. Changes in respiratory physiology that are part of normal aging are an important exposure feature. Further, declines in respiratory function associated with disease (chronic obstructive pulmonary disease COPD, asthma, bronchitis) may produce even larger deviation from normal air flow and ventilation rate in different airway regions. To the extent that disease states are included in an EFH, this would be an important consideration.

- Lung clearance mechanisms may diminish with advancing age such that particle retention may increase. This is an area of some uncertainty and of minimal data and, therefore, is an important research need.
- There are conflicting data on whether the barrier function of the skin is altered in normal aging, but wound healing is diminished, leading to greater opportunity for transdermal penetration via damaged skin. This factor may not be readily amenable to quantitative incorporation into risk assessments. However, blood flow to the skin appears to diminish; this factor can be used in PBTK modeling to simulate how chemical absorption across the skin may diminish with age. Skin penetration studies involving aged individuals are warranted, both in vivo and in vitro.
- Skin surface area is a function of body size and can be estimated from NHANES height and weight data for various age groups including aged individuals. One caveat is that the elasticity of the skin decreases which may affect surface area, but the workshop participants were not aware of data in this regard.
- Cardiovascular function decreases with advancing age such that the chronotropic and ionotropic responses of the heart to sympathetic stimulation decrease. Further, there is an age-associated decrease in the distensibility of the arteries that causes an increase in systolic blood pressure and pulse pressure. Consideration should be given to how these changes and more severe changes that lead to vascular diseases or congestive heart failure may affect cardiac output and organ blood flows.
- Renal function decreases as part of the aging process with NHANES data showing that glomerular filtration rate (GFR) declines roughly 2 fold between the age range of 20s and 70s in healthy adults. Drug clearance studies involving renally cleared drugs (e.g., many antibiotics, furosemide) provide a good indication of diminishing xenobiotic clearance from the kidneys with age.
- Creatinine clearance or the daily excretion of creatinine declines with age. There can be numerous reasons for this, involving both renal function and muscle mass/wasting. Since the creatinine concentration in urine is often used as a normalization factor for biomonitoring results, modification of creatinine levels with aging has implications for the interpretation of NHANES/CDC biomonitoring data.
- Obesity is common to most age groups; while it may represent a particular physiologic stress to aged individuals, there does not seem to be a strong rationale for including this as a separate exposure factor. Body mass index is not a highly

useful parameter in old age because the loss in lean muscle mass can be counterbalanced by increased fat stores leading to a similar BMI to that seen in younger ages that does not reflect the changes in body composition.

- Body composition is important to report in an EFH because of its influence on chemical distribution. Therefore, changes in body lipid, water and muscle mass that occur as part of the aging process would be valuable information. The volume of distribution (Vd) of water soluble chemicals may go down because of lower total body water while the Vd for fat soluble compounds may go up. Levels of albumin are slightly lower in the aged who are free of liver disease so protein binding, another factor governing Vd, may be less in this life stage. However, these PK factors are not incorporated into the current handbooks.
- Menopause is a physiological change that involves shifting hormone levels and body remodeling, in particular bone resorption that can lead to release of lead and other metals stored in bone. While this is not a factor that affects intake of new chemical exposures, it may merit some mention in the handbook.
- The amount of work needed to perform a basic function such as climbing a flight of stairs or vacuuming may be greater in the older population in comparison to young adults. This physiologic change is related to decreased lean muscle mass. Therefore, the manner in which activities are assigned numeric values for activity level, ventilation rate, and energy utilization will need to be examined for every age group; this may be an important research need.
- There can be many different reasons for loss of physical activity. Data on physiological changes that create barriers to activity, such as loss of eyesight, loss of limbs, arthritis, etc., may be useful to collect in this handbook.
- Physiological parameters for a truly random sample of the total older population would be useful information to include in the handbook, rather than just the healthy older population.

The NHANES dataset is an important source of physiological data across life stages. Price et al. (2003) have evaluated individuals from NHANES III to build a PBTK parameter database that describes individuals rather than the population. Through simulations, these individuals can be analyzed as a group to develop an understanding of population distributions. This analytical approach has the advantage where, for parameters which are correlated (e.g., height and weight or respiration and cardiac output), their assignment to individuals based upon actual measurements will maintain the correlations and safeguard against simulating individuals who are physiologically unlikely (someone who is very tall and very light) (Price, et al. 2003). The workshop participants recommend that EPA explore this technique as a way to establish population distributions of physiological parameters where such individual data are available (e.g., NHANES).

There are numerous physiological changes in aged individuals that can affect toxicokinetic (decreased hepatic and renal clearance, altered body composition, protein binding changes, altered blood flows, possible altered partition coefficients) and toxicodynamic (decreased cellular defense mechanisms, antioxidant and glutathione levels, functional reserve capacity) vulnerabilities to chemical exposure. These factors may best be summarized in a companion vulnerability factors handbook rather than incorporation into this handbook.

Numerous physiological changes can be described, but their relevance to exposure and risk assessment is not always clear. To the extent possible, the handbook should describe how particular parameters (e.g., lean muscle mass decrements) are related to differential exposure in this life stage relative to others. EPA may wish to organize the available data to develop qualitative guidance on what is known about the ageing process in each of the organ systems and the implications for exposure assessment. Special emphasis should be given to the organ systems relevant to intake and uptake (the GI tract, lungs, and skin) and metabolism and excretion (liver and kidneys).

3.1.3 *What information is available on diet and medication use in the aging population? What research is currently being conducted in these areas? What are the data gaps and research needs?*

Response:
Medication use is extensive in the aging population due to the greater number of medical conditions experienced by this life stage. The existence of polypharmacy, generally defined as 4 or more medications at one time in one individual, is on the order of 20% or more, depending upon the population under study (e.g., nursing homes vs community residents). This leads to a greater likelihood of adverse drug reactions (ADRs), drug-drug interactions, and drug-environmental chemical interactions. However, this is a complex topic that is highly variable due to all the different combinations of drugs, drug dosages, and disease states that one may experience. Data are sometimes reported as the number of inappropriate medications based upon prescribing criteria in the elderly.
To date, information on medication use has not been incorporated in the current Exposure Factors Handbooks, even though this can be an important co-exposure at any age. While this issue rises to new levels of importance in the aged, it may not be appropriate to single out one group for this data reporting. Rather than try to capture the toxicokinetic and toxicodynamic factors that are associated with polypharmacy in aging individuals, the EPA may want to provide some discussion of this issue in the handbook and then refer to other sources for more information. The workshop participants discussed the desirability of a separate analysis of the potential interactions between heavily prescribed drugs and environmental chemicals to complement a handbook.
Any assessment of medication use should not lose sight of the fact that many people, including the aging population, take supplements and herbal remedies that may contain toxicants or may predispose in some manner to susceptibility and adverse health outcomes. This can be difficult information to collect as usage may be more sporadic and ingredients less standardized than with the intake of pharmaceuticals.

Dietary intake of calories, nutrients and specific foods generally declines with advancing age with numerous datasets showing evidence of these declines. However data on the intake of specific contaminant-bearing foods (e.g., swordfish, tuna) in specific age groups may not be as readily available. The intake of individual nutrients in the aged is described in the Institute of Medicine report while the CSFII reports describe the consumption of specific foods. The Institute of Medicine reports on the intake of individual nutrients (calories, vitamins, supplements, salt, electrolytes) for different age groups, including 51-70 and 70+. These datasets need to be explored to fill in essential information for a handbook. However, it is important to keep in mind that food surveys have inherent limitations and recall bias. Short-term surveys may not be highly representative unless a large number of people are sampled, while longer-term dietary diaries or surveys have compliance or recall issues.

Aged individuals are more likely to eat a narrower range of foods and thus could represent an upper end of a meal frequency tail. This could be due to shopping for the easiest and most convenient or inexpensive foods, and less interest in trying new foods. Therefore, it is important to accurately characterize the distribution of geriatric eating patterns.

Drinking water ingestion may not vary greatly in healthy older adults compared to young adults, although the thirst recognition trigger is not as acute as in younger ages. This trigger is the dehydration point at which thirst becomes noticeable. The aged are more likely to receive their drinking water from at home sources rather than the typical combination of workplace, transportation site, convenience store/restaurant and other locations more common at younger ages. Therefore, exposure to contaminants in household tap water may be greater in old adults, although the general default of 2 L/day for a 70 Kg adult at one particular residence may cover the upper end of the water intake rate in aged individuals as well.

CHARGE QUESTION NO. 2 – Age Bins

3.2 ***Individuals over the age of 65 are often divided into categories based solely on chronological age, such as young-old (65-74 years), old-old (75-84 years), and oldest-old (85 years and older). However, the aging population is a highly heterogeneous group, and age-related changes in behavior and physiological function may be more a function of biological age than chronological age. This may be an important distinction in evaluating risk of exposure to environmental chemicals as changes in behavior and physiology directly affect exposure as well as the resulting internal dose. With this in mind, please discuss the following questions:***

3.2.1 ***In conducting exposure/risk assessments, is it appropriate to divide the aging population into age groups or "bins?" If so, what factors should be considered in determining these groups?***

Response:
Workshop participants agreed that binning a diverse group such as the aging population into subcategories can be useful for risk assessment. Heterogeneity in the population

over 65 is too great to establish all inclusive population distributions that do not obscure important features in certain individuals that may predispose to exposure and risk. The idea of binning is to break the data into groups that have less variability than the population as a whole. Multi-modal population distributions for key parameters would be an indication of the need to create subdivisions. However, even without distributional analysis certain natural divisions may be suggested by activity and physiological considerations. The workshop participants considered a number of factors that might help determine the construction of such bins:

- Chronological age: this has several advantages as it is the most easily obtained parameter, would conform with the type of binning that is done for children, and provides an obvious indication of the number of years someone has these characteristics (the size of the age bin corresponds to the number of years of that exposure classification). However, there are major disadvantages, most notably that chronological age often does not reflect biological age in aged populations. People age at different rates, with activities and function greatly affected by diseases, medications, pre-existing exercise regimen, retirement and socialization. This leads to great heterogeneity within any age category, such that age alone is likely to be a poor discriminator of breakpoints in key exposure parameters. The workshop participants concluded that categorization based upon age alone is inappropriate and is likely to obscure key functional, behavioral and exposure differences among aged individuals.
- Functional status: this category is a composite of physiology and activity as it describes the extent to which the individual is physically capable of participating in a range of activities. This has merit for segregating the aged population into subgroups because it relates to changes in physiology and behavior that can directly affect exposure. One parameter that may be particularly useful in this regard is changes in gait, as measured in standard gait tests.
- Lean muscle mass: this parameter has some attraction for binning because it reliably decreases with aging and the possibility of developing cutpoints of lean muscle mass that correspond to functional capabilities and exposure potential (e.g., below a certain muscle mass, mowing the lawn is highly unlikely). Skin fold thickness measurements are readily available as a surrogate index of lean muscle mass and body fat load.
- Living situation: the type of residence – single family private residence, versus condominium/apartment versus assisted living versus rehab/hospital versus nursing home may be a way to characterize an individual's health/disease status, function and activity level. However, there is still likely to be considerable variability within any one of these settings.
- Metabolic and clearance functions: these are physiologic functions that tend to decrease in aged individuals, leading to greater internal dose and longer retention of drugs and environmental chemicals. Such toxicokinetic factors can affect internal concentration and so, in a way, represents an exposure factor. However, this may not be the proper grouping basis for the handbook since its main focus is on

activity-based contact with chemical media and not on chemical processing once taken up.

- The workshop participants recognized that some information is lost when individuals are collapsed into bins based upon age or any other feature. The bins average across a range of parameter values limiting the ability to perform a full variability analysis. The workshop participants discussed the possibility of continuous exposure models in which physiologic and activity parameters are described in equations or coded in lookup tables as a continuous function of age. This approach works well where the change in a parameter fits a continuous function such that a single equation predicts the parameter value at any given age. Equations or lookup tables can also be designed to portray step functions if transitions are not a smooth function of age. However, as described above, age may not always be the best descriptor of a change in exposure characteristics and even step functions may poorly predict what is occurring in select subgroups.
- The workshop participants discussed the need for all individual or raw data that go into any binning process be made available to analysts so that they can go beyond the predetermined bins and organize the data differently and also more completely explore interindividual variability.

3.2.2 *Are there behavioral changes that occur in the aging which lend themselves to characterization using age group categories?*

Response:
The workshop participants did not identify any specific behavioral factors that, on their own, would constitute a good basis for subdividing the aged into groups. As mentioned above, living situation and overall activity level may be useful considerations in choosing categories. It can also be argued that retirement is a major factor governing the types of activities participating in and the exposures someone is likely to receive. Some of these factors are governed by changes in physiology which may affect participation in the full array of adult activities. Therefore, it may be better to use physiological measures for segregating the aged population into subgroups and then describe the types of living arrangements, behaviors and activity patterns that go with the physiologically defined group.

3.2.3 *Are there physiological changes that occur in the aging which lend themselves to characterization using age group categories?*

The workshop participants recognized that it is very difficult to define biological age as there are numerous parameters and the gerontologists often disagree about which parameters are most associated with different life stages. Rather than try to identify a set of physiologic characteristics, they agreed upon a set of functional characteristics that can be used to segregate the elderly into groups that are descriptive of activities and exposure potential. The recommended focus is on the ability to perform tasks by groups as follows:

Group 1: Aged individuals who are active and capable of exercise, leisure and social activities, and can perform a wide array of routine tasks (instrumental activities of daily living (IADLs), activities of daily living (ADLS)) plus more difficult chores such as yard work, painting, etc. They may be affected by diseases such as hypertension, diabetes or arthritis, but their conditions do not impair their functional level with respect to basic tasks. These individuals would be part of the population distribution extended from younger age groups and may not need a separate grouping based upon some age cutpoint.

Group 2: Aged individuals whose functional activity is limited such that the IADLs have become an issue and cannot do one or more of the following: stoop/kneel, reach over head, write, walk 2-3 blocks, lift 10 lbs or any one of the IADLs without assistance.

Group 3: Aged individuals whose functional capacity is diminished such that the ADLs cannot be performed without assistance. The ADL refers to walking, going outside, bathing, dressing, using the toilet, getting in and out of a bed or a chair, and eating. Group 3 would comprise 15 to 20% of the United States population over age 65. Although Group 3 is heavily weighted by the oldest old, it would also have a significant fraction of all age groups over age 65. The frail elderly and the institutionalized elderly would primarily be in this group. This group's activities and exposures are expected to be governed more by their functional status than by their age or where they live (e.g., at home with caretaker vs institutionalized).

This categorization scheme would capture functional disabilities that can affect exposure potential whether it was due to the normal aging process, disease, or injury. It would also be useful as a predictor of health status and longevity as those who can engage in physical activity tend to maintain good health and have less rapid erosion of functional capabilities. The challenge in implementing this framework will be to find datasets relevant to these categories that describe exposure factors such as dietary habits, ventilation rates, water ingestion, and other parameters. Therefore, an important task will be to describe these categories in both physiologic and behavioral terms. A variety of sources are likely to already exist. For example, standard physiological data for aging individuals typically are from healthy, independent subjects and so are most relevant to Group 1, while data available for nursing home patients may be a source of information for Group 3. The Senior Fitness Test, a comprehensive physiology and functions battery, has been applied to large numbers of older adults (Rikli and Jones, 2001). Data from such testing should help define these categories more precisely.

The manner in which these categories would be incorporated into the handbook is open to several different possibilities. In each case, the workshop participants recommend that aged adults be included in the same handbook as younger adults and presented as a separate line (or series of lines) in parameter tables. In this case, Group 1 could be presented as a central estimate and distribution percentiles for all people of a single gender over a particular age. Alternatively, the Group 1 aged population can be lumped in 5 or 10 year increments to better portray changing parameter values with advancing age. It would be anticipated that Groups 2 and 3 would be presented as a central tendency and distribution percentiles without further breakdown by age. This assumes that people in Groups 2 and 3 have similar exposure traits regardless of age, which may be a good assumption for many parameters.

Another way in which these groupings can be presented is within chronological age categories. For example, one may construct aging categories of 65-74, 75-84, 85-94, and >94. Within each category, the healthy (Group 1) data can be presented, together with information on the percentage of that age group that is Group 2 and Group 3. This could facilitate the creation of a mixed or multi-modal distribution for each age category where all three groups would be represented in their respective percentages. This approach has the advantage of unifying the analysis around age groups along with analyzing the variability within age groups. It has the potential disadvantage of obscuring a small percentage of the population that may have a large difference in exposure potential. Such groups may be best represented by a separate distribution so that they can receive a special focus in the risk assessment.

Finally, the workshop noted that the handbook need not be limited to these pre-determined groupings, but could also create a new category based upon some unique living situation or circumstance that involved a sizable group of aged individuals. This would be analogous to having subsistence fishers as a separate exposure category in the current handbooks. The possibility that such readily definable and uniquely exposed groups exist should be carefully considered when filling in the handbook framework.

3.2.4 *In the context of exposure/risk assessment among the aging, how should "frailty" be defined? Should "frail" older adults be considered separately from "healthy" older adults?*

Frailty is a problematic term because of vague and sometimes conflicting definitions. The workshop participants did not attempt to settle the definition of frailty, but rather advised steering away from such a general phrase. The grouping framework described previously captures frail individuals, primarily within Group 3 (described in Section 3.2.3).

CHARGE QUESTION NO. 3 – Potential Users, Use in Exposure and Risk Assessments, Factors to Include, Data Presentation

3.3 *It has been proposed that an Exposure Factors Handbook for Aging populations be developed to provide more detailed information on factors used in assessing exposure among this potentially sensitive subpopulation. Before initiating this project, the following issues must be considered:*

3.3.1 *Who are the potential users of an Exposure Factors Handbook for the Aging?*

Response:
The primary user of an EFHA will not change from the current users of the existing Exposure Factors Handbooks: risk assessors in government, industry, academia, and consulting firms. The workshop participants expect that researchers interested in exposure analysis and biomonitoring (e.g., at CDC) will find this document useful as they evaluate how best to characterize exposure to the aged population. By describing exposure characteristics, it may help the designers of biomonitoring studies determine which subgroups to oversample and when to get a representative or worst case sample. Clearly PBTK modelers will find the physiology and activity data critical in building more accurate exposure and dosimetry models. This is true even if the document excludes the standard toxicokinetic parameters (see response to Charge Question 2).

3.3.2 *How would an Exposure Factors Handbook for the Aging be applied in conducting exposure and risk assessments?*

Response:
Exposure factors data for aged individuals would be applied as other data in the current handbooks; risk assessors will look for both the supporting data and chapter recommendations in developing exposure assessments. Assessors may choose to use bounding estimates of parameter values (e.g., 95^{th} percentile) in constructing screening level analyses, or may perform refined assessments involving sensitivity analysis using a range of parameter values or develop a complete distributional analysis. Finally, an analyst may wish to present the exposures for a particular subgroup to separately analyze this group's risk in comparison to the remainder of the population. In this manner, the analyst may be able to explore the range of exposures possible in the population and further prioritize a particular lifestage or subgroup for a more detailed risk assessment. The data to support each of these activities needs to be readily available.

The EFH data base will be used to explore exposure variability and uncertainty across the population. To the extent possible, the EFH should describe the degree of uncertainty in the underlying datasets in terms of numbers of individuals, measurement error, degree of variability, agreement between datasets and issues of combining across datasets to create a unified table of parameter values. This will help analysts understand the level of confidence in the dataset and allow them to explore development of a more formal uncertainty analysis.

The workshop participants also noted that understanding exposure pathways and their contribution to risk can assist in the area of risk communication. It may be very important to educate aging populations and their caregiver institutions how exposures come about and lead to increased risk, especially if this occurs in susceptible subgroups. The EFH can be critical as supporting documentation of exposure differentials between subgroups, especially if the data are presented in a manner that allows ready comparison from younger adults through the various aged categories described in the workshop report.

3.3.3 *What factors should be included?*

Response:
The workshop participants had a lively discussion over whether the EFH should be limited to the traditional exposure factors currently compiled in the EFH and CS-EFH, or whether the list should be expanded to include toxicokinetic and possibly even some vulnerability factors (e.g., disease states, polypharmacy). A concern is that the EFH and CS-EFH already include many factors, some of which may need special guidance for their application and use in risk assessment. If the EFH for adults is expanded by incorporating detailed information for aged individuals, then it would not be wise to further expand the document by incorporating other types of parameters. They also discussed how there is rationale for including toxicokinetic factors (absorption, metabolism, clearance, cardiac output, body composition, protein binding sites) since they govern internal exposure which is a key link to health risk.

The workshop participants concluded that toxicokinetic and toxicodynamic factors that affect aged individuals should be mentioned in the handbook, and the implications of these factors briefly described. In particular, some mention is worthwhile regarding the possibility that groupings based upon age or functionality as described in Question No. 2, may not be the best way to organize the data in terms of toxicokinetic break points or windows of toxicodynamic vulnerability. These issues should be brought up in the EFH, but a separate applications document is likely needed to interface the EFH with toxicokinetic and vulnerability issues. The potential for polypharmacy, ADRs, and disease states to exist in aged citizens and affect exposure/vulnerability should be described qualitatively with reference to outside documents that allow analysts to go beyond standard exposure factors.

As mentioned in the response to the previous question, an EFH needs to supply qualitative and possibly also quantitative information on the uncertainties in the datasets used to populate the database.

3.3.4 *How should the data be presented in order to be most beneficial to exposure assessors?*

Response:
As described in previous responses, exposure parameter data both in terms of recommended values, distributional statistics, individual studies, should be provided and where possible, the raw data be made available. The raw data may help analysts derive continuous distributions of the data according to age or some other parameter rather than use the pre-determined groupings presented in the EFH and CS-EFH. The workshop participants do not recommend separating the elderly into a separate EFH. Rather, data for aging populations should be presented in summary tables with younger adults such that ready comparison can be made across lifestages and functional subgroups, together with the degree of variability within any subgroup.

4. SUMMARY OF DATA GAPS AND RESEARCH NEEDS

The workshop identified a number of research needs, in particular surrounding the development of aging subcategories as follows:

- Indices of activity and behavior - data are limited with respect to comparisons across sub-categories of older adults (ethnicities, living situation, functional category); data on water exposure activities such as frequency and time spent bathing, showering, washing clothing, dishes; potential exposure to soil and house dust – hand-to-mouth frequency, time spent gardening, home cleaning practices; types of products used around the home; hobbies engaged in – how often and what products are used, with a focus on hobbies that may involve toxic chemicals, physical labor, or time spent in specific microenvironments (e.g., dark room, ceramics workshop). Also, more objective measures of physical activity are needed for validation of activity surveys.
- Dermal penetration - studies across the skin of older as compared to younger individuals, both in vitro and in vivo (due to possibly altered barrier function and lowered skin blood flow), are warranted.
- Classification of functional status – since the ability to perform activities of daily living is recommended as a key criterion, it will be important to have clear scale of functionality to discriminate between categories. The categories suggested by the workshop in response to the Charge Question No. 2 (in Section 3.2.3) are still rather broad and may need further refinement. The scale with which to do this may already exist (e.g., in the Senior Fitness Test) or may need to be derived for the purpose of the EFH.
- Derivation of exposure correlates to functional categories – each of the 3 categories identified in response to the Charge Question No. 2 will have unique physiologic and functional properties that affect exposure potential. These exposure characteristics will have to be sought in the literature and perhaps demand new studies. For example, the ventilation rate or food intake of aged individuals may not be characterized from the perspective of functional categories (e.g., ventilation rate, fish consumption, water ingestion may not be known for Category 3 individuals in Section 3.2.3) although that information may be available for specific age groups. However, these data may be adapted to the functional groupings by further evaluation of the studied population.
- Estimation of longevity in the geriatric age/functionality groupings — an important exposure consideration is how long someone with that profile will receive exposure in that manner. Some default exposure scenarios assume 70 years when exposure begins early in life, but when beginning with an older individual it is appropriate to assume a considerably shorter exposure period based upon life expectancy.
- Evaluation of variability – Any grouping of the data should be evaluated in terms of the degree of within-group variability; the framework should strive to minimize inter-subject variability and maximize between group variability.

- How will special conditions like dementia affect behavior and exposure rates? Will forgetful or aberrant behavior lead to changes in soil/housedust ingestion, food ingestion, water ingestion, etc?
- How will toxicokinetic and toxicodynamic vulnerabilities affect the types of geriatric age groupings needed for particular chemicals – age-related changes in clearance pathways, polypharmacy and disease incidence may affect internal exposure and health risk. These factors may govern the cut points needed for grouping the aging population, but special analysis of these factors will be needed to determine if they drive different cutpoints than what one gets with the functional categories outlined above.
- Specific limitations in the data and research needs will likely emerge from a more thorough review of the data as it is compiled into a comprehensive structured database.

5. RECOMMENDATIONS

The workshop participants provide the following recommendations for how EPA may wish to proceed in terms of characterizing and documenting exposure factors for the geriatric population:

- Aged individuals can be very different than younger adults in terms of exposure factors and thus do merit special attention in an Exposure Factors Handbook.
- It is probably better to not present this material as a separate EFH, but rather join the information on aged individuals into the current EFH to form an expanded handbook. This will enable ready comparison of parameter values across life stages.
- Geriatric populations can be binned based upon a wide variety of parameters; however, it may be most useful from an exposure assessment standpoint to group aged populations on the basis of functional categories according to the 3 groups described above. Chronological age can still be part of the grouping framework by developing age bins that are informed by the percentage of people that are within the full functioning (Group 1), compromised functioning (Group 2) or low functioning (Group 3) categories (Section 3.2.3).
- Frailty, per se, should not be used as a discriminator for binning aged adults.
- Make as much of the individual study data and raw data available so that analysts can more fully examine variability and uncertainty and potentially develop other subgroups for specific risk assessment purposes.
- There are numerous pharmacokinetic factors that differ between aged individuals and younger adults that could affect internal dose and risk. The EFH should include a qualitative discussion of these but then refer to another document (still needs to be developed) for more detailed information.
- There are numerous physiologic and behavioral factors that can affect susceptibility to toxicants (e.g., disease states, polypharmacy, ADRs); these are not exposure factors in the traditional sense (e.g., that would help quantitate exposure dose) and so should be described in a separate document on vulnerability factors in aged individuals.
- As provided in the current handbooks, confidence and uncertainties in the exposure parameters should be made explicit.
- The handbook should focus on mobility as providing a key set of activity/functional parameters that distinguish elderly individuals from the remainder of the population. These mobility parameters include daily mobility (e.g., to and from work or recreation), long-term mobility (how long one resides in the same house) and physical mobility (capability to walk and perform activities).
- Physiological parameters for a truly random sample of the older population would be useful information to include in the handbook, rather than just the healthy older population.

- EPA should examine the databases described in this document along with data from epidemiology studies, biomonitoring datasets and longitudinal studies on behavior and physiological status; this information should be used to populate the handbook with data that paint a broad picture of the potential for environmental exposures in the geriatric population and its key subgroups in comparison to the exposure potential in younger adults.
- There are many complex vulnerability factors and they may not line up well with exposure factors in terms of age or other types of bins. Rather than complicate the exposure handbook with this information, it was agreed to recommend that vulnerability factors in aged individuals merit their own document.
- Price et al. (2003) have evaluated individuals from NHANES III to build a PBTK parameter database that describes individuals rather than the population. Through simulations, these individuals can be analyzed as a group to develop an understanding of population distributions. The workshop participants recommend that EPA explore this technique as a way to establish population distributions of physiological parameters where such individual data are available (e.g., NHANES).
- Finally, the workshop recommends that the handbook be as forward-thinking as possible. As risk assessment has changed greatly in the last few years, developing a forward-looking document that anticipates new developments may be worthwhile. Even if the document includes data that cannot be used now, the data may be usable in the future.

APPENDIX A

LIST OF ATTENDEES

Expert Panelists

Joyce Donohue .... USEPA, OW
Jeff Evans .... USEPA, OPPTS
Elaine Faustman .... Institute for Risk Analysis and Risk Communication
Michael Firestone .... USEPA, OCHP
Stiven Foster .... USEPA, OSWER
Andrew Geller .... USEPA, NHEERL
Gary Ginsberg .... Connecticut Department of Public Health
Dale Hattis .... Center for Technology Environment and Development
Bob MacPhail .... USEPA, NHEERL
Kyriakos Markides .... University of Texas Medical Branch
Edward Masoro .... University of Texas Health Science Center at San Antonio
Tom McCurdy .... USEPA, NERL
Keith Meyer .... University of Wisconsin-Madison, Department of Medicine
Haluk Ozkaynak .... USEPA, NERL
Paul Price .... Dow Chemical Company
Deborah Riebe .... University of Rhode Island
Bob Sonawane .... USEPA, NCEA
Alan Stern .... New Jersey DEP
Kathy Sykes .... USEPA, OCHP
Lauren Zeise .... California EPA/OEHHA

Observers

Doug Johns .... USEPA, NCEA
Jackie Moya .... USEPA, NCEA
Jeff Frithsen .... USEPA, NCEA
Susan Arnold .... The LifeLine Group, Inc.
Gary Bangs .... USEPA, OSA
Vernon Benignus .... USEPA, NHEERL
Evelyn Chao .... USEPA, NERL
David Chen .... USEPA, OCHP
Karen Yokley .... USEPA, NHEERL
Kent Thomas .... USEPA, NERL

APPENDIX B

CHARGE TO PANELISTS
PRE-WORKSHOP REFERENCE LIST

AGING WORKSHOP CHARGE QUESTIONS

1. Age-related changes in activity patterns, behavior, and physiology may have a significant impact on exposures to environmental chemicals. In order to better characterize these changes, please discuss the following:

   - What information is available on activity patterns and behaviors in the aging? Specifically, what is known regarding: 1) where older adults spend their time, and 2) what activities older adults are engaged in? What research is currently being conducted in these areas? What are the data gaps and research needs?
   - What information is available on age-related changes in physiological parameters such as inhalation rate, body composition, and body weight? What research is currently being conducted in these areas? What are the data gaps and research needs?
   - What information is available on diet and medication use in the aging population? What research is currently being conducted in these areas? What are the data gaps and research needs?

2. Individuals over the age of 65 are often divided into categories based solely on chronological age, such as young-old (65-74 years), old-old (75-84 years), and oldest-old (85 years and older). However, the aging population is a highly heterogeneous group, and age-related changes in behavior and physiological function may be more a function of biological age than chronological age. This may be an important distinction in evaluating risk of exposure to environmental chemicals as changes in behavior and physiology directly affect exposure as well as the resulting internal dose. With this in mind, please discuss the following questions:

   - In conducting exposure/risk assessments, is it appropriate to divide the aging population into age groups or "bins?" If so, what factors should be considered in determining these groups?
   - Are there behavioral changes that occur in the aging which lend themselves to characterization using age group categories?
   - Are there physiological changes that occur in the aging which lend themselves to characterization using age group categories?
   - In the context of exposure/risk assessment among the aging, how should "frailty" be defined? Should "frail" older adults be considered separately from "healthy" older adults?

3. It has been proposed that an Exposure Factors Handbook for Aging populations be developed to provide more detailed information on factors used in assessing exposure among this potentially sensitive subpopulation. Before initiating this project, the following issues must be considered:

- Who are the potential users of an Exposure Factors Handbook for the Aging?
- How would an Exposure Factors Handbook for the Aging be applied in conducting exposure and risk assessments?
- What factors should be included?
- How should the data be presented in order to be most beneficial to exposure assessors?

PRE-WORKSHOP REFERENCE LIST

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Websites of Interest:

Department of Health and Human Services – Administration on Aging
http://www.aoa.gov/

National Institute on Aging
http://www.nia.nih.gov/

U.S. Census Bureau
http://www.census.gov/

USDA Agricultural Research Service – Food Surveys Research
http://www.ars.usda.gov/main/site_main.htm?modecode=12-35-50-00

U.S. EPA – Aging Initiative
http://www.epa.gov/aging/

APPENDIX C

AGENDA

Issues Related to the Development of an Exposures Factors Handbook for the Aging Workshop Agenda

DAY 1: February 14, 2007

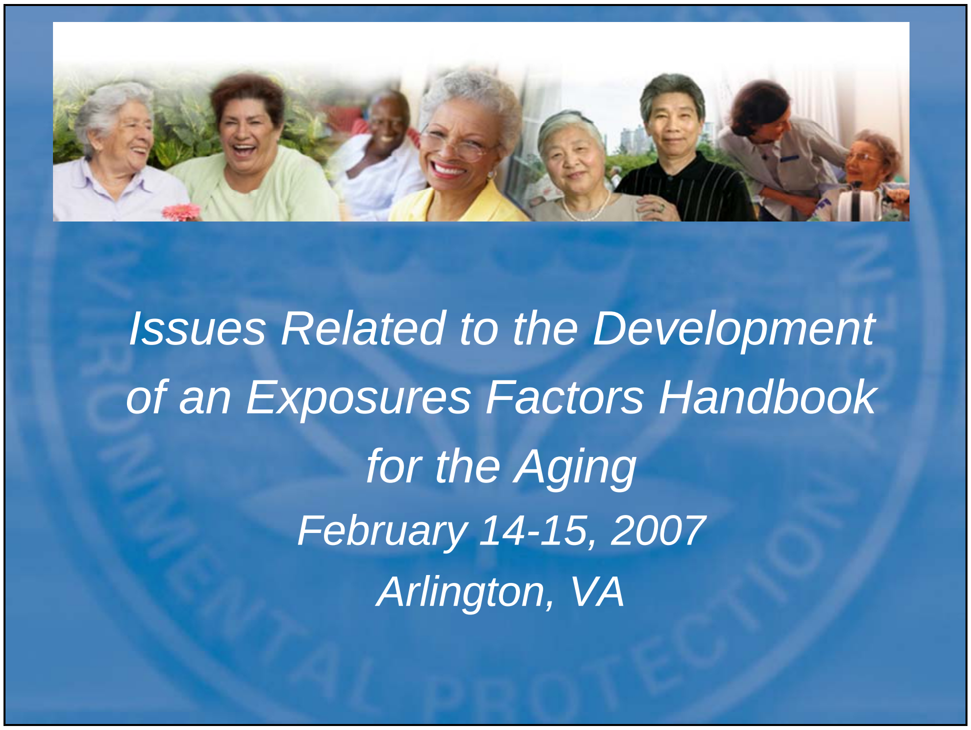
8:15 AM	Registration/Check-in *Versar, Inc.*
8:40 AM	Welcome Remarks and Introductions *Bob Sonawane, National Center for Environmental Assessment, U.S. EPA*
8:45 AM	Background and Workshop Objectives *Gary Ginsberg, Workshop Chair, Connecticut Department of Public Health*
9:00 AM	U.S. EPA Aging Initiative *Kathy Sykes, Office of Children's Health Protection, U.S. EPA*
9:20 AM	History and Use of the Exposure Factors Handbooks *Jacqueline Moya, National Center for Environmental Assessment, U.S. EPA*
9:40 AM	U.S. EPA Charge to Panel Experts *Gary Ginsberg*
9:55 AM	Break
10:10 AM	Summary and Discussion of Pre-Meeting Comments *Expert Panel*
11:00 AM	Panel Discussion of Charge Question 1
12:30 PM	Lunch
1:30 PM	Continued Panel Discussion of Charge Question 1
2:30 PM	Panel Discussion of Charge Question 2
3:30 PM	Break
3:45 PM	Continued Panel Discussion of Charge Question 2
5:00 PM	Observer Comments
5:30 PM	Adjourn

DAY 2: February 15, 2007

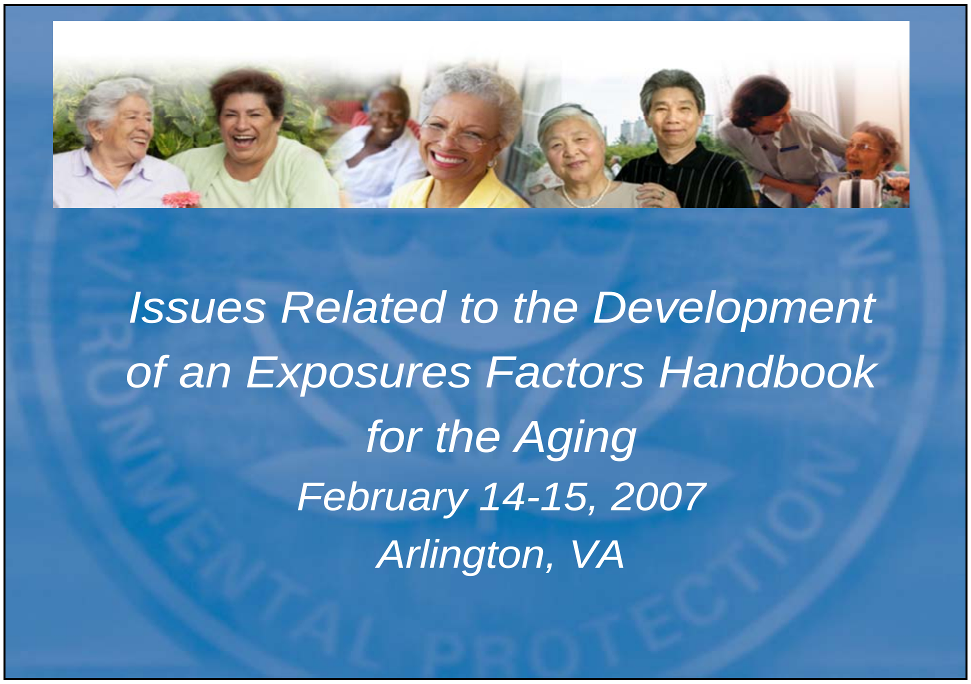
8:15 AM	Summary of Day 1 and Further Discussion of Unresolved Issues *Gary Ginsberg*
9:15 AM	Panel Discussion of Charge Question 3
10:30 AM	Break
10:45 AM	Continued Panel Discussion of Charge Question 3
12:00 PM	Lunch
1:00 PM	Observer Comments and Open Discussion of Unresolved Issues
2:15 PM	Closing Remarks *Gary Ginsberg*
2:30 PM	Adjourn

APPENDIX D

PRESENTATION OVERHEADS


Issues Related to the Development
of an Exposures Factors Handbook
for the Aging
February 14-15, 2007
Arlington, VA

BOB SONAWANE


Issues Related to the Development
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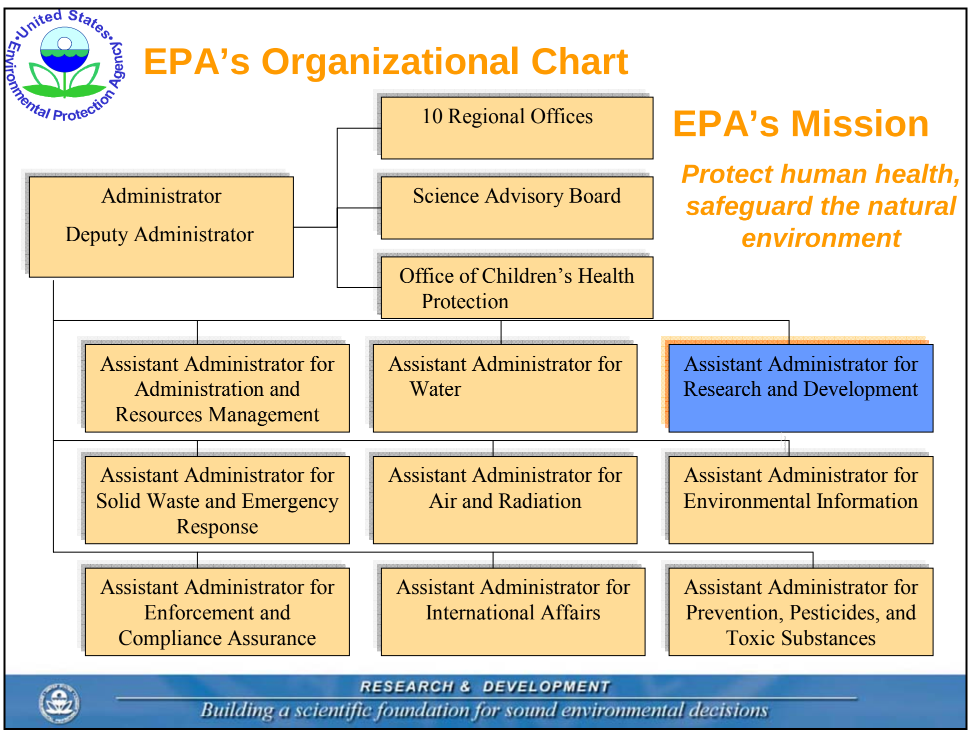
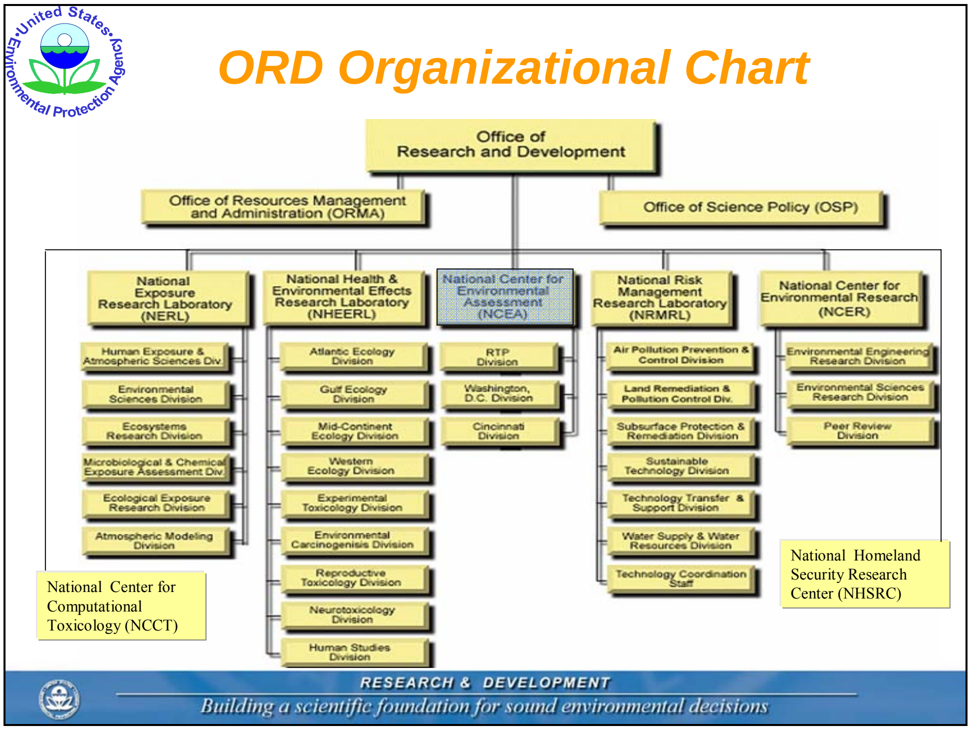
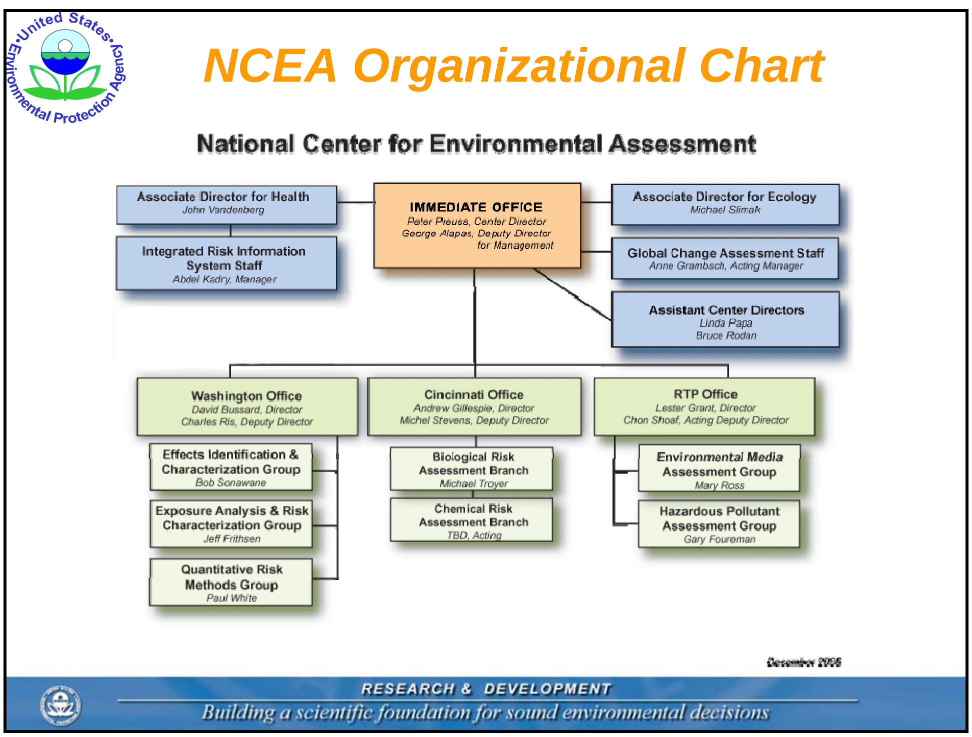
for the Aging
February 14-15, 2007
Arlington, VA


United States Environmental Protection Agency
EPA's Organizational Chart
10 Regional Offices
Science Advisory Board
Office of Children's Health Protection
Administrator
Deputy Administrator
EPA's Mission
Protect human health, safeguard the natural environment
Assistant Administrator for Administration and Resources Management
Assistant Administrator for Water
Assistant Administrator for Research and Development
Assistant Administrator for Solid Waste and Emergency Response
Assistant Administrator for Air and Radiation
Assistant Administrator for Environmental Information
Assistant Administrator for Enforcement and Compliance Assurance
Assistant Administrator for International Affairs
Assistant Administrator for Prevention, Pesticides, and Toxic Substances
RESEARCH & DEVELOPMENT
Building a scientific foundation for sound environmental decisions


ORD Organizational Chart
Office of Research and Development
Office of Resources Management and Administration (ORMA)
Office of Science Policy (OSP)
National Exposure Research Laboratory (NERL)
National Health & Environmental Effects Research Laboratory (NHEERL)
National Center for Environmental Assessment (NCEA)
National Risk Management Research Laboratory (NRMRL)
National Center for Environmental Research (NCER)
Human Exposure & Atmospheric Sciences Div.
Environmental Sciences Division
Ecosystems Research Division
Microbiological & Chemical Exposure Assessment Div.
Ecological Exposure Research Division
Atmospheric Modeling Division
Atlantic Ecology Division
Gulf Ecology Division
Mid-Continent Ecology Division
Western Ecology Division
Experimental Toxicology Division
Environmental Carcinogenesis Division
Reproductive Toxicology Division
Neurotoxicology Division
Human Studies Division
RTP Division
Washington, D.C. Division
Cincinnati Division
Air Pollution Prevention & Control Division
Land Remediation & Pollution Control Div.
Subsurface Protection & Remediation Division
Sustainable Technology Division
Technology Transfer & Support Division
Water Supply & Water Resources Division
Technology Coordination Staff
Environmental Engineering Research Division
Environmental Sciences Research Division
Peer Review Division
National Center for Computational Toxicology (NCCT)
National Homeland Security Research Center (NHSRC)
RESEARCH & DEVELOPMENT
Building a scientific foundation for sound environmental decisions


NCEA Organizational Chart
National Center for Environmental Assessment
Associate Director for Health
John Vandenberg
Integrated Risk Information System Staff
Abdel Kadry, Manager
IMMEDIATE OFFICE
Peter Preuss, Center Director
George Alapas, Deputy Director for Management
Associate Director for Ecology
Michael Slimak
Global Change Assessment Staff
Anne Grambsch, Acting Manager
Assistant Center Directors
Linda Papa
Bruce Rodan
Washington Office
David Bussard, Director
Charles Ris, Deputy Director
Cincinnati Office
Andrew Gillespie, Director
Michel Stevens, Deputy Director
RTP Office
Lester Grant, Director
Chon Shoaf, Acting Deputy Director
Effects Identification & Characterization Group
Bob Sonawane
Exposure Analysis & Risk Characterization Group
Jeff Frithsen
Quantitative Risk Methods Group
Paul White
Biological Risk Assessment Branch
Michael Troyer
Chemical Risk Assessment Branch
TBD, Acting
Environmental Media Assessment Group
Mary Ross
Hazardous Pollutant Assessment Group
Gary Foureman
RESEARCH & DEVELOPMENT
Building a scientific foundation for sound environmental decisions

Exposure Factors

- Exposure Factors Handbooks
- Susceptible subpopulations
  - Children
  - Older Adults
- Expert Panel
  - "Think tank" session
  - Characterization of age-related changes in physiology and behavior
  - Use of an Exposure Factors Handbook for the Aging
  - Are older adults different enough to warrant a separate handbook?

