

US EPA ARCHIVE DOCUMENT

EPA/630/R-00/005
December 2000

**Summary Report of the Technical Workshop on Issues
Associated with Considering Developmental Changes in
Behavior and Anatomy when Assessing Exposure to
Children**

U.S. Environmental Protection Agency
Washington, DC
July 26–27, 2000

Risk Assessment Forum

U.S. Environmental Protection Agency
Washington, DC 20460
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FOREWORD

This report presents information and materials from a peer involvement workshop organized by EPA's risk Assessment Forum. The meeting was held in Washington, DC on July 26 and 27, 2000. The meeting discussions focused on how to consider age related changes in behavior and physical development when assessing childhood exposures to environmental contaminants. These discussions are part of EPA's ongoing efforts to improve the assessment of risks to children.

The 1993 National Academy of Sciences (NAS) report "Pesticides in the Diets of Infants and Children" highlights important differences between children and adults with respect to risks posed by pesticides. Some of the principles in the NAS report provided the foundation for the Food Quality Protection Act of 1996 (FQPA) and the President's Executive Order 13045, Protection of Children from Environmental Health Risks and Safety Risk. FQPA requires the consideration of aggregate exposure to children when establishing pesticide tolerances (legal limits for residues in food). Executive Order 13045 broadens consideration of impacts on children by stating that "each Federal agency: shall ensure that its policies, programs, activities, and standards address disproportionate risks to children that result from environmental health risks or safety risks." Many of the comments the EPA received on the Proposed Guidelines for Carcinogen Risk Assessment relate to the implementation of Executive Order 13045. In response to these comments and regulatory initiatives, EPA has been investigating ways to improve Agency risk assessments for children.

An Agency workgroup convened under the auspices of the Risk Assessment Forum has been exploring children's exposure assessment issues. This workgroup has concluded that a major issue facing Agency assessors is how to consider age related changes in behavior and physiology when preparing exposure assessments for children. Children's behavior changes over time in ways that can have an important impact on exposure. Further, children's physiology changes over time in ways that can impact both their exposures and their susceptibility to certain health effects. There are two aspects to these physiological changes. First, there are anatomical changes resulting from physical growth. Second, there are changes in pharmacokinetics and pharmacodynamics which affect the absorption, distribution, excretion and effects of environmental contaminants. The Agency is examining the pharmacokinetic/pharmacodynamic changes in children through other efforts and future meetings on this topic are anticipated. The July 26 and 27, 2000 workshop focused on incorporating age related changes in behavior and anatomy into Agency exposure assessments.

BILL WOOD

EXECUTIVE SUMMARY

On July 26 to 27, 2000, the U.S. Environmental Protection Agency (EPA) sponsored a workshop to discuss issues associated with considering developmental changes in behavior and anatomy when assessing exposure to children. The workshop panel comprised 22 experts in toxicology, exposure assessment, risk assessment, and pediatrics from universities, state and federal government, industry, and medical centers.

An opening plenary session provided background on the workshop's purpose as well as EPA's activities and the availability of data regarding exposure factors for children's exposure assessment. Panelists then divided into two discussion groups—one focusing on behavioral changes during childhood and their impact on exposure to environmental contaminants, and the other focusing on anatomical and physiological changes during childhood and their impact on exposure to environmental contaminants. Each discussion group met for about 8 hours to define and characterize the important behavioral and anatomical facets of child development related to exposure, to discuss how best to incorporate scientific and medical knowledge about childhood development into the practice of exposure assessment, and to suggest what research should be conducted to fill critical data gaps and enhance child-related exposure assessment. The conclusions and recommendations developed by each group were presented in a final plenary session. Key conclusions and recommendations included the following:

- # Both groups noted the limitations inherent in using age bins to characterize developmental change during childhood. They emphasized that while development is a series of discrete events, these events occur along a number of continua. There is considerable variability about when a change begins and ends, and some behavioral patterns, once initiated, may never end. Race, ethnicity, culture, and socioeconomic factors, as well as genetics, may contribute to the variability. For these reasons, developmental change for both behavior and anatomy should ideally be characterized as distributions.
- # Bins may be useful as a guide to the development of exposure scenarios, but EPA should always keep in mind that bins are only a crude approximation of an underlying distribution. Age bins, if used uncritically during exposure assessment, could lead to significant error. Exposure assessors need to have an understanding of the biological phenomena underlying age bins.
- # Both groups offered preliminary ideas about possible bins for developmental change related to exposure. However, they emphasized that these were based on very limited discussion, working from general knowledge, and were provided only as a starting point for further work. Even after further work, research would be needed to refine and validate those bins over time.
- # Data for both behavioral and anatomical exposure factors are limited in terms of both quality and coverage. The adequacy of current data sets is highly variable, and some of the data may

not be useful because they were gathered using outdated methods or because lifestyle changes since the study was conducted make the results less relevant to today's conditions. More up-to-date data would be useful for refining distributions of critical developmental periods.

- # Despite the limitations of current data sets, more extensive use of available data on child development relative to exposure will likely greatly reduce the enormous errors currently made when such data are ignored. An age bin approach would therefore be an improvement over the status quo, however, in the longer term, the panel would prefer a distributional approach.
- # To identify and fill data gaps, EPA should first have developmental specialists in the areas of behavior and anatomy/physiology conduct an in-depth review of the literature to determine what data are available and to evaluate the data in terms of methodology, reliability, sample size, relationship to current exposure conditions, and variability. The experts felt that a considerable amount of useful information already exists, albeit somewhat dispersed, in the literature. A short-term goal could be to assemble this information to examine what we know about distributions underlying the bins that might be utilized pending development of models that can incorporate distribution.
- # A long-term project would be the development of integrated data sets (combining information about children's behavior and anatomy, their estimated exposure, their biomarkers for particular chemicals, and their health) to be used to evaluate the relative importance of different kinds of exposure in order to identify exposure pathways that appear to be associated with the most significant risks. Future research can then be focused on developing data for exposure factors that appear to have the greatest significance for risk. The long-term goal should be to develop good statistical data on distributions for behavioral and anatomical change that can account for the variability inherent in childhood development; the statistical data would be correlated with biomarkers and clinically important endpoints.
- # Any physiological data for children will be inextricably linked to toxicokinetic and toxicodynamic issues that must be taken into account when considering age bins.
- # Although the indirect exposure assessment approach can be valuable when direct data are not available, some panelists felt that direct assessments are not necessarily too expensive or too difficult to be conducted. This was thought to be feasible at least for the more prevalent toxic chemicals and for the more prevalent exposures. Such studies should incorporate information about both exposure and biomarkers of exposure.
- # Prenatal development was not discussed since it was outside the scope of the workshop, but both groups strongly recommended that EPA look closely at maternal-fetal exposure, since in utero development is such a critical and sensitive period.

- # Panelists felt that the interdisciplinary nature of the panel contributed significantly to the quality of the discussion and recommended that the agency continue to involve a broad range of specialists, including pediatric and obstetrical subspecialists, public health specialists, exposure and risk assessors, and toxicologists in further discussion about children's exposure.

1. INTRODUCTION

1.1 Workshop Purpose

The Technical Workshop on Issues Associated with Considering Developmental Changes in Behavior and Anatomy When Assessing Exposure to Children was held on July 26 and 27, 2000, in Washington, D.C. The workshop was sponsored by the U.S. Environmental Protection Agency's (EPA's) Risk Assessment Forum, which has been exploring children's exposure assessment issues. The purpose of the workshop was to discuss issues associated with considering developmental changes in behavior and anatomy when assessing children's exposure to environmental contaminants.

1.2 Workshop Participants

Panelists at the workshop consisted of 22 experts, including pediatricians, toxicologists, risk assessors, and public health professionals from industry, universities, consulting, and state and federal government agencies. Over 50 observers attended the workshop. Panelists and observers are listed in Appendices A and B, respectively.

1.3 Charge to the Panel

The complete charge to panelists is provided in Appendix C. Both behavioral and anatomical changes over time can affect children's exposure; anatomical changes can also affect children's susceptibility to certain health effects. Panelists were asked to focus their discussions on defining and characterizing the important facets of behavioral and anatomical development during childhood and on how best to estimate children's exposure given the limitations in existing exposure information. They were asked to focus on broad issues (rather than specific methodologies) and not to address pharmacokinetic issues, since these are being evaluated in a separate effort. They were also asked to consider whether existing

exposure information is adequate and what research should be conducted to enhance children's exposure assessment.