RESEARCH & DEVELOPMENT
Building a scientific foundation for sound environmental decisions

GARY GINSBERG

A Third Exposure Factors Handbook??

- EFH and CS-EFH – key resources in RA
  - Standardized data source, excellent review, recommends values appropriate for RA
- Concern that not all potentially susceptible populations covered in existing docs
- Elderly may present unique exposure and risk issues that merit a separate database
- Obvious physiologic, functional and behavioral changes

Existing EFHs Cover

- Basic Physiology
  - Body weight
  - Inhalation rate, volume
  - Skin surface area and soil adherence
- Behaviors
  - Food ingestion
  - Water ingestion
  - Soil ingestion
  - Time/activity patterns

Existing EFHs Do Not Cover

- Clearance pathways – metabolism, renal
- Other pharmacokinetic modeling parameters
  - Organ weights, blood flows
- Disease states
- Drug intake
- Type of housing

Objectives of Workshop

- What do we know about the elderly?
  - Physiology
  - Behavior/activity
- How should the elderly be defined
  - Chronologic age groups?
  - Function (ability to perform basic tasks)?
  - Physiologic parameters (lean muscle mass?)
  - Special conditions (dx, frailty, meds use)?
- Who will use the document and how?

Additional Thought Questions

- Do we even need separate EFH for the elderly?
  - Are they so different from younger adults?
  - Are they generally exposed less?
    - Less food intake, soil ingestion, breathing vols
    - Less likely to have occupational exposure
    - Exposure pattern different - more time at home/indoors
  - Elderly EFH can be of value if
    - Elderly exposures are sufficiently different
    - Elderly vulnerability is unique – will need to analyze elderly for TD reasons so need to how to estimate doses
    - Certain elderly subgroups are very different
      - Should we create a Vulnerable Population EFH?

Additional Questions

- Does USEPA need a **<u>Risk</u>** Factors Handbook instead of EFH for the elderly
  - Encompass exposure factors
  - Toxicokinetics
  - Vulnerability
    - Disease states
    - Polypharmacy
    - Diminished reserve/defenses
    - Aging neurologic and other systems more vulnerable?

Charge Questions

- Age-related changes in activity patterns, behavior, and physiology may have a significant impact on exposures to environmental chemicals. In order to better characterize these changes, please discuss the following:
- 1.1 What information is available on activity patterns and behaviors in the aging? Specifically, what is known regarding: 1) where older adults spend their time, and 2) what activities older adults are engaged in? What research is currently being conducted in these areas? What are the data gaps and research needs?
- 1.2 What information is available on age-related changes in physiological parameters such as inhalation rate, body composition, and body weight? What research is currently being conducted in these areas? What are the data gaps and research needs?
- 1.3 What information is available on diet and medication use in the aging population? What research is currently being conducted in these areas? What are the data gaps and research needs?

Charge Questions

- Individuals over the age of 65 are often divided into categories based solely on chronological age, such as young-old (65-74 years), old-old (75-84 years), and oldest-old (85 years and older). However, the aging population is a highly heterogeneous group, and age-related changes in behavior and physiological function may be more a function of biological age than chronological age. This may be an important distinction in evaluating risk of exposure to environmental chemicals as changes in behavior and physiology directly affect exposure as well as the resulting internal dose. With this in mind, please discuss the following questions:

Charge Questions

- 2.1 In conducting exposure/risk assessments, is it appropriate to divide the aging population into age groups or "bins?" If so, what factors should be considered in determining these groups?
- 2.2 Are there behavioral changes that occur in the aging which lend themselves to characterization using age group categories?
- 2.3 Are there physiological changes that occur in the aging which lend themselves to characterization using age group categories?
- 2.4 In the context of exposure/risk assessment among the aging, how should "frailty" be defined? Should "frail" older adults be considered separately from "healthy" older adults?

Charge Questions

- It has been proposed that an Exposure Factors Handbook for Aging populations be developed to provide more detailed information on factors used in assessing exposure among this potentially sensitive subpopulation. Before initiating this project, the following issues must be considered:
- 3.1 Who are the potential users of an Exposure Factors Handbook for the Aging?
- 3.2 How would an Exposure Factors Handbook for the Aging be applied in conducting exposure and risk assessments?
- 3.3 What factors should be included?
- 3.4 How should the data be presented in order to be most beneficial to exposure assessors?

Additional Questions

- Do the elderly or elderly subgroups warrant a separate EFH?
- How do we incorporate aging changes into an EFH?
  - Less muscle mass – does it relate to activity pattern, vent rates
  - Less clearance
  - Frailty
  - Polypharmacy
  - Diseases of aging
- Do we know enough about variability in elderly?
- Do we need an elderly Risk Factors Handbook?
- Do we need a separate PBPK parameters database for elderly?
- What can we learn from epi studies or biomonitoring studies of environment-aging effects that can be brought into EFH??

Charge Question

Discussion Points

Charge Question Discussion Points

1.1 What is known about activity/behavior
- – More leisure time – gardening, golf (PP)
- – Less heavy exercise, less function
  - How does this translate into specific activity patterns?
  - How does this translate into different resp volumes
  - How different is this all from younger adults?
- – Do we have enough specific info from NHANES on diet in elderly?
- – Water ingestion for elderly – EFH includes some data – doesn't appear to be large differences from younger

Charge Question Discussion Points

1.2 What is known about physiology in aging

- Hattis comment that Price modeling framework can derive elderly parameters from NHANESIII intra-subject database
  - How would this work?
- How do changes in physiology relate to changes in exposure parameters?
  - How does elevated BP relate to organ bld flows?
- Are elderly phys parameters part of adult distribution or are they clearly different
  - Subgroups that are clearly different?
- Should menopause or bone remodeling (Pb reexposure) be included in EFH?
- How different are antioxidant levels/GSH

Charge Question Discussion (1.2 Continued)

- What do we know about skin surface area and blood flow (EM)
- What do we know about changes in lung clearance (KM)
- Several reviewers mentioned obesity – should it be a separate consideration in elderly? – its not in other EFHs
- Should frail be a separate group

Charge Question #2 Points

- Grouping the elderly into age categories
  - Since aging occurs throughout adulthood, is it arbitrary to start elderly definition at a particular age?
- Is it better to have continuous models of parameter change – lookup tables– rather than age cutoffs
  - Is it better to have functional rather than chronological cutpoints (ADL vs IADL)?
    - Can certain phys factors such as lean muscle mass, grip strength, respiratory volume, etc., be used as a key age binning parameter? Senior fitness test?

Charge Q#2 Points (cont)

- If we consider ADME, disease states, polypharm in elderly, why not younger age groups as well?
- Fragility – is it too vague/undefined to make into a separate condition – better to specify diseases and more specific conditions?

Charge Q #3 Discussion Points

- How to apply elderly parameters:
  - Should an elderly scenario be constructed – elderly parameters overlain with some drug use and disease(s) – how would this affect exposure and risk?

KATHY SYKES

Protecting the Health of Older Americans

US EPA Aging Initiative

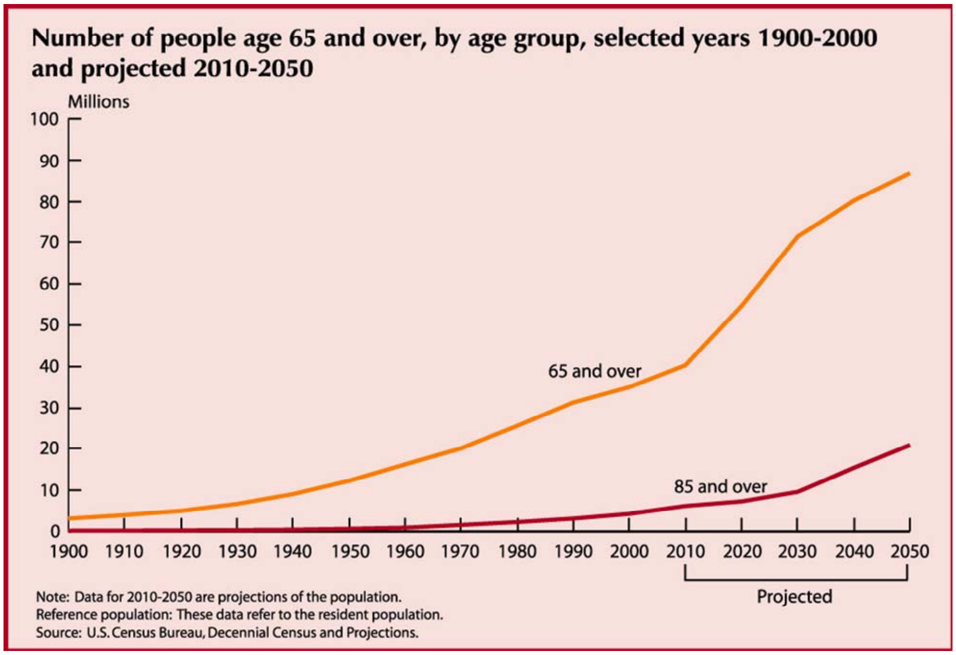
Kathy Sykes,
Senior Advisor
USEPA Aging Initiative
February 14, 2007

Demographic Shift: Growing Aging Population in USA

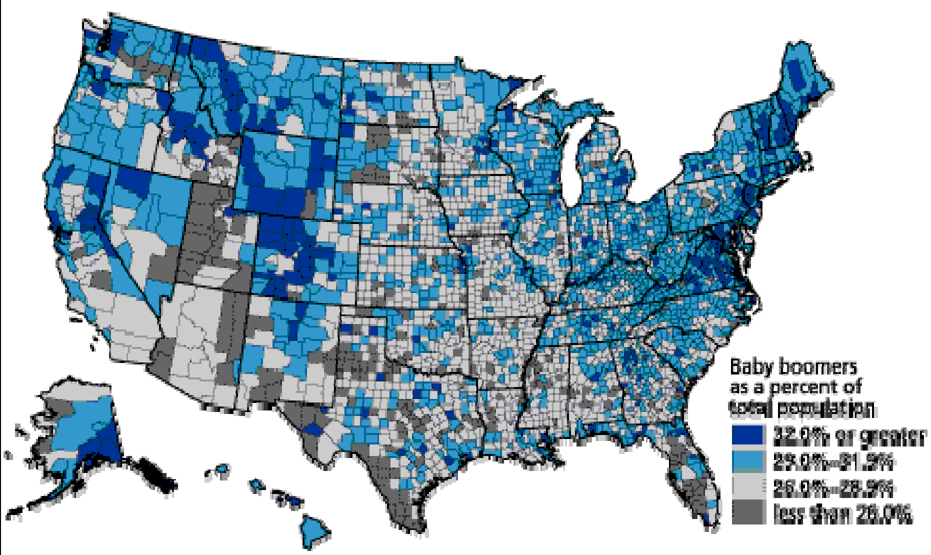
- **In 2000, 35 M 65+**
  - **4.2 M 85+**
- **By 2030, 71.5M 65+**
  - **9.6 M 85+**
- **85+ fastest growing age cohort**

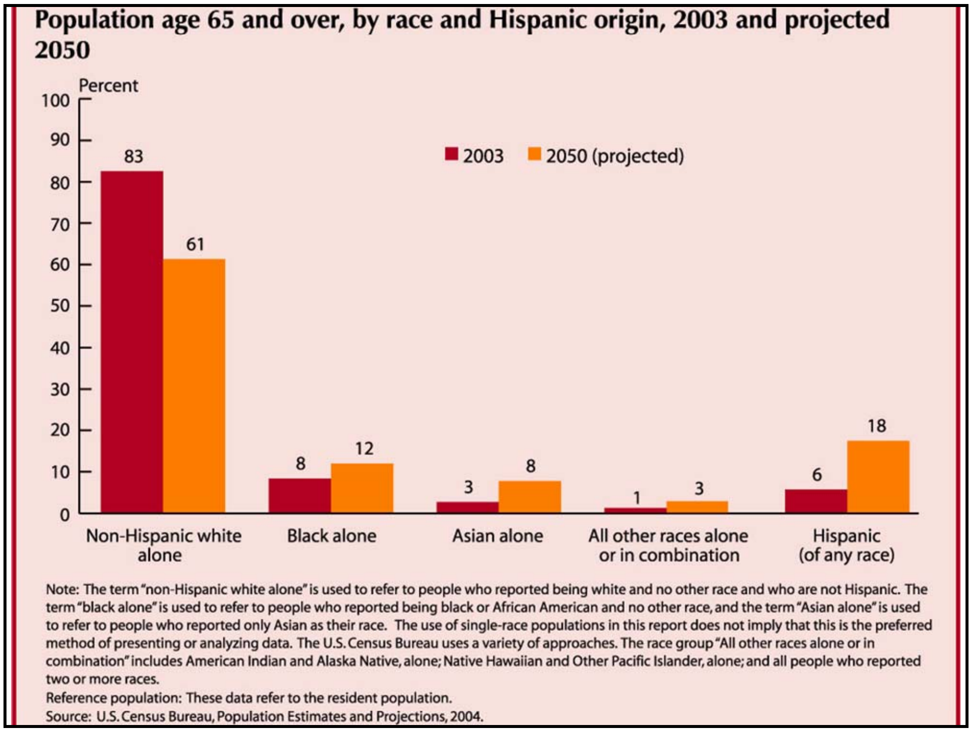
Source: US Census 2004

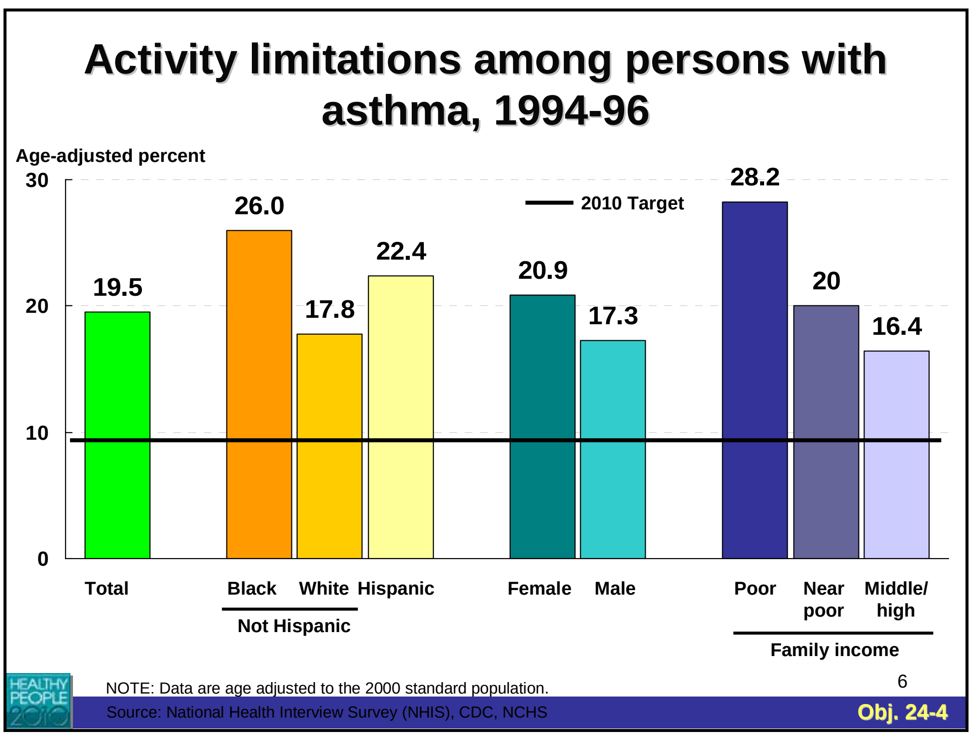
2

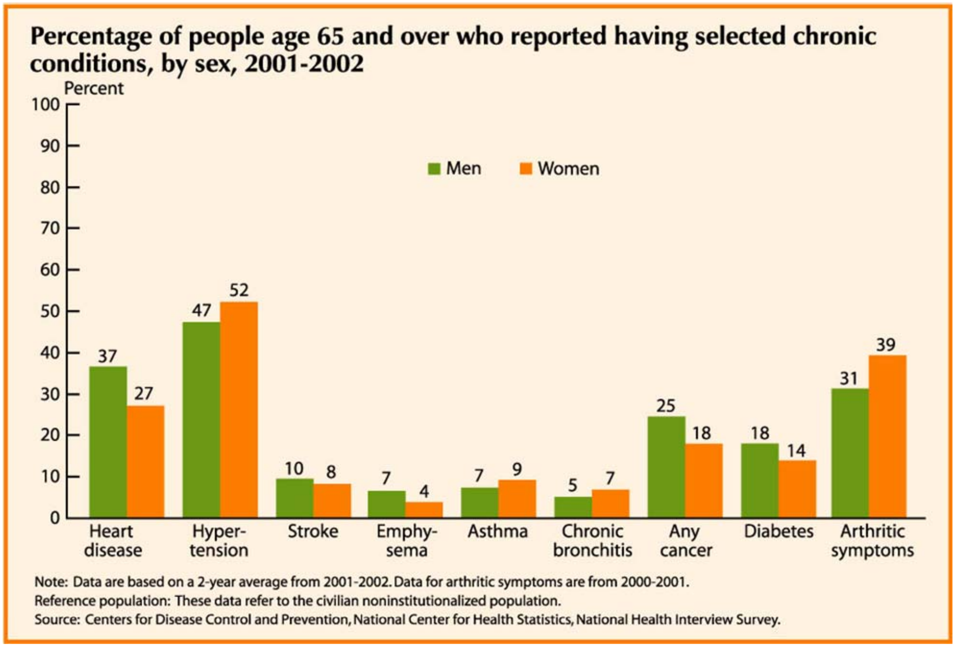


Baby Boomers as a Percent of the Total Population




Population age 65 and over, by race and Hispanic origin, 2003 and projected 2050
Percent
100
90
80
70
60
50
40
30
20
10
0
2003
2050 (projected)
83
61
8
12
3
8
1
3
6
18
Non-Hispanic white alone
Black alone
Asian alone
All other races alone or in combination
Hispanic (of any race)
Note: The term "non-Hispanic white alone" is used to refer to people who reported being white and no other race and who are not Hispanic. The term "black alone" is used to refer to people who reported being black or African American and no other race, and the term "Asian alone" is used to refer to people who reported only Asian as their race. The use of single-race populations in this report does not imply that this is the preferred method of presenting or analyzing data. The U.S. Census Bureau uses a variety of approaches. The race group "All other races alone or in combination" includes American Indian and Alaska Native, alone; Native Hawaiian and Other Pacific Islander, alone; and all people who reported two or more races.
Reference population: These data refer to the resident population.
Source: U.S. Census Bureau, Population Estimates and Projections, 2004.


Activity limitations among persons with asthma, 1994-96
Age-adjusted percent
30
20
10
0
2010 Target
19.5
26.0
17.8
22.4
20.9
17.3
28.2
20
16.4
Total
Black
White
Hispanic
Not Hispanic
Female
Male
Poor
Near poor
Middle/ high
Family income
NOTE: Data are age adjusted to the 2000 standard population.
Source: National Health Interview Survey (NHIS), CDC, NCHS
6
Obj. 24-4

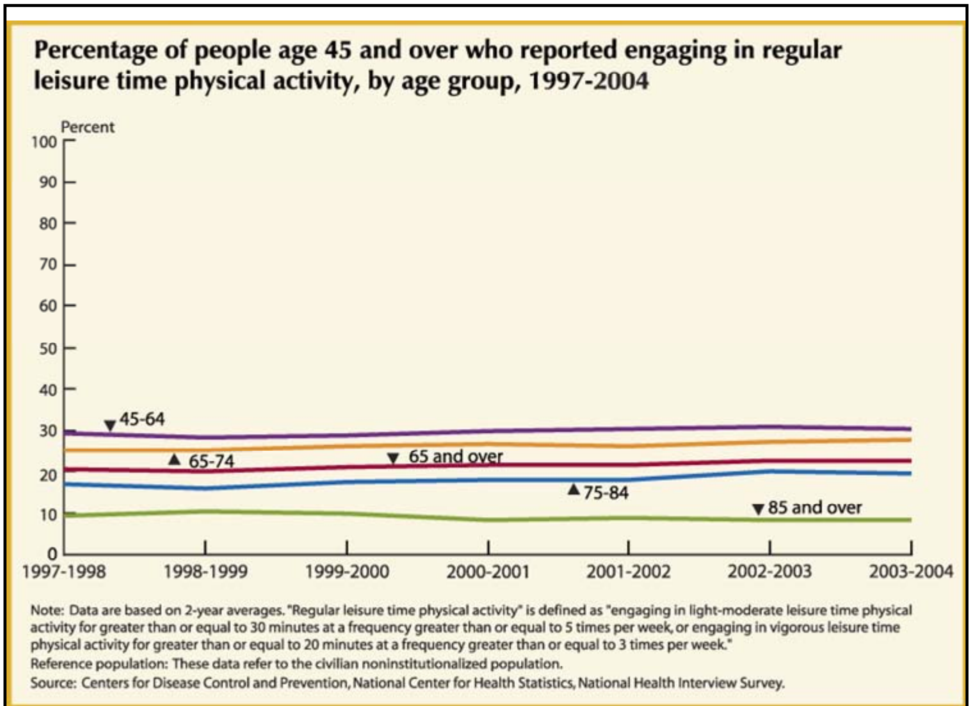


Aging and Health

- **88% of persons over 65 yrs of age have at least one chronic health condition.**
- **21% of over 65 have chronic disabilities.**
- **In 2002, 49% of person 65+ lived in a county with poor air quality.**

Sources Bullets 1 and 2: NIA 2000
Bullet 3: Federal Interagency Forum on Aging Related Statistics 2004

8



National Agenda for the Environment and the Aging

1. **Identify research gaps in environmental health**
2. **Translate research findings into public health prevention strategies**
3. **Create tools to address the impact a rapidly aging society will have on the environment**
4. **Provide opportunities for older adults to become environmental stewards in their communities**

10

Why Focus on Older Adults?

- **Decrease in organ function & reserves**
- **Impaired chemical clearance and detoxification**
- **Vulnerable to medication-environment adverse interactions (example - heat/psychotropic drugs)**
- **Legacy of past occupational and environmental cumulative exposures to persistent agents.**

11

Poison Control Center Data 1993-1998

- Older adults accounted for a small percentage of poison control center reported incidents (2.8%).
- However, they accounted for 5.9% of all cases with a moderate to major medical outcome and 28% of the deaths.

Source: Dr. Jerry Blondell OPPTS, EPA

12

PM a Major Public Health Risk

- Diabetes ~ 60,000 people die annually in the US
- End-stage Renal Disease: ~ 60,000 deaths/yr
- Particle Pollution: ~ 60,000 deaths/yr

Source: Wayne E. Cascio, MD, Professor of Medicine and Chief, Division of Cardiology, Brody School of Medicine, East Carolina University

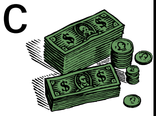
13

Ozone and Particulate Matter (PM)

- **Ozone & PM have the greatest potential to affect the health of older adults.**
- **PM is linked to premature death, cardiac arrhythmias, heart attacks, asthma attacks, and development of chronic bronchitis.**

14

Economic Burden of Chronic Diseases

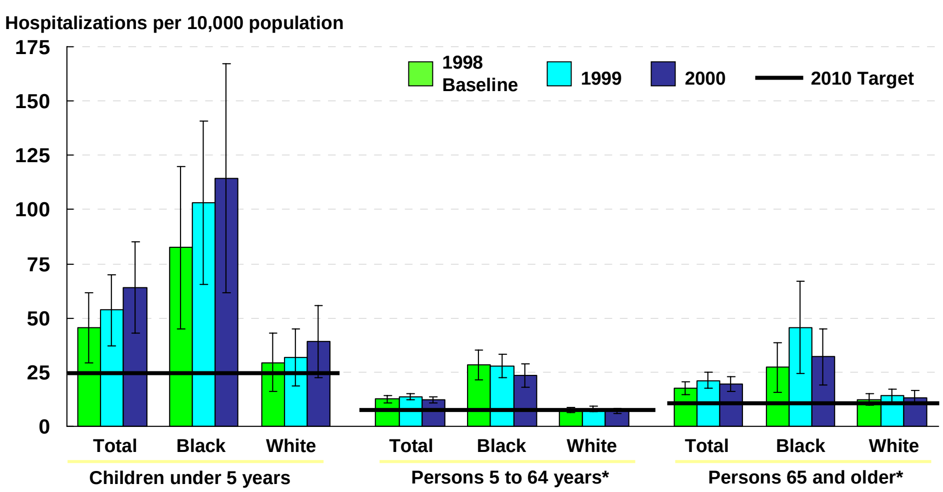


- Air pollution can exacerbate stroke, heart disease, stroke & chronic lung diseases.
- In 2002, these conditions cost $250 billion in direct medical costs and $9 billion in lost productivity.

- Source: Morbidity & Mortality: 2002 Chart book on Cardiovascular Lung and Blood Diseases, National Institutes of Health, NHLBI, May 2002

15

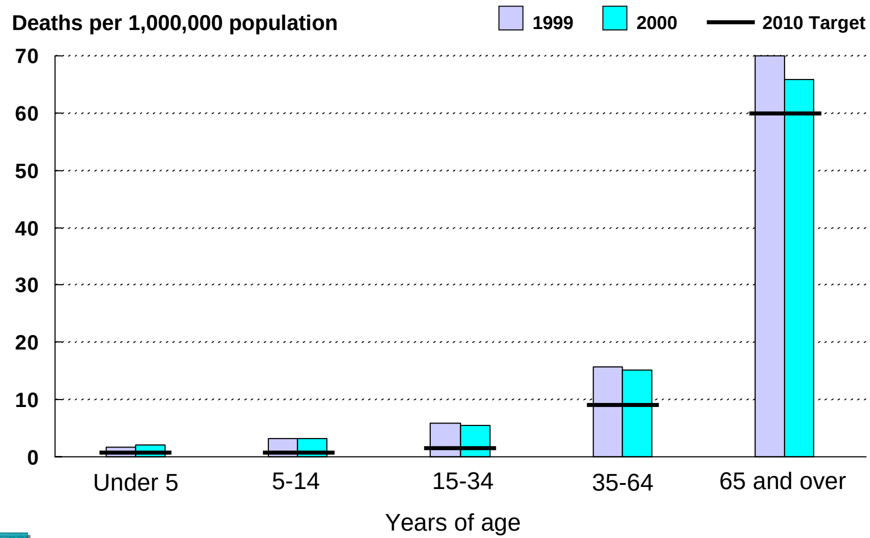
Hospitalizations for asthma, 1998-2000



I = 95% confidence interval
Note: *Data are age adjusted to the 2000 standard population.
Data for Hispanics, American Indians, Alaska Natives, Asians and Pacific Islanders are unreliable.
Source: National Hospital Discharge Survey (NHDS), CDC, NCHS

Obj. 24-2 a, b, c

Asthma deaths by age, 1999-2000



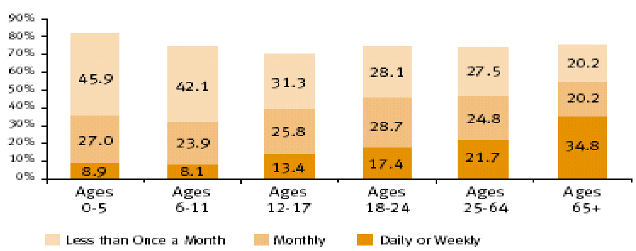
HEALTHY PEOPLE 2010

Source: National Vital Statistics System, CDC, NCHS.

Obj. 24-1 a-e

Highest rate of symptoms in older adults (California HIS)

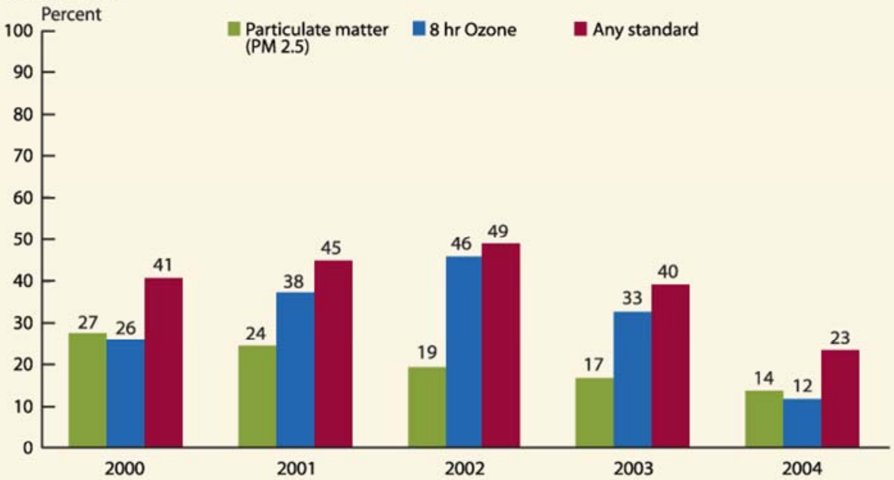
Exhibit 2
Asthma Symptoms in the Past 12 Months by Age, Persons Who Have Been Diagnosed With Asthma, 2001



Source: 2001 California Health Interview Survey

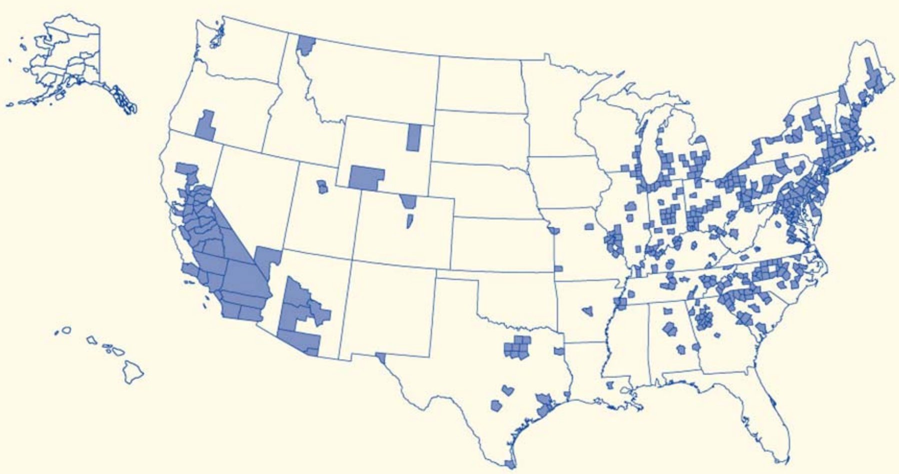
18

Percentage of people age 65 and over living in counties with "Poor air quality," 2000-2004



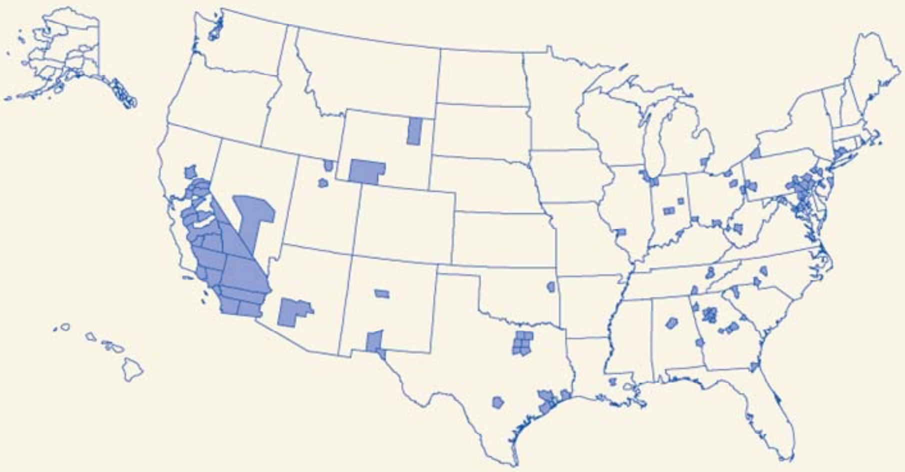
Note: The term "Poor air quality" is defined as air quality concentrations above the level of the National Ambient Air Quality Standards (NAAQS). The term "Any standard" refers to any NAAQS for ozone, particulate matter, nitrogen dioxide, sulfur dioxide, carbon monoxide, and lead.
Reference population: These data refer to the resident population.
Source: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Air Quality System; U.S. Census Bureau, Population Projections, 2000-2002.

Counties with "Poor air quality" for any standard in 2002



Note: The term "Poor air quality" is defined as air quality concentrations above the level of the National Ambient Air Quality Standards (NAAQS). The term "Any standard" refers to any NAAQS for ozone, particulate matter, nitrogen dioxide, sulfur dioxide, carbon monoxide, and lead.
Reference population: These data refer to the resident population.
Source: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Air Quality System; U.S. Census Bureau, Population Projections, 2002.

Counties with "Poor air quality" for any standard in 2004



Note: The term "Poor air quality" is defined as air quality concentrations above the level of the National Ambient Air Quality Standards (NAAQS). The term "Any standard" refers to any NAAQS for ozone, particulate matter, nitrogen dioxide, sulfur dioxide, carbon monoxide, and lead.
Reference population: These data refer to the resident population.
Source: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Air Quality System; U.S. Census Bureau, Population Projections, 2004.

Chronic Obstructive Pulmonary Disease (COPD)

- COPD is the 4th leading cause of death in the US, claiming 119,000 lives each year
- In 2000, COPD was responsible for 726,000 hospitalizations, 1.5 million hospital emergency room visits and 8 million doctor visits.

22

Gastrointestinal Illness in the U.S.

- **211 million episodes of acute gastrointestinal illness occur each year in the US.**
  - **Result in more than 900,000 hospitalizations & 6,000 deaths (Mead 1999).**
- **Many of these cases may be of infectious origin due to food or waterborne transmission.**

Slide provided by : Jack Colford, UC Berkley

23

Burden of Waterborne Disease

Studies have found that 1/3 of GI illness cases are related to drinking water, suggesting that up to 70 million cases of GI illness may be caused by waterborne pathogens.

Source: Payment 1991 & 1997

24

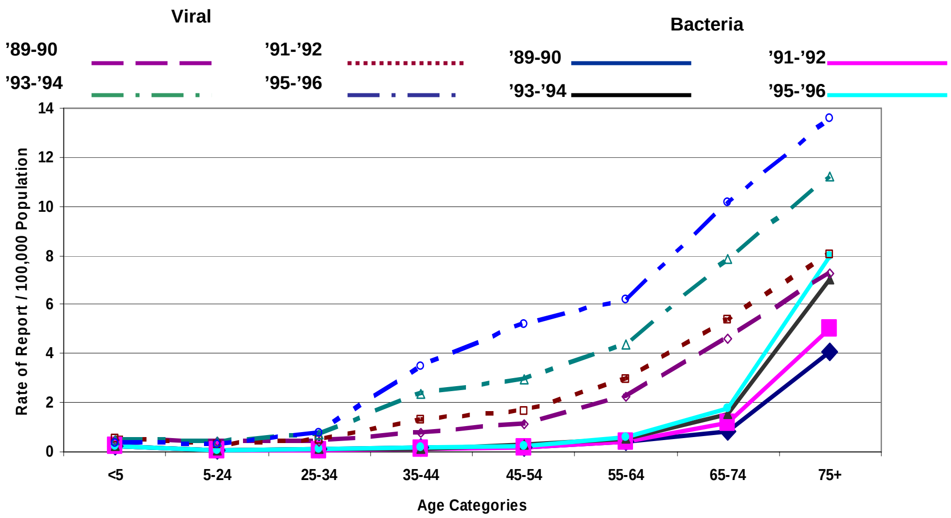
Older Adults at Increased Risk for GI

Older adults may be at increased risk for infectious GI illness, severe diarrhea, or dying from diarrheal illness.

Source: Peterson 2003, Mounts 1999, Gerba 1996, Lew 1991

25

Bacterial and Viral Enteric Diseases as Contributing Causes of Death by Age, 1989 - 1996



26

Hospitalizations and Death

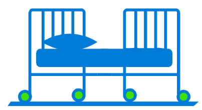
- Older adults are at the highest risk of dying during an gastroenteritis related hospitalization, even when compared to infants.