1.4 Agenda

The workshop agenda is provided in Appendix D. The workshop began with welcoming remarks; a presentation about EPA's Risk Assessment Forum; and a presentation on the current practices and future needs of EPA's Office of Children's Health Protection with respect to the conduct of children's exposure assessments. These were followed by two technical presentations. The first, given by a member of EPA's National Exposure Research Laboratory, described the algorithms and parameters currently used to conduct indirect exposure assessments. The second, given by a member of the Harvard Center for Risk Analysis, discussed how well the different parameters mentioned in the previous presentation are currently documented in the research literature.

The formal charge to the experts was then presented and the participants divided into two discussion groups corresponding to the two sections of the charge. One discussion group was charged to consider developmental changes in children's behavior-related exposure factors and the other was charged to consider developmental changes in children's anatomical exposure factors. (Discussion group chairs and members are listed in Section 2.6.) The discussion groups met for 3 hours and then reconvened in a brief plenary session to summarize their progress before adjourning for the evening. The discussion groups resumed their work the next day and, after 6 hours of further deliberation, presented their findings to each other at the final plenary session. Open discussion among the full panel of experts continued after the presentations.

1.5 Workshop Summary

This report summarizes the workshop presentations and discussions and is organized as follows:

- # Section 2 of this report summarizes the presentations. Overheads used by the chairperson, EPA presenters, and a commenting observer are provided in Appendix E. The background papers that the presenters refer to are provided in Appendices G and H.
- # Section 3 and 4 report the conclusions that the two discussion groups (concerned with behavior-related and anatomy-based exposure factors, respectively) presented at the conclusion of the conference. Overheads used by the behavior-related discussion group in presenting their results can be found in Appendix F.
- # Section 5 summarizes the final plenary discussion on issues related to assessing children's exposure.

2. SUMMARY OF OPENING REMARKS

2.1 Welcome

Jan Connery of Eastern Research Group, Inc. (ERG), opened the workshop by welcoming participants and observers. She introduced Dr. Kimberly Thompson, the workshop chair, and asked other workshop participants to introduce themselves to the group. Dr. Thompson added her own welcome to the participants and began the introductions. After the introductions, Ms. Connery reviewed the workshop agenda and introduced the first speaker.

2.2 Background on EPA's Risk Assessment Forum

Bill Wood, Executive Director of EPA's Risk Assessment Forum (RAF), provided background on the RAF and its broad goals in sponsoring the workshop. The RAF is a standing committee within EPA that is responsible for providing agency-wide guidance in the area of risk assessment. This workshop is one part of a larger consensus-building process that the RAF is undertaking to improve its understanding of children's risks from environmental contaminants.

The RAF is currently revising EPA's cancer risk assessment guidelines. It is engaged in an ongoing discussion with EPA's Science Advisory Board (SAB) about improvements that could be made to these guidelines so as to better address children's cancer risks. The results of these discussions should be released soon. In parallel with RAF's efforts to incorporate the issue of children's risks into existing cancer risk assessment guidelines, there are several other agency-wide programs to better address children's risks. The RAF, in this and previous workshops, is trying to capture the kinds of expertise that are rapidly emerging (both within and outside EPA) in connection with children's risk assessment.

At present, there is some consistency and some variation in how EPA's different departments consider children's risks. The variations are rooted in the different kinds of data, decisions, and pieces of legislation with which the different departments work. The RAF would like to take a broader perspective as it develops agency-wide guidance pertaining to these risks, and it recognizes that such a perspective ought to be carefully developed in a consensus-building process. Dr. Wood concluded by thanking the RAF Technical Panel for their assistance in this regard. The Technical Panel is an advisory group composed of senior scientists from across the Agency.

2.3 Children's Exposure Assessment at EPA: Current Practices and Future Needs

2.3.1 Presentation

Next, Dr. Michael Firestone, Science Director at EPA's Office for Children's Health