Case fatality rates

65-74yrs: 14.4 deaths/1,000 discharges

75+: 24.9 deaths/1,000 discharges

Source: Mounts 1999



27

Grants: Making a Difference for the Environment & Health of Older Adults

<u>Funded 19 projects in 2005-- $462,180</u>

- Smart growth (5-6 projects)
- Intergernerational (5 projects)
- Leadership training (7 projects)
- Targets socio-economically disadvantaged elders (5 projects)

28

Fact Sheets
Environmental Health and Older Adults
www.epa.gov/aging

- ***Age Healthier, Breathe Easier***
- ***Effective Control of Household Pests***
- ***It's Too Darn Hot--Planning for Excessive Heat Events***
- ***Environmental Hazards Weigh Heavy on the Heart***
- **Water Works**
- **Coming soon: diabetes and environmental factors**

Translations: Spanish, Portuguese, Chinese, Korean, Vietnamese, Russian, Italian, French, Japanese, and Haitian Creole

Purple Series: for people with limited reading ability

29

Aging Initiative List Serve

Join the EPA Aging Initiative List serve for monthly updates

www.epa.gov/aging

Questions? sykes.kathy@epa.gov or 202.564.3651

30

JACKIE MOYA

History and Use of the Exposure Factors Handbook

Jacqueline Moya
NCEA, ORD, U.S. EPA, Washington, DC

Issues Related to the Development of an Exposures Factors Handbook for the Aging
February 14-15, 2007
Arlington, VA

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

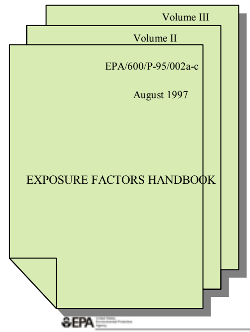
Outline

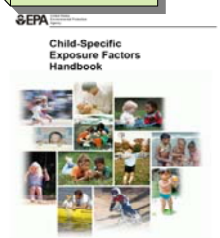
- Exposure Factors Handbook
- Child-Specific Exposure Factors Handbook
- Evolution of Exposure Factors Program
- Areas of high priority
- Examples of adult data
- Next steps

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

- Two major products:
  - Exposure Factors Handbook
  - Child-Specific Exposure Factors Handbook





RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Goals of the Exposure Factors Program

- Update the *Child-Specific Exposure Factors Handbook* and the *Exposure Factors Handbook* by 2007 (ERD 2006) and 2008, respectively
- Keep the handbook up-to-date through yearly updates to the Guide to Current Literature in the Exposure Factors Program Homepage
- Provide companion documents to the Handbooks to assist clients in the use of exposure factors data in exposure assessments
- Consultation services to clients on the use of the data and development of exposure scenarios

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Exposure Factors Handbook

- First published in 1989 and updated in 1997
- Published in CD-ROM format in 1999
- Guide to current literature published in the NCEA homepage in 2001
- Next update planned for 2008

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Impact of EFH

- Over 2,000 paper copies distributed since 1997
- Over 500 copies of CD-ROM distributed
- Frequently cited in risk assessment in the Agency and outside (nationally and internationally)
- Used by the Program Offices in their assessments
  - Office of Pesticides
  - Toxics
  - OSWER/RCRA program
  - Office of Water

Child-Specific Exposure Factors Handbook

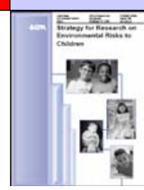
Children's Risk Policy

Executive Order 13045

Interim Final Child-Specific Exposure Factors Handbook

1995	1996	1997	2000	2002	2006

Food Quality Protection Act



ORD's Children's Research Strategy

External Review Draft Child-Specific Exposure Factors Handbook

Then…we focused our attention on children

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

First Steps to Achieve Goals

- Exposure Factors Program Colloquium held June 7-8, 2004 (EPA only)
- Established an Exposure Factors team within NCEA
- Established an Agency-wide Exposure Factors Advisory Group

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Charge to the Exposure Factors Advisory Group

- Assist NCEA in identifying areas where research is necessary
- Assist NCEA in setting priorities for research
- Assist in planning future activities
- Provide feedback on program goals and products

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

High Priority Areas Identified by Advisory Group

- Soil ingestion rates for adults and children
- Mouthing behavior data
- Defining "high-end" exposed populations
- Develop guidance on the use of fish consumption data
- Developing longitudinal data and methods

- Farmers
- Subsistence
- Aging

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Are older adults different than younger adults in physiology and behavior?

- Are there exposure data available to characterize differences?
  - Sample size may be limited for older adults
- What age groups are important?
  - For children there is a specific set of age groups recommended by EPA
  - For adults there is no consistent set of age groups
- Factors other than age important to define aging populations?

Example Table from EFH 1997

Table 3-9. Per Capita Intake of Total Vegetables (g/kg-day as consumed)

Population Group	Percent Consuming	MEAN	SE	P1	P5	P10	P25	P50	P75	P90	P95	P99
Total	96.5%	4.52	0.03	0.00	0.51	1.14	2.22	3.71	5.81	8.57	10.83	18.66
Age (years)												
0-5 months	22.3%	2.34	0.86	0.00	0.00	0.00	0.00	0.00	0.00	10.40	17.86	25.28
6-12 months	91.5%	12.08	0.91	0.00	0.00	0.80	5.90	11.24	15.13	24.18	29.00	49.00
< 01	54.7%	6.90	0.72	0.00	0.00	0.00	0.00	2.34	12.23	17.86	24.18	36.28
01-02	95.3%	9.53	0.21	0.00	0.47	1.93	4.53	8.01	12.58	18.72	23.28	33.46
03-05	93.3%	7.30	0.16	0.00	0.00	1.35	3.41	6.23	9.69	13.93	18.27	28.99
06-11	93.9%	5.34	0.12	0.00	0.00	1.12	2.48	4.33	7.10	10.44	13.54	21.21
12-19	98.4%	4.03	0.09	0.00	0.63	1.12	2.14	3.40	5.15	7.40	9.35	14.68
20-39	98.1%	4.09	0.05	0.00	0.73	1.26	2.15	3.54	5.42	7.33	9.24	14.36
40-69	97.2%	3.96	0.04	0.00	0.58	1.17	2.17	3.45	5.22	7.31	8.73	12.06
70 +	97.9%	4.17	0.08	0.00	0.62	1.14	2.24	3.69	5.46	7.75	9.27	13.46

Adults were grouped into ages 20 – 39, 40 – 69 and 70+ years

Data from Continuing Survey of Food Intake by Individuals (CSFII 94-96)

Example of Revisions to EFH

Age Category	*Daily Average Ventilation Rate for **Males** (m3/day-kg)*				*Daily Average Ventilation Rate for **Females** (m3/day-kg)*			
	Mean	5th%	Median	95th%	Mean	5th%	Median	95th%
<1 year	1.09	0.91	1.08	1.29	1.14	0.97	1.13	1.38
1 year	1.19	0.96	1.17	1.48	1.20	1.01	1.18	1.47
2 years	0.95	0.78	0.87	1.13	0.96	0.84	0.96	1.11
3<6 years	0.70	0.52	0.61	0.92	0.69	0.54	0.68	0.92
6<11 years	0.44	0.32	0.38	0.58	0.43	0.31	0.43	0.58
11<16 years	0.29	0.21	0.25	0.38	0.25	0.20	0.25	0.34
16<21 years	0.23	0.17	0.20	0.30	0.21	0.17	0.21	0.28
21<31 years	0.23	0.16	0.19	0.32	0.21	0.16	0.20	0.28
31<41 years	0.24	0.16	0.20	0.34	0.21	0.15	0.20	0.30
41<51 years	0.24	0.17	0.20	0.34	0.22	0.16	0.22	0.31
51<61 years	0.24	0.16	0.20	0.34	0.22	0.16	0.21	0.30
61<71 years	0.21	0.17	0.19	0.25	0.18	0.15	0.17	0.23
71<81 years	0.20	0.17	0.19	0.24	0.18	0.15	0.17	0.23
>81 years	0.20	0.17	0.19	0.25	0.18	0.15	0.18	0.22

More recent analysis grouped adults into categories of 10 years after age 21

Example of Activity Pattern Data

Statistics for 24-Hour Cumulative Number of Minutes Spent Indoors in a Residence										
Age (yrs)	N	Mean	SD	5th	25th	50th	75th	90th	95th	99th
1 -4	498	1,211	219	795	1,065	1,260	1,410	1,440	1,440	1,440
5 - 11	700	1,005	222	686	845	975	1,165	1,334	1,413	1,440
12 - 17	588	970	242	585	812	950	1,155	1,310	1,405	1,440
18 - 64	6,022	948	273	540	750	900	1,165	1,350	1,428	1,440
> 64	1,348	1,175	229	760	1,030	1,210	1,375	1,440	1,440	1,440
Statistics for 24-Hour Cumulative Number of Minutes Spent at a Park/Golf Course										
1 -4	21	150	176	25	50	85	150	360	425	755
5 - 11	54	208	184	35	70	125	275	555	635	665
12 - 17	52	238	242	15	60	148	338	590	840	1,065
18 - 64	314	198	186	20	60	150	270	440	580	870
> 64	55	189	183	20	30	120	300	510	570	735

Sample size is an issue

Data from National Human Activity Pattern Surevey (NHAPS) grouped ages 18 – 64 and > 64 years old

How are older adults spending their time?

Next Steps

- Obtain recommendations from the workshop participants
- Determine exposure factors data needs and gaps
- Continue working with other parts of the Agency and identify areas of collaboration

APPENDIX E

PRE-MEETING COMMENTS BY CHARGE QUESTIONS WITH SUGGESTED ADDITIONAL REFERENCES

RESPONSE TO CHARGE

1.0 Age-related changes in activity patterns, behavior, and physiology may have a significant impact on exposures to environmental chemicals. In order to better characterize these changes, please discuss the following:

E.J. Masoro

My expertise is limited to addressing question 1.2. However, based on the literature provided, I feel that I should mention here what I think is too limited a view for the development of an exposure factors handbook for the aging. In my opinion, what first needs to be considered is what we know and what we don't know about the biology of aging.

A good starting place is to consider how biogerontologists define *aging,* a term that they use as a synonym for *senescence*. It is defined as: *the progressive deteriorative changes, during adult life, which underlie an increasing vulnerability to challenges, thereby decreasing the ability of the organism to survive.* This definition makes clear that not only should the proposed handbook focus on how aging influences the extent of exposure to harmful agents, but should also consider how aging influences the responses to such agents.

By the above definition, aging starts at least by the early 30s in both genders; this is based on the decreasing performance ability for most sports by that age. However, its effects are dramatic in centenarians, almost all of whom need assistance to perform the basic tasks of living. This phenotype also occurs in a small fraction of the population as early as the seventh decade of life with that fraction increasing as the cohort progresses in age towards that of centenarians. Rowe and Kahn (*Successful Aging,* Pantheon Books, New York, 1998) point out that there are people in the seventh, eighth, and even the ninth decade of life, exhibiting minimal physiological deterioration, which they call "Successful Aging." Others in the same age-range exhibit deterioration in all physiological systems while in still others, only some of the systems are affected. This heterogeneity is another important factor that needs to be considered and I gather this has been fully recognized. However, I find somewhat unsettling the view that this problem can be addressed by using biomarkers of aging.

Most biogerontologists agree that the rate of aging varies greatly among individuals and embrace the concept that biological age is different than chronological age. The problem is how to measure the rate and extent of biological aging of individuals. Many attempts have been made to develop a panel of biomarkers of aging to do so. As of yet, a generally agreed upon panel has not emerged (see McClearn, *Exp. Gerontol.*32: 87-94, 1997). Indeed even the time-honored use of Gompertz analysis for population aging has recently been challenged (see Driver, *Biogerontology* 4: 325-327, 2003).

Most evolutionary biologists don't believe that aging is an evolutionary adaptation with a genetic program similar to that of development. Rather they feel that aging occurs because following sexual maturation, the force of natural selection decreases with increasing age (see Rose, *Evolutionary Biology of Aging,* Oxford University Press, New York, 1991). This makes using the Child-Specific Exposure Factors Handbook as a template for the Aging Handbook problematic.

The literature references sent to us provide little discussion of age-associated diseases. This is surprising because aging in the absence of such diseases is a rarity and much of the physiological deterioration with advancing age is secondary to such diseases. Age-associated diseases are defined as those that usually don't cause morbidity or mortality until advanced ages. They may be chronic or acute and in the latter case, they result from a long-term process such as atherogenesis. Examples of age-associated diseases are: coronary artery disease, stroke, many types of cancer, type II diabetes, osteoarthritis, osteoporosis, cataracts, Alzheimer's disease, and Parkinson's disease to name a few. In the mid-twentieth century, several age-associated deteriorations of heart function were described; it subsequently has been shown that most of this deterioration is secondary to occult coronary artery disease. Currently, there is debate as to whether age-associated diseases are an integral part of the aging process (see Chapter 2 in Masoro and Austad, eds., Handbook of the Biology of Aging, 6th edition, Elsevier, San Diego, 2006). Whether an integral part of the aging process or not, age-associated diseases are important to consider in depth in an Exposure Factors Handbook for the Aging.

1.1 What information is available on activity patterns and behaviors in the aging? Specifically, what is known regarding: 1) where older adults spend their time, and 2) what activities older adults are engaged in? What research is currently being conducted in these areas? What are the data gaps and research needs?

Kyriakos Markides

We know that more than 60% of older people in the US do not engage in physical activity and that 31% are sedentary. Men are more active than women. Older members of minority groups such as African Americans and Hispanics are less active. This is a problem partly because of high rates of diabetes in these populations. Physical activity is highly important for diabetics in order to prevent complications and other negative outcomes. Older people who exercise are more likely to participate in aerobic exercise than in strength training. Walking is by far the most popular activity. Older Black and Hispanics are less likely to engage in walking partly because they are more likely to live in unsafe environments, i.e., poor or non-existent sidewalks as well as high crime rates.

Other correlates of low participation in physical activity include smoking and poor health, older age, rural residence, living alone, and lower educational attainment.

With respect to environmental factors it is known that living neighborhoods with heavy traffic and trash/litter is associated with lower levels of physical activity.

Keith Meyer

In general, less time is spent outside ones dwelling and less time is spent exercising.

1. Where do older adults spend their time?

Compared to younger adults, more time is spent indoors, but there is considerable interindividual variation that is influenced by weather/climate and physiologic condition.

Older adults are much less likely to be exposed to industry/commercial environments due to retirement.

2. What activities do older adults engage in?

This appears to vary quite a bit by socioeconomic status and health status

3. What research is being conducted concerning activity patterns and behaviors in the aging?

Current research seems to focus on exercise and conditioning.

4. What are the data gaps and research needs?

Paul Price

The impression from the literature provided by EPA is that there are extensive data available on the activity patterns of the aged; however, these data have not always been appropriately analyzed. For example, activity pattern data reported in Leech et al. (2002) have not been analyzed for differences between adults <65 and adults >65. In addition, many surveys have collected data on activity levels but only reported data in terms of a total activity "score". Such studies imply that considerable additional data

were collected but not reported. EPA should take steps to obtain access to the raw data from such surveys and reanalyze the results for the relevant exposure factors.
Finally, there is a need to define when changes in the capacity for physical activity will preclude or change exposure-related behaviors. In many instances the magnitude of exposure will be directly related to the ability to perform moderate or high levels of effort over extended periods of time (painting the interior of a large house, swimming for several hours in a pool, etc.) that are not within the capacity of certain portions of the *aged* population.

Deborah Riebe

Data from the Baltimore Longitudinal Study of Aging (BSLA; Verbrugge et al., 1996) showed that older men and women spent the greatest amount of time in obligatory activities and passive leisure and the least amount of time on committed activities and active leisure. There is diversity across people, but the data suggests less diversity among older adults as the repertoire of activities is narrowed. Another study of individuals aged 70-105 years showed that 17% of the day is spent watching television, 15% is spent completing IADLs, and 12% is spent on other leisure activities. This study also showed that 80% of waking hours were spent inside the home (Horgas et al., 1998). However, similar to BLSA, there was substantial variety in how older adults spent their time.

The National Health Interview Survey reports that in 2003-2004, 27.5% of adults aged 65-74 years, 19.4% of adults aged 75-84 years, and 8.4% of adults over 85 participate in regular leisure time activity (defined as engaging in at least 30 minutes of light-moderate intensity physical activity 5 days per week or engaging in vigorous intensity physical activity for at least 20 minutes, 3 times per week). Despite overwhelming evidence that regular physical activity decreases the risk of some chronic diseases, may relieve symptoms of depression, enhances overall quality of life, and helps to maintain independent living, the number of older adults participating has remained stagnant for the past 10 years. It should be noted that, like many surveys, physical activity is measured by self-report. Over-reporting physical activity is common in all age groups.

Physical activity decreases with age. In the SENIOR project, approximately 62 percent of adults aged 65-74 reported participating in regular exercise using stages of change (ie., in action or maintenance), compares to 51% of those aged 75-84 years and 43% of those over 85 years. This was confirmed by the Yale Physical Activity Survey (YPAS) summary score (37.8, 33.6, 27.2 for ages 65 – 74, 75-84 and 85+, respectively) and energy expenditure scores (7580, 6048, 5472 kcal/week for ages 65 – 74, 75-84 and 85+, respectively). Again, physical activity and stage of change were measured by self-report, so the possibility of response and recall bias are inherent (Riebe et al., 2005). However, this study also measured physical function using the Up-and-Go test and found that physical function was poorer with increasing age and as stage moved from maintenance to precontemplation, suggesting self-reported stage of change reflected habitual activity. Manuscripts containing longitudinal outcomes are currently under review and the SENIOR II project is being conducted with the same subjects.

More research using objective measures of exercise and physical activity are needed to quantify the overall amount of physical activity older adults participate in. The use of accelerometers and other portable measuring devices will help to expand our knowledge in this area, but these devices still need to be refined.

Lauren Zeise

The workshop organizers provided several references that addressed activity patterns and behavior in the aging. This included references showing fraction of time spend in different activities in nursing homes and assisted living. The one data gap I would add that has not been discussed is activities leading to exposures to dust.

1.2 What information is available on age-related changes in physiological parameters such as inhalation rate, body composition, and body weight? What research is currently being conducted in these areas? What are the data gaps and research needs?

Dale Hattis

To begin to respond to this very open-ended set of questions, I briefly scanned the reference sources that were supplied to us as PDFs. Appendix A is my quick evaluation of the potential usefulness of each as a source of data (or references to data sources) that might be compiled in an aging-related exposure factors handbook analogous to the child-related handbook that has been produced.

In addition I would like to highlight several other sources not included in the PDFs supplied to the work group:

- Price et al. (2003) have developed formulae for translating measurements made by NHANES III researchers into estimates of parameters needed for PBPK modeling. After comparisons with measured data, where available, these estimates could be used to develop expected distributions of key PBPK parameters for older people.[1]
- Brochu and coworkers have recently compiled data from over 1000 doubly labeled water measurements of total metabolism for individuals of all ages (including some measurements of people in their 90s). In addition to three published papers in Human and Ecological Risk Analysis, they provide considerably detailed summary statistics for their findings within age categories in accessible web sites. Some detail from these sources is compiled in Appendix B. Even better detail might be possible for compilation if the authors were persuaded to supply the underlying data themselves for inclusion in an EPA compilation. Even in their present form, these "gold standard" metabolic rate data can be used to detect and correct biases in metabolic rate/breathing rate data from other more extensive sources.
- About a year ago I participated with Kannan Krishnan in a project funded by Dr. Sonawane of EPA to compile and analyze statistical distributions of a number of pharmacokinetic/ functional parameters in older people. My summary analysis report has not to my knowledge appeared in any final published document, but may be in process in the EPA/NCEA. Some excerpts related to body and organ weights, kidney glomerular filtration rates, diabetes, and hypertension are included for reference as Appendix C.

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1 Price PS, Conolly RB, Chaisson CF, Gross EA, Young JS, Mathis ET, Tedder DR. 2003. Modeling interindividual variation in physiological factors used in PBPK models of humans. Crit Rev Toxicol. 2003;33(5):469-503.

Modeling interindividual variation in internal doses in humans using PBPK models requires data on the variation in physiological parameters across the population of interest. These data should also reflect the correlations between the values of the various parameters in a person. In this project, we develop a source of data for human physiological parameters where (1) the parameter values for an individual are correlated with one another, and (2) values of parameters capture interindividual variation in populations of a specific gender, race, and age range. The parameters investigated in this project include: (1) volumes of selected organs and tissues; (2) blood flows for the organs and tissues; and (3) the total cardiac output under resting conditions and average daily inhalation rate. These parameters are expressed as records of correlated values for the approximately 30,000 individuals evaluated in the NHANES III survey. A computer program, Physiological Parameters for PBPK Modeling (P3M), is developed that allows records to be retrieved randomly from the database with specification of constraints on age, sex, and ethnicity. P3M is publicly available. The database and accompanying software provide a convenient tool for parameterization models of interindividual variation in human pharmacokinetics.

Kyriakos Markides
Obesity in middle-age or earlier is known to be a significant risk factor for a variety of health problems in old age, including diabetes, cardiovascular disease, and disability. Obesity among older people appears to be less detrimental to their health, partly because obese older people are selected survivors". Obesity (BMI 30+) does not appear to be related to mortality in older people and may be protective of mortality in African Americans and Hispanics.

At the same time, obesity appears to be related to subsequent disability. More needs to be known regarding the mechanisms linking obesity to health outcomes.

E. J. Masoro
Many changes occur in the physiological systems with increasing age (see *Handbook of Physiology, Section 11, Aging*, American Physiological Society, 1995). However, it must be reiterated that particular age changes vary among individuals from imperceptible to incapacitating. The following are the physiological changes that are of most concern in regard to the Exposure Factors Handbook for the Aging:

1. Intake of Harmful Agents; 2. Distribution of Harmful Agents; 3. Elimination of Harmful Agents; 4. Sensitivity to Harmful Agents.
The intake of harmful agents relates to the following physiological processes: 1.Food and water intake and the gastrointestinal system; 2. Respiratory function; 3. Skin function. NHANES III showed that food intake (measured as energy intake) decreases progressively from age 20 through age 80+. Similar findings have been reported from several smaller studies (Flynn et al, *J. Am. Coll. Nutr.* 11: 660-672, 1992; Drewnowski & Evans, *J. Gerontol.* 56A: Suppl. 2, 89-94, 2001; Wakimoto & Block, *J. Gerontol.* 56A, Suppl. 2, 65-80, 2001). In healthy elderly, the gastrointestinal system functions just about as effectively as in the young; however, this fact has to be tempered by the fact that gastrointestinal problems are the second most common reason for hospital admission of elderly patients. Although, it was long believed that there is an age-associated decrease in gastric secretion of hydrochloric acid, it is now recognized that this belief relates to the increased prevalence of atrophic gastritis in the elderly and that healthy elderly have a normal level of gastric acid secretion. Although respiratory failure is not uncommon in the elderly, in the absence of respiratory disease, only minor changes in respiratory function occur with increasing age. However, the clearance of particles in the airways is diminished at advanced ages, because of the diminished functioning of the cilia embedded in the lining layer of mucus. Also because of the increased dead space in the pulmonary system (see Zeleznik *Clin. Geriatr. Med.* 19: 1-18, 2003), the elderly have to inhale a greater amount of air than the young to obtain the same rate of alveolar ventilation. On the other hand, both the basal energy expenditure and the use of energy for physical activities are decreased with advancing age (see Di Pietro, *J. Gerontol.* 56A: Suppl. 2, 13-22, 2001); Drewnowski & Evans, *J. Gerontol.* 56A: Suppl. 2, 89-94, 2001; Hallfrisch et al, *J. Gerontol.* 45: M186-M191, 1990); this reduction in energy expenditure acts to decrease the rate of pulmonary ventilation. Geller and Zenck (*Envir. Health Perspect.* 113: 1257-1262, 2005) state the barrier function of the skin decreases with advancing age. In contrast, Chuttani and Gilchrest (see Chapter 11 in the *Handbook of the Physiology, Section 11, Aging,* American Physiological Society, 1995) state that the barrier function of the skin either increases or doesn't change with age depending on the chemical nature of the substance. Moreover, Balin (*The Encyclopedia of Aging,* 3rd ed, vol. 2, Springer Publishing Co., New York, 2001, pp. 933-935). points out that the blood supply to the skin decreases with advancing age, which decreases the rate of entry into the body of substances placed on the skin.

The distribution of harmful agents is influenced by the following: the percent body fat content, the composition of the blood, and the blood-brain barrier. Body fat content, expressed as percent of body weight, increases with increasing age through the seventh decade of life (see Kohrt et al, *Med. Sci. Sports*

Exerc. 24: 832-837, 1992). During the eighth decade and older, body fat content tends to decrease, but of course there is also concomitantly a loss of lean body mass. Body fat sequesters lipophilic compounds, thereby increasing their half-life in the body. There is a small but significant decrease in the blood plasma level of albumin (see McLean & Couteur, *Pharmacol. Rev.* 56: 163-184, 2004). Serum albumin binds lipophilic compound; thereby its level influences the free concentration of such substances. Aging also changes the blood-brain barrier (see Geller & Zenick, *Envir. Health Perspect.* 113: 1257-1262, 2005) and this change alters the access of toxic substances to the brain. The cardiovascular system is tangentially related to the bodily distribution of substances. There are age-changes in the functioning of the cardiovascular system in the elderly free of cardiovascular disease. The aging heart exhibits a reduced chonotropic and inotropic response to sympathetic system innervation. (see Chapter 17 in the *Handbook of Physiology, Section 11, Aging,* American Physiological Society, 1995). In addition, there is an age-associated decrease in the distensibility of the arteries that causes an increase in systolic blood pressure and pulse pressure (see Lakatta & Levy, *Circulation* 107: 139-146, 2003). Moreover, many elderly suffer severe malfunctioning of the cardiovascular system because of age-associated diseases -- coronary artery disease, cerebrovascular disease, heart failure, and peripheral vascular disease.

The elimination of harmful agents involves their metabolism by the liver and their excretion by the kidneys, the biliary pathway and if volatile by the lungs. Liver mass and blood flow significantly decrease with increasing age and hepatic sinusoidal function is altered (see McLean et al, *Pharmacol. Rev.* 56: 163-184, 2004). As a result, hepatic clearance of many harmful substances is decreased. Whether an alteration in the hepatic cytochrome P450 enzymes is also involved is controversial (see Geller & Zenick, *Envir. Health Perspect.* 113: 1257-1262, 2005).Biliary excretion is decreased somewhat by advancing age. A marked decrease in renal glomerlar filtration rate with advancing age has been reported in cross-sectional studies. However, in a longitudinal study involving the subjects of the Baltimore Longitudinal Study of Aging, about one-third of the subjects did not exhibit an age-associated decrease in the glomerular filtration rate (see Lindeman et al, *J. Am. Geriatr. Soc.* 33: 278-285, 1985). I haven't encountered information on the effects of age on the elimination of harmful substances by the pulmonary route.

One would expect that aging would affect the sensitivity to harmful agents. Indeed, it is known that the cellular signaling systems are altered with advancing age. Examples are the blunted skeletal muscle response to insulin and the blunted cardiac responses to adrenergic stimulation. In addition to the altered cellular signaling responses to chemical agents, the reduced ability of repair systems with advancing age should augment any effect a harmful agent has on a cell. The issue of the effect of age on the response of cells to chemical agents (pharmacodynamics) has been addressed to a limited extent in regard to the therapeutic use of drugs. However, I am not aware that toxicodynamics has been directly studied in humans and doubt that such studies are ethically possible. I suspect that the best that can be hoped for are extrapolations from pharmacodynamic studies and animal model studies. Both of these approaches can mislead rather than inform.
Since I don't do research in any of these areas, I can't say what the ongoing research activities are in any of the above areas. I can say that much of the kind of research needed in these areas has not been well supported by the NIH in recent years. In regard to Exposure Factors Handbook for Aging, the need is for descriptive physiological aging studies. In recent years, NIH has tended to primarily support mechanistic hypothesis-driven research at the molecular level.

There are many knowledge gaps and research needs. Age changes in respiratory function have not been extensively studied nor have the alterations in the skin barrier function. The longitudinal study indicating that a significant number of people do not exhibit an age-associated decrease in glomerular filtration involved subjects in the Baltimore Longitudinal Study of Aging. This is a very select population that may not be at all typical. To my knowledge, this kind of longitudinal study has not been extended to make sure that this is also true for most populations. Much more research is needed on the effect of age on the blood-brain barrier and on the hepatic P450 enzymes. The subject of the effect of age on toxicodynamics is of great importance, but I am at a loss as to how to address it.

Keith Meyer
Inhalation rate:
It is unclear what this term refers to. Data on respiration and changes in respiratory function generally focus on static pulmonary function tests (e.g. spirometry values, lung volumes, diffusion capacity). As age advances, chest wall compliance decreases and lung compliance tends to increase, with the net result being a decline in both forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). With advancing age, breaths/minute tend to increase. However, I am not aware of any specific studies that have measured "inhalation rate" for older compared to younger individuals. A study on rats suggests that old rats challenged with ozone inhalation display more of a rapid, shallow breathing pattern than young rats, which suggests that exposure to irritants might do the same to older humans and increase the "inhalation rate." Confounding factors include an age-associated decline in mucociliary clearance as well as a decline in alveolar-capillary clearance.

Body composition and weight:
Weight and body mass index (BMI) will vary according to the health status and activities (sedentary vs. active, regular exercise vs. lack of exercise, etc.) of individuals, but there is progressive decline in muscle mass (and muscle strength and contraction velocity) as part of the aging process. Similarly, bone mineral density decreases. Progressive increases in body fat and decreases in fat-free mass have been observed, and individuals who are more sedentary or disabled tend to have greater decline in fat-free mass. Additionally, weight and BMI measurements may not track very well with fat-free mass. Increased physical activity tends to prevent loss of fat-free mass and increases in BMI that are associated with aging.

Current research:
Other key physiological parameters that change with aging and can be assessed via various measurements include:

a.) cardiovascular function:

b.) cataract formation

c.) respiratory function including respiratory muscle strength

Data gaps and research needs:

Paul Price
The impression from the literature provided, is that there are numerous *studies of* age-related changes in physiology; however, the data have not been analyzed for the change in the physiological factors related to exposure assessment. EPA should seek to obtain the raw data from these studies and include them in the handbook. In addition, EPA may well wish to organize the available data to develop qualitative guidance on what is know about the ageing process in each of the organ systems and the implications for exposure assessment. Special emphasis should be given to the organ systems relevant to intake and uptake (the GI tract, lungs, and skin) and metabolism and excretion (liver and kidneys).

Deborah Riebe
The prevalence of obesity is increasing in all age groups, including older persons. Using the customary BMI of 30.0 kg/m2 or more to define obesity, the prevalence of obesity has increased to more than 22% in persons aged 60-69 years and 15% of persons aged 70 years and older in 2000 (Mokdad, 2001). The prevalence further increased tin 2001, to 25% and 17%, respectively (Mokdad, 2003). It should be noted that data on individuals over the age of 80 was obtained for the first time in NHANES III. In this age

group, the prevalence of obesity was low compared to younger age groups in the NHANES database (8.0% for males and 15.1% in females).

Large population studies show that mean body weight and BMI increase during most of adult life and reach peak values at 50-59 years of age in both men and women. The National Health Examination Survey (NHES I) and the National Health and Nutrition Examination Surveys (NHANES) from 1960 to 1994 demonstrated that weight gain occurs at different times in life for men and women. The increase in obesity in men, over this 34 year period, ranged from a 25% increase in 20- to 29-year-olds to a 115% increase in 50- to 59-year olds. For women, the largest increase in obesity, 139%, occurred in 20- to 29-year olds, with less increase in obesity seen in older age groups.

After the age of 60 years, mean body weight and BMI tend to decrease. The lower prevalence rates in this group may again be due to selective survival or to the higher frequency of diseases in this age group. The observation of lower weight in cross-sectional studies should be interpreted with caution, because obese persons have higher mortality rates at younger ages (Manson, 1995). Therefore, premature mortality of obese young and middle-aged adults would tend to decrease mean body weight and BMI in older adults.

Much attention has been paid to the unusual or sudden loss of body weight in the elderly, as it is the single best predictor for risk of death in older adults (World Health Organization, 1998). Involuntary weight loss occurs in approximately 13% of those over the age of 65 years (Morley, 1996) Precipitous weight loss is unexplained in 24% of cases but is associated with the onset of cancer (16%) depression (18%), gastrointestinal ailments (11%), an overactive thyroid gland (9%), neurological problems (7%) and the effects of or responses to medication (9%) (Thompson and Morris, 1991).

The shape of the association between BMI and mortality in the elderly has been shown to be U-shaped or J-shaped. Other studies have found a positive linear association, a negative linear association, or no association. However, "Obesity in Older Adults: Technical Review and Position Statement of the American Society for Nutrition and NASSO, The Obesity Society" states that collectively, data suggests that the absolute mortality risk associates with increased BMI increases up to 75 years of age and that the health complications due to obesity increase linearly with increasing BMI until the age of 75.

Obesity is associated with metabolic abnormalities, arthritis, pulmonary function abnormalities, urinary incontinence and cancer in older adults. Obesity has important functional implications in older adults, as it can exasperate the age-related decline in physical function. Mobility is markedly diminished in overweight and obese older adults compared to lean elderly adults (Galanos, 1994; Launer, 1994). Villareal et al (2004) demonstrated that obesity is an important cause of frailty in older persons. This study also showed that obesity is also associated with significant impairment in health-related quality of life.

BMI is a common measure used in large population studies due to its simplicity and ease of use. Caution must be used when interpreting BMI data. Height and weight are often self-reported. It is common for weight to be underestimated, especially in the obese population. An overestimation of height is also possible in the older population as they may not realize the decreases in height with age. Further, age related changes in body composition may result in the misclassification of some individuals; most notably those with high levels muscle (ex., body builders) and those with low levels of lean tissue and high levels of fat (older adults). BMI is not a direct measure of fatness and does not reflect fat patterning. In fact a large waist circumference was found to be a better predictor of all-cause mortality in non-smokers than a high BMI (Seidell & Visscher, 2000). Cross-sectional data from the Baltimore Longitudinal Study of Aging showed increases in body weight and adiposity in both men and women up through middle age. In men, the decrease in body weight after the fifth decade was primarily due to a decrease in muscle mass.

In very old men in their eighties and nineties, both muscle and fat mass decrease thus resulting in a large decrease in body weight. Women increased body weight through the sixth decade, primarily due to a continuous increase in fat mass. Although the increase in the fat mass was the major influence on body weight, muscle mass also declined. Both men and women lose muscle mass after age 25 but also put on fat during the next 3 decades, so there may be little change in BMI. Measures of BMI should not be discounted, just interpreted with caution.

Aging is associated with considerable changes in body composition. After age 20-30 years fat free mass (FFM) steadily declines in both men and women, whereas fat mass increases. The loss of FFM is primarily attributable to muscle atrophy. Because most of our knowledge about aging effects on FFM is derived from cross-sectional studies, and few have included individuals over the age of 70, the loss of FFM with age is not well documented. Loses of 5% per decade in men and 2.5% per decade in women have been reported. However, one longitudinal study of older adults (age 60 at baseline) showed a 2% loss in men and no change in women over a 10-year period. What is clear is that sarcopenia is highly prevalent in older adults, with as high as 40% in individuals more than 80 years of age, and is strongly associated with weakness, disability, and morbidity (Baumgartner, 2000).

Older adults at greatest risk for disability are those who are simultaneously sarcopenic and obese, and the prevalence of this combination of low muscle mass and excess fat increases form 2% in those 60 to 69 years of age to 10% in those more that 80 years old (Baumgartner, 2000). With obesity rates on the rise, this combination may also become more prevalent.

Regular exercise is important in the maintenance of optimal body composition with aging. Recent reviews of aerobic training in older adults reported that aerobic training was effective in reducing weight and FM in 20 or 22 studies and there was an apparent dose-response relationship. The fat loss occurred preferentially in the central regions of the body. Aerobic training was not effective for increasing muscle mass (Fiatarone Singh, 1998; Toth et al., 1999). Resistance exercise was also effective in decreasing body fat in older individuals participating in 12 to 52 weeks of training. At the same time, most studies show an increase in FFM. Further, energy needs during resistance training increased by about 15% in healthy elderly people, suggesting an increase in food intake may be necessary to stabilize weight.

Lauren Zeise

There were papers in the background materials provided to the committee that addressed body weight

Drewnowski and Evans:

- More body fat
- Reduced muscle mass
- Glucose tolerance related to inactivity and age
- Altered thirst, hunger and -- adoption of monotonous diet changes in gustatory and olfactory function

1.3 What information is available on diet and medication use in the aging population? What research is currently being conducted in these areas? What are the data gaps and research needs?

Gary Ginsberg

Medication Use in the Elderly - Polypharmacy

This is an area of large differences relative to younger adults. With increasing age there is a natural increase in the number of medical diagnoses, and many of these diagnoses are associated with pharmacologic intervention. Rates of most major diseases, including cardiovascular, pulmonary, renal, hormonal (diabetes) and cancer increase with aging (Mclean and LeCouteur, 2004). Each condition can be associated with multiple drugs and the side effects of these drugs can lead to other medications. The elderly also take a large amount of CNS-active medications either because of neurodegenerative disease (e.g., Parkinson's disease) or because of clinical states such as depression. Finally, pain medications are common in the elderly.

The manner in which polypharmacy is described is in terms of the number of drugs taken at a given time per patient, the classes of drugs given most often, the number of inappropriate drugs based upon criteria of pharmacologic intervention in the elderly, and the incidence of adverse drug reactions. The latter statistic can be a function of the number of drugs given per patient, the types of drugs and how they interact, and the age of the patient.

A quick search of the literature found a limited number of studies reporting on the number of drugs prescribed per individual. A 1987 study from Dublin reported on the mean number of drugs prescribed per person receiving medications from a survey of community pharmacies, with the number increasing from 1.5/person in children to 2.8/person in those over 80 (Nolan and O'Malley, 1987). Analysis of a Medicaid database in Georgia over a wide age range showed the peak in drug prescriptions in the 70-80 group (Kotzan, et al., 1989). Analysis of a prescription drug database in Denmark found that polypharmacy, defined as at least 2 drug prescriptions at one time, was more prevalent in the elderly than the rest of the population with 2/3rds of those over 70 receiving multiple medications while in the general population the frequency of polypharmacy was much less frequent (<10%) (Bjerrum, et al., 1998). Polypharmacy tends to be greatest in the elderly, women and in those who had recent hospitalization, with an estimate of elderly drug use (on average) being 2-6 prescribed and 1-3 non-prescribed medications per day (Routledge, et al., 2004). A more recent study of patients coming to a geriatric day clinic in the Netherlands reported 4.7 medications per person with that number going up somewhat after receiving further diagnosis and treatment at the clinic (Frankfort, et al., 2006). When polypharmacy is defined as >4 medications taken per person per day, the frequency in the elderly is estimated at 20-40% (McLean and LeCoteur, 2004). These types of studies consistently show that both in-patient and outpatient medication use goes up with age and that polypharmacy becomes a much more common phenomenon, and at times problem, in the elderly. A more thorough search of the literature is warranted in an attempt to obtain the population distribution of the number of drugs taken in the elderly and in elderly subgroups (frail, institutionalized, having certain diagnoses, etc.). However, it is not obvious that the data needed to construct such a distribution are available.

Regarding the types of drugs which the elderly tend to take, this may also differ from younger age groups. The analysis of the Denmark medication database mentioned above showed that those affected by polypharmacy tend to have unique medication profiles making it difficult to generalize which drugs are most involved in this syndrome (Bjerrum, et al., 1998). However, cardiovascular drugs and analgesics tended to be more common in elderly profiles while anti-ulcer, asthma and psychotropic drugs were more common in polypharmacy in younger adults. An older study generally found that psychotropics, diuretics and cardiovascular drugs were the most commonly prescribed drugs in the elderly (Nolan and O'Malley, 1987).

The frequency of inappropriate drug administration has been an increasing focus as criteria for drug prescribing in the elderly have been developed to attempt to curb polypharmacy and adverse drug reactions. The Beers drug prescribing in the elderly criteria were initially established in 1997 and updated in 2002 (van der Hooft, et al., 2005). These criteria point out inappropriate prescribing based upon contraindications due to age or disease state, or due to inappropriate dose level or drug combination. The frequency of inappropriate drug prescribing has been estimated at 15-20%, that being the odds of a geriatric patient receiving an improper prescription at least once per year (van der Hooft, et al., 2005). The drugs most frequently involved in these situations were nitrofurantoin, long-acting benzodiazepines, amitriptyline, promethazine and cimetidine. In terms of the drugs most frequently prescribed in unnecessarily high doses, temazepam and zolpidem were most common. The most frequent contraindicated prescription was for conventional NSAIDs in persons with a history of ulcer. A study of inappropriate dosing of an outpatient veteran group found a 23% rate with pain relievers, benzodiazepines, antidepressants, and musculoskeletal agents constituting the majority of these cases (Pugh, et al., 2005). As expected, the frequency of inappropriate drug use increases with increasing numbers of drugs prescribed per patient (greater degrees of polypharmacy (Steinman, et al., 2006). These types of studies point to specific areas of drug therapy in the elderly that may be of special interest to risk assessors because they involve drugs that shouldn't be used at all, are being used at inappropriate dose levels, or that could lead to drug interactions. These situations might be cases of special concern for drug/toxicant interaction on a pharmacokinetic or pharmacodynamic basis. These particular dosing situations would need to be described more thoroughly for potential incorporation into an Exposure Factors Handbook or in geriatric risk assessments.

Finally, the subject of polypharmacy in the elderly leads to the higher rates of adverse drug reactions (ADRs). ADRs are a concern in any age group and therapeutic arena because many drugs have effects that go beyond the anticipated therapeutic effect. It was originally believed that ADRs were more common in the elderly because at advanced age there is less functional reserve and homeostatic regulation and so the system is less able to kinetically or dynamically handle the challenge of a pharmacologic agent (Turnheim, 2004). ADR examples due to this type of phenomenon are postural hypotension with agents that lower blood pressure, dehydration and electrolyte disturbances in response to diuretics, bleeding complications with oral anticoagulants, hypoglycemia with antidiabetics, and gastrointestinal irritation with non-steroidal anti-inflammatory drugs. Further, the CNS can be especially sensitive in old age such that CNS-active drugs (psychotropic s, anticonvulsants, centrally acting antihypertensives) may impede intellectual function and motor coordination much more so than at younger ages (Turnheim, 2006). .However, evidence has accumulated that ADRs may be more related to polypharmacy than to age per se (Begaud, et al., 2002; Routledge, et al., 2004; Nguyen, et al., 2006). The types of ADRs can vary widely with neurologic effects fairly common, in some cases leading to a documented increase in falls (French, et al., 2006). The drugs implicated in increased risk of falls are cardiovascular, CNS and musculoskeletal. The oberservation and study of ADRs may have important implications for risk assessors because they show ways in which the elderly are more sensitive to xenobiotics and they point to a particularly sensitive exposure scenario in which polypharmacy leads to neurologic and other types of ADRs that may predispose to pharmacokinetic or dynamic sensitivity.

The medication prescribing trends in geriatric patients may present useful data for risk assessors, although currently the standard risk assessment practice does not take into account concomitant drug exposure. An argument can be made for this in the elderly due to the prevalence of drug use which is one of the factors that sets this age group apart from others. However, the number and type of drugs taken, as well as the treatment regimen (dose, frequency) are likely to be highly individualized so it may be difficult to generalize about what drugs the elderly are taking and how that could interface with environmental risk factors. One possibility may be to construct a prototypic polypharmacy treatment regimen that could be used as an exposure input factor. The drugs in this regimen could be evaluated separately and in combination for potential interactive effects with a given toxicant to which there is elderly exposure. Particular focus could be given to drugs which tend to be given inappropriately to the elderly or for which an interaction can be expected with the toxicant on the basis of protein binding, clearance mechanisms or the types of ADR produced. The data to develop a prototypic elderly drug regimen can likely be obtained from studies of prescribing databases that rely upon insurance company records. These records might also provide some indication of regimen compliance in that the frequency of refills can be matched against the unit supply per prescription. Inclusion of medication-taking behavior in a geriatric EFH should only come after careful consideration of how the data might be used by risk assessors. This can dictate the type, quality and quantity of data needed for the EFH.

Diet in the Elderly

With aging body weight tends to increase due to the rise in body fat (Hughes, et al., 2002). This doesn't mean that the elderly take in more calories since activity level is generally diminished in old age. In fact, in spite of increasing body weight, caloric intake steadily declines with aging (Wakimoto and Block, 2001). This may lead to nutrient deficiencies. Food consumption patterns may shift as there is evidence of less red meat, whole milk or fatty foods in the elderly, and instead an increase in fruits and vegetables (Wakimoto and Block, 2001). The existing EFH displays data for elderly consumers (>65) in relation to everyone else. These tables suggest that the elderly consume slightly lower amounts of fruits and vegetables with bigger drops in red meat. However, the data tables for fish ingestion do not break down older age groups, lumping everyone over 45. There is a need for more specific reporting of elderly dietary data and options should be considered on how to express it: total amount ingested, vs ingested per body wt vs ingested vs lean muscle mass. It would appear that ingestion of food/body weight would be considerably lower in the elderly given their decreasing food intake and larger body weight. However, more studies along these lines and with elderly subgroups (age bins, other categories) should be included. Special focus on fatty foods and fish may be particularly valuable given concern about toxicants in these foods. These data may be available from NHANES and other large-scale population datasets.

Drinking Water in the Elderly

The EFH already shows data derived from CSFII (1989-1991) for drinking of water and related beverages across decades of life, with the oldest age bin being >80. The mean ingestion data presented do not show obvious differences between younger and older adults (Table 3-21). While this would suggest similar water ingestion rates across the adult age span, water ingestion is also tied to activity and exertion level. The more sedentary pattern of the elderly may lead to less water ingestion at the upper ends of the distribution in which water ingestion may be driven by activity level with this being less of a factor in the elderly. However, the distribution of water ingestion in elderly subgroups compared to younger adults should be analyzed to the extent possible from sources cited in the EFH and elsewhere. Recent datasets that evaluate age-related changes in water ingestion (e.g., Raman, et al., 2004) should be reviewed to further evaluate the elderly and relevant subgroups within the elderly. However, care must be given to ensure data are obtained for tap water ingestion rate as this is most relevant to chemical exposure and risk. Some papers combine water, beverage and food moisture content for a total water ingestion rate. It may be appropriate to analyze both tap water only and tap water + beverage in this regard, but food moisture should be left out of the calculation.

Keith Meyer

Diet and medication use in the elderly:

Again, many factors affect diet, including health status, dental situation, and socioeconomic status. Elderly individuals frequently take many medications, although compliance may often be an issue.

Paul Price
No comment.

Lauren Zeise
From the NHANES dietary food survey data one can get diet intake information at the individual level. It will include older individuals in the survey. However, because of the design of the NHANES and CSFII surveys do not provide information on individuals food intake over time. As Drewnowski and Evans (2001) point out, because of altered sensations of thirst, hunger and satiety, many aged adopt a monotonous diet. Thus some of the approaches that have been used for example by the pesticide program to randomize individual food intakes may not lead to good estimates of the higher intake levels. On the other hand private firms conduct market surveys to determine eating habits. There is a wide range of foods for which market survey data is collected; food producers also commission surveys and the EPA could potentially commission surveys on food types of concern. The aging population has been a focus of some food surveys because they represent a large and growing market for food producers. The NPD Food Group, a commercial market survey group has focused on the elderly. See for example, the article at http://www.npdinsights.com/archives/october2005/cover_story.html NPD surveys and surveys by other commercial groups provide much better information on longitudinal eating habits for certain food than does NHANES.

Certain dietary supplements can also pose a health concern. Lead in calcium supplements has been an issue. In fish oil persistent lipophilic contaminants can concentrate. A small survey of supplement intake found that 51% of the elderly population took supplements, with fish oil being one of them. The extent that the elderly may consume supplements that contain environmental pollutants should be evaluated. For those supplements such as fish oil that are consumed by the elderly and have can have high levels of environmental contaminants, information on the range of intake and if possible distributional values would be of value to have in a handbook for this age group.

We tend to think about the young as being a vulnerable group for effects to lead and track behaviors and diet leading to exposure. Lead along with cadmium is of concern to the aging population especially given issues of remobilization from bone and changes in fat stores during aging and diseases that occur during aging. Intake information on foods and other products that may contain high levels for example of lead, cadmium, and lipophilic compounds should be targets for data collection and research so they can be included in a handbook.

2.0 Individuals over the age of 65 are often divided into categories based solely on chronological age, such as young-old (65-74 years), old-old (75-84 years), and oldest-old (85 years and older). However, the aging population is a highly heterogeneous group, and age-related changes in behavior and physiological function may be more a function of biological age than chronological age. This may be an important distinction in evaluating risk of exposure to environmental chemicals as changes in behavior and physiology directly affect exposure as well as the resulting internal dose. With this in mind, please discuss the following questions:

E. J. Masoro
Since individuals over age 65 vary greatly in physiological characteristics, there is a need to divide them into categorical groups. It is clear that dividing them by chronological age is not the answer since a few in the seventh decade of life will have a phenotype similar to most centenarians. In theory, using biological age to group them would appear to be the answer. However, to do so would require the ability to measure biological age and at this time, there is not a panel of biomarkers to do so that most biogerontologists

agree on. It is not due to a failure of the National Institute on Aging (NIA) to make available resources to generate such a panel of biomarkers. In 1988, the NIA initiated a 10 year study aimed at generating such a panel and enlisted leading gerontological laboratories to carry out the studies. This initiative failed to achieve this goal; the results of the initiative were published in the Nov and Dec 1999 issues of the *J. Gerontology,* Series A. It is such an important gerontologic issue that currently the NIA may well have an ongoing program; I suggest that the NIA be contacted in this regard.

2.1 In conducting exposure/risk assessments, is it appropriate to divide the aging population into age groups or "bins?" If so, what factors should be considered in determining these groups?

Gary Ginsberg

The concept of binning age groups may be borrowed from children's risk assessment where this has been deemed to be appropriate. Binning is usually most applicable to where physiologic or behavioral (exposure) factors change in a step function rather than as a smooth continuous and gradual trend. Bins could be established based upon age cut points where such apparent steps occur. One parameter for governing these cut points is frailty, a feature which likely becomes more significant with increasing age and disease. Disease rates and the associated polypharmacy also may increase in step function with age. I would think these are the most likely types of bins or subgroups to create – frail vs non-frail, # of major diseases, # of medications taken. Other parameters such as diet, water consumption, respiratory rate, etc. may have a smoother change with age and not as easily binned. I disagree with binning just for the sake of splitting of a population group such as the elderly.

There are many physiological factors to consider for including in a geriatric EFH. If one were to include toxicokinetic and clearance factors, you should also consider including glutathione content in the central compartment. There is evidence that this goes down in RBC and likely also in tissues, which can help explain the buildup of lipofuscin, a waste product reflecting oxidative damage (Singh, 2002). Given the importance of GSH as a cellular defense mechanism, risk assessors should be aware of the data, implications and information gaps with respect to the content of GSH and other antioxidants.

Dale Hattis

Binning is a convenience, but it necessarily loses information that may be in the component data sets. In general it would be better to derive age-dependencies in a continuous fashion with variability about the central tendencies. In practice using a single set of consistent age bins is difficult because the authors of different studies have used different/inconsistent bins for summarizing their data.

E. J. Masoro

Given the heterogeneity of the aging population, it is essential to do so. The problem is what basis can be used to do it? Clearly age categories such as young-old, old-old and oldest-old are not the way to go. Using biological age would be, if we knew how to measure it. I believe that at this time the best way to categorize the aging population is to base it on the ability to function. I would utilize the following functional assessments:

Group 1 would be comprised of those not able to do the ADL (Activities of Daily Living) without assistance. The ADL refers to walking, going outside, bathing, dressing, using the toilet, getting in and out of a bed or a chair, and eating. Group 1 would comprise 15 to 20% of the United States population over age 65. Although Group 1 is heavily weighted by the oldest old, it would also have a significant fraction of all age groups over age 65 (see page 28 in *Older Americans, Update 2006).* The frail elderly and the institutionalized elderly would primarily be in Group 1. Group 2 would be comprised of those not able to do one or more of the following: stoop/kneel, reach over head, write, walk 2-3 blocks, lift 10 lbs. or any one of the IADL (Instrumental Activities of Daily Living) without assistance. The IADL refers to using the telephone, traveling via car or public transportation, shopping for food and clothes, preparing a meal, doing housework, using medications and managing money. Group 2 would be comprised of about 20% of the men and 30% of the women in the USA over the age of 65 (see pages 28 and 29 of the *Older Americans, Update)*. Group 3 would be comprised of the rest of the United States population over the age of 65.

Keith Meyer

Considerable variation exists within this population. Exposure to environmental substances via inhalation and ingestion will vary greatly according to:

a) health status (i.e. free-living in community, chronic health problems confined to indoors, institutionalized, the presence of significant organ dysfunction due to chronic disease such as COPD or congestive heart failure)

b) physical activity

c) dietary habits (i.e. quality and consistency of foods, amounts and types of liquids consumed)

d) outdoor vs. indoor dwelling

e) geographic location (i.e. inner city, areas of the U.S. with poorer air quality, residence near emitters of atmospheric contaminants (incinerator, coal-fired power plants, smelter, heavy/constant vehicular traffic area, etc.)

f) tobacco addiction

Therefore, it is difficult to segregate the aging population into distinct groups on the basis of specific parameters.

Factors to consider:

Health status, exposure to atmospheric contaminants in ambient air

Paul Price

The goal of creating groups or bins is to identify objective criteria for grouping individuals that produce groups having significantly different values for one or more exposure factors. There are a number of problems with defining bins that are solely based on age.

In the past, EPA held workshops on developing age bins for children (Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants" ERG 2003, and Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants EPA/630/P-03/003F November 2005). The conclusion from these efforts is that age base binning of exposure factors is a valuable approach but that there were a number of difficulties with using age as the only criteria for bins.

- Growth rates in children vary with the individual (some children going through growth spurts at earlier ages some at later ages). Grouping data into age bins smears out this variation and leads to under estimates of the rate of changes in weight in specific individuals.

- Changes in different behaviors follow different patterns with age. Bins that make sense on the basis of diet may be very misleading when it comes to factors such as mobility or activity patterns. Thus, the use of a single set of age bins can introduce errors into screening risk assessments.

These problems present a greater challenge to the idea of using age to characterize factors among the aged than for characterizing factors among children. This suggests that age may have less value as the basis for binning the aged than for binning children. Some of the reasons why age is less of a predictor of exposure factors in the aged include the following.

First, growth is biologically determined aging is not. In order to predict the changes in an individual all that is required is knowledge of the status of the child at a point in time. That is to say, the characteristics of the child (age, developmental status, height, and weight) determine what the status of the child will be in the future (3-5 year olds have higher weights than 1-2 year olds). This occurs because growth follows a consistent sequence of events dictated by the goal of producing an adult capable of reproducing.
In contrast, aging has no goal and is characterized by the highly variable progressive failure of different biological systems over time. Thus, there is much less of a regular biological pattern to aging (Zeleznik, 2003). This absence of a regular pattern (other than menopause) makes the aging population much more variable.

Second, as indicated in many of the papers provided to the reviewers, physiological factors in the aged are influenced by individual personal behavior. Many physiological factors are influenced by diet and exercise. Third, as discussed by a number of papers provided to the reviewers, the U.S. aged population is dynamic. Public health and societal changes at all ages of U.S. society result in constant secular changes in aged individuals. Examples of this are the changes in life expectancy, body weights, and rates of specific diseases in individuals' of specific ages over the last 50 years. Because of these factors, EPA should thoroughly explore the option of defining bins in terms of categories other than age that may more accurately reflect differences in individuals' exposure factors.

A specific concern is that the tails of inter individual distributions of age bins in the elderly will be the same. This could happen because a fraction of individuals in each age group will be in a "frail" condition and because becoming frail radically changes behavior and physiology. An example of the problems this could cause in a screening exposure assessment is as follows. Consider an exposure to a specific source (pesticide on a golf course) and a sensitive individual (low blood clearance rate). Using age bins the upper tail on golfing and urinary output for "young old" could result in the combination of data on behavior that come from a "non-frail" individual and clearance rates that come from "frail" individuals.

Deborah Riebe
The simplest way to describe age is to categorize it. Age categories are divisions of chronological age that are used for discussion and classification in gerontological research. An inconsistency in gerontological research is that is that age categories have not been standardized. In physical activity research, studies have defined older adults as age 50+, 55+, 60+ and 65+. This makes it difficult to interpret research or to compare “old” subjects to “young” subjects when there has been no consistency at to what old means. Divisions of older adulthood have been created so that the growing number of older adults (the young-old), by virtue of remaining active, have continued behaving as young and middle-aged people.

Categorizing by age alone has flaws. There are many individual differences which arise form many sources including genetics, lifestyle, disease, gender, differential rates of aging of physiological systems, culture, education, socioeconomic status, and compensatory behaviors. For example, people differ in the extent to which they experience disease because each unique genotype supports different types and frequencies of pathologies, different vulnerabilities to certain environmental challenges and different level of immune function effectiveness.

Individual differences can be better represented by using biological (functional) age rather than chronological age. Biological aging is a group of processes that cause the eventual breakdown of mammalian homeostasis with the passage of time and is expresses as a progressive decrease in viability and an increase in vulnerability with the passage of time (Spiraduso, 2005). The non-scientific approach of simple observation demonstrates that individuals differ dramatically in the way that they age. Someone may seem “young for their age” while someone else might seem much older than their peers. Essentially, biological age has been used to describe the individual differences seen on variables within chronological age groups. It can be defined as the difference between an individual’s score on a biomarker of aging and the mean score for their chronological age cohort. However, to quantify human biological aging, a battery of biomarkers would need to be identified and measured. It is likely that there is a variety of mechanisms that cause aging. Even if all the contributors to biological aging were identified, measuring them to for the purpose of categorizing older adults would likely be impossible.

Categorizing individuals for any reason is primarily done for the purposes of convenience and generalizing research results. Making conclusions based on data that includes individuals placed into categories is useful. It helps researchers understand “the norm” and in most cases appropriate decisions based on norms can be made. It is up to those who use research results to understand that there will always be individual differences.

Lauren Zeise
Binning is appropriate; the question is whether it should be by age, other features, or a mix. Factor to consider in determining these groups:

- How well does the distinguisher (e.g., age) enable the differentiation among exposures?
- Can the distinguisher enable significantly better understanding of high vs common exposure levels? Does it provide the basis for elucidating the tails of the distribution – e.g., middle vs 85, 90, 95, 97.5, 99, 99.9%-tiles?
- To what extent are data available to identify the exposure parameter in question (e.g., inhalation rate) for the distinguisher?
- At what cost and to what extent can research address gaps in knowledge if that distinguisher is used?
- Exposure tables should support scenario risk assessment approaches. For parameters for which some special groups within the elderly population (e.g., frail) are linked to “high end” exposure that are linked to special characteristics of functionality a different treatment should be pursued to support the risk assessment. Studies should be sought out to identify at least central tendency and upper end values for those special groups so they can be adequately addressed in relevant risk assessments.
- Possible groups to consider – menopause, frailty

2.2 Are there behavioral changes that occur in the aging which lend themselves to characterization using age group categories?

Dale Hattis
Yes, particularly related to residence/lifestyles like decreased activity. Alternatively, some sources allow use of residential/lifestyle categories as the primary independent variable for assessing distributions of activity and other factors among elderly people in broad age ranges.

Kyriakos Markides
There is no doubt that "biological age" may be a better marker of aging than chronological age. Unfortunately it is not clear what a good measure of biological age is. Geriatricians would argue that 'old

age' nowadays begins at age 75. So conventional categorizations of people into ages 65 to 74, 75 to 74, and 85 and above remain useful.

Behavioral or medical factors that correlate with these age groups include comorbidities, disability rates, and cognitive declines, the latter being very prevalent among persons aged 85 and over.

And rates of 'frailty' are highly associated with age as measured above. Yet frailty is not necessarily due to aging. Major causes such as sarcopenia, atherosclerosis, malnutrition, and to a more limited extent, cognitive impairment can be prevented or reversed with appropriate interventions.

I am not certain whether frail vs 'healthy' older adults should be considered separately in the content of exposure/risk assessment.

Keith Meyer
Physical activity and outdoor activities decrease with advancing age, for one.

Paul Price

Not to my knowledge.
Age related changes in behavior in the elderly provide less support for age bins than changes in children. In the case of children, the transition from preschool to school changed a wide range of exposure factors such as activity patterns and diet. This suggests separating the pre and post 5 year olds into different bins. In the aged, there are no transitions that occurred at fixed ages. The largest change in activity patterns in the aged is from full time employment to post full time employment. This change will clearly affect individuals' activity patterns. However, while mandatory school attendance is generally required at age five, retirement is not tied to a specific age. Thus, a 58 year old who is retired may have an activity pattern that is more in common with a 68-year-old retiree than a 68-year-old employed individual.

Deborah Riebe
Physical inactivity is one of the strongest predictors of physical disability among older persons (Carlson & Harshman, 1999). Several longitudinal studies reveal that regular exercise extends longevity and reduces the risk of disability in later life (Ferruccci et al., 1999; Leveille et al., 1999; Wu, Leu & Li, 1999). Many of the age-related physiologic decrements older adults experience are not inevitable. Cardiorespiratory fitness, muscular strength and endurance, power, flexibility, balance, and body composition has a role in preserving physical function, reducing the risk of chronic disease, and averting disability with age.

Adults become less physically active with age so that by 75 years of age, 54% of men and 66% of women report no physical activity, defined as the lack of participation in any leisure-time physical activity for as long as ten minutes. Individuals who remain active into older adulthood will have lower levels of disability compared to those who are sedentary.

Participation in exercise is a behavior that has been widely investigated. Much attention has paid to determining the mediators and moderators of physical activity participation. Older adults exercise for different reasons compared to young adults. Further they identify different barriers to exercise, such as fear of falling. While the fear of falling is not considered as important in the young-old population, it becomes considerable more important as an individual ages and becomes more vulnerable to falls.

When examining population means, participation in physical activity, an important health behavior, differs among older age groups. As age increases, physical activity decreases. Mediators and moderators may change as a person ages, but much more research needs to be done in this area. Using age groups categories to describe physical activity participation is possible. However, there are many individual differences. Masters athletes train and compete into very old age, although empirical evidence suggests that even masters' competitors reduce both the frequency and intensity with which they train. An individual who has exercised throughout life will still experience age-related declines in fitness, performance, and physiological parameters. However, because they built such high levels of fitness when they were young, various physiological measures remain at much higher levels compared to the average older adult. For example, a distance runner might have such a high VO_2max that despite the age related decline of approximately 1% per year (which may accelerate after age 65), they may have better cardiorespiratory fitness compared to some sedentary younger and middle-aged individuals. If strength training is done throughout life, strength levels peak at significantly higher levels compared to untrained individuals and decrements in muscle strength across time occur at a slower rate. Strength-trained individuals have a better functional ability, reduced risk for falls and lower the development of some chronic diseases such as osteoporosis.

When considering exercise behavior, age group categories are convenient to use and represent "the norm". Age group categories will never be accurate to represent exercise behavior for the entire older adult population. Further, the type of exercise that one participates in (moderate versus vigorous; aerobic training versus resistance training) further differentiate between individuals.

Lauren Zeise

- Within the older population, there are behavioral changes (e.g., related to Alzheimer's disease) that increase with age. It may be preferable to focus on the populations with different behavioral characteristics that may result in higher end exposure than to try to capture these in general age categories.

2.3 Are there physiological changes that occur in the aging which lend themselves to characterization using age group categories?

Dale Hattis

Yes—need data on age related changes in a whole host of chronic cumulative functional changes, e.g. breathing rates, metabolism rates; dietary habits.

E. J. Masoro

If by age group categories, what is meant is chronological age, the answer is very few since there is great heterogeneity in most age groups in the extent of physiological deterioration and the occurrence and extent of pathophysiological processes. The only ones that I can think of that exhibit relative homogeneity in regard to chronologic age are menopause and presbyopia and I don't feel either provides the kind of information needed for the Handbook. In contrast, I believe that the categories suggested in 2.1 will divide the population in regard to the effects of age on the physiological systems and on effect of age-associated pathophysiology. It is these physiological changes and pathophysiologic processes that influence exposure to and physiological processing and biological actions of harmful environmental agents.

Keith Meyer

1) grip strength (or respiratory muscle force)
2) Bone density, muscle mass, and fat-free mass can be measured via DEXA scanning
3) Cardiovascular function could be characterized by measuring systemic blood pressure or via 6-minute walk test distance

4) Respiratory function can be assessed via spirometry

Paul Price
Not to my knowledge.

Age related changes in physiology in the elderly provide less support for age bins than changes in children. As discussed in many of the papers, biological age in the aged can differ markedly from the calendar age (a 65 year old may have a biological age of 55). This is not true for children (15 year olds never have biological ages of 5).

In addition, the aged (and to a lesser extent all adults) fall into physiological states (fragility and morbid obesity) which radically change behavior and physiology but are not strictly age related. This suggests that for the aged it may be important to define these as separate populations perhaps treating them in the same way as "asthmatics" and not lump them into age bins.

Deborah Riebe
Most physiological systems undergo decrements with age. To a degree, these decrements in physiology are reflected in decreases in health-related physical fitness, functional fitness and motor skill performance (ex., speed, power, hand-eye coordination). A precedent has been set to categorize physical performance in older adults. The Senior Fitness Test (Rikli and Jones, 2001) is a widely used measure of functional fitness for individuals over the age of 60. It includes assessment of lower body strength, upper body strength, aerobic endurance, lower body flexibility, upper body flexibility and agility and dynamic balance. Both normative and criterion-referenced standards are available for ages 60-94, broken into 5-year age categories. The criterion performance scores are particularly helpful as an older adult can determine if they are above average, in the normal range, or below average. The level at which an individual is at risk for loss of functional mobility has also been determined. A female aged 70-74 years is in the normal range for the 6-minute walk test if they walk between 490 and 610 yards compares to 290 to 450 yards for a woman aged 90-94. Functional disability begins when a woman cannot walk more than 350 yards in six minutes. Although these norms are available and quite useful, in both research and practice, there will continue to be individual differences. A frail 74-year old will score well below average while a high-functioning 90-year-old may be far above the norm for her age group. Age categories are widely used in determining health-related and/or functional fitness levels in age groups. Again, norms will not represent individual differences – those individuals above or below what is expected.

Lauren Zeise
There is a general decline in certain physiological characteristics with age. However within an age group there can be greater variability in parameters linked to these physiological characteristic than the variability in central tendency values across age groups.

2.4 In the context of exposure/risk assessment among the aging, how should “frailty” be defined? Should “frail” older adults be considered separately from “healthy” older adults?

Gary Ginsberg
Frailty is characterized by a major diminution of activities and independence that is associated with loss of appetite, weight loss, decreased energy expenditure, slower drug clearance and other factors that set this condition apart. It can occur at a range of calendar ages and so shouldn’t be divided out based upon age but upon the presence of absence of frailty. Given that this group may be more susceptible to environmental toxicants, risk assessors may need to quantitate exposure separately for this group. Thus, both exposure and toxicodynamic features may make this group important to analyze. There are common

definitions in the geriatric literature for frailty (decreased activity, weight loss, loss of independence) that can be used for the purpose of identifying this subgroup for the EFH.

E. J. Masoro

The definition of frailty is problematic since it has been evolving rapidly since 1990 and probably will continue to evolve for some time (see Spini et al, *Encyclopedia of Gerontology,* 2nd edition, vol. 1, J. Birren, ed., Elsevier, San Diego, 2007, pp. 572-579). From a biomedical point of view, the papers by Bortz (*J. Gerontol.* 57A: M283-M288, 2002) and Fried et al (*J. Gerontol.* 56A: M146-M156, 2001) provide similar definitions but fail to consider the recent developing psychosocial point of view. I feel that at the present time, it is not wise for the Exposure Factor Handbook to try to provide a definition of frailty nor is it necessary.

In regard to the question of considering the frail elderly separately from the "healthy" elderly, I presume by "healthy" elderly is meant what gerontologists refer to as normal aging. They define normal aging as aging in the absence of chronic diseases. Many gerontologists feel that normal aging is a figment (see Chapter 2, *Handbook of the Biology of Aging,* 6th edition, E. Masoro & S. Austad, eds., Elsevier, San Diego, 2006) since normal aging defined in this way is a rarity. A separate category for the frail elderly is simply not warranted, since Category 1 of my classification will capture most, if not all, of the frail elderly as well as others with severe chronic diseases. I see no reason to muddy the waters with a separate "frailty" category.

Keith Meyer
Definition of frailty:
If an aged individual is frail, does that place them at greater risk of adverse consequences from environmental exposures? I think that this is the case for inhaled substances such as PM or ozone. However, differentiating frail elderly from non-frail elderly is not necessarily straightforward, and a definition remains elusive. Furthermore, the presence of comorbid conditions or a disability complicate this differentiation.

The best correlate of frailty appears to be musculoskeletal function and measurement of strength and mobility (e.g. geriatric status scale, Barthel index, or PULSES profile) and may represent the best way to differentiate frail from non-frail elderly. Fried et al. (J Gerontol 2001;56A:M146-M156) defined frailty as a syndrome with ≥3 of 5 criteria (unintentional weight loss of ≥10 lbs over previous year, self-reported exhaustion, weak grip strength, slow walking speed, and low physical activity), and this definition appeared to correlate reasonably with identifying frailty in community-dwelling older adults.
Should “frail” older adults be considered separately from “healthy” older adults?

I am not sure that this should be done for all exposures. However, one could argue that certain exposures such as respiratory exposure to airborne and respired particular (which have been shown to have significant effects on cardiovascular, respiratory, and cerebrovascular function in the elderly) may have a much more profound effect on frail elderly individuals.

Paul Price
Frailty should be looked at in terms of both the physiological changes (energy expenditures) and the ability to perform exposure related behaviors (jogging, gardening, golfing, swimming, etc.). As indicted above, categories should be defined in ways that group populations in the elderly into relatively homogeneous groups that distinctly differ from one another. The value of age in defining such groups is not clear.

Yes, the aged "non-frail" should be separated from the aged "frail". Similar consideration should be given to separately evaluating the morbidly obese.

Lauren Zeise
For certain parameters there appear to be relatively large differences that depend on whether the older adult is frail or functionally impaired or not, for example physical activity, affects food consumption, body fat, muscle mass, BMI, water consumption. Other categories may turn out to be important, for example menopause.

3.1 Who are the potential users of an Exposure Factors Handbook for the Aging?

Elaine Faustman
I would assume that the same users of the manual would exist as currently exists for within agency risk assessors. In addition such information may be useful for pharmacists and other health care providers.

Gary Ginsberg
The potential users are exposure and risk analysts, which can include PBTK and Monte Carlo modelers. The EFH may be useful in a range of applications from qualitative risk characterization and uncertainty analysis thru fully quantitative/distributional analyses.

Keith Meyer
Government agencies, municipalities (especially those with air quality problems), toxicologists, epidemiologists.

Deborah Riebe
Although my expertise is not in exposure, after reviewing articles on the reference list, I would like to make one comment. Any individual who prescribes exercise to older adults (exercise physiologists, nutritionists, health care workers) would benefit from information in the Exposure Factors Handbook for Aging Populations. Exercise physiologists closely consider environmental challenges with exercise, but most of the work is done in the areas of heat, cold, and altitude. An individual may be more exposed to toxins in the environment during exercise as breathing rate increases. Functional capacity decreases with age, and sedentary older adults may have very low functional capacities. Therefore, even every day activities such as slow walking become quite vigorous when considered relative to the maximal capacity. Although this is well understood in the exercise science community, the increased exposure to environmental toxins is not likely something they would think about.

Paul Price
Assessments of a wide number of exposure sources will benefit from the handbook. Specifically assessments of exposures to components of products used by the aged or are used in environments where the aged are present.

Alan H. Stern
Both in my understanding and in my professional experience with the existing U.S.EPA Exposure Factors Handbook (EFH), the primary use of that document is to provide default and generic information on specific exposure assessment parameters (e.g., body weight, ventilation rate, pool use) that can be used in the in quantitative descriptions of exposure scenarios that are, themselves, used in the development of generic risk assessment standards and guidelines. Toxicokinetic, toxicodynamic and physiologic parameters, as well as general health status can be important determinants of risk. These can generally be characterized as parameters of sensitivity or susceptibility. As such, however, they are generally not relevant parameters for the exposure assessment portion of risk assessments. An obvious exception to this is when health status and more specifically, the ability to change locations, and participate in various activities may be a determinant in the construction of representative and generic exposure scenarios.

However, judging by the papers made available for the workshop and, to a lesser extent, by the charge questions, it may be that exposure factors are being conflated with factors predictive of sensitivity and susceptibility. Thus, for example, frailty is relevant to exposure assessment only to the extent that it either increases or limits contact with a contaminant in the environment, or the ability to translate an external dose into an internal dose.

From my standpoint as a user of the EFH, and as an advocate for the appropriate use of distributional information in exposure assessment, I think that a major issue in the construction of an Exposure Factors Handbook for the Ageing is the apparent large variability in common exposure parameters. This is not necessarily surprising as overall health status can vary greatly even within a relatively narrow age range among the relatively aged. A large variability per se, may not be an impediment to the useful quantitative description of an exposure parameter as long as the variability describes a more or less regular distribution. It is not even necessary for that distribution to be a close approximation of a common parametric distribution (e.g., lognormal). However, among the papers provided, I see evidence that the variability in the ageing population is not necessarily regular, but is, in some cases, highly bi-or polymodal, probably as a result of the parallel existence of physically robust and physically frail individuals of the same sex and age. Therefore, from my perspective, I think that a major challenge for the construction of an EFH for the ageing will be how to represent and summarize such data on a way that makes it both accessible and useful for distributional assessment. Can, for instance, stratifying the population produce more or less regular distributions? A related issue, is how would such information be used to construct exposure scenarios that reflect the most sensitive sub-groups in a population? Would, for instance, the frail sub-population be more at less at risk from an outdoor source of a contaminant, given that they are likely to spend less time outdoors?

Lauren Zeise

- Those that do site specific risk assessments
- Those that develop standards and other regulatory guidance (e.g., drinking water)
- Those that characterize dose response relationships to the extent the handbook provides useful parameters.

3.2 How would an Exposure Factors Handbook for the Aging be applied in conducting exposure and risk assessments?

Elaine Faustman
I would see this in two ways: First as inputs to the exposure assessment to see if exposures would exceed those for other age categories i.e. in a sensitivity analysis to determine who are the most highly exposed populations? Second, do these coincide with the most dynamically sensitive populations? Third, as I stated above, issues of fragility and other underlying disease states should be considered separately from the issue of exposure factors for aged. Fourth, issues of co-exposures i.e. mixtures or poly pharmacy should be further discussed at the meetings. I feel that these also should be handled as part of a continuum not issues only for the aged.

Gary Ginsberg
One possibility is that a bounding assessment of the elderly could be conducted in which the most extreme but still realistic geriatric parameters would be used (e.g., for the frail group?) to determine whether there would be a substantially different exposure dose or risk outcome than if the standard adult scenario was run. Alternatively, the various elderly subgroups could be combined with the younger adult group to develop a Monte Carlo distribution of exposures and risks in which the elderly were more completely assessed. Some parameters could be used directly in exposure assessment (e.g., body wt, water ingestion rate, food ingestion rates, breathing rate and volume, etc) while other parameters might only be useful for PBTK modeling (e.g., metabolic clearance rate). Medication use presents more of a challenge as it doesn't relate directly to chemical exposure or TK or TD vulnerabilities. However, it may be possible to develop methods to analyze how interactions between therapeutic drugs and environmental chemicals can occur on the TK and TD levels.

Dale Hattis
Preferably in a full probabilistic mode integrating information on external exposures, internal doses, and age-dependent changes in vulnerability to effects.

Keith Meyer
I defer to other panel members, but I think that this handbook could be particularly helpful for identifying and gauging inhalational exposure risks.

Paul Price
No comment.

Lauren Zeise
The Handbook would provide supplementary information on the aging population that could support the same kind of analysis that the existing Exposure Factors Handbook does, but would provide for better coverage of the aging subpopulation. It would therefore support:

- Scenario driven exploration of sensitive subgroups in the aging population – e.g., those frail, either living in nursing homes or at home that essentially spend 24 hours a day in the same location
- Populations – e.g., the individual exposure parameters can interact – the person with the large bodyweight may have lower metabolism, be more sedentary,
- Microenvironments – indoor v outdoor, size of residence, 24 hr exposures
- In dose response analyses, for example in looking at variability among humans using a PBPK approach, variability in body fat content and body weight can be important. In calculating cancer potency from epidemiological data the age structure of the population in the Exposure Factors Handbook can be used.

3.3 What factors should be included?

Elaine Faustman
I think we can answer this question once we have discussed the points identified from above.

Dale Hattis
That depends on the scope of the age-related probabilistic variability analyses that are to be supported. Minimally, one should try to include media consumption rates (ingestion of water, food products; inhalation by characteristics such as living arrangements.

Keith Meyer
Exposures via inhalation of ambient air should be a prominent component (e.g. exposure to particulates such as PM 2.5, ozone, oxides of nitrogen, sulfur compounds)

Paul Price
The factors in the handbook should include those factors used by PBPK modeling. These include tissue and compartment volumes and fractional blood flows. The other handbooks should be revised to include these factors as well.

Lauren Zeise

- For parameters that one would expect significant differences between older ages and those captured in the existing Exposure Factors Handbook.
- Could advise on exposure modifiers – sensitivity factors - to get at changes in renal clearance, hepatic processing, blood flow, (e.g., for particle deposition - lung elasticity, ventilation rate, COPD), polypharmacy, combination of age modified physiologic and pharmacokinetic parameters. Ventilation as elimination.
- Information on the correlation across time for dietary intake of certain kinds of food items. Because the elderly can be considerably more monotonous in their eating habit than other adults, some accounting for that would be useful. Random Monte Carlo approaches that are sometimes used in dietary exposures estimation could result in

substantial mischaracterizations for some elderly who eat the same food day in and day out.

- Outdoor/indoor – A fraction of individuals will spend virtually all their time indoors and at the same location (e.g., in nursing homes)
- Dust exposure could potentially be quite important for some substances (e.g., PBDEs), so exposure factors that would address behavior such as frequent hand to mouth activities in some subpopulations of the elderly.

3.4 How should the data be presented in order to be most beneficial to exposure assessors?

Gary Ginsberg

The data presentation should be as complete as possible, showing the mean, median, gm, sd, gsd, and various percentiles of the distribution. The shape of parameter distributions should be described (e.g, normal, log normal, etc.) . Subgroups should have separate data presentations. It would be helpful to have young adult data presented side-by-side with the geriatric data for ready comparison.

Keith Meyer

I defer to other panel members.

Paul Price

Access to the raw data is critical. Summary tables and summary descriptors are useful but the handbook should have a way to link back to the raw data on which the information is based. This can be done by setting up data bases that can be downloaded from the EPA web page or providing direct links to web pages where the data can be downloaded. EPA should give high priority to obtaining supporting date for all studies listed in the handbook. Wherever possible, EPA should require that data from publicly funded on studies be made publicly available.

EPA should develop both a paper copy of the handbook and an internet version. The FDA has established guidance on data submissions made electronically that would be a useful goal in the web-based version of the handbook. FDA has required that the raw data that supports any number be accessible within three mouse "clicks". Ideally, no more than three mouse clicks on a summary value in the handbook should bring the user to an electronic version the raw data of each study.

Lauren Zeise

So as not to introduce unnecessary uncertainty, when relevant parameters can be normalized by bodyweight - because they are derived from databases where data on individuals are available – they should be (e.g., drinking water intake as ml/kg-bw/day).

Where possible present data in such a way as to enable pairing of high exposure with high inherent sensitivity when they co-occur

The following points do not directly address the question but are provided as input as EPA considers approaches for improving the way it addresses risk characterizations that cover the elderly.

- Some work is needed to determine how EPA can best give guidance regarding increased susceptibility and varied pharmacokinetic handling of environmental xenobiotics due to heavy pharmaceutical use in the elderly. Guidance is clearly needed but it is unclear whether this is best done through the exposure guidance being considered.
- Just as age susceptibility factors have been introduced for infant and child assessments in the EPA Supplemental Guidance for conducting cancer risk assessment, factors that could serve as default in certain circumstances could be considered for the elderly. They may

pertain to exposure and be pertinent to an exposure factors handbook for the aged for example for internal chemical exposures impacted by renal clearance. Some single source for risk assessors to turn to aid systematic thinking on issues to consider and factors to entertain in conducting assessments for the aging population would be quite useful. The separation between internal and external dosimetry is to some extent artificial. A source to turn to for insights on pharmacodynamic considerations regarding susceptibility as well as pharmacokinetic and external exposure factors could be quite useful.

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APPENDIX F

PRE-MEETING COMMENTS BY EXPERT PANEL MEMBER INCLUDING SUPPLEMENTAL INFORMATION

PEER REVIEWER COMMENTS FROM

JOYCE DONOHUE

Issues Related to the Development of an Exposure Factors Handbook for the Aging

WORKSHOP CHARGE QUESTIONS

Joyce Donohue

(*Responses italicized*.)

1. Age-related changes in activity patterns, behavior, and physiology may have a significant impact on exposures to environmental chemicals. In order to better characterize these changes, please discuss the following:

   - What information is available on activity patterns and behaviors in the aging? Specifically, what is known regarding: 1) where older adults spend their time, and 2) what activities older adults are engaged in? What research is currently being conducted in these areas? What are the data gaps and research needs?
   - What information is available on age-related changes in physiological parameters such as inhalation rate, body composition, and body weight? What research is currently being conducted in these areas? What are the data gaps and research needs?
     - *There are considerable anthropometric data (height and weight) on the elderly from the NHANES surveys that are used in nutritional assessment.*
   - What information is available on diet and medication use in the aging population? What research is currently being conducted in these areas? What are the data gaps and research needs?
     - *I cannot provide specific citations but the Journal of the American Dietetic Association (JADA) publishes articles in nutrient intakes by elderly populations. There is also considerable information of deficiencies of specific nutrients among the free living and institutionalized older Americans. In the Reading list, I noted one articles from the American Journal of Clinical Nutrition but not from other nutrition publications such as JADA and the Journal of Nutrition*
     - *The Institute of Medicine Dietary Reference Intake volumes provide age specific information on essential nutrients from the Continuing Survey of Food Intakes by Individuals, NHANES, and the FDA total Diet Study.*
     - *The challenges posed by various dietary regimes for increased or restricted intakes of specific food groups should be considered as part of the dietary component of this effort.*

2. Individuals over the age of 65 are often divided into categories based solely on chronological age, such as young-old (65-74 years), old-old (75-84 years), and oldest-old (85 years and older). However, the aging population is a highly heterogeneous group, and age-related changes in behavior and physiological function may be more a function of biological age than chronological age. This may be an important distinction in evaluating risk of exposure to environmental chemicals as changes in behavior and physiology directly affect exposure as well as the resulting internal dose. With this in mind, please discuss the following questions:

- In conducting exposure/risk assessments, is it appropriate to divide the aging population into age groups or "bins?" If so, what factors should be considered in determining these groups?
- Are there behavioral changes that occur in the aging which lend themselves to characterization using age group categories?
- Are there physiological changes that occur in the aging which lend themselves to characterization using age group categories?
    - *The Dietary reference Intakes for Canadians and Americans subdivide the adult population into those from ages 50 to 70 and >70 years. The over 70 group was separated from the 50-70 year group based on changes in physiological function (i.e. nutrient absorption, kidney function) and physical activity (most are retired from full time employment).*
- In the context of exposure/risk assessment among the aging, how should "frailty" is defined? Should "frail" older adults be considered separately from "healthy" older adults?
    - *The there are number of chronic disorders such as high blood pressure, diabetes, atherosclerosis, Alzheimer's disease, osteoporosis, etc., that beset the elderly. This does not always place them in a category that one could label "frail. However, it does influence what they do and how they live. Chronic disease among the elderly population is an aspect of aging that I feel should be considered in the exposure factors handbook because it impacts physiology, exercise, diet and medicine*

3. It has been proposed that an Exposure Factors Handbook for Aging populations be developed to provide more detailed information on factors used in assessing exposure among this potentially sensitive subpopulation. Before initiating this project, the following issues must be considered:

- Who are the potential users of an Exposure Factors Handbook for the Aging?

- *Risk assessors, especially for consideration of sensitive population issues*
- *Exposure assessors*

- How would an Exposure Factors Handbook for the Aging be applied in conducting exposure and risk assessments?
  - *Age-specific parameters for use in estimating exposures*
  - *Identification sensitizing factors (physiological and life-style) that increase risk for the elderly. In my opinion, those sensitizing factors related to the pharmaceuticals they take are particularly important.*
- What factors should be included?
- How should the data be presented in order to be most beneficial to exposure assessors?
  - *I am not sure since I an not a frequent user of the Exposure Factors Handbook.*

PEER REVIEWER COMMENTS FROM

JEFFREY EVANS

Charge Question 1.2: What information is available on age-related changes in physiological parameters such as inhalation rate, body composition, and body weight? What research is currently being conducted in these areas? What are the data gaps and research needs?

OPP uses the following age groups in aggregate and cumulative assessments: The diets are based on the CSFII survey data.

Table X. Results of Acute Dietary (Food Only, Food and Drinking Water, or Drinking Water Only) **Exposure Analysis Using DEEM FCID**

Population Subgroup	aPAD (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
General U.S. Population							
All Infants (< 1 year old)							
Children 1-2 years old							
Children 3-5 years old							
Children 6-12 years old							
Youth 13-19 years old							
Adults 20-49 years old							
Adults 50+ years old							
Females 13-49 years old							

** Report %PADs to 2 significant figures*

Elderly

The elderly are identified as a life stage that may be comparatively more susceptible to effects from exposure to exogenous chemicals. At present, a 10-fold uncertainty factor is used in risk assessments to account for a wide range of possible susceptible populations, including the elderly. A primary concern is that metabolism and renal clearance is slower in the elderly. However, there are only limited experimental data as to the exacerbation of chemical toxicity in the elderly; these studies are primarily subacute toxicity evaluations of kidney function following exposure to antibiotics and mycotoxins (Janssen et al., 1993; Dormans et al., 1996; Peters-Volleberg et al., 1999; Dortant et al., 2001). The data indicate that the severity and/or incidence seen in older rats was generally not greater than three- or four-fold that seen in young animals. Dorne et al. (2002) looked at a very small group of humans for age differences in CYP2D6 metabolism and found that although the rate of metabolism was reduced in the elderly, it was only less by 1.2-fold. Human variability in renal excretion kinetics has been quantified (Dorne et al., 2004) using a database of 15 compounds excreted extensively by the kidney (>60% of a dose) to develop renal excretion-related uncertainty factors for the risk assessment of environmental contaminants handled via this route. Kinetic data for the renal excretion pathway in subgroups of the population were abstracted and compared to the mean and variability for the healthy adult data. The default uncertainty factor for renal excretion with oral administration was 3.16 for most subgroups, but, for the elderly subgroup, a slightly higher renal excretion-related factor of 4.2 would be required to cover up to 99% of the subgroup. **Consequently, the consensus of the ACSA Life Stages Task Force is that the proposed systemic toxicity studies on young adult animals adequately identify endpoints of concern relevant for the elderly and that, in general, the 10-fold uncertainty factor for susceptible populations adequately protects the elderly. Reducing the uncertainty factor should be considered only if the risk assessor is confident that the elderly are not especially sensitive.** However, specific investigations may be triggered to assess risks in the elderly if the reserve capacity is exceeded for other endpoints of concern (e.g., renal, immune system, nervous system, endocrine system, cardiovascular system, and liver) (Cooper et al., 1991). This is particularly so for the kidney, because function decreases normally with age due to anatomical and physiological alterations. Concern would also be triggered if the chemical structure resembles an existing chemical that is known to be toxic in elderly or aged animals.

Charge Question 2.1: In conducting exposure/risk assessments, is it appropriate to divide the aging population into age groups or "bins?" If so, what factors should be considered in determining these groups?
See table above.

Charge Question 2.2: Are there behavioral changes that occur in the aging which lend themselves to characterization using age group categories?

A few aging factors that may lead to increased potential for pesticide exposure are: Pesticide marketing is increasingly focusing on aging adults since they get more involved in gardening as children leave home. Other factors that need to be considered for the aging are: increased pet ownership and increased number of golfing events

Charge Question 2.3: Are there physiological changes that occur in the aging which lend themselves to characterization using age group categories?

Yes. The changes in diet are captured in our dietary surveys. Other information regarding breathing rates would be important and amount of time spent indoors/outdoors.

Charge Question 3.2: How would an Exposure Factors Handbook for the Aging be applied in conducting exposure and risk assessments?

Activity pattern information, pesticide use survey information and breathing rates have and can continue to be used in aggregate and cumulative assessments.

Charge Question 3.3: What factors should be included?

See above.

PEER REVIEW COMMENTS FROM

ELAINE FAUSTMAN

Exposure Factors Handbook for the Aging

General comments: I have reviewed all the papers and reports provided for this workshop and have emphasized my detailed reviews on Geller and Zenick, 2005; Ginsberg et al 2005;Kinirons and Crome, 1997; and Mc Lean and Le Couteur, 2004. I have however several questions.

First, has the team defined the search criteria that were used to identify these papers? I notice that absent from this list of references are examples of where environmental impacts were noted in aged human populations. Don't we need to review some of that literature in order to get the exposure factors on target? It would seem to be beneficial to see what factors in those epi studies best correlated with response. Several recent air particulate exposures and mortality or morbidity would be good for reference.

Research papers on menopause seem to be missing in this database. What about bone-remodeling during these times and increased Pb exposure from this unique age-specific source?

Second, I am concerned that as we start to consider differences in underlying disease state that we do this not only for the aged population but for other life stages as well. For example, although renal failure is higher in aged populations it can occur at most other ages. Likewise, hepatic function changes frequently occur in the elderly but jaundice is a very common issue prenatally. Thus, consideration of organ function and its impact on exposure and kinetic factors affecting ADME parameters should be defined across ages and only differentially considered as a different proportion of the population would need to be evaluated at each life stage. Likewise onset of many neuropsychiatric conditions occurs at adolescence not in aged populations yet we have several papers that consider these conditions just in the aged. I think we need to agree up front on how we will handle these cross-cutting life stage issues.

In a similar vein, the concepts of fragility could also be considered in pre-mature births and I am not a proponent of such "undefined" concepts for risk assessment. I would like us to identify specific conditions and disease states that constitute fragility and to use these disease states specifically rather than general wellbeing terms.

In the area of nutrition I think another across life stage issue is present and would press to consider this in general and not an issue just for the aged. Excellent examples exist for Pb and Ca deficiency as contributing to greater sensitivity in children so perhaps the questions should be broaden to see how nutritional exposure factors across life stages should be handled?

As I more frequently work with life stage specific differences in dynamics perhaps I need to see some of these considerations placed in a risk assessment framework for the aged to understand how the agency has considered using this information. I know that when I was involved with linking the physiological considerations with the exposure behaviors factors across children's risk assessment that such broader considerations helped me answer similar charge questions. In fact, I sometimes think that we should be doing an up-front sensitivity analysis to id key drivers in these risk equations so that we can better refine our inputs. Perhaps we can spend some of our face to face time doing this.

Response to charge questions in category 3:

3.1 Users of the manual—I would assume that the same users of the manual would exist as currently exists for within agency risk assessors. In addition such information may be useful for pharmacists and other health care providers.

3.2 See some of my comments above: I would see this in two ways: First as inputs to the exposure assessment to see if exposures would exceed those for other age categories i.e. in a sensitivity analysis to determine who are the most highly exposed populations? Second, do these coincide with the most dynamically sensitive populations? Third, as I stated above, issues of fragility and other underlying disease states should be considered separately from the issue of exposure factors for aged. Fourth, issues of co-exposures i.e. mixtures or poly pharmacy should be further discussed at the meetings. I feel that these also should be handled as part of a continuum not issues only for the aged.

3.3 Regarding display—I think we can answer this question once we have discussed the points identified from above.

PEER REVIEWER COMMENTS FROM

GARY GINSBERG

Response to Geriatric Workshop Charge Questions

Gary Ginsberg – January 26, 2007

1.3 What information is available on diet and medication use in the aging population? What research is currently being conducted in these areas? What are the data gaps and research needs?

GG Response:

Medication Use in the Elderly - Polypharmacy

This is an area of large differences relative to younger adults. With increasing age there is a natural increase in the number of medical diagnoses, and many of these diagnoses are associated with pharmacologic intervention. Rates of most major diseases, including cardiovascular, pulmonary, renal, hormonal (diabetes) and cancer increase with aging (Mclean and LeCouteur, 2004). Each condition can be associated with multiple drugs and the side effects of these drugs can lead to other medications. The elderly also take a large amount of CNS-active medications either because of neurodegenerative disease (e.g., Parkinson's disease) or because of clinical states such as depression. Finally, pain medications are common in the elderly.

The manner in which polypharmacy is described is in terms of the number of drugs taken at a given time per patient, the classes of drugs given most often, the number of inappropriate drugs based upon criteria of pharmacologic intervention in the elderly, and the incidence of adverse drug reactions. The latter statistic can be a function of the number of drugs given per patient, the types of drugs and how they interact, and the age of the patient.

A quick search of the literature found a limited number of studies reporting on the number of drugs prescribed per individual. A 1987 study from Dublin reported on the mean number of drugs prescribed per person receiving medications from a survey of community pharmacies, with the number increasing from 1.5/person in children to 2.8/person in those over 80 (Nolan and O'Malley, 1987). Analysis of a Medicaid database in Georgia over a wide age range showed the peak in drug prescriptions in the 70-80 group (Kotzan, et al., 1989). Analysis of a prescription drug database in Denmark found that polypharmacy, defined as at least 2 drug prescriptions at one time, was more prevalent in the elderly than the rest of the population with 2/3rds of those over 70 receiving multiple medications while in the general population the frequency of polypharmacy was much less frequent (<10%) (Bjerrum, et al., 1998). Polypharmacy tends to be greatest in the elderly, women and in those who had recent hospitalization, with an estimate of elderly drug use (on average) being 2-6 prescribed and 1-3 non-prescribed medications per day (Routledge, et al., 2004). A more recent study of patients coming to a geriatric day clinic in the Netherlands reported 4.7 medications per person with that number going up somewhat after receiving further diagnosis and treatment at the clinic (Frankfort, et al., 2006). When polypharmacy is defined as >4 medications taken per person per day, the frequency in the elderly is estimated at 20-40% (McLean and LeCoteur, 2004). These types of studies consistently show that both in-patient and outpatient medication use goes up with age and that polypharmacy becomes a much more common phenomenon, and at times problem, in the elderly. A more thorough search of the literature is warranted in an attempt to obtain the population distribution of the number of drugs taken in the elderly and in elderly subgroups (frail, institutionalized, having certain diagnoses, etc.). However, it is not obvious that the data needed to construct such a distribution are available.

Regarding the types of drugs which the elderly tend to take, this may also differ from younger age groups. The analysis of the Denmark medication database mentioned above showed that those affected by polypharmacy tend to have unique medication profiles making it difficult to generalize which drugs are most involved in this syndrome (Bjerrum, et al., 1998). However, cardiovascular drugs and analgesics tended to be more common in elderly profiles while anti-ulcer, asthma and psychotropic drugs were more common in polypharmacy in younger adults. An older study generally found that psychotropics, diuretics and cardiovascular drugs were the most commonly prescribed drugs in the elderly (Nolan and O'Malley, 1987).

The frequency of inappropriate drug administration has been an increasing focus as criteria for drug prescribing in the elderly have been developed to attempt to curb polypharmacy and adverse drug reactions. The Beers drug prescribing in the elderly criteria were initially established in 1997 and updated in 2002 (van der Hooft, et al., 2005). These criteria point out inappropriate prescribing based upon contraindications due to age or disease state, or due to inappropriate dose level or drug combination. The frequency of inappropriate drug prescribing has been estimated at 15-20%, that being the odds of a geriatric patient receiving an improper prescription at least once per year (van der Hooft, et al., 2005). The drugs most frequently involved in these situations were nitrofurantoin, long-acting benzodiazepines, amitriptyline, promethazine and cimetidine. In terms of the drugs most frequently prescribed in unnecessarily high doses, temazepam and zolpidem were most common. The most frequent contraindicated prescription was for conventional NSAIDs in persons with a history of ulcer. A study of inappropriate dosing of an outpatient veteran group found a 23% rate with pain relievers, benzodiazepines, antidepressants, and musculoskeletal agents constituting the majority of these cases (Pugh, et al., 2005). As expected, the frequency of inappropriate drug use increases with increasing numbers of drugs prescribed per patient (greater degrees of polypharmacy (Steinman, et al., 2006). These types of studies point to specific areas of drug therapy in the elderly that may be of special interest to risk assessors because they involve drugs that shouldn't be used at all, are being used at inappropriate dose levels, or that could lead to drug interactions. These situations might be cases of special concern for drug/toxicant interaction on a pharmacokinetic or pharmacodynamic basis. These particular dosing situations would need to be described more thoroughly for potential incorporation into an Exposure Factors Handbook or in geriatric risk assessments.

Finally, the subject of polypharmacy in the elderly leads to the higher rates of adverse drug reactions (ADRs). ADRs are a concern in any age group and therapeutic arena because many drugs have effects that go beyond the anticipated therapeutic effect. It was originally believed that ADRs were more common in the elderly because at advanced age there is less functional reserve and homeostatic regulation and so the system is less able to kinetically or dynamically handle the challenge of a pharmacologic agent (Turnheim, 2004). ADR examples due to this type of phenomenon are postural hypotension with agents that lower blood pressure, dehydration and electrolyte disturbances in response to diuretics, bleeding complications with oral anticoagulants, hypoglycemia with antidiabetics, and gastrointestinal irritation with non-steroidal anti-inflammatory drugs. Further, the CNS can be especially sensitive in old age such that CNS-active drugs (psychotropic s, anticonvulsants, centrally acting antihypertensives) may impede intellectual function and motor coordination much more so than at younger ages (Turnheim, 2006). .However, evidence has accumulated that ADRs may be more related to polypharmacy than to age per se (Begaud, et al., 2002; Routledge, et al., 2004; Nguyen, et al., 2006). The types of ADRs can vary widely with neurologic effects fairly common, in some cases leading to a documented increase in falls (French, et al., 2006). The drugs implicated in increased risk of falls are cardiovascular, CNS and musculoskeletal. The oberservation and study of ADRs may have important implications for risk assessors because they show ways in which the elderly are more sensitive to xenobiotics and they point to a particularly sensitive exposure scenario in which polypharmacy leads to neurologic and other types of ADRs that may predispose to pharmacokinetic or dynamic sensitivity.

The medication prescribing trends in geriatric patients may present useful data for risk assessors, although currently the standard risk assessment practice does not take into account concomitant drug exposure. An argument can be made for this in the elderly due to the prevalence of drug use which is one of the factors that sets this age group apart from others. However, the number and type of drugs taken, as well as the treatment regimen (dose, frequency) are likely to be highly individualized so it may be difficult to generalize about what drugs the elderly are taking and how that could interface with environmental risk factors. One possibility may be to construct a prototypic polypharmacy treatment regimen that could be used as an exposure input factor. The drugs in this regimen could be evaluated separately and in combination for potential interactive effects with a given toxicant to which there is elderly exposure. Particular focus could be given to drugs which tend to be given inappropriately to the elderly or for which an interaction can be expected with the toxicant on the basis of protein binding, clearance mechanisms or the types of ADR produced. The data to develop a prototypic elderly drug regimen can likely be obtained from studies of prescribing databases that rely upon insurance company records. These records might also provide some indication of regimen compliance in that the frequency of refills can be matched against the unit supply per prescription. Inclusion of medication-taking behavior in a geriatric EFH should only come after careful consideration of how the data might be used by risk assessors. This can dictate the type, quality and quantity of data needed for the EFH.

Diet in the Elderly

With aging body weight tends to increase due to the rise in body fat (Hughes, et al., 2002). This doesn't mean that the elderly take in more calories since activity level is generally diminished in old age. In fact, in spite of increasing body weight, caloric intake steadily declines with aging (Wakimoto and Block, 2001). This may lead to nutrient deficiencies. Food consumption patterns may shift as there is evidence of less red meat, whole milk or fatty foods in the elderly, and instead an increase in fruits and vegetables (Wakimoto and Block, 2001). The existing EFH displays data for elderly consumers (>65) in relation to everyone else. These tables suggest that the elderly consume slightly lower amounts of fruits and vegetables with bigger drops in red meat. However, the data tables for fish ingestion do not break down older age groups, lumping everyone over 45. There is a need for more specific reporting of elderly dietary data and options should be considered on how to express it: total amount ingested, vs ingested per body wt vs ingested vs lean muscle mass. It would appear that ingestion of food/body weight would be considerably lower in the elderly given their decreasing food intake and larger body weight. However, more studies along these lines and with elderly subgroups (age bins, other categories) should be included. Special focus on fatty foods and fish may be particularly valuable given concern about toxicants in these foods. These data may be available from NHANES and other large-scale population datasets.

Drinking Water in the Elderly

The EFH already shows data derived from CSFII (1989-1991) for drinking of water and related beverages across decades of life, with the oldest age bin being >80. The mean ingestion data presented do not show obvious differences between younger and older adults (Table 3-21). While this would suggest similar water ingestion rates across the adult age span, water ingestion is also tied to activity and exertion level. The more sedentary pattern of the elderly may lead to less water ingestion at the upper ends of the distribution in which water ingestion may be driven by activity level with this being less of a factor in the elderly. However, the distribution of water ingestion in elderly subgroups compared to younger adults should be analyzed to the extent possible from sources cited in the EFH and elsewhere. Recent datasets that evaluate age-related changes in water ingestion (e.g., Raman, et al., 2004) should be reviewed to further evaluate the elderly and relevant subgroups within the elderly. However, care must be given to ensure data are obtained for tap water ingestion rate as this is most relevant to chemical exposure and risk. Some papers combine water, beverage and food moisture content for a total water ingestion rate. It may be appropriate to analyze both tap water only and tap water + beverage in this regard, but food moisture should be left out of the calculation.

2.1 In conducting exposure/risk assessments, is it appropriate to divide the aging population into age groups or "bins?" If so, what factors should be considered in determining these groups?

GG Response: The concept of binning age groups may be borrowed from children's risk assessment where this has been deemed to be appropriate. Binning is usually most applicable to where physiologic or behavioral (exposure) factors change in a step function rather than as a smooth continuous and gradual trend. Bins could be established based upon age cut points where such apparent steps occur. One parameter for governing these cut points is frailty, a feature which likely becomes more significant with increasing age and disease. Disease rates and the associated polypharmacy also may increase in step function with age. I would think these are the most likely types of bins or subgroups to create – frail vs non-frail, # of major diseases, # of medications taken. Other parameters such as diet, water consumption, respiratory rate, etc. may have a smoother change with age and not as easily binned. I disagree with binning just for the sake of splitting of a population group such as the elderly.

There e are many physiological factors to consider for including in a geriatric EFH. If one were to include toxicokinetic and clearance factors, you should also consider including glutathione content in the central compartment. There is evidence that this goes down in RBC and likely also in tissues, which can help explain the buildup of lipofuscin, a waste product reflecting oxidative damage (Singh, 2002). Given the importance of GSH as a cellular defense mechanism, risk assessors should be aware of the data, implications and information gaps with respect to the content of GSH and other antioxidants.

2.4 In the context of exposure/risk assessment among the aging, how should "frailty" be defined? Should "frail" older adults be considered separately from "healthy" older adults?

GG Response: Frailty is characterized by a major diminution of activities and independence that is associated with loss of appetite, weight loss, decreased energy expenditure, slower drug clearance and other factors that set this condition apart. It can occur at a range of calendar ages and so shouldn't be divided out based upon age but upon the presence of absence of frailty. Given that this group may be more susceptible to environmental toxicants, risk assessors may need to quantitate exposure separately for this group. Thus, both exposure and toxicodynamic features may make this group important to analyze. There are common definitions in the geriatric literature for frailty (decreased activity, weight loss, loss of independence) that can be used for the purpose of identifying this subgroup for the EFH.

3.2 Who are the potential users of an Exposure Factors Handbook for the Aging?

GG Response: The potential users are exposure and risk analysts, which can include PBTK and Monte Carlo modelers. The EFH may be useful in a range of applications from qualitative risk characterization and uncertainty analysis thru fully quantitative/distributional analyses.

3.2 How would an Exposure Factors Handbook for the Aging be applied in conducting exposure and risk assessments?

GG Response: One possibility is that a bounding assessment of the elderly could be conducted in which the most extreme but still realistic geriatric parameters would be used (e.g., for the frail group?) to determine whether there would be a substantially different exposure dose or risk outcome than if the standard adult scenario was run. Alternatively, the various elderly subgroups could be combined with the younger adult group to develop a Monte Carlo distribution of exposures and risks in which the elderly were more completely assessed. Some parameters could be used directly in exposure assessment (e.g., body wt, water ingestion rate, food ingestion rates, breathing rate and volume, etc) while other parameters might only be useful for PBTK modeling (e.g., metabolic clearance rate). Medication use presents more of a challenge as it doesn't relate directly to chemical exposure or TK or TD vulnerabilities. However, it may be possible to develop methods to analyze how interactions between therapeutic drugs and environmental chemicals can occur on the TK and TD levels.

3.5 How should the data be presented in order to be most beneficial to exposure assessors?

GG Response: The data presentation should be as complete as possible, showing the mean, median, gm, sd, gsd, and various percentiles of the distribution. The shape of parameter distributions should be described (e.g, normal, log normal, etc.) . Subgroups should have separate data presentations. It would be helpful to have young adult data presented side-by-side with the geriatric data for ready comparison.

References

Begaud B, Martin K, Fourrier A, Haramburu F. 2002. Does age increase the risk of adverse drug reactions? Br J Clin Pharmacol 54:548-552

Bjerrum L et al., (1998) Polypharmacy correlations with sex, age, and drug regimen. A prescription database study. Eur J Clin Pharmacol 54: 197-202.

Frankfort, S.V. et al. (2006) Evaluation of pharmacotherapy in geriatric patients performing complete geriatric assessment at a diagnostic day clinic. Clin Drug Invest 26: 169-174.

French, et al. (2006) Drugs and falls in community-dwelling older people: a national veterans study. Clin Ther 28: 619-630.

Hughes, et al. (2002) Longitudinal changes in body composition in older men and women: role of body weight change and physical activity. Am J Clin Nutr 76: 473-481.

Kotzan, L et al. (1989) Influence of age, sex, and race on prescription drug use among Georgia Medicaid recipients. Am J Hosp Pharm 46: 287-290.

Mclean, AJ and LeCouteur, DG (2004) Aging biology and geriatric clinical pharmacology. Pharmacol Rev 56: 163-184.

Nolan L and O'Malley, K (1987) Age-related prescribing patterns in general practice. Compr Gerontol 1: 97-101.

Nguyen, JK, et al., (2006) Polypharmacy as a risk factor for adverse drug reactions in geriatric nursing home residents. Am J Geriatr Pharmacother 4: 36-41.

Pugh, MJ et al. (2005) Potentially inappropriate prescribing in elderly veterans: are we using the wrong drug, wrong dose, or wrong duration? J Am Geriatr Soc 53: 1282-1289. Raman, A., et al., (2004) Water turnover in 458 American adults 40-79 yr of age. Am J Physiol Renal Physiol 286: F394-401.

Routledge PA, O'Mahony MS, Woodhouse KW. 2004. Adverse drug reactions in elderly patients. Br J Clin Pharmacol 57:121-126Steinman, et al., 2006

Singh, RJ (2002) Glutathione: a marker and antioxidant for aging. J Lab Clin Med 140: 380-381.

Turnheim, K (2004) Drug therapy in the elderly. Exp Gerontol 39: 1731-1738.

van der Hooft, CS et al. (2005) Inappropriate drug prescribing in older adults: the updated 2002 Beers criteria – a population-based cohort study. Br J Clin Pharmacol 60: 137-144.

Wakimoto, P and Block, G (2001) Dietary intake, dietary patterns and changes with age: an epidemiological perspective. J Gerontol 56A, Suppl 2: 65-80.

PEER REVIEWER COMMENTS FROM

DALE HATTIS

1.2 What information is available on age-related changes in physiological parameters such as inhalation rate, body composition, and body weight? What research is currently being conducted in these areas? What are the data gaps and research needs?

To begin to respond to this very open-ended set of questions, I briefly scanned the reference sources that were supplied to us as PDFs. Appendix A is my quick evaluation of the potential usefulness of each as a source of data (or references to data sources) that might be compiled in an aging-related exposure factors handbook analogous to the child-related handbook that has been produced.

In addition I would like to highlight several other sources not included in the PDFs supplied to the work group:

- Price et al. (2003) have developed formulae for translating measurements made by NHANES III researchers into estimates of parameters needed for PBPK modeling. After comparisons with measured data, where available, these estimates could be used to develop expected distributions of key PBPK parameters for older people.2

- Brochu and coworkers have recently compiled data from over 1000 doubly labeled water measurements of total metabolism for individuals of all ages (including some measurements of people in their 90s). In addition to three published papers in Human and Ecological Risk Analysis, they provide considerably detailed summary statistics for their findings within age categories in accessible web sites. Some detail from these sources is compiled in Appendix B. Even better detail might be possible for compilation if the authors were persuaded to supply the underlying data themselves for inclusion in an EPA compilation. Even in their present form, these "gold standard" metabolic rate data can be used to detect and correct biases in metabolic rate/breathing rate data from other more extensive sources.

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2 Price PS, Conolly RB, Chaisson CF, Gross EA, Young JS, Mathis ET, Tedder DR. 2003. Modeling interindividual variation in physiological factors used in PBPK models of humans. Crit Rev Toxicol. 2003;33(5):469-503.

Modeling interindividual variation in internal doses in humans using PBPK models requires data on the variation in physiological parameters across the population of interest. These data should also reflect the correlations between the values of the various parameters in a person. In this project, we develop a source of data for human physiological parameters where (1) the parameter values for an individual are correlated with one another, and (2) values of parameters capture interindividual variation in populations of a specific gender, race, and age range. The parameters investigated in this project include: (1) volumes of selected organs and tissues; (2) blood flows for the organs and tissues; and (3) the total cardiac output under resting conditions and average daily inhalation rate. These parameters are expressed as records of correlated values for the approximately 30,000 individuals evaluated in the NHANES III survey. A computer program, Physiological Parameters for PBPK Modeling (P3M), is developed that allows records to be retrieved randomly from the database with specification of constraints on age, sex, and ethnicity. P3M is publicly available. The database and accompanying software provide a convenient tool for parameterization models of interindividual variation in human pharmacokinetics.

- About a year ago I participated with Kannan Krishnan in a project funded by Dr. Sonawane of EPA to compile and analyze statistical distributions of a number of pharmacokinetic/functional parameters in older people. My summary analysis report has not to my knowledge appeared in any final published document, but may be in process in the EPA/NCEA. Some excerpts related to body and organ weights, kidney glomerular filtration rates, diabetes, and hypertension are included for reference as Appendix C.

2.1 In conducting exposure/risk assessments, is it appropriate to divide the aging population into age groups or "bins?" If so, what factors should be considered in determining these groups?

Binning is a convenience, but it necessarily loses information that may be in the component data sets. In general it would be better to derive age-dependencies in a continuous fashion with variability about the central tendencies. In practice using a single set of consistent age bins is difficult because the authors of different studies have used different/inconsistent bins for summarizing their data.

2.2 Are there behavioral changes that occur in the aging which lend themselves to characterization using age group categories?

Yes, particularly related to residence/lifestyles like decreased activity. Alternatively, some sources allow use of residential/lifestyle categories as the primary independent variable for assessing distributions of activity and other factors among elderly people in broad age ranges.

2.3 Are there physiological changes that occur in the aging which lend themselves to characterization using age group categories?

Yes—need data on age related changes in a whole host of chronic cumulative functional changes, e.g. breathing rates, metabolism rates; dietary habits.

3.2 How would an Exposure Factors Handbook for the Aging be applied in conducting exposure and risk assessments?

Preferably in a full probabilistic mode integrating information on external exposures, internal doses, and age-dependent changes in vulnerability to effects.

3.3 What factors should be included?

That depends on the scope of the age-related probabilistic variability analyses that are to be supported. Minimally, one should try to include media consumption rates (ingestion of water, food products; inhalation by characteristics such as living arrangements.

SUPPLEMENTAL INFORMATION PROVIDED BY DALE HATTIS

Overview of PDF reference resources.

Berk et al. (2006). Changes in exercise level and subsequent disability among seniors: a 16 year followup. Great variability (10 fold+ in minutes of exercise per week)

Bortz (2002) Frailty conceptual framework. 30% of normal function represents a threshold for adequate function. (20% = mortality). Dubious dichotomization in principle, and likely overgeneralization of "disability" idea across many disparate functions.

Dergance (2005). Longitudinal aging project comparing Mexican Americans and European Americans. Slightly less than 30% difference observed in leisure time physical activity energy expenditure measured in kcal/week. All assessments seem to be based on interviews—no physiological studies.

DiPietro (2001). Literature review of large population-based studies of activity in older people. Moderate activity said to provide protection. Mostly helpful as a guide to prior literature supporting an association between reported activity and health risks of various types.

Drewnowski (2001). No data. Not obviously directly helpful.

Flynn (1992)—20 year prospective study of physiologic and dietary parameters. Includes coverage of dietary kilocalories/day based on 4-day diaries, % body fat, blood pressures, fat free weight, serum cholesterol and other blood lipids, and total potassium in males by decade of age (e.g. 61-70). Cross-sectional results within each group presented as means,, standard deviations, and number of observations. Longitudinal changes over 20 years are also shown for time windows beginning 30, 40, 50, and 60 years of age. Very helpful.

Fried (2001). Another "Frailty" paper—defines frailty as a syndrome with three or more of the following:

> Unintentional weight loss of 10 lbs in the past year,
>
> Self-reported exhaustion (responses to 2 standard questions)
>
> Weakness (grip strength in the lowest 20% at baseline adjusted for gender and BMI)
>
> Slow walking speed (slowest 20% of the population adjusted for gender and standing height)
>
> Low physical activity (based on a weighted score of kilocalories expended per week, based on the lowest quintile for each gender)

The classification of people into 3 categories of frailty (Frail, intermediate, not frail) based on 3/5 indicators based on scores that are themselves interpreted dichotomously seems like a serious waste of information in the underlying continuous data. Why wouldn't it be better to devise a continuous index of Frailty that was some weighted combination of the continuous measures of the component factors?

Furniss (1998). Medication use in nursing homes by elderly people. Elderly nursing home residents receive "up to" 4X the prescription drugs as elderly outside of nursing homes. Literature review; no tabular data.

Geller (2005). Review primarily of PK changes broken down by ADME categories.

Ginsberg (2005). Classical PK data analysis for drugs; broken down into 10-year age groups. Raw data also available on a web site: http://www2.clarku.edu/faculty/dhattis

Hallfrisch 1990. Baltimore longitudinal study of aging. 7-day diet records from 105 free-living men in the 1960s, 70s and 80s. Cross-sectional and longitudinal data similar to Flynn (1992) except in this paper the cross sectional data are presented in calendar-year intervals; indicating secular changes in some important parameters. Good data but limited N.

Horgas (1998). Daily life in very old age. Data from the Berlin aging study (Germany). Probability sample of 485 people broken down by age groups (70-84 and 85-103), sex marital status, education level, and residential status, and income. All categories are dichotomous except residential status where the division is private dwelling (subdivided by private house vs Apartment building) and Long term care (subdivided by assisted living vs nursing home) Many different activities included as % reporting/day and groups of activities expressed in terms of % time or absolute minutes on average day. Results given in terms of means, standard deviations and ranges (in minutes) as well as frequency. Relationships given by age decade, gender marital status, education, long term care and income. Correlation coefficients with age sex, and long term care are also given. Very helpful, except that the data apply most directly to Germany.

Hughes 2002. Body composition changes (fat mass and fat free mass) in men and women in relation to weight change and physical activity, derived from cross-sectional data. N=148. Under water weighing measurements.

Kinirions (1997). Frail elderly alleged to have reduced drug metabolism—see ref 73 (Woodhouse et al. (1988), Who are the frail elderly? (Q J Med)—contrary to observations from the Ginsberg et al. data base.

Leech (2002). Canadian vs American time-activity patterns\, based on large population surveys. Doesn't appear to be much breakout data for elderly.

Mcauley (2000)—randomized controlled exercise trial. Outside correlations from background data, doesn't seem very helpful.

McCurdey (2000)—description of CHAD. Overview paper. Elderly specific data would need to be isolated from the underlying database.

Mclean (2004). Good discussion, source of some types of PK-related data, and reference source for other PK data.

Metter (1992). Excellent empirical data on the selection effects that may distort comparisons between healthy 60 and healthy 80 year old men.

Moya (2002). Good discussion of the current use of information from the exposure factors handbook. Emphasis is on Superfund site cleanup assessments.

Moya (2004). Discusses early life exposure differences in the form of percentile distributions for different age groups (with all adults lumped into a >20 category). No data from seniors groups are included, but illustrate the composition and potential of an elderly parameters database.

Riebe (2005). Yale physical activity survey. A modest amount of potentially helpful current execrcise data by 10-year age groups. Less helpful attitudinal/intentional data on future exercise; not cross-tabulated by age.

Satariano (2002). Potentially very helpful information from 55+ yr residents of a rural California town on leisure time physical activity in relation to living arrangements. 2/3 participation rate. Good background data for the cross-sectional sample as a whole for men vs women I n lives alone, lives with spouse or lives with others only for men and women separately averaging 70 years of age. Unfortunately the ratings of physical activity are on a 4 category scale of "brisk," "less than brisk, "moderately vigorous, or highly vigorous" rather than something that is readily translatable into quantitative measures (e.g. kcal/day).

Smith (1998). Another paper from the Berlin Aging study. Survey to assess gender-related differences in constructs representing social status, physical health, functional capacity and other measurements. Without detailed study of the components of the constructs it is not clear that any are directly useful for risk analyses. Data presented in the form of 11 Clusters of parameters whose meaning and significance is unclear.

Stewart (1994). Polypharmacy in the Aged. No tabular data.

Talbot (2000). Baltimore Longitudinal Aging Study. Focus is on maximal VO2 and peak intensity. Not as useful for dosimetry as some integral of leisure time minutes X intensity, or leisure exercise kcal. (Exception: assessments for very short term exposure events, such as a chlorine leak from a tank car.) However a desirable breakdown of minutes at 3 levels of intensity is provided in Table 1 for men and women separately. Also scatter plots in figure 1 show individual data and overall regression analyses for each sex of total daily leisure-time energy expenditures. Tables 3 and 5 show energy expenditures in three very broad age groups (<40, 40-60, and >= 60 for 3 intensity levels. Better conclusions may be possible within the 60+ age group if the raw data can be obtained..

Verbrugge (1996). Another Baltimore Longitudinal Aging study paper. Activities and activity changes by age. Extensive data presented in graphical form by Age decades. Access to raw data would be essential for serious analysis of age related differences in trends for time spent in various activities.

Wakimoto (2001). Dietary intakes and changing dietary patterns with age. Data from NHANES III and other national studies. Table 4 gives helpful data for secular changes in total energy intake by 11-year age groups. Tables 5-7 summarize data from NHANES III for major macronutrients, minerals and micronutrients/vitamins, further detailed by gender and race/ethnicity groups. Table 8-9 gives helpful percentile distribution data for energy and other dietary parameters from CSFII data for different 10 year age ranges. Table 10 breaks down the products that are the sources of dietary energy into food product categories for 20-29 vs 70+ age groups.

Zeleznik (2003). Potentially useful survey of data sources for lung function and related parameters.

Tables and Reference Sources for Brochu Data Base on Doubly Labeled Water Metabolism Rate Measurements

Brochu tables introduction downloaded from web site http://www.mddep.gouv.qc.ca/air/inhalation/resumea_en.htm:

Physiological Daily Inhalation Rates

Free-Living Individuals Aged 1 Month to 96 Years, using Data from Doubly Labeled Water Measurements : A Proposal for Air Quality Criteria, Standard Calculations and Health Risk Assessment

Tables http://www.mddep.gouv.qc.ca/air/inhalation/resumea_en.htm#1

(http://www.mddep.gouv.qc.ca/air/inhalation/brochua-en.pdf, 94 ko)

Figure syntheses http://www.mddep.gouv.qc.ca/air/inhalation/resumea_en.htm#2

(PDF http://www.mddep.gouv.qc.ca/air/inhalation/Fig1-2en.pdf, 417 ko)

Reported disappearance rates of doubly labeled water (^2H_2O and $H_2{}^{18}O$) in urine, monitored by gas-isotope-ratio mass spectrometry for an aggregate period of over 30,000 days and completed with indirect calorimetry and nutritional balance measurements, have been used to determine physiological daily inhalation rates for 2210 individuals aged 3 weeks to 96 years. Rates in m^3/kg-day for healthy normal-weight individuals (n=1252) were higher by 6 to 21% compared to their overweight/obese counterparts (n=679). Rates for healthy normal-weight males and females drop by about 66 to 75% within the course of a lifetime. Infants and children between the age of 3 weeks to less than 7 years inhale 1.6 to 4.3 times more air (0.395 ± 0.048 to 0.739 ± 0.071 m^3/kg-day, mean ± S.D., n=581) than adults aged 23 to 96 years (0.172 ± 0.037 to 0.247 ± 0.039 m^3/kg-day, n=388). The 99th percentile rate of 0.725 m^3/kg-day based on measurements for boys aged 2.6 to less than 6 months is recommended for air quality criteria and standard calculation for non-carcinogenic compounds pertaining to individuals of any age or gender (normality confirmed using the Shapiro-Wilk test, $p \geq 0.05$). This rate is 2.5 fold more protective than the daily inhalation estimate of 0.286 m^3/kg-day published by the Federal Register in 1980 (i.e. 20 m^3/day for a 70-kg adult). It ensures that very few newborns aged 1 month and younger, less than 1% of infants aged 2.6 to less than 6 months and of course no older individuals up to 96 years of age inhale more toxic chemicals than associated safe doses which are not anticipated to result in any adverse effects in humans, when air concentration reaches the resulting air quality criteria and standard values. This rate is also protective for underweight, overweight and obese individuals. Finally, as far as newborns are concerned, a rate of 0.956 m^3kg-day based on the 99th percentile estimates is recommended for short-term criteria and standard calculations for toxic chemicals that yield adverse effects over instantaneous to short-term duration.

Reference to be cited:

BROCHU, Pierre, Jean-François DUCRÉ-ROBITAILLE and Jules BRODEUR. 2006a. Physiological daily inhalation rates for free-living individuals aged 1 month to 96 years, using data from doubly labeled water measurements: a proposal for air quality criteria, standard calculations and health risk assessment. *International Journal of Human and Ecological Risk Assessment*. HERA 12(4):675-701

[1]These tables are cited in the publications but were not published in the articles. These tables present energy expenditures and other measurement data that were used to determine physiological daily inhalation rates.

[2]These figure syntheses are not cited and were not published in the articles. These figure syntheses present the variations in physiological daily inhalation rates for different susceptible groups of the population as a function of age.

Substantive summary downloaded from http://www.mddep.gouv.qc.ca/air/inhalation/resumec_en.htm

Physiological Daily Inhalation Rates

Free-Living Individuals Aged 2.6 Months to 96 Years Based on Doubly Labeled Water Measurements: Comparison with Time-Activity-Ventilation and Metabolic Energy Conversion Estimates

Tables http://www.mddep.gouv.qc.ca/air/inhalation/resumec_en.htm#1

(PDF http://www.mddep.gouv.qc.ca/air/inhalation/brochuc-en.pdf, 49 ko)

Figure syntheses http://www.mddep.gouv.qc.ca/air/inhalation/resumec_en.htm#2

(PDF http://www.mddep.gouv.qc.ca/air/inhalation/Fig3-10en.pdf, 118 ko)

In the first part of this article, a critical review of traditional approaches used to estimate daily inhalation rates as a function of age for health risk assessment purposes shows that such rates are not totally reliable due to various biases introduced by both quantitative and qualitative deficiencies regarding certain input parameters. In the second part, the magnitude of under- and overestimations of published inhalation rates derived from each approach is described by a comparison with new sets of physiological daily inhalation rates and distribution percentile values based on total daily energy expenditures (TDEEs) measured by the doubly labeled water (DLW) method. TDEEs are derived from the analysis of deuterium (^{2}H) and heavy oxygen-18 (^{18}O) in urine samples by gas-isotope-ratio mass spectrometry during an aggregate period of over 20,000 days for unrestrained free-living normal-weight individuals aged 2.6 months to 96 years (n=1252). Regarding physiological values based on DLW measurements, opposite tendencies have been observed between two sets of estimates using time-activity patterns both biased by conservative input data assumptions during sleep and light activities: most of estimates based on the time-activity-ventilation approach are overestimated, while most of those using metabolic equivalent approach are underestimated. Erroneous food intakes have clearly lead to underestimated rates when used in daily food-energy intake (EFD) and Parameter A approaches. With the latter approach, overestimated basal metabolic rates (BMRs) used in EFD/BMR ratios contribute to the underestimation of inhalation values. Few mean daily inhalation rates and Monte Carlo simulation percentiles based on traditional approaches (57 out of 253) are close to physiological values within a gap of ±5% or less. Aggregate errors in all estimates (in m^3/day and m^3/kg-day) vary from –52 to +126%. The most accurate daily inhalation rates are those based on

DLW measurements with an error of about ±5%, as calculated in previous studies for free-living males and females aged 1 month to 96 years and pregnant and lactating adolescents and women aged 11 to 55 years during real-life situations in their normal surroundings. or additional information please do not hesitate to contact me.

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N.B.

Brochu P, Ducré-Robitaille JF, Brodeur J. 2006a. Physiological daily inhalation rates for free-living individuals aged 1 month to 96 years, using data from doubly labeled water measurements: a proposal for air quality criteria, standard calculations and health risk assessment. Hum Ecol Risk Assess 12(4):675-701

Tables Web-1 to Web-12 and 2 figures are also available in English at:

http://www.mddep.gouv.qc.ca/air/inhalation/resumea_en.htm

or in French at:

http://www.mddep.gouv.qc.ca/air/inhalation/resumea.htm

Brochu P, Ducré-Robitaille JF, Brodeur J. 2006b. Physiological daily inhalation rates for free-living pregnant and lactating adolescents and women aged 11 to 55 years, using data from doubly labeled water measurements for use in health risk assessment. Hum Ecol Risk Assess 12(4):702-735

Tables Web-1 to Web-13 and 2 figures are also available in English at:

http://www.mddep.gouv.qc.ca/air/inhalation/resumeb_en.htm

or in French at:

http://www.mddep.gouv.qc.ca/air/inhalation/resumeb.htm

Brochu P, Ducré-Robitaille JF, Brodeur J. 2006c. Physiological daily inhalation rates for free-living individuals aged 2.6 months to 96 years based on doubly labeled water measurements: comparison with time-activity-ventilation and metabolic energy conversion estimates. Hum Ecol Risk Assess 12(4):736-761

Tables Web-1 to Web-5 and 8 figures are also available in English at:

http://www.mddep.gouv.qc.ca/air/inhalation/resumec_en.htm

or in French at:

http://www.mddep.gouv.qc.ca/air/inhalation/resumec.htm

Excerpts from Krishnan, K., Hattis, D. Tardif, R., and Alagappan, M. "Physiological Parameters in the Healthy and Diseased Aged Populations," Report to the U.S. Environmental Protection Agency under Purchase Order EP05W002158, December 2005.

5. DISTRIBUTIONAL ANALYSIS

Studies of the distributional analyses of selected data in the database were undertaken during this project. These analyses, primarily to exemplify one end use of the database, were conducted with GFR, body weight and BMI for:

- Characterizing the distributional form of these parameters in elderly people, and in subsets of people with known chronic conditions (e.g., diabetes, hypertension) and
- Where possible, make limited comparisons of distributional forms for inter-individual variability in elderly subjects with distributional forms seen for the same parameters in younger age groups.

1.1. 5.1. Glomerular Filtration Rate (GFR)

Coresh et al. (2003) is a rich source of information on GFR in elderly. However, one problem with this study is that the subgroup analyses excluded 25 individuals whose estimated glomerular filtration rates were less than 15 ml/min-1.73 m^2 of body surface area. The authors report that they did this because they are concerned that people with such a low level of kidney function (probably consistent with a need for dialysis) might have lower rates of participation than people with higher kidney function. While this is likely to be correct, excluding these people from the sample creates an even worse distortion in estimates of the numbers of people in lower ranges of kidney function. Therefore we have analyzed the distributional data of Coresh et al. (2003) with and without use of a simple procedure to estimate the missing numbers of very low kidney function people in various subgroups. The procedure is to assume that the numbers of people under 15 ml/min-1.73 m^2 are roughly proportional to the numbers in the next higher group (those with 15-29 ml/min-1.73 m^2). The whole population sample contained 52 people in this higher (but still very depressed) range of function. Therefore, we derived improved estimates of the numbers of people in the <30 GFR functional group by multiplying the numbers in the 15-29 ml group by (25 + 52)/52.

Figures 10-13 show normal and lognormal probability plots of the overall population GFR distributions implied by the Coresh et al. data. * It can be seen that the normal plots provide a good description of the data—better than the corresponding lognormal plots. Because of this we will summarize variability in the GFR parameter using the coefficient of variation, the simple standard deviation (estimated by the slope in the normal probability plots) divided by the mean (estimated by the intercept in the normal probability plots).

1.1.1 5.1.1. Effects of Age

Figures 14 and 15 show normal and lognormal probability plots of the GFR distributions within specific age groups—in both cases including estimates of the numbers of individuals with estimated GFRs < 15 ml/min-1.73 m^2. It can be seen that normal distributions continued to provide superior descriptions of these data for narrower age groups. Looking among the specific age groups, it can be seen that the normal plots produce almost perfect descriptions of the data for the oldest age group; but the fidelity of the points to the regression line deteriorates as one proceeds from older to younger groups. This suggests an interpretation that with advancing age, the factors that cause differences in GFR among people tend to act additively in changing GFR across the entire population. However, at younger ages there seem likely to be some special pathological processes that act only on a small minority of people to produce severely depressed GFR in one or more subgroups.

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* In a plot of this type the general correspondence of the points to the line is a quick visual indication of how well an assumed normal or lognormal distribution describes the data. Normal distributions are to be expected when there are many factors that cause different people to be different in the measured parameters and the individual factors tend to have additive effects. Lognormal distributions are similarly expected when there are multiple factors affecting variability but they tend to affect the measured parameter multiplicatively. In each fitted regression line in this type of plot, the intercept represents an estimate of the mean of the parameter (either untransformed, or in log form) and the slope represents an estimate of the standard deviation of the same parameter. An advantage of probability plotting analyses is that comparisons with theoretical distributions and unbiased estimates of summary statistics (e.g., means and standard deviations) can be derived from truncated data (e.g. data where there are some number of non-detects or other source of censoring--as in this case with the exclusion of the < 15 ml/min-surface area group) or histogram representations data (as is also present in the fact that we are only given the percentages of people in different ranges of glomerular filtration, not the full raw data themselves.)

Based on the normal plots in Figure 14, Table 45 compares the age-related changes in the estimated means and coefficients of variation of the age-specific GFR data. It can be seen that the spreading of the population distribution (as indicated by the coefficient of variation) increase at older ages—suggesting an additive GFR loss process that operates at different rates in different people. Overall, the data in the last column indicates that age-related losses proceed at an average rate of approximately 1 ml/min-1.73 m^2/year.

1.1.2 5.1.2. Effects of Diabetes

Figure 16 and Table 46 show the differences in GFR distributions for people who do and do not report a history of diabetes. It can be seen that the absolute standard deviation of the two distributions is almost identical. This leads to a slightly higher coefficient of variation for the diabetic subpopulation, although the major effect is clearly a nearly 15 ml/min-1.73 m^2 change in the mean GFR.

1.1.3 5.1.3. Effects of Hypertension

Figures 17 and 18 as well as Table 47 show the effects of hypertension (with or without current medication) on the population distribution of GFR. In some contrast with the influence of diabetes, a diagnosis of hypertension is associated with both a decrease in mean GFR and an increase in the absolute standard deviation of the GFR distribution. This pattern is likely to be related to the fact that hypertension is a direct cause of kidney damage (and kidney damage can in turn contribute to hypertension).

5.2. Body weight and BMI

Figures 19 and 20 show distributions of body weight for elderly age groups, based on NHANES 3 data. On calculating the CVs all three male groups have similar ratios of standard deviation to mean at about 0.176; all three female groups have CVs that are slightly higher at about 0.22. Close examination of the normal plots for females in particular reveals a tendency for the data points to turn upward. This is characteristic of data that are better described by lognormal, rather than normal distributions. Therefore Figures 21 and 22 show lognormal probability plots of the same data; which are indeed somewhat better descriptions of the distributions in five out of six cases (as judged by comparisons of the R^2 statistics).

Figures 23 and 24 show normal probability plots of fat mass distributions given in percentile form by Kyle et al. (2001) for the three oldest age groups for men and women, respectively. Figures 25 and 26 show similar plots for three selected groups of younger people. The peak of the median fat mass/person occurs between the 55-64 and 65-74 year age groups. Therefore the order of the age groups shown in

Figures 23 and 24 is the opposite of the order used for Figures 25 and 26. We should also note the reversal of order for the oldest age group, but it should be borne in mind that the extreme percentiles of the distribution for this age group are based on relatively few observations. The normal distributions represented by the straight lines in these plots are generally reasonable, but not all perfect, descriptions of the data. The derived regression relationships can provide guidance for estimating other percentiles of the distributions than were directly given in the Kyle et al (2001) paper.

For essentially the same population, Figures 27 and 28 show normal probability plots of the distributions of the "fat mass index"—individual fat mass normalized to height^2 (a proxy for surface area). These distributions also seem to be reasonably well described as normal in form, with larger means and standard deviations for the older age groups (although the slight bend in the concave-upward direction suggests that lognormal plots might be even better descriptions of the data in some cases).

Such analyses cannot be performed for all physiological parameters due to the limited individual data or lack of characterization of the dispersion of data except for standard deviations within highly selected groups. However, such data from various studies may be investigated for possible pooling.

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Table 45: Age-Related Changes in GFR Distributions as Inferred from the Data of Coresh et al. (2003)

Age group	Approx Mean Age	Estimated Mean GFR	Estimated Std. Dev GFR	Est CV	Estimated Mean GFR Change/ Year Age From Prior Period (ml/min-1.73 m2-year)
20-39	30	120.76	26.778	0.222	
40-59	50	95.101	20.283	0.213	1.28
60-69	65	85.586	21.194	0.248	0.63
70+	75	74.968	21.876	0.292	1.06
Average Change 70+ vs 20-39 Group:	.	.	.	.	1.02

Table 46: Differences in GFR Distributions Associated with Diabetes as Inferred from the Data of Coresh et al. (2003)

	Estimated Mean GFR	Estimated Std. Dev GFR	Est CV	Mean GFR Change Associated with Diabetes
Without diabetes	100.9	24.8	0.245	
With diabetes	86.2	25.5	0.296	14.7

Table 47: Differences in GFR Distributions Associated with Hypertension as Inferred from the Data of Coresh et al. (2003)

	Estimated Mean GFR	Estimated Std. Dev GFR	Est CV	Mean GFR Change Associated with Hypertension
Without Hypertension	100.7	18.8	0.186	
With Unmedicated Hypertension	89.9	22.9	0.255	10.8
With Medicated Hypertension	81.1	23.3	0.287	19.6

Table 48: Comparative Weighted Regression Analysis Results for Mean Body and Organ Weights vs Age for Female Danish vs Japanese Autopsy Subjects—Data of Puggard et al (2002) and Inoue and Otsu (1987)

Population and Dependent	Regression	Regression Slope (Weight Units Per	Age 65 Predicted	Age 65 % Organ Weight/Body	% Age 65 Weight

Variable	Intercept	Year of Age)	Value	Weight	Decline/Yr
Danish Body Weight (kg)	78.7	-0.261	61.8		0.422
Japanese Body Weight (kg)	52.8	-0.202	39.7		0.508
Danish Brain Weight (g)	1609	-4.51	1316	2.13	0.343
Japanese Brain Weight	1440	-3.60	1206	3.04	0.298
Danish Heart Weight (g)	366	-0.330	344	0.557	0.096
Japanese Heart Weight	300	0.1227	308	0.777	-0.040
Danish Liver Weight (g)	2246	-12.81	1414	2.29	0.906
Japanese Liver Weight	1806	-11.63	1050	2.64	1.107
Danish Spleen Weight (g)	193.9	-1.138	120.0	0.194	0.949
Japanese Spleen Weight	145.6	-1.063	76.5	0.193	1.391
Danish Both Kidney Man Weight (g)	436	-2.92	246	0.398	1.186
Japanese Both Kidney Mean Weight	181.9	-0.959	119.6	0.301	0.802

Table 49: Weighted Regression Analysis Results for Mean Body Weights and Mean Body Mass Index In Relation to Age from the U.S. NHANES 3 Data for 60-90 Year Old Subjects—Comparison with Autopsy Data Derived from Danish and Japanese Women Autopsy Subjects

Population and Dependent Variable	Regression Intercept	Regression Slope (Weight Units Per Year of Age)	Age 65 Predicted Value	% Age 65 Decline/Yr
NHANES Male 60+ Body Weight (kg)	116.1	-0.512	82.8	0.618
NHANES Female 60+ Body Weight	104.4	-0.513	71.0	0.723
Danish Female Body Weight (kg)	78.7	-0.261	61.8	0.422
Japanese Female Body Weight (kg)	52.8	-0.202	39.7	0.508
NHANES Male 60+ BMI	33.8	-0.100	27.3	0.366
NHANES Female 60+ BMI	35.4	-0.119	27.7	0.431

Table 50: Comparison of Expectations from Regressions Derived From NHANES 3 Data for 60-90 Year Old Subjects vs Mean Observations of Kyle for Mean Body Weight and Mean Body Mass Index

Approximate Midpoint of Kyle (2001) Age Ranges (Yrs)	60	70	80	90
Predictions from NHANES 3 Male 60+ Body Weight Regression (Kg)	85.4	80.3	75.2	70.0
Kyle (2001) Male Mean Body Weight (Kg)	75.2	75.9	72.6	71.6
Predictions from NHANES 3 Male 60+ BMI Regression	27.8	26.8	25.8	24.8
Kyle (2001) Male Mean BMI	25.0	25.7	24.9	26.2
Kyle (2001) Male Std Error BMI	0.2	0.3	0.3	0.6
Predictions from NHANES 3 Female 60+ Body Weight Regression (Kg)	73.6	68.4	63.3	58.2
Kyle (2001) Female Mean Body Weight (Kg)	62.8	65.6	62.6	59.1
Predictions from NHANES 3 Female 60+ BMI Regression	28.3	27.1	25.9	24.7
Kyle (2001) Female Mean BMI	24.3	25.9	25.3	25.2
Kyle (2001) Female Std Error BMI	0.3	0.3	0.3	0.7

Figure 2: Population-Weighted Differences in Mean Weight for NHANES3 Subjects of Different Ages

2.

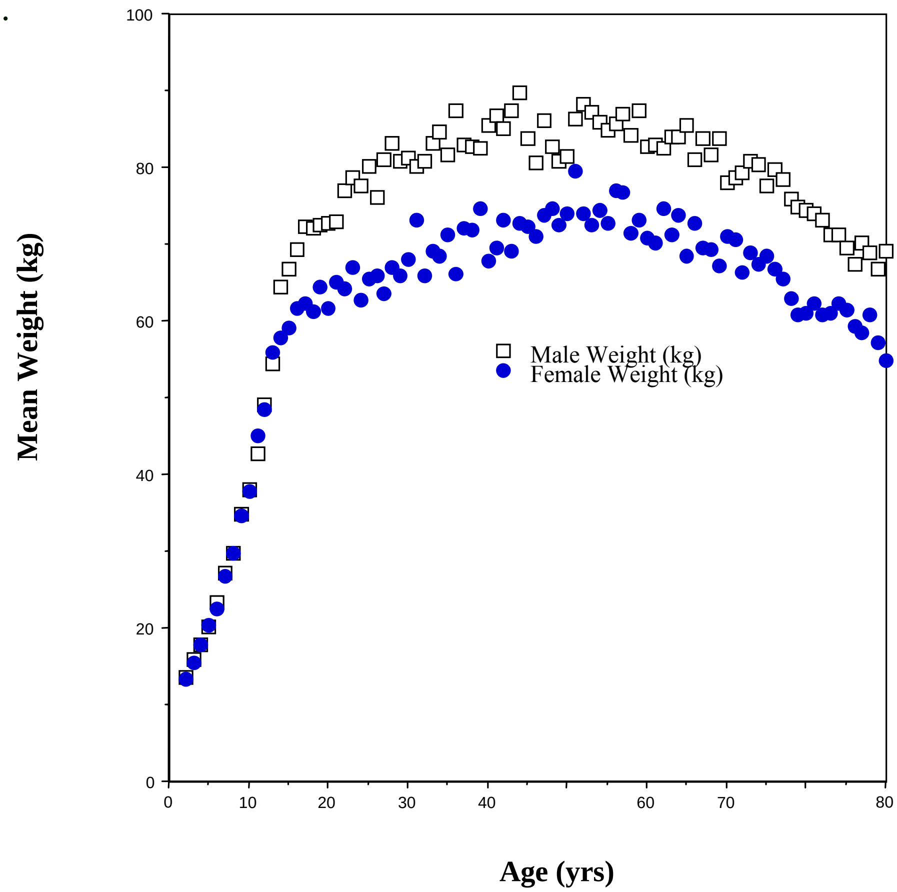


Figure 3: Population-Weighted differences in Mean Body Mass Index for NHANES3 Subjects of Different Ages

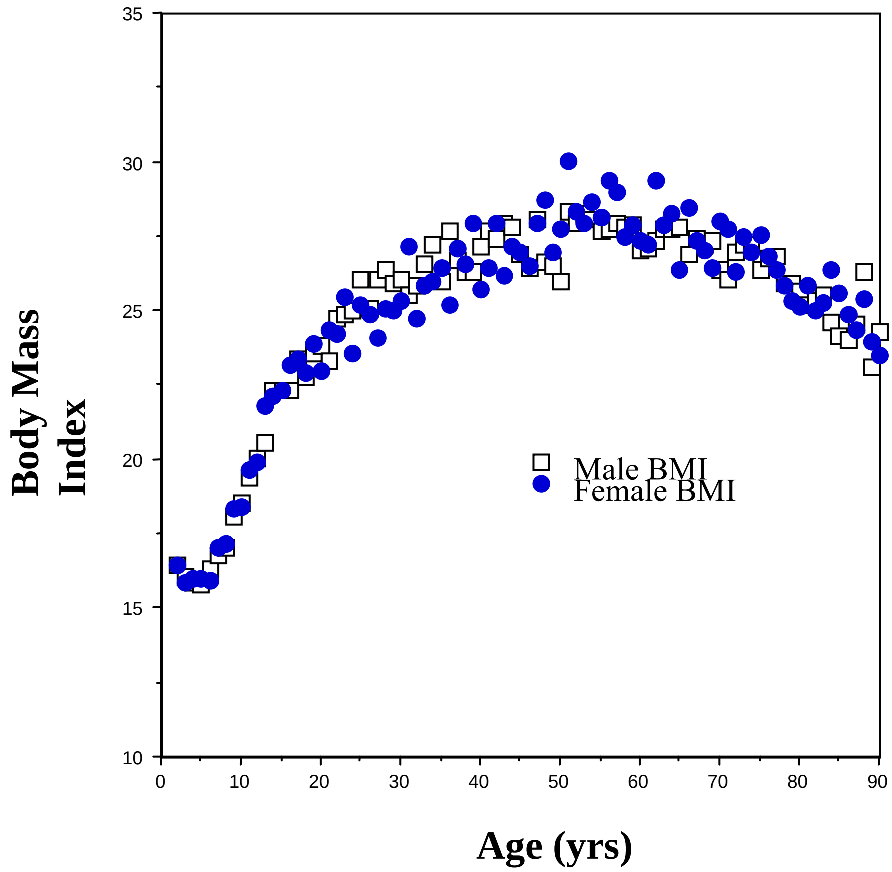


Figure 4: Comparison of Age-Related Declines in Liver Weight with Age in Male U.S. vs Japanese Autopsy Subjects. Data from Calloway et al. (1965) and Inoue and Otsu (1987)

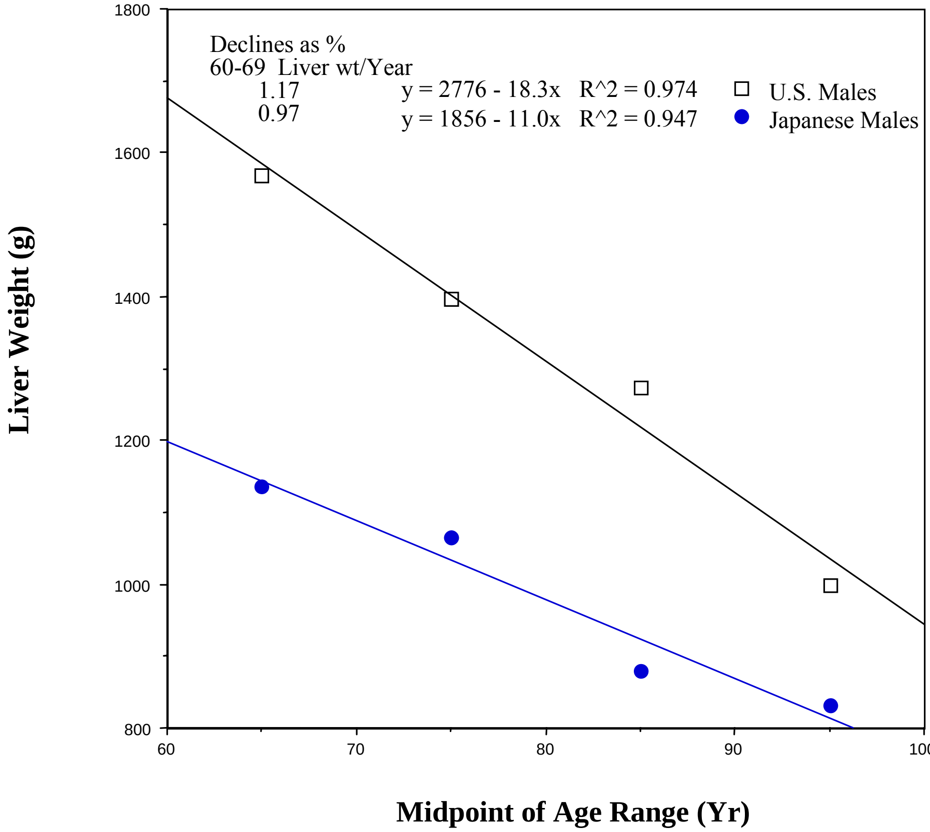


Figure 5: Comparison of Age-Related Declines in Heart Weight with Age in U.S. vs Japanese Autopsy Subjects. Data from Calloway et al. (1965) and Inoue and Otsu (1987)

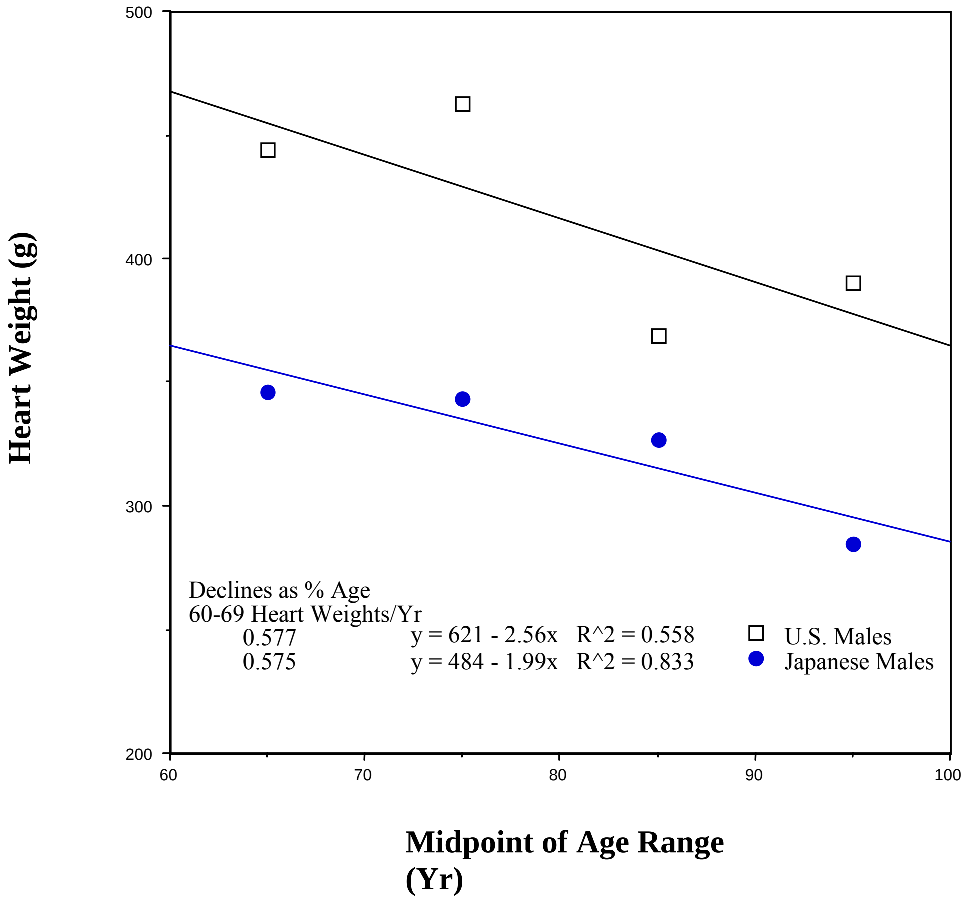


Figure 6: Comparison of Age-Related Declines in Right Kidney Weight with Age in Male U.S. vs Japanese Autopsy Subjects. Data from Calloway et al. (1965) and Inoue and Otsu (1987)

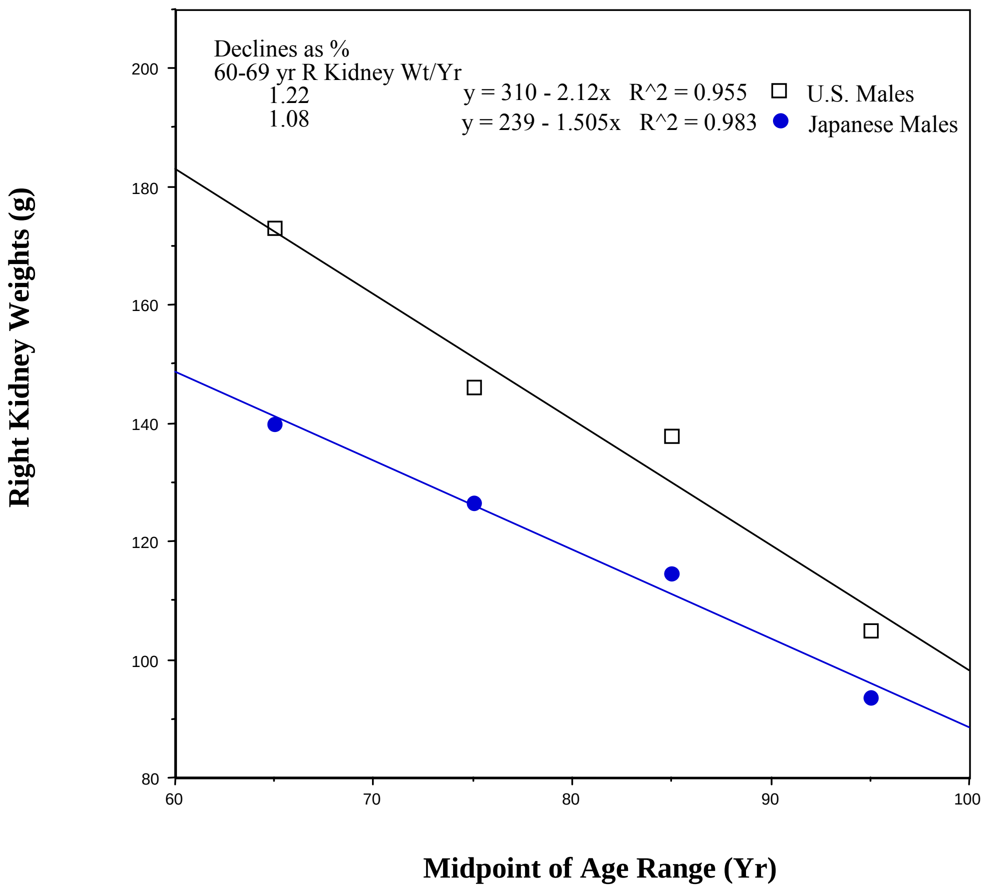


Figure 7: Comparison of Age-Related Declines in Left Kidney Weight with Age in Male U.S. vs Japanese Autopsy Subjects. Data from Calloway et al. (1965) and Inoue and Otsu (1987)

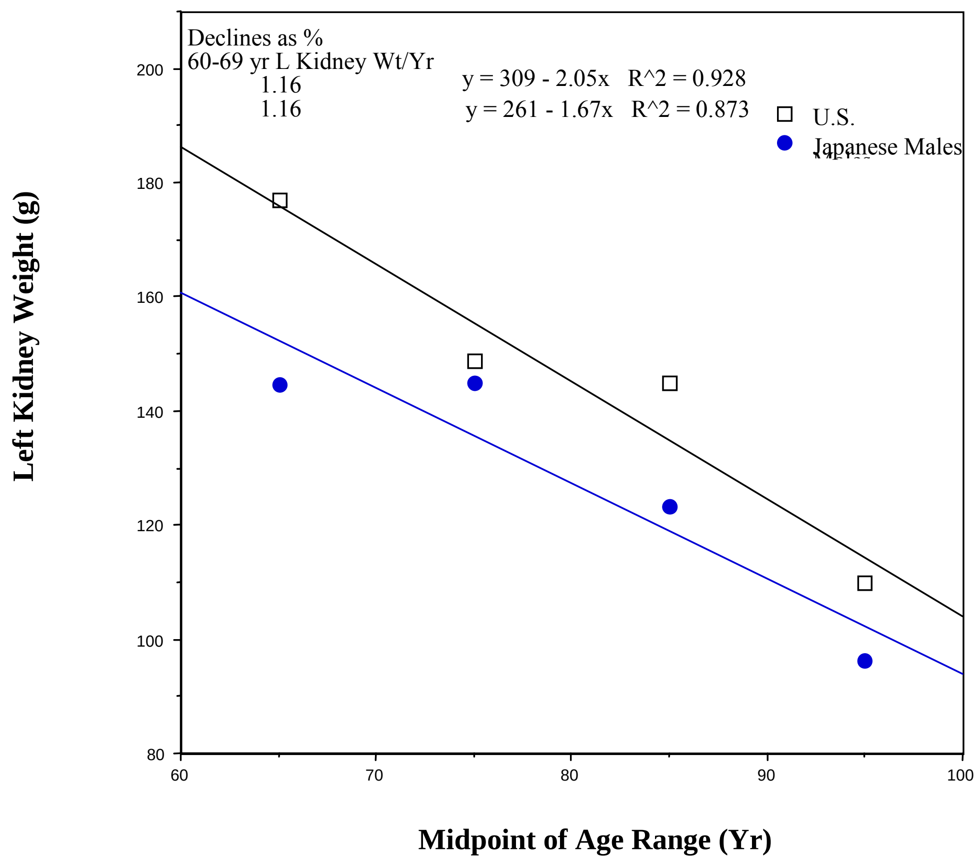


Figure 8: Comparison of Age-Related Declines in Brain Weight with Age in Male U.S. vs Japanese Autopsy Subjects. Data from Calloway et al. (1965) and Inoue and Otsu (1987)

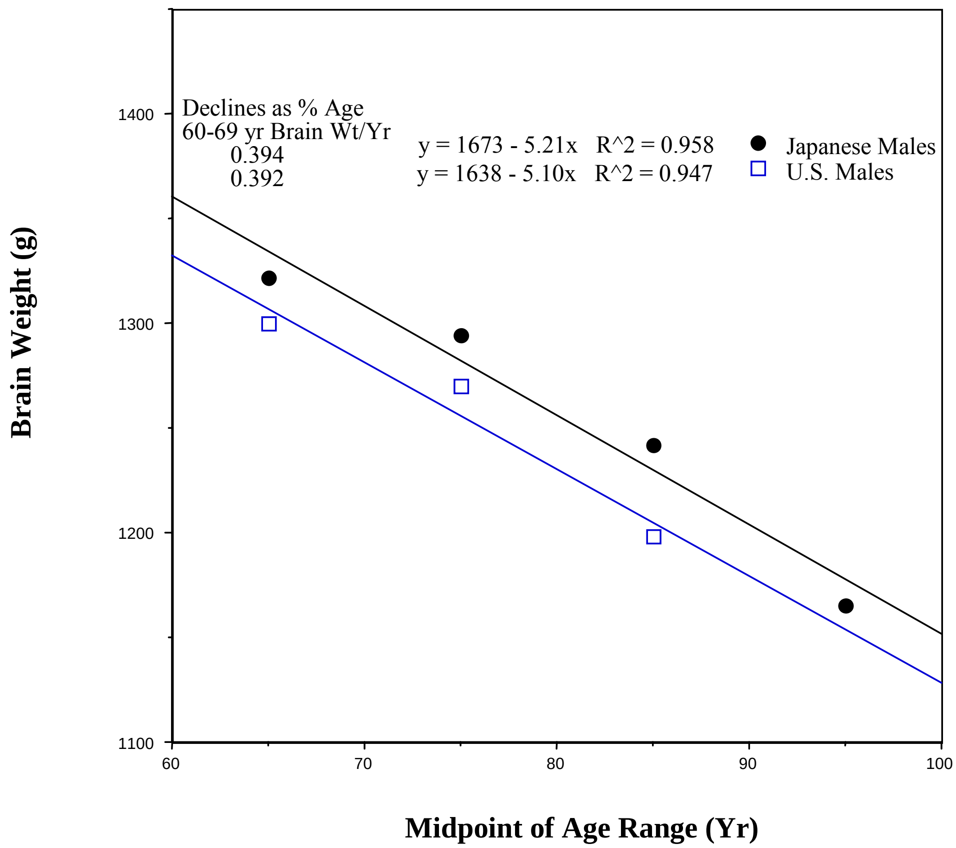


Figure 9: Comparison of Age-Related Declines in Spleen Weight with Age in Male U.S. vs Japanese Autopsy Subjects. Data from Calloway et al. (1965) and Inoue and Otsu (1987)

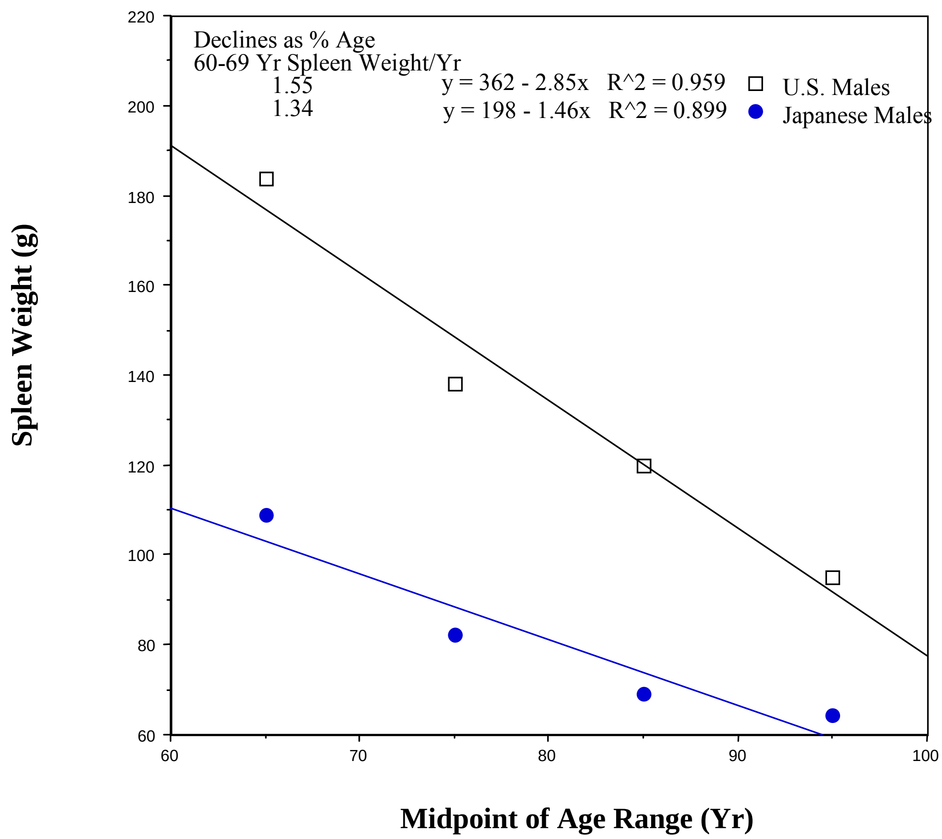


Figure 10: Normal Plot of the Distribution of Estimated Glomerular Filtration Rates for the U.S. Adult Noninstitutionalized Civilian Population—Data of Coresh et al. 2003 Excluding People <15 ml/min-1.73 m^2

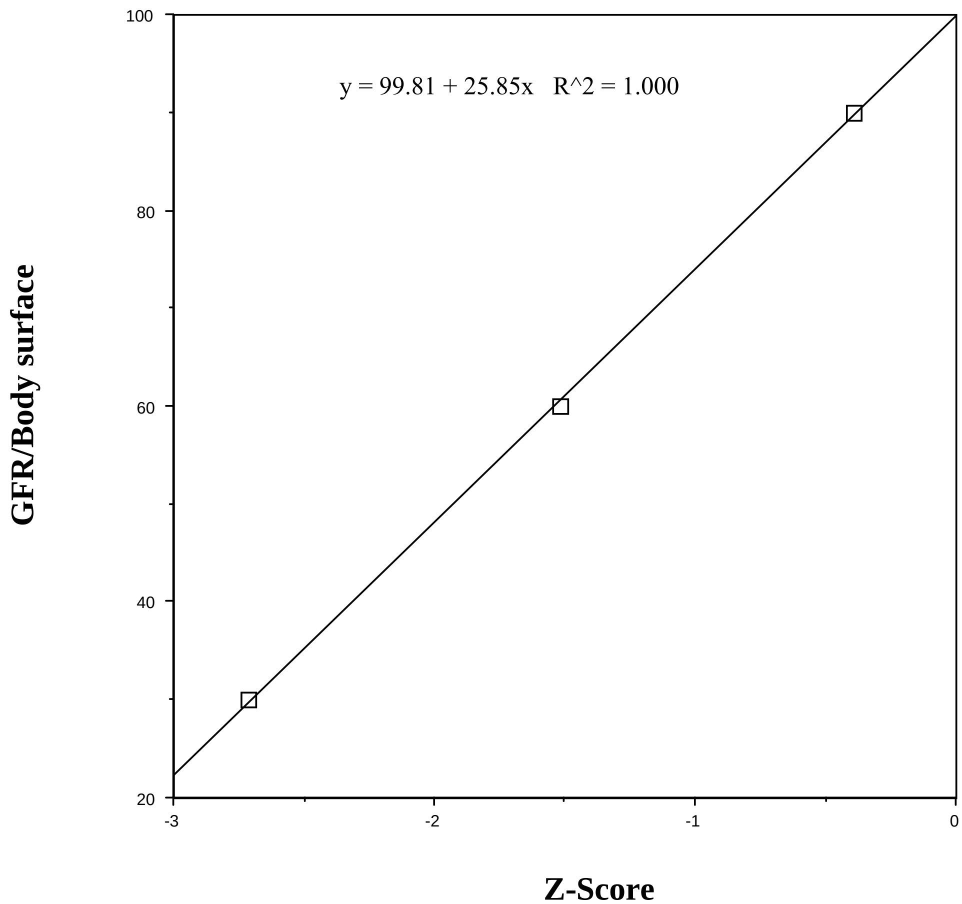


Figure 11: Normal Plot of the Distribution of Estimated Glomerular Filtration Rates for the U.S. Adult Noninstitutionalized Civilian Population—Data of Coresh et al. 2003 Including People <15 ml/min-1.73 m^2

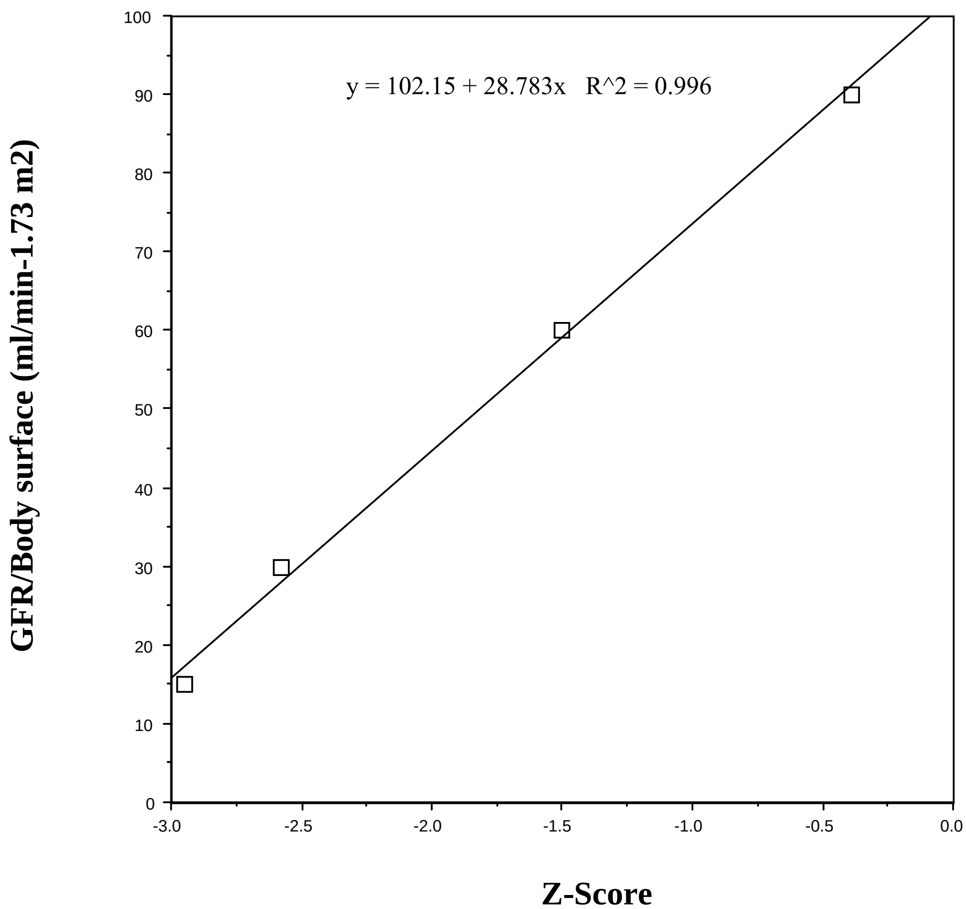


Figure 12: Lognormal Plot of the Distributions of Estimated Glomerular Filtration Rates for the U.S. Adult Noninstitutionalized Civilian Population—Data of Coresh et al. 2003 Excluding Estimated Numbers of People <15 ml/min 1.73 m^2

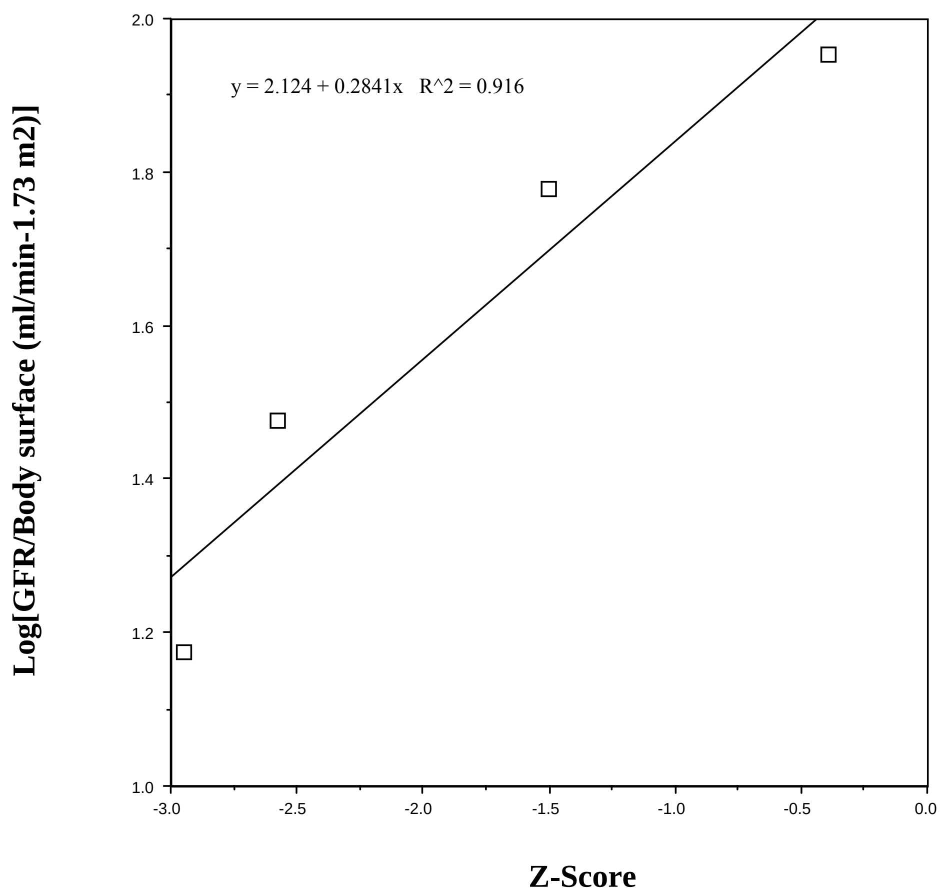


Figure 13: Lognormal Plot of the Distribution of Estimated Glomerular Filtration Rates for the U.S. Adult Noninstitutionalized Civilian Population—Data of Coresh et al. 2003 Including Estimated Numbers of People <15 ml/min 1.73 m^2

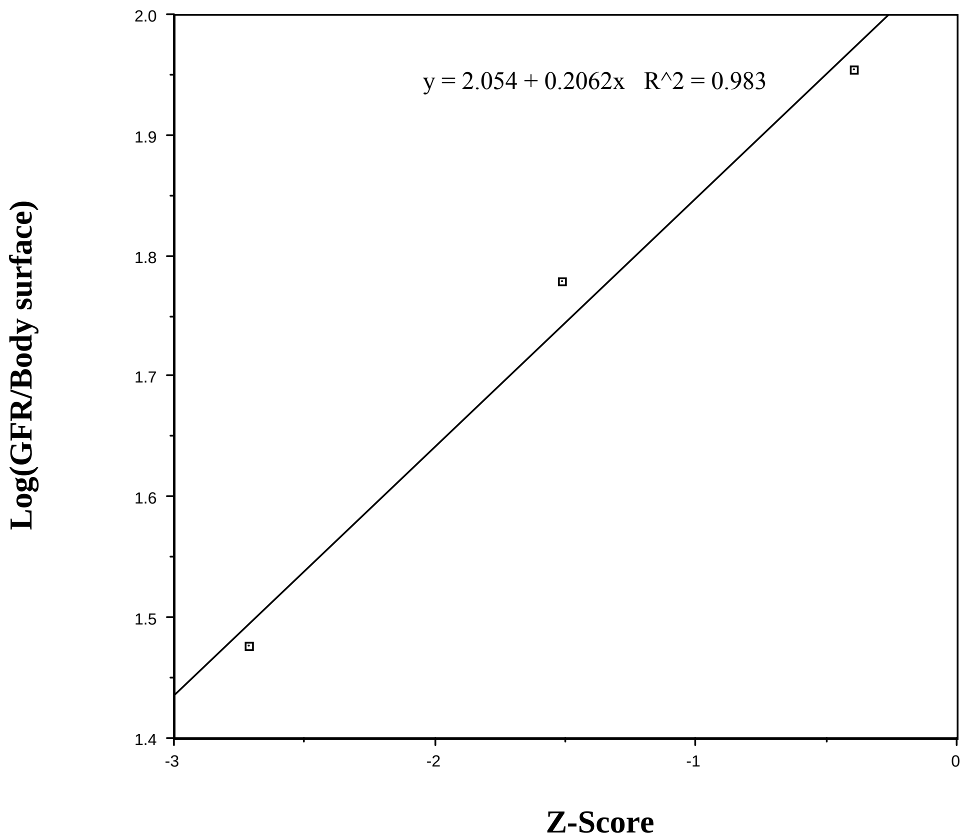


Figure 14: Age-Specific Normal Plots of the Distributions of Estimated Glomerular Filtration Rates for the U.S. Adult Noninstitutionalized Civilian Population—Data of Coresh et al. 2003 After Restoring Estimated Numbers of People <15 ml/min 1.73 m²

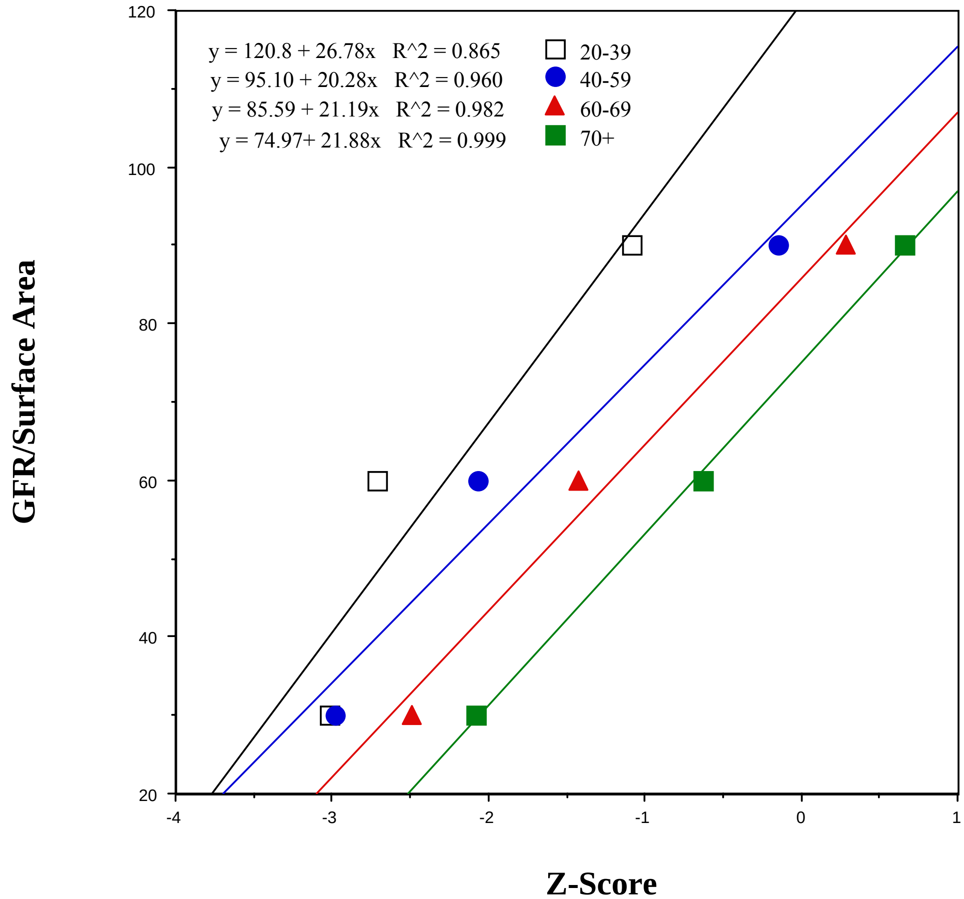


Figure 15: Age-Specific Lognormal Plots of the Distributions of Estimated Glomerular Filtration Rates for the U.S. Adult Nonistitutionalized Civilian Population—data of Coresh et al. 2003 After Restoring Estimated Numbers of People < 15 ml/min-1.73 m^2

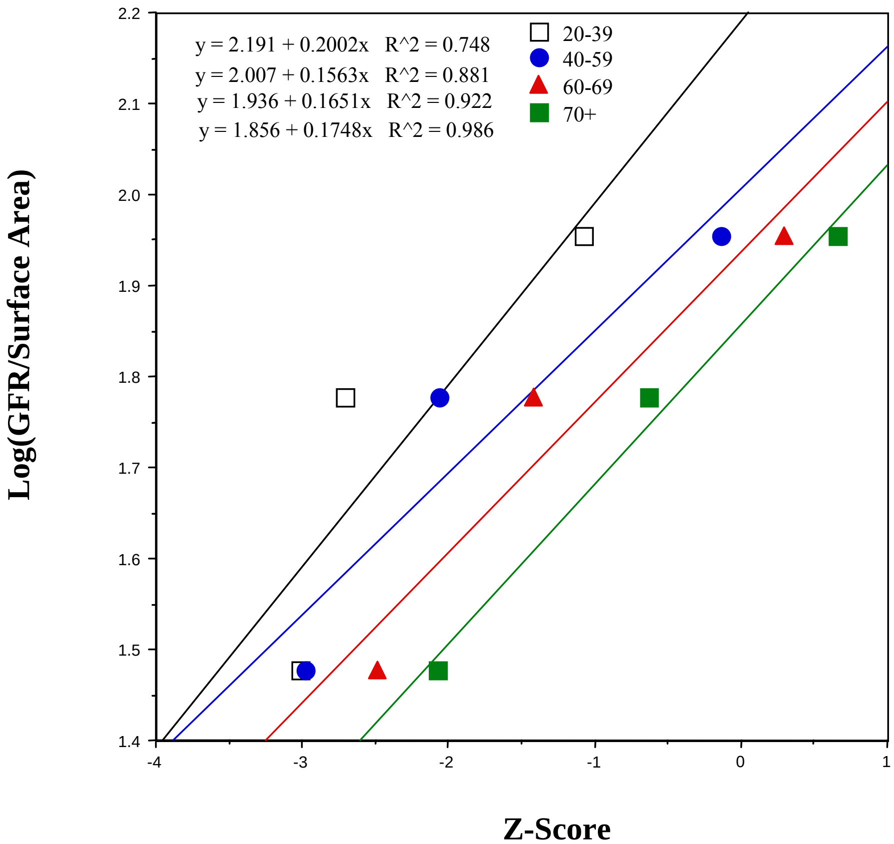


Figure 16: Normal Plots of the Population Distributions of Estimated Glomerular Filtration Rate/Body Surface Area for People With and Without Diagnosed Diabetes—Data of Coresh et al. 2003 Including Estimates of Those < 15 ml/min-1.73 m²

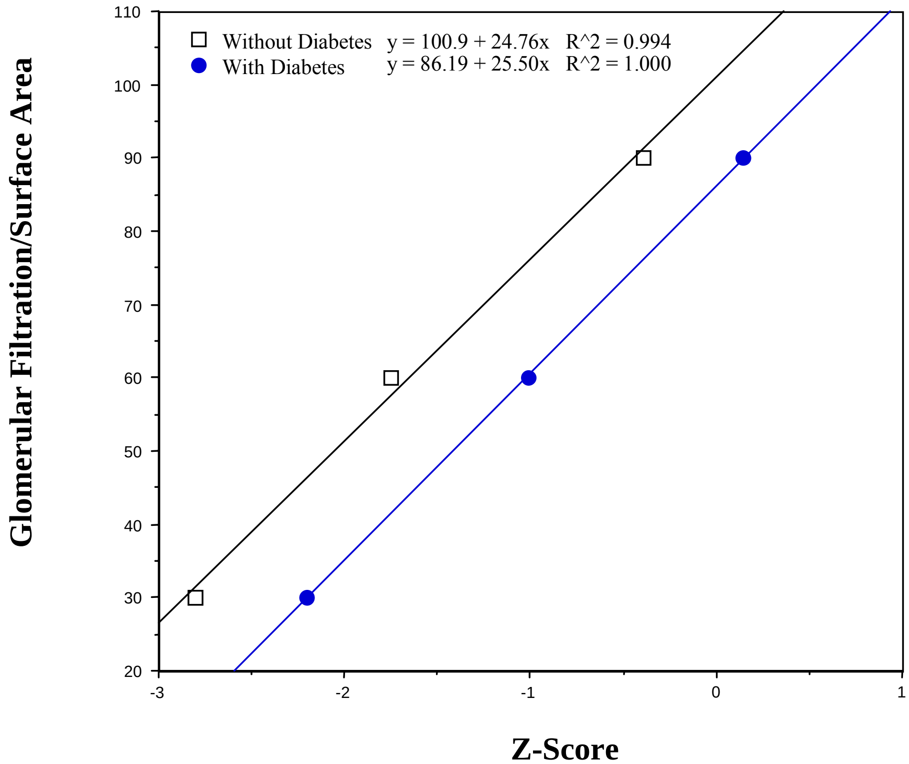


Figure 17: Normal Plots of the Population Distributions of Estimated Glomerular Filtration Rate/Body Surface Area for People by Hypertension Status - Data from Coresh et al. 2003 Excluding Those < 15 ml/min-1.73 m^2

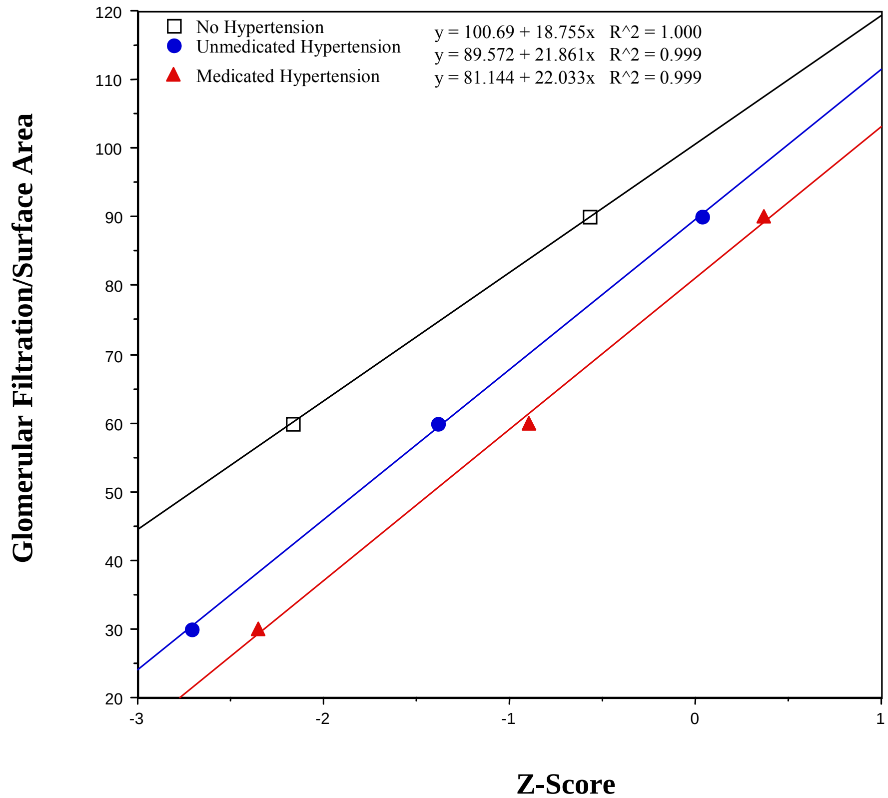


Figure 18: Normal Plots of the Population Distributions of Estimated Glomerular Filtration Rate/Body Surface Area for People by Hypertension status—Data of Coresh et al. 2003 Including those < 15 ml/min-1.73 m^2

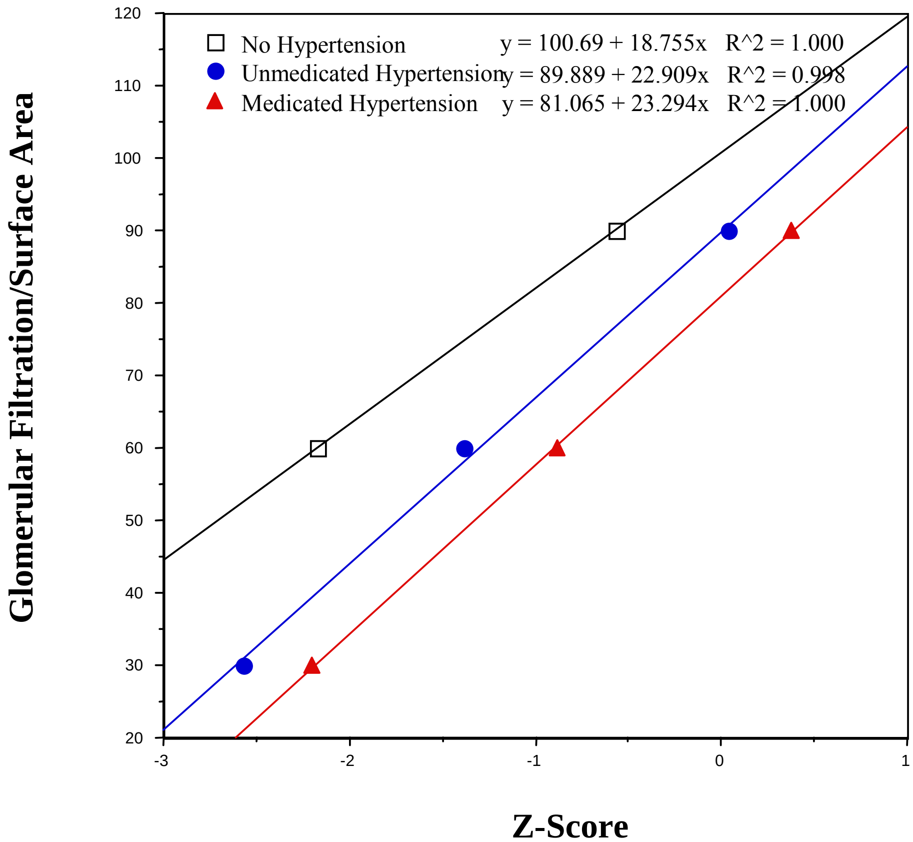


Figure 19: Normal Probability Plots of Population-Weighted NHANES 3 Body Weight Data for Older Male Age Groups

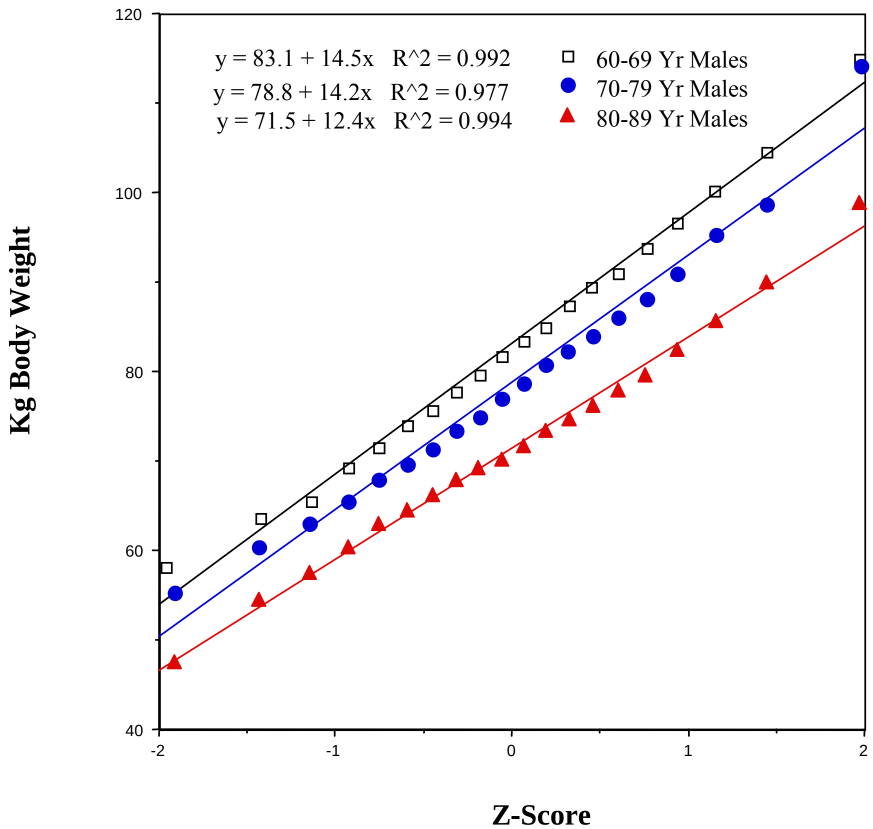


Figure 20: Normal Probability Plots of Population-Weighted NHANES 3 Body Weight Data for Older Female Age Groups

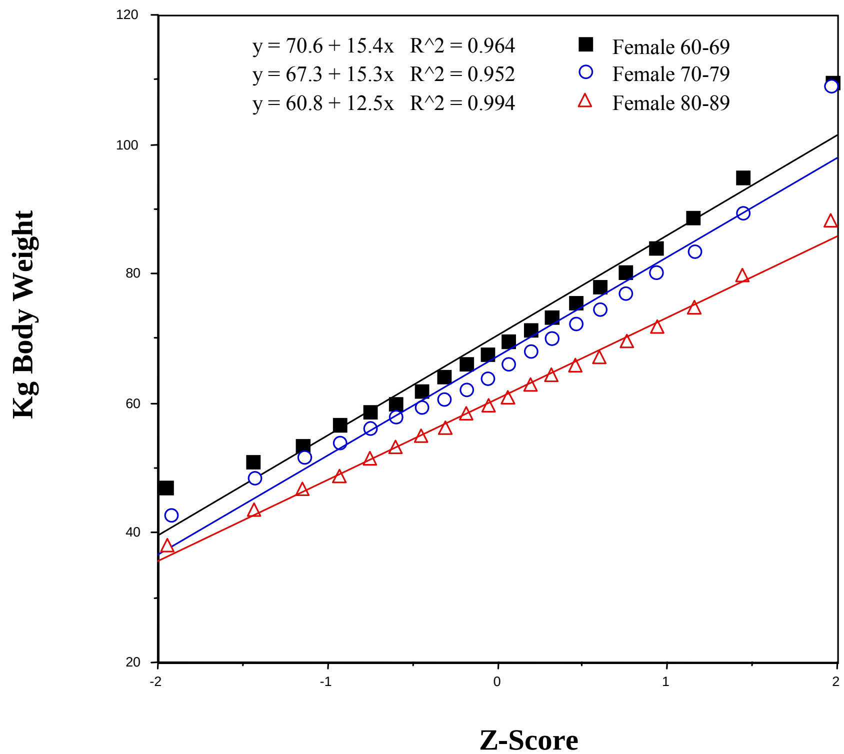


Figure 21: Lognormal Probability Plots of Population-Weighted NHANES 3 Body Weight Data for Older Male Age Groups

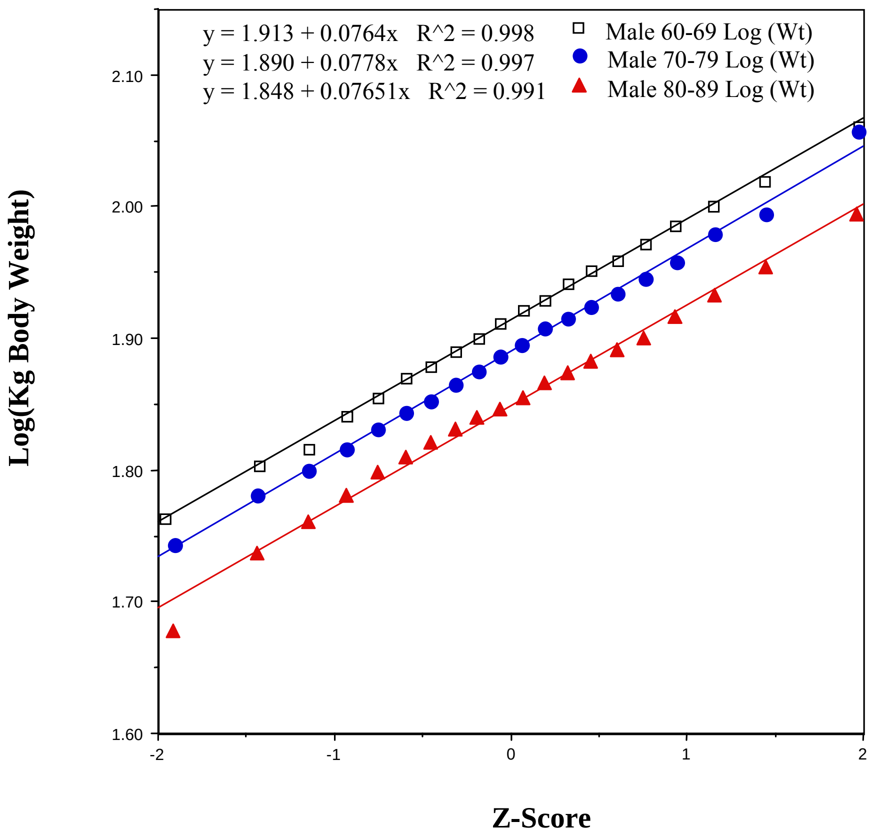


Figure 22: Lognormal Probability Plots of Population-Weighted NHANES 3 Body Weight Distributions for Older Female Age Groups

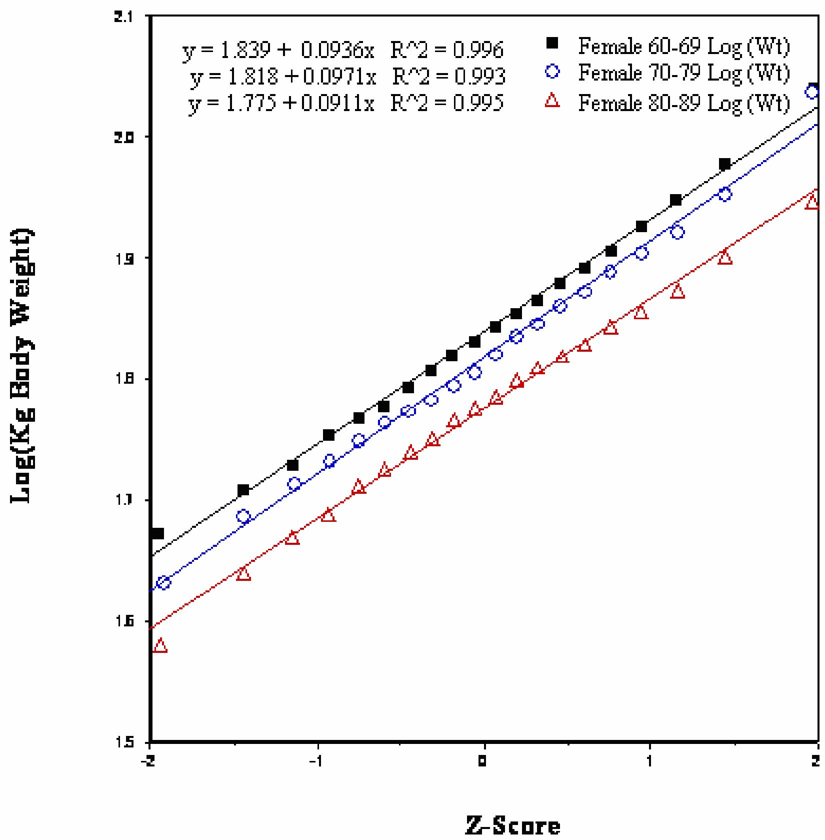


Figure 23: Normal Probability Plots of Fat Mass Percentile Distribution Data of Kyle et al. (2001) for Older Male Age Groups

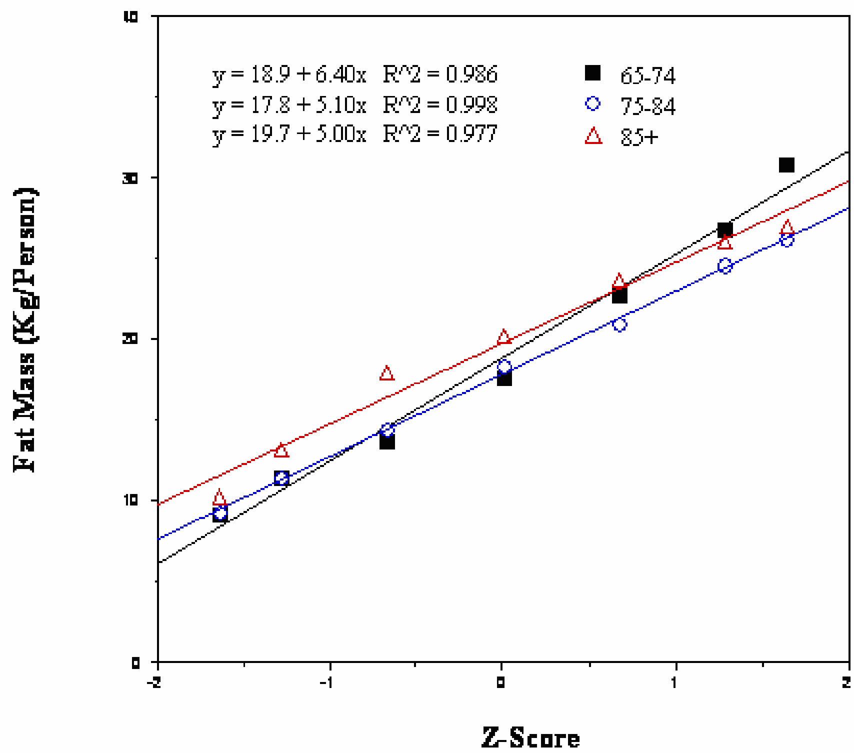


Figure 24: Normal Probability Plots of Fat Mass Percentile Distribution Data of Kyle et al. (2001) for Older Female Age Groups

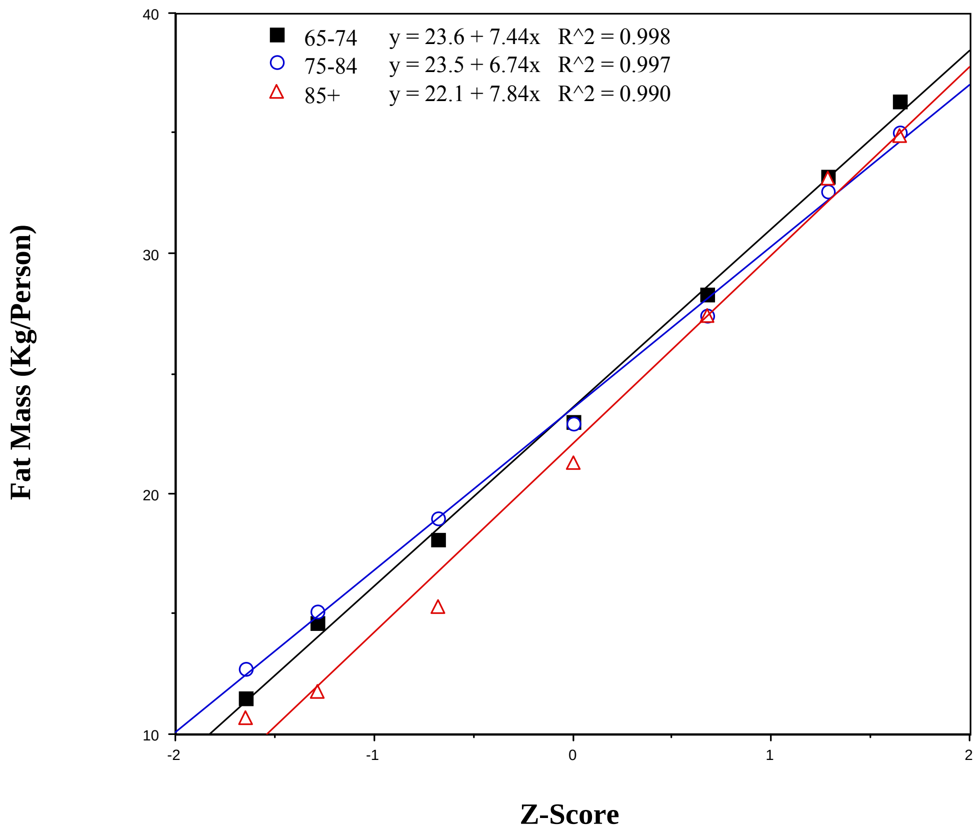


Figure 25: Normal Probability Plots of Fat Mass Percentile Distribution Data of Kyle et al. (2001) for Younger Male Age Groups

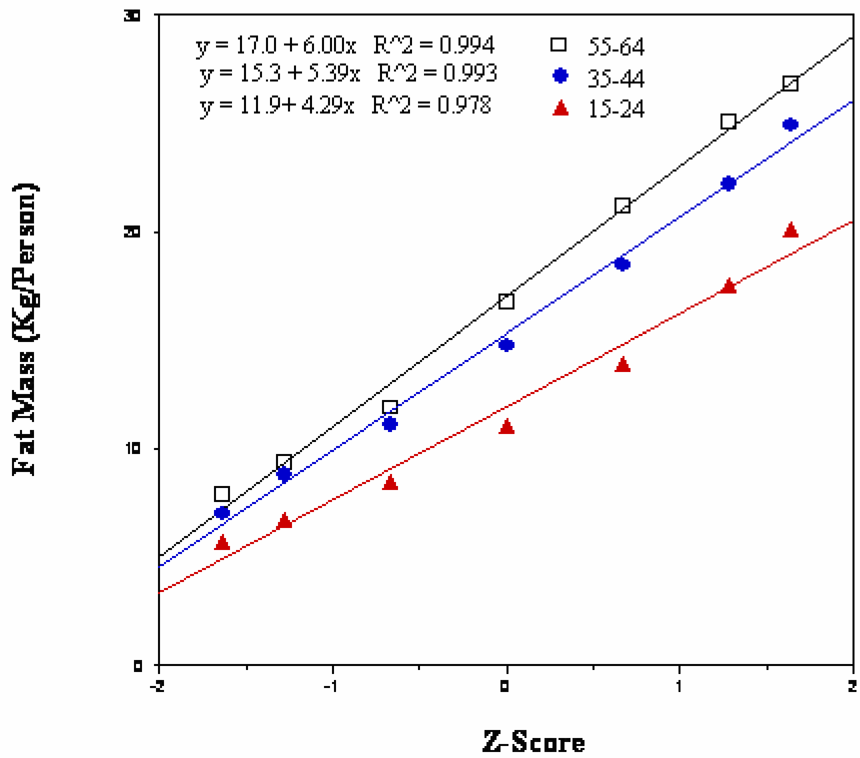


Figure 26: Normal Probability Plots of Fat Mass Percentile Distribution Data of Kyle et al. (2001) for Younger Female Age Groups

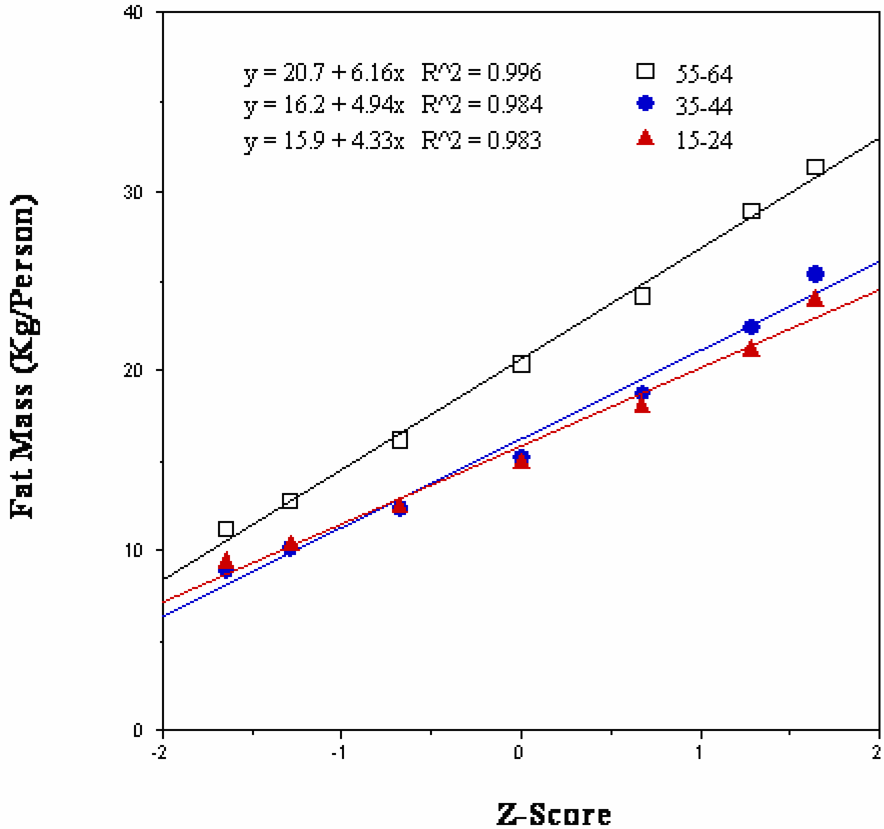


Figure 27: Normal Plots of Fat Mass Index Percentile Data for Ambulatory Swiss Men—Data of Schultz et al. (2002)

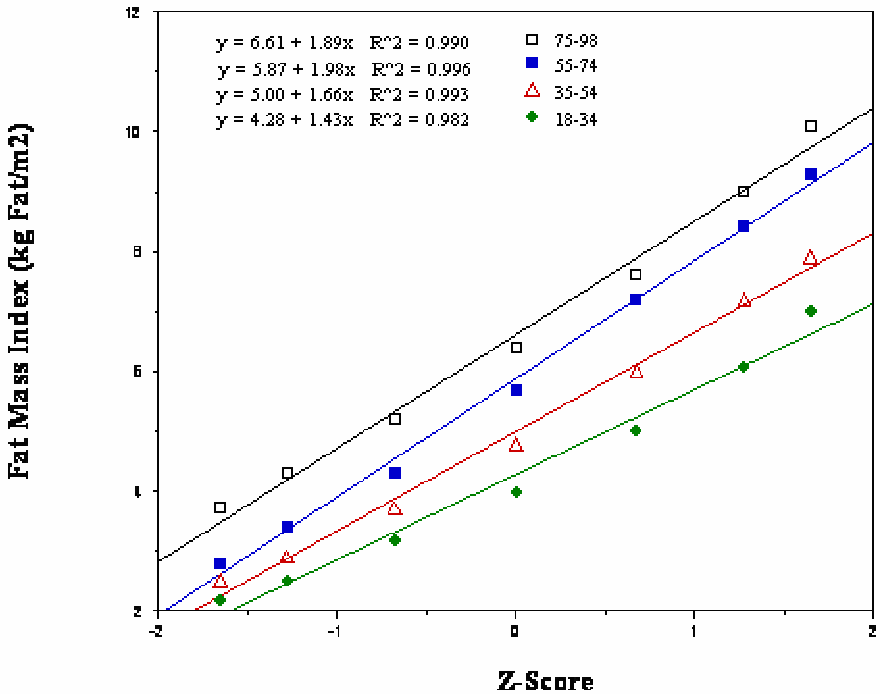
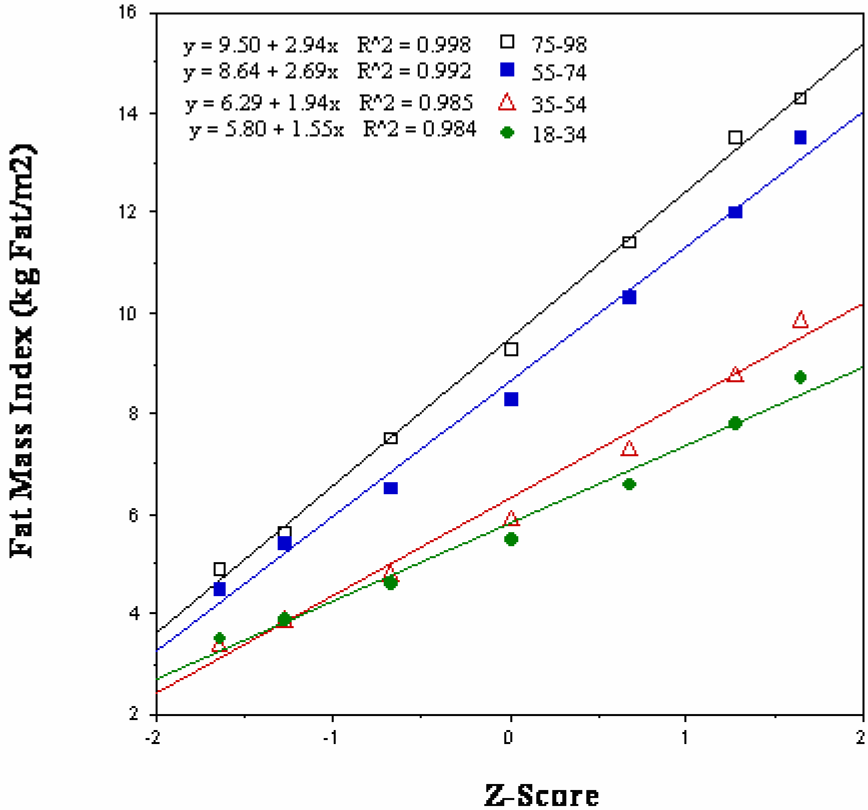


Figure 28: Normal Plots of Fat Mass Index Percentile Data for Ambulatory Swiss Women—Data of Schultz et al. (2002)



PEER REVIEWER COMMENTS FROM

KYRIAKOS MARKIDES

Markides, Kyriakos S.

Here are some comments relevant to the charge questions that I feel comfortable with. As you know I am a social/behavioral scientist with considerable experience win aging but with no experience on exposures. I am particularly knowledgeable about minority populations especially Hispanics and I hope to contribute in this area.

We know that more than 60% of older people in the US do not engage in physical activity and that 31% are sedentary. Men are more active than women. Older members of minority groups such as African Americans and Hispanics are less active. This is a problem partly because of high rates of diabetes in these populations. Physical activity is highly important for diabetics in order to prevent complications and other negative outcomes.

Older people who exercise are more likely to participate in aerobic exercise than in strength training. Walking is by far the most popular activity. Older Black and Hispanics are less likely to engage in walking partly because they are more likely to live in unsafe environments, i.e., poor or non-existent sidewalks as well as high crime rates.

Other correlates of low participation in physical activity include smoking and poor health, older age, rural residence, living alone, and lower educational attainment.

With respect to environmental factors it is known that living neighborhoods with heavy traffic and trash/litter is associated with lower levels of physical activity.

Promising areas for future research include more attention to developing programs and interventions especially for minority populations. Other people to be targeted include caregivers, the recently widowed, and the recently retired.

Sarcopenia, or loss of muscle mass with aging is very common. Muscle loss is related to declines in physical activity among other factors. It appears that exercise can increase muscle mass even in frail and very old people. Also beneficial is weight gain from energy and protein intake. Other interventions such as anabolic hormone therapy have yielded mixed results.

Obesity in middle-age or earlier is known to be a significant risk factor for a variety of health problems in old age, including diabetes, cardiovascular disease, and disability. Obesity among older people appear to be less detrimental to their health, partly because tbese older people are selected "survivors". Obesity (BMI 30+) does not appear to be related to mortality in older people and may be protective of mortality in African Americans and Hispanics. At the same time, obesity appears to be related to subsequent disability. More needs to be known regarding the mechanisms linking obesity to health outcomes.

There is no doubt that "biological age" may be a better marker of aging than chronological age. Unfortunately it is not clear what a good measure of biological age is. Geriatricians would argue that 'old age' nowadays begins at age 75. So conventional categorizations of people into ages 65 to 74, 75 to 74, and 85 and above remain useful.

Behavioral or medical factors that correlate with these age groups include comorbidities, disability rates, and cognitive declines, the latter being very prevalent among parsons aged 85 and over. And rates of 'frailty' are highly associated with age as measured above. Yet frailty is not necessarily due to aging. Major causes such as sarcopenia, atherosclerosis, malnutrition, and to a more limited extent, cognitive impairment can be prevented or reversed with appropriate interventions. I am not certain whether frail vs 'healthy' older adults should be considered separately in the context of exposure/risk assessment.

PEER REVIEWER COMMENTS FROM

KEITH MEYER

1.1 What information is available on activity patterns and behaviors in the aging? Specifically, what is known regarding: 1) where older adults spend their time; 2) what activities older adults are engaged in; 3) what research is currently being conducted in these areas; and 4) what are the data gaps and research needs?	**In general, less time is spent outside ones dwelling and less time is spent exercising.** **1. Where do older adults spend their time?** Compared to younger adults, more time is spent indoors, but there is considerable interindividual variation that is influenced by weather/climate and physiologic condition. Older adults are much less likely to be exposed to industry/commercial environments due to retirement. **2. What activities do older adults engage in?** This appears to vary quite a bit by socioeconomic status and health status **3. What research is being conducted concerning activity patterns and behaviors in the aging?** Current research seems to focus on exercise and conditioning. **4. What are the data gaps and research needs?**
1.2 What information is available on age-related changes in physiological parameters such as inhalation rate, body composition, and body weight? What research is currently being conducted in these areas? What are the data gaps and research needs?	**Inhalation rate:** It is unclear what this term refers to. Data on respiration and changes in respiratory function generally focus on static pulmonary function tests (e.g. spirometry values, lung volumes, diffusion capacity). As age advances, chest wall compliance decreases and lung compliance tends to increase, with the net result being a decline in both forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). With advancing age, breaths/minute tend to increase. However, I am not aware of any specific studies that have measured "inhalation rate" for older compared to younger individuals. A study on rats suggests that old rats challenged with ozone inhalation display more of a rapid, shallow breathing pattern than young rats, which suggests that exposure to irritants might do the same to older humans and increase the "inhalation rate." Confounding factors include an age-associated decline in mucociliary clearance as well as a decline in alveolar-capillary clearance. **Body composition and weight:** Weight and body mass index (BMI) will vary according to the health status and activities (sedentary vs. active, regular exercise vs. lack of exercise, etc.) of individuals, but there is progressive decline in muscle

	mass (and muscle strength and contraction velocity) as part of the aging process. Similarly, bone mineral density decreases. Progressive increases in body fat and decreases in fat-free mass have been observed, and individuals who are more sedentary or disabled tend to have greater decline in fat-free mass. Additionally, weight and BMI measurements may not track very well with fat-free mass. Increased physical activity tends to prevent loss of fat-free mass and increases in BMI that are associated with aging. **Current research:** Other key physiological parameters that change with aging and can be assessed via various measurements include: d.) cardiovascular function: e.) cataract formation f.) respiratory function including respiratory muscle strength **Data gaps and research needs:**
1.3 What information is available on diet and medication use in the aging population? What research is currently being conducted in these areas? What are the data gaps and research needs?	**Diet and medication use in the elderly:** Again, many factors affect diet, including health status, dental situation, and socioeconomic status. Elderly individuals frequently take many medications, although compliance may often be an issue. **Current research:** **Data gaps and research needs:**
2.1 In conducting exposure/risk assessments, is it appropriate to divide the aging population into age groups or "bins?" If so, what factors should be considered in determining these groups?	Considerable variation exists within this population. Exposure to environmental substances via inhalation and ingestion will vary greatly according to: g) health status (i.e. free-living in community, chronic health problems confined to indoors, institutionalized, the presence of significant organ dysfunction due to chronic disease such as COPD or congestive heart failure) h) physical activity i) dietary habits (i.e. quality and consistency of foods, amounts and types of liquids consumed) j) outdoor vs. indoor dwelling k) geographic location (i.e. inner city, areas of the U.S. with poorer air quality, residence near emitters of atmospheric contaminants (incinerator, coal-fired power plants, smelter, heavy/constant vehicular traffic area, etc.)

	l) tobacco addiction Therefore, it is difficult to segregate the aging population into distinct groups on the basis of specific parameters. **Factors to consider:** Health status, exposure to atmospheric contaminants in ambient air
2.2 Are there behavioral changes that occur in the aging which lend themselves to characterization using age group categories?	Physical activity and outdoor activities decrease with advancing age, for one.
2.3 Are there physiological changes that occur in the aging which lend themselves to characterization using age group categories?	5) Loss of muscle mass is reflected by measuring grip strength (or respiratory muscle force) 6) Bone density, muscle mass, and fat-free mass can be measured via DEXA scanning 7) Cardiovascular function could be characterized by measuring systemic blood pressure or via 6-minute walk test distance 8) Respiratory function can be assessed via spirometry
2.4 In the context of exposure/risk assessment among the aging, how should "frailty" be defined? Should "frail" older adults be considered separately from "healthy" older adults?	**Definition of frailty:** If an aged individual is frail, does that place them at greater risk of adverse consequences from environmental exposures? I think that this is the case for inhaled substances such as PM or ozone. However, differentiating frail elderly from non-frail elderly is not necessarily straightforward, and a definition remains elusive. Furthermore, the presence of comorbid conditions or a disability complicate this differentiation. The best correlate of frailty appears to be musculoskeletal function, and measurement of strength and mobility (e.g. geriatric status scale, Barthel index, or PULSES profile) may represent the best way to differentiate frail from non-frail elderly. Fried et al. (J Gerontol 2001;56A:M146-M156) defined frailty as a syndrome with ≥3 of 5 criteria (unintentional weight loss of ≥10 lbs over previous year, self-reported exhaustion, weak grip strength, slow walking speed, and low physical activity), and this definition appeared to correlate reasonably with identifying frailty in community-dwelling older adults. Should "frail" older adults be considered separately from "healthy" older adults?

	I am not sure that this should be done for all exposures. However, one could argue that certain exposures such as respiratory exposure to airborne and respired particular (which have been shown to have significant effects on cardiovascular, respiratory, and cerebrovascular function in the elderly) may have a much more profound effect on frail elderly individuals.
3.1 Who are the potential users of an Exposure Factors Handbook for the Aging?	Government agencies, municipalities (especially those with air quality problems), toxicologists, epidemiologists
3.2 How would an Exposure Factors Handbook for the Aging be applied in conducting exposure and risk assessments?	I defer to other panel members, but I think that this handbook could be particularly helpful for identifying and gauging inhalational exposure risks.
3.3 What factors should be included?	Exposures via inhalation of ambient air should be a prominent component (e.g. exposure to particulates such as PM 2.5, ozone, oxides of nitrogen, sulfur compounds)
3.4 How should the data be presented in order to be most beneficial to exposure assessors?	I defer to other panel members

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PEER REVIEWER COMMENTS FROM

PAUL PRICE

Response to Charge Questions
As required under Task Order # 4996.001,
Versar Job Number: 104700.4996.001.01
Peer Involvement Workshop for Development of an
Exposure Factors Handbook for the Aging

General Comments

The Exposure Factors Handbook and the Child-Specific Exposure Factors Handbook are useful resources for a wide range of exposure and risk assessment activities. The development of an Exposure Factors Handbook for the elderly will be a useful additional resource for exposure and risk assessors.

Accurate characterization of exposures to the aged is important in the evaluation of chemical exposures. For certain sources of exposure, the aged individuals will be the sub-population with the highest long-term exposures. For example, exposures to local point sources of air emissions, the aged make up a disproportionate share of the "most exposed" individuals. The reasons for this are that mobility tends to decline with age and the fraction of time spent at home increases with age. Thus, the individuals with the longest duration exposures will be the aged. In addition, certain activities such as gardening and golf are known to be associated with aged populations. Accurate and well-organized information on the aged will improve assessments of exposures to these sources.

Response to Charge Questions

1. **Age-related changes in activity patterns, behavior, and physiology may have a significant impact on exposures to environmental chemicals. In order to better characterize these changes, please discuss the following:**

   What information is available on activity patterns and behaviors in the aging? Specifically, what is known regarding: 1) where older adults spend their time, and 2) what activities older adults are engaged in? What research is currently being conducted in these areas? What are the data gaps and research needs?

The impression from the literature provided by EPA is that there are extensive data available on the activity patterns of the aged; however, these data have not always been appropriately analyzed. For example, activity pattern data reported in Leech et al. (2002) have not been analyzed for differences between adults <65 and adults >65. In addition, many surveys have collected data on activity levels but only reported data in terms of a total activity "score". Such studies imply that considerable additional data were collected but not reported. EPA should take steps to obtain access to the raw data from such surveys and reanalyze the results for the relevant exposure factors.

Finally, there is a need to define when changes in the capacity for physical activity will preclude or change exposure-related behaviors. In many instances the magnitude of exposure will be directly related to the ability to perform moderate or high levels of effort over extended periods of time (painting the interior of a large house, swimming for several hours in a pool, etc.) that are not within the capacity of certain portions of the *aged* population.

What information is available on age-related changes in physiological parameters such as inhalation rate, body composition, and body weight? What research is currently being conducted in these areas? What are the data gaps and research needs?

The impression from the literature provided, is that there are numerous *studies of* age-related changes in physiology; however, the data have not been analyzed for the change in the physiological factors related to exposure assessment. EPA should seek to obtain the raw data from these studies and include them in the handbook. In addition, EPA may well wish to organize the available data to develop qualitative guidance on what is know about the ageing process in each of the organ systems and the implications for exposure assessment. Special emphasis should be given to the organ systems relevant to intake and uptake (the GI tract, lungs, and skin) and metabolism and excretion (liver and kidneys).

What information is available on diet and medication use in the aging population? What research is currently being conducted in these areas? What are the data gaps and research needs?

No comment.

2. **Individuals over the age of 65 are often divided into categories based solely on chronological age, such as young-old (65-74 years), old-old *(75-84* years), and oldest-old (85 years and older). However, the aging population is a highly heterogeneous group, and age-related changes in behavior and physiological function may be more a function of biological age than chronological age. This may be an important distinction in evaluating risk of exposure to environmental chemicals as changes in behavior and physiology directly affect exposure as well as the resulting internal dose. With this in mind, please discuss the following questions:**

In conducting exposure/risk assessments, is it appropriate to divide the aging population into age groups or "bins?" If so, what factors should be considered in determining these groups?

The goal of creating groups or bins is to identify objective criteria for grouping individuals that produce groups having significantly different values for one or more exposure factors. There are a number of problems with defining bins that are solely based on age.

In the past, EPA held workshops on developing age bins for children (Guidance on Selecting the Appropriate Age Groups for Assessing Childhood Exposures to Environmental Contaminants" ERG 2003, and Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants EPA/630/P-03/003F November 2005). The conclusion from these efforts is that age base binning of exposure factors is a valuable approach but that there were a number of difficulties with using age as the only criteria for bins.

- Growth rates in children vary with the individual (some children going through growth spurts at earlier ages some at later ages). Grouping data into age bins smears out this variation and leads to under estimates of the rate of changes in weight in specific individuals.
- Changes in different behaviors follow different patterns with age. Bins that make sense on the basis of diet may be very misleading when it comes to factors such as mobility or activity patterns. Thus, the use of a single set of age bins can introduce errors into screening risk assessments.

These problems present a greater challenge to the idea of using age to characterize factors among the aged than for characterizing factors among children. This suggests that age may have less value as the basis for binning the aged than for binning children. Some of the reasons why age is less of a predictor of exposure factors in the aged include the following.

First, growth is biologically determined aging is not. In order to predict the changes in an individual all that is required is knowledge of the status of the child at a point in time. That is to say, the characteristics of the child (age, developmental status, height, and weight) determine what the status of the child will be in the future (3-5 year olds have higher weights than 1-2 year olds).

This occurs because growth follows a consistent sequence of events dictated by the goal of producing an adult capable of reproducing.

In contrast, aging has no goal and is characterized by the highly variable progressive failure of different biological systems over time. Thus, there is much less of a regular biological pattern to aging (Zeleznik, 2003). This absence of a regular pattern (other than menopause) makes the aging population much more variable.

Second, as indicated in many of the papers provided to the reviewers, physiological factors in the aged are influenced by individual personal behavior. Many physiological factors are influenced by diet and exercise. Third, as discussed by a number of papers provided to the reviewers, the U.S. aged population is dynamic. Public health and societal changes at all ages of U.S. society result in constant secular changes in aged individuals. Examples of this are the changes in life expectancy, body weights, and rates of specific diseases in individuals' of specific ages over the last 50 years.

Because of these factors, EPA should thoroughly explore the option of defining bins in terms of categories other than age that may more accurately reflect differences in individuals' exposure factors.

A specific concern is that the tails of inter individual distributions of age bins in the elderly will be the same. This could happen because a fraction of individuals in each age group will be in a "frail" condition and because becoming frail radically changes behavior and physiology. An example of the problems this could cause in a screening exposure assessment is as follows.

Consider an exposure to a specific source (pesticide on a golf course) and a sensitive individual (low blood clearance rate). Using age bins the upper tail on golfing and urinary output for "young old" could result in the combination of data on behavior that come from a "non-frail" individual and clearance rates that come from "frail" individuals.

Are there behavioral changes that occur in the aging which lend themselves to characterization using age group categories?

Not to my knowledge.

Age related changes in behavior in the elderly provide less support for age bins than changes in children. In the case of children, the transition from preschool to school changed a wide range of exposure factors such as activity patterns and diet. This suggests separating the pre and post 5 year olds into different bins. In the aged, there are no transitions that occurred at fixed ages. The largest change in activity patterns in the aged is from full time employment to post full time employment.

This change will clearly affect individuals' activity patterns. However, while mandatory school attendance is generally required at age five, retirement is not tied to a specific age. Thus, a 58 year old who is retired may have an activity pattern that is more in common with a 68-year-old retiree than a 68-year-old employed individual.

Are there physiological changes that occur in the aging which lend themselves to characterization using age group categories?

Not to my knowledge.

Age related changes in physiology in the elderly provide less support for age bins than changes in children. As discussed in many of the papers, biological age in the aged can differ markedly from the calendar age (a 65 year old may have a biological age of 55). This is not true for children (15 year olds never have biological ages of 5).

In addition, the aged (and to a lesser extent all adults) fall into physiological states (fragility and morbid obesity) which radically change behavior and physiology but are not strictly age related.

This suggests that for the aged it may be important to define these as separate populations perhaps treating them in the same way as "asthmatics" and not lump them into age bins.

In the context of exposure/risk assessment among the aging, how should "frailty" be defined? Should "frail" older adults be considered separately from "healthy" older adults?

Frailty should be looked at in terms of both the physiological changes (energy expenditures) and the ability to perform exposure related behaviors (jogging, gardening, golfing, swimming, etc.). As indicted above, categories should be defined in ways that group populations in the elderly into relatively homogeneous groups that distinctly differ from one another. The value of age in defining such groups is not clear.

Yes, the aged "non-frail" should be separated from the aged "frail". Similar consideration should be given to separately evaluating the morbidly obese.

3. **It has been proposed that an Exposure Factors Handbook for Aging populations be developed to provide more detailed information on factors used in assessing exposure among this potentially sensitive subpopulation. Before initiating this project, the following issues must be considered:**
   - **Who are the potential users of an Exposure Factors Handbook for the Aging?**

Assessments of a wide number of exposure sources will benefit from the handbook. Specifically assessments of exposures to components of products used by the aged or are used in environments where the aged are present.

How would an Exposure Factors Handbook for the Aging be applied in conducting exposure and risk assessments?

No comment.

. **What factors should be included?**

The factors in the handbook should include those factors used by PBPK modeling. These include tissue and compartment volumes and fractional blood flows. The other handbooks should be revised to include these factors as well.

- **How should the data be presented in order to be most beneficial to exposure assessors?**

Access to the raw data is critical. Summary tables and summary descriptors are useful but the handbook should have a way to link back to the raw data on which the information is based. This can be done by setting up data bases that can be downloaded from the EPA web page or providing direct links to web pages where the data can be downloaded. EPA should give high priority to obtaining supporting date for all studies listed in the handbook. Wherever possible, EPA should require that data from publicly funded on studies be made publicly available.

EPA should develop both a paper copy of the handbook and an internet version. The FDA has established guidance on data submissions made electronically that would be a useful goal in the web-based version of the handbook. FDA has required that the raw data that supports any number be accessible within three mouse "clicks". Ideally, no more than three mouse clicks on a summary value in the handbook should bring the user to an electronic version the raw data of each study.

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Zeleznik, J. (2003). Normative aging of the respiratory system. *Clin. Geriatr. Med.* ***19,*** **1-**1

PEER REVIEWER COMMENTS FROM

DEBORAH RIEBE

Deborah Riebe, Ph.D.

University of Rhode Island

Aging Workshop Specific Charge Question 1

Section 1.1. Data from the Baltimore Longitudinal Study of Aging (BSLA; Verbrugge et al., 1996) showed that older men and women spent the greatest amount of time in obligatory activities and passive leisure and the least amount of time on committed activities and active leisure. There is diversity across people, but the data suggests less diversity among older adults as the repertoire of activities is narrowed. Another study of individuals aged 70-105 years showed that 17% of the day is spent watching television, 15% is spent completing IADLs, and 12% is spent on other leisure activities. This study also showed that 80% of waking hours were spent inside the home (Horgas et al., 1998). However, similar to BLSA, there was substantial variety in how older adults spent their time.

The National Health Interview Survey reports that in 2003-2004, 27.5% of adults aged 65-74 years, 19.4% of adults aged 75-84 years, and 8.4% of adults over 85 participate in regular leisure time activity (defined as engaging in at least 30 minutes of light-moderate intensity physical activity 5 days per week or engaging in vigorous intensity physical activity for at least 20 minutes, 3 times per week). Despite overwhelming evidence that regular physical activity decreases the risk of some chronic diseases, may relieve symptoms of depression, enhances overall quality of life, and helps to maintain independent living, the number of older adults participating has remained stagnant for the past 10 years. It should be noted that, like many surveys, physical activity is measured by self-report. Over-reporting physical activity is common in all age groups.

Physical activity decreases with age. In the SENIOR project, approximately 62 percent of adults aged 65-74 reported participating in regular exercise using stages of change (ie., in action or maintenance), compares to 51% of those aged 75-84 years and 43% of those over 85 years. This was confirmed by the Yale Physical Activity Survey (YPAS) summary score (37.8, 33.6, 27.2 for ages 65 – 74, 75-84 and 85+, respectively) and energy expenditure scores (7580, 6048, 5472 kcal/week for ages 65 – 74, 75-84 and 85+, respectively). Again, physical activity and stage of change were measured by self-report, so the possibility of response and recall bias are inherent (Riebe et al., 2005). However, this study also measured physical function using the Up-and-Go test and found that physical function was poorer with increasing age and as stage moved from maintenance to precontemplation, suggesting self-reported stage of change reflected habitual activity. Manuscripts containing longitudinal outcomes are currently under review and the SENIOR II project is being conducted with the same subjects.

More research using objective measures of exercise and physical activity are needed to quantify the overall amount of physical activity older adults participate in. The use of accelerometers and other portable measuring devices will help to expand our knowledge in this area, but these devices still need to be refined.

Section 1.2. The prevalence of obesity is increasing in all age groups, including older persons. Using the customary BMI of 30.0 kg/m2 or more to define obesity, the prevalence of obesity has increased to more than 22% in persons aged 60-69 years and 15% of persons aged 70 years and older in 2000 (Mokdad, 2001). The prevalence further increased tin 2001, to 25% and 17%, respectively (Mokdad, 2003). It should be noted that data on individuals over the age of 80 was obtained for the first time in NHANES III. In this age group, the prevalence of obesity was low compared to younger age groups in the NHANES database (8.0% for males and 15.1% in females).

Large population studies show that mean body weight and BMI increase during most of adult life and reach peak values at 50-59 years of age in both men and women. The National

Health Examination Survey (NHES I) and the National Health and Nutrition Examination Surveys (NHANES) from 1960 to 1994 demonstrated that weight gain occurs at different times in life for men and women. The increase in obesity in men, over this 34 year period, ranged from a 25% increase in 20- to 29-year-olds to a 115% increase in 50- to 59-year olds. For women, the largest increase in obesity, 139%, occurred in 20- to 29-year olds, with less increase in obesity seen in older age groups.

After the age of 60 years, mean body weight and BMI tend to decrease. The lower prevalence rates in this group may again be due to selective survival or to the higher frequency of diseases in this age group. The observation of lower weight in cross-sectional studies should be interpreted with caution, because obese persons have higher mortality rates at younger ages (Manson, 1995). Therefore, premature mortality of obese young and middle-aged adults would tend to decrease mean body weight and BMI in older adults.

Much attention has been paid to the unusual or sudden loss of body weight in the elderly, as it is the single best predictor for risk of death in older adults (World Health Organization, 1998). Involuntary weight loss occurs in approximately 13% of those over the age of 65 years (Morley, 1996) Precipitous weight loss is unexplained in 24% of cases but is associated with the onset of cancer (16%) depression (18%), gastrointestinal ailments (11%), an overactive thyroid gland (9%), neurological problems (7%) and the effects of or responses to medication (9%) (Thompson and Morris, 1991).

The shape of the association between BMI and mortality in the elderly has been shown to be U-shaped or J-shaped. Other studies have found a positive linear association, a negative linear association, or no association. However, "Obesity in Older Adults: Technical Review and Position Statement of the American Society for Nutrition and NASSO, The Obesity Society" states that collectively, data suggests that the absolute mortality risk associates with increased BMI increases up to 75 years of age and that the health complications due to obesity increase linearly with increasing BMI until the age of 75.

Obesity is associated with metabolic abnormalities, arthritis, pulmonary function abnormalities, urinary incontinence and cancer in older adults. Obesity has important functional implications in older adults, as it can exasperate the age-related decline in physical function. Mobility is markedly diminished in overweight and obese older adults compared to lean elderly adults (Galanos, 1994; Launer, 1994). Villareal et al (2004) demonstrated that obesity is an important cause of frailty in older persons. This study also showed that obesity is also associated with significant impairment in health-related quality of life.

BMI is a common measure used in large population studies due to its simplicity and ease of use. Caution must be used when interpreting BMI data. Height and weight are often self-reported. It is common for weight to be underestimated, especially in the obese population. An overestimation of height is also possible in the older population as they may not realize the decreases in height with age. Further, age related changes in body composition may result in the misclassification of some individuals; most notably those with high levels muscle (ex., body builders) and those with low levels of lean tissue and high levels of fat (older adults). BMI is not a direct measure of fatness and does not reflect fat patterning. In fact a large waist circumference was found to be a better predictor of all-cause mortality in non-smokers than a high BMI (Seidell & Visscher, 2000). Cross-sectional data from the Baltimore Longitudinal Study of Aging showed increases in body weight and adiposity in both men and women up through middle age. In men, the decrease in body weight after the fifth decade was primarily due to a decrease in muscle mass. In very old men in their eighties and nineties, both muscle and fat mass decrease thus resulting in a large decrease in body weight. Women increased body weight through the sixth decade, primarily due to a continuous increase in fat mass. Although the increase in the fat mass was the major influence on body weight, muscle mass also declined. Both men and women lose muscle mass after age 25 but also put on fat during the next 3 decades, so there may be little change in BMI. Measures of BMI should not be discounted, just interpreted with caution.

Aging is associated with considerable changes in body composition. After age 20-30 years fat free mass (FFM) steadily declines in both men and women, whereas fat mass increases. The loss of FFM is primarily attributable to muscle atrophy. Because most of our knowledge about aging effects on FFM is derived from cross-sectional studies, and few have included individuals over the age of 70, the loss of FFM with age is not well documented. Loses of 5% per decade in men and 2.5% per decade in women have been reported. However, one longitudinal study of older adults (age 60 at baseline) showed a 2% loss in men and no change in women over a 10-year period. What is clear is that sarcopenia is highly prevalent in older adults, with as high as 40% in individuals more than 80 years of age, and is strongly associated with weakness, disability, and morbidity (Baumgartner, 2000).

Older adults at greatest risk for disability are those who are simultaneously sarcopenic and obese, and the prevalence of this combination of low muscle mass and excess fat increases form 2% in those 60 to 69 years of age to 10% in those more that 80 years old (Baumgartner, 2000). With obesity rates on the rise, this combination may also become more prevalent.

Regular exercise is important in the maintenance of optimal body composition with aging. Recent reviews of aerobic training in older adults reported that aerobic training was effective in reducing weight and FM in 20 or 22 studies and there was an apparent dose-response relationship. The fat loss occurred preferentially in the central regions of the body. Aerobic training was not effective for increasing muscle mass (Fiatarone Singh, 1998; Toth et al., 1999). Resistance exercise was also effective in decreasing body fat in older individuals participating in 12 to 52 weeks of training. At the same time, most studies show an increase in FFM. Further, energy needs during resistance training increased by about 15% in healthy elderly people, suggesting an increase in food intake may be necessary to stabilize weight.

Aging Workshop Specific Charge Question 2

Section 2.1. The simplest way to describe age is to categorize it. Age categories are divisions of chronological age that are used for discussion and classification in gerontological research. An inconsistency in gerontological research is that is that age categories have not been standardized. In physical activity research, studies have defined older adults as age 50+, 55+, 60+ and 65+. This makes it difficult to interpret research or to compare "old" subjects to "young" subjects when there has been no consistency at to what old means. Divisions of older adulthood have been created so that the growing number of older adults (the young-old), by virtue of remaining active, have continued behaving as young and middle-aged people.

Categorizing by age alone has flaws. There are many individual differences which arise from many sources including genetics, lifestyle, disease, gender, differential rates of aging of physiological systems, culture, education, socioeconomic status, and compensatory behaviors. For example, people differ in the extent to which they experience disease because each unique genotype supports different types and frequencies of pathologies, different vulnerabilities to certain environmental challenges and different level of immune function effectiveness.

Individual differences can be better represented by using biological (functional) age rather than chronological age. Biological aging is a group of processes that cause the eventual breakdown of mammalian homeostasis with the passage of time and is expresses as a progressive decrease in viability and an increase in vulnerability with the passage of time (Spiraduso, 2005). The non-scientific approach of simple observation demonstrates that individuals differ dramatically in the way that they age. Someone may seem "young for their age" while someone else might seem much older than their peers. Essentially, biological age has been used to describe the individual differences seen on variables within chronological age groups. It can be defined as the difference between an individual's score on a biomarker of aging and the mean score for their chronological age cohort. However, to quantify human biological aging, a battery of biomarkers would need to be identified and measured. It is likely that there is a variety of mechanisms that cause aging. Even if all the contributors to biological aging were identified, measuring them to for the purpose of categorizing older adults would likely be impossible.

Categorizing individuals for any reason is primarily done for the purposes of convenience and generalizing research results. Making conclusions based on data that includes individuals placed into categories is useful. It helps researchers understand "the norm" and in most cases appropriate decisions based on norms can be made. It is up to those who use research results to understand that there will always be individual differences.

Section 2.2. Physical inactivity is one of the strongest predictors of physical disability among older persons (Carlson & Harshman, 1999). Several longitudinal studies reveal that regular exercise extends longevity and reduces the risk of disability in later life (Ferruccci et al., 1999; Leveille et al., 1999; Wu, Leu & Li, 1999). Many of the age-related physiologic decrements older adults experience are not inevitable. Cardiorespiratory fitness, muscular strength and endurance, power, flexibility, balance, and body composition has a role in preserving physical function, reducing the risk of chronic disease, and averting disability with age.

Adults become less physically active with age so that by 75 years of age, 54% of men and 66% of women report no physical activity, defined as the lack of participation in any leisure-time physical activity for as long as ten minutes. Individuals who remain active into older adulthood will have lower levels of disability compared to those who are sedentary.

Participation in exercise is a behavior that has been widely investigated. Much attention has paid to determining the mediators and moderators of physical activity participation. Older adults exercise for different reasons compared to young adults. Further they identify different barriers to exercise, such as fear of falling. While the fear of falling is not considered as important in the young-old population, it becomes considerable more important as an individual ages and becomes more vulnerable to falls.

When examining population means, participation in physical activity, an important health behavior, differs among older age groups. As age increases, physical activity decreases. Mediators and moderators may change as a person ages, but much more research needs to be done in this area. Using age groups categories to describe physical activity participation is possible. However, there are many individual differences. Masters athletes train and compete into very old age, although empirical evidence suggests that even masters competitors reduce both the frequency and intensity with which they train. An individual who has exercised throughout life will still experience age-related declines in fitness, performance, and physiological parameters. However, because they built such high levels of fitness when they were young, various physiological measures remain at much higher levels compared to the average older adult. For example, a distance runner might have such a high VO_2max that despite the age related decline of approximately 1% per year (which may accelerate after age 65), they may have better cardiorespiratory fitness compared to some sedentary younger and middle-aged individuals. If strength training is done throughout life, strength levels peak at significantly higher levels compared to untrained individuals and decrements in muscle strength across time occur at a slower rate. Strength-trained individuals have a better functional ability, reduced risk for falls and lower the development of some chronic diseases such as osteoporosis.

When considering exercise behavior, age group categories are convenient to use and represent "the norm". Age group categories will never be accurate to represent exercise behavior for the entire older adult population. Further, the type of exercise that one participates in (moderate versus vigorous; aerobic training versus resistance training) further differentiate between individuals.

Section 2.3. Most physiological systems undergo decrements with age. To a degree, these decrements in physiology are reflected in decreases in health-related physical fitness, functional fitness and motor skill performance (ex., speed, power, hand-eye coordination). A precedent has been set to categorize physical performance in older adults. The Senior Fitness Test (Rikli and Jones, 2001) is a widely used measure of functional fitness for individuals over the age of 60. It includes assessment of lower body strength, upper body strength, aerobic endurance, lower body flexibility, upper body flexibility and agility and dynamic balance. Both normative and criterion-referenced standards are available for ages 60-94, broken into 5-year age categories. The criterion performance scores are particularly helpful as an older adult can determine if they are above average, in the normal range, or below average. The level at which an individual is at risk for loss of functional mobility has also been determined. A female aged 70-74 years is in the normal range for the 6-minute walk test if they walk between 490 and 610 yards compares to 290 to 450 yards for a woman aged 90-94. Functional disability begins when a woman cannot walk more than 350 yards in six minutes. Although these norms are available and quite useful, in both research and practice, there will continue to be individual differences. A frail 74-year old will score well below average while a high-functioning 90-year-old may be far above the norm for her age group.

Age categories are widely used in determining health-related and/or functional fitness levels in age groups. Again, norms will not represent individual differences – those individuals above or below what is expected.

Aging Workshop Specific Charge Question 3

Section 3.1. Although my expertise is not in exposure, after reviewing articles on the reference list, I would like to make one comment. Any individual who prescribes exercise to older adults (exercise physiologists, nutritionists, health care workers) would benefit from information in the Exposure Factors Handbook for Aging Populations. Exercise physiologists closely consider environmental challenges with exercise, but most of the work is done in the areas of heat, cold, and altitude. An individual may be more exposed to toxins in the environment during exercise as breathing rate increases. Functional capacity decreases with age, and sedentary older adults may have very low functional capacities. Therefore, even every day activities such as slow walking become quite vigorous when considered relative to the maximal capacity. Although this is well understood in the exercise science community, the increased exposure to environmental toxins is not likely something they would think about.

PEER REVIEWER COMMENTS FROM

ALAN H. STERN

Pre-meeting Comments

Alan H. Stern, Dr.P.H., DABT

Both in my understanding and in my professional experience with the existing U.S.EPA's Exposure Factors Handbook((EFH), the primary use of that document is to provide default and generic information on specific exposure assessment parameters (e.g., body weight, ventilation rate, pool use) that can be used in the in quantitative descriptions of exposure scenarios that are, themselves, used in the development of generic risk assessment standards and guidelines. Toxicokinetic, toxicodynamic and physiologic parameters, as well as general health status can be important determinants of risk. These can generally be characterized as parameters of sensitivity or susceptibility. As such, however, they are generally not relevant parameters for the exposure assessment portion of risk assessments. An obvious exception to this is when health status and more specifically, the ability to change locations, and participate in various activities may be a determinant in the construction of representative and generic exposure scenarios. However, judging by the papers made available for the workshop and, to a lesser extent, by the charge questions, it may be that exposure factors are being conflated with factors predictive of sensitivity and susceptibility. Thus, for example, frailty is relevant to exposure assessment only to the extent that it either increases or limits contact with a contaminant in the environment, or the ability to translate an external dose into an internal dose.

From my standpoint as a user of the EFH, and as an advocate for the appropriate use of distributional information in exposure assessment, I think that a major issue in the construction of an Exposure Factors Handbook for the Ageing is the apparent large variability in common exposure parameters. This is not necessarily surprising as overall health status can vary greatly even within a relatively narrow age range among the relatively aged. A large variability per se, may not be an impediment to the useful quantitative description of an exposure parameter as long as the variability describes a more or less regular distribution. It is not even necessary for that distribution to be a close approximation of a common parametric distribution (e.g., lognormal). However, among the papers provided, I see evidence that the variability in the ageing population is not necessarily regular, but is, in some cases, highly bi-or polymodal, probably as a result of the parallel existence of physically robust and physically frail individuals of the same sex and age. Therefore, from my perspective, I think that a major challenge for the construction of an EFH for the ageing will be how to represent and summarize such data on a way that makes it both accessible and useful for distributional assessment. Can, for instance, stratifying the population produce more or less regular distributions? A related issue, is how would such information be used to construct exposure scenarios that reflect the most sensitive sub-groups in a population. Would, for instance, the frail sub-population be more at less at risk from an outdoor source of a contaminant, given that they are likely to spend less time outdoors?

PEER REVIEWER COMMENTS FROM

LAUREN ZEISE

AGING WORKSHOP CHARGE QUESTIONS

1. Age-related changes in activity patterns, behavior, and physiology may have a significant impact on exposures to environmental chemicals. In order to better characterize these changes, please discuss the following:

- What information is available on activity patterns and behaviors in the aging? Specifically, what is known regarding: 1) where older adults spend their time, and 2) what activities older adults are engaged in? What research is currently being conducted in these areas? What are the data gaps and research needs?

The workshop organizers provided several references that addressed activity patterns and behavior in the aging. This included references showing fraction of time spend in different activities in nursing homes and assisted living. The one data gap I would add that has not been discussed is activities leading to exposures to dust.

- What information is available on age-related changes in physiological parameters such as inhalation rate, body composition, and body weight? What research is currently being conducted in these areas? What are the data gaps and research needs?

There were papers in the background materials provided to the committee that addressed body weight

  - o *Drewnowski and Evans:*
    - *More body fat*
    - *Reduced muscle mass*
    - *Glucose tolerance related to inactivity and age*
    - *Altered thirst, hunger and -- adoption of monotonous diet changes in gustatory and olfactory function*

- What information is available on diet and medication use in the aging population? What research is currently being conducted in these areas? What are the data gaps and research needs?

From the NHANES dietary food survey data one can get diet intake information at the individual level. It will include older individuals in the survey. However, because of the design of the NHANES and CSFII surveys do not provide information on individuals food intake over time. As Drewnowski and Evans (2001) point out, because of altered sensations of thirst, hunger and satiety, many aged adopt a monotonous diet. Thus some of the approaches that have been used for example by the pesticide program to randomize individual food intakes may not lead to good estimates of the higher intake levels. On the other hand private firms conduct market surveys to determine eating habits. There is a wide range of foods for which market survey data is collected; food producers *also commission surveys and the EPA could potentially commission surveys on food types of concern. The aging population has been a focus of some food surveys because they represent a large and growing market for food producers. The NPD Food Group, a commercial market survey group has focused on the elderly. See for example, the article at http://www.npdinsights.com/archives/october2005/cover_story.html NPD surveys and surveys by other commercial groups provide much better information on longitudinal eating habits for certain food than does NHANES.*

Certain dietary supplements can also pose a health concern. Lead in calcium supplements has been an issue. In fish oil persistent lipophilic contaminants can concentrate. A small survey of supplement intake found that 51% of the elderly population took supplements, with fish oil being one of them. The extent that the elderly may consume supplements that contain environmental pollutants should be evaluated. For those supplements such as fish oil that are consumed by the elderly and have can have high levels of environmental contaminants, information on the range of intake and if possible distributional values would be of value to have in a handbook for this age group.

We tend to think about the young as being a vulnerable group for effects to lead and track behaviors and diet leading to exposure. Lead along with cadmium is of concern to the aging population especially given issues of remobilization from bone and changes in fat stores during aging and diseases that occur during aging. Intake information on foods and other products that may contain high levels for example of lead, cadmium, and lipophilic compounds should be targets for data collection and research so they can be included in a handbook.

2. Individuals over the age of 65 are often divided into categories based solely on chronological age, such as young-old (65-74 years), old-old (75-84 years), and oldest-old (85 years and older). However, the aging population is a highly heterogeneous group, and age-related changes in behavior and physiological function may be more a function of biological age than chronological age. This may be an important distinction in evaluating risk of exposure to environmental chemicals as changes in behavior and physiology directly affect exposure as well as the resulting internal dose. With this in mind, please discuss the following questions:

- In conducting exposure/risk assessments, is it appropriate to divide the aging population into age groups or "bins?" If so, what factors should be considered in determining these groups?

Binning is appropriate, the question is whether it should be by age, other features, or a mix. Factor to consider in determining these groups:

- o *How well does the distinguisher (e.g., age) enable the differentiation among exposures?*

- *Can the distinguisher enable significantly better understanding of high vs common exposure levels? Does it provide the basis for elucidating the tails of the distribution – e.g., middle vs 85, 90, 95, 97.5, 99, 99.9%-tiles?*
- *To what extent are data available to identify the exposure parameter in question (e.g., inhalation rate) for the distinguisher?*
- *At what cost and to what extent can research address gaps in knowledge if that distinguisher is used?*
- *Exposure tables should support scenario risk assessment approaches. For parameters for which some special groups within the elderly population (e.g., frail) are linked to "high end" exposure that are linked to special characteristics of functionality a different treatment should be pursued to support the risk assessment. Studies should be sought out to identify at least central tendency and upper end values for those special groups so they can be adequately addressed in relevant risk assessments.*
- *Possible groups to consider – menopause, frailty*

- Are there behavioral changes that occur in the aging which lend themselves to characterization using age group categories?
    - *Within the older population, there are behavioral changes (e.g., related to Alzheimer's disease) that increase with age. It may be preferable to focus on the populations with different behavioral characteristics that may result in higher end exposure than to try to capture these in general age categories.*
- Are there physiological changes that occur in the aging which lend themselves to characterization using age group categories?
    - *There is a general decline in certain physiological characteristics with age. However within an age group there can be greater variability in parameters linked to these physiological characteristic than the variability in central tendency values across age groups.*
- In the context of exposure/risk assessment among the aging, how should "frailty" be defined? Should "frail" older adults be considered separately from "healthy" older adults?
    - *For certain parameters there appear to be relatively large differences that depend on whether the older adult is frail or functionally impaired or not, for example physical activity, affects food consumption, body fat, muscle mass, BMI, water consumption. Other categories may turn out to be important, for example menopause.*

3. It has been proposed that an Exposure Factors Handbook for Aging populations be developed to provide more detailed information on factors used in assessing exposure among this potentially sensitive subpopulation. Before initiating this project, the following issues must be considered:

- Who are the potential users of an Exposure Factors Handbook for the Aging?
    - *Those that do site specific risk assessments*
    - *Those that develop standards and other regulatory guidance (e.g., drinking water)*
    - *Those that characterize dose response relationships to the extent the handbook provides useful parameters.*
- How would an Exposure Factors Handbook for the Aging be applied in conducting exposure and risk assessments?

  The Handbook would provide supplementary information on the aging population that could support the same kind of analysis that the existing Exposure Factors Handbook does, but would provide for better coverage of the aging subpopulation. It would therefore support:

    - *Scenario driven exploration of sensitive subgroups in the aging population – e.g., those frail, either living in nursing homes or at home that essentially spend 24 hours a day in the same location*
    - *populations – e.g., the individual exposure parameters can interact – the person with the large bodyweight may have lower metabolism, be more sedentary,*
    - *Microenvironments – indoor v outdoor, size of residence, 24 hr exposures*
    - *In dose response analyses, for example in looking at variability among humans using a PBPK approach, variability in body fat content and body weight can be important. In calculating cancer potency from epidemiological data the age structure of the population in the Exposure Factors Handbook can be used.*
- What factors should be included?
    - *For parameters that one would expect significant differences between older ages and those captured in the existing Exposure Factors Handbook.*
    - *Could advise on exposure modifiers – sensitivity factors - to get at changes in renal clearance, hepatic processing, blood flow, (e.g., for particle deposition - lung elasticity, ventilation rate, COPD), polypharmacy, combination of age modified physiologic and pharmacokinetic parameters. Ventilation as elimination.*
    - *Information on the correlation across time for dietary intake of certain kinds of food items. Because the elderly can be considerably more monotonous in their eating habit than other adults, some accounting for that would be useful. Random Monte*

Carlo approaches that are sometimes used in dietary exposures estimation could result in substantial mischaracterizations for some elderly who eat the same food day in and day out.

- *Outdoor/indoor – A fraction of individuals will spend virtually all their time indoors and at the same location (e.g., in nursing homes)*
- *Dust exposure could potentially be quite important for some substances (e.g., PBDEs), so exposure factors that would address behavior such as frequent hand to mouth activities in some subpopulations of the elderly.*

It is not clear where the following comment should go – it to some extent relates to the sum total of an individuals life style behavior and activity patterns. The issue relates to the concept of "background additivity" and can either be framed as an exposure issue - accumulated and concurrent exposures - or a dose response issue. The impact of any particular exposure to an agent or mixture depends on an individual's concurrent body burden of that and other exogenous and xenobiotic exposures that also can modulate the toxicological process in question, in addition to things like loss of reserve from past exposures, and predisposing genetic and other factors in the aged individual. Non-cancer dose response analyses typically do not explicitly address this issue and, unless based on vulnerable exposed human populations, implicitly do not assess contributions from background. An example of this issue for the elderly is cadmium and nephrotoxicity. The half life of cadmium is over 20 in humans and thus cadmium accumulates with age. Environmental levels of cadmium are associated with nephrotoxic effects in the aged. Lead (also a long half life), other chemicals and additional exposures to cadmium can all impact on kidney function. Both lead and cadmium have very long half lives and can be remobilized with aging, and indeed nephrotoxicity is observed and associated with relatively low concentrations of lead and cadmium. Susceptible populations include those with hypertension, diabetes and chronic kidney disease, conditions over represented in the elderly (see e.g., Muntner et al. Kidney Int. 63:1044-50, 2003; Ekong et al. Kidney Int. 70:2074-84).

- How should the data be presented in order to be most beneficial to exposure assessors?

So as not to introduce unnecessary uncertainty, when relevant parameters can be normalized by bodyweight - because they are derived from databases where data on individuals are available – they should be (e.g., drinking water intake as ml/kg-bw/day).

Where possible present data in such a way as to enable pairing of high exposure with high inherent sensitivity when they co-occur

The following points do not directly address the question but are provided as input as EPA considers approaches for improving the way it addresses risk characterizations that cover the elderly.

- *Some work is needed to determine how EPA can best give guidance regarding increased susceptibility and varied pharmacokinetic handling of environmental xenobiotics due to heavy pharmaceutical use in the elderly. Guidance is clearly needed but it is unclear whether this is best done through the exposure guidance being considered.*
- *Just as age susceptibility factors have been introduced for infant and child assessments in the EPA Supplemental Guidance for conducting cancer risk assessment, factors that could serve as default in certain circumstances could be considered for the elderly. They may pertain to exposure and be pertinent to an exposure factors handbook for the aged for example for internal chemical exposures impacted by renal clearance. Some single source for risk assessors to turn to aid systematic thinking on issues to consider and factors to entertain in conducting assessments for the aging population would be quite useful. The separation between internal and external dosimetry is to some extent artificial. A source to turn to for insights on pharmacodynamic considerations regarding susceptibility as well as pharmacokinetic and external exposure factors could be quite useful.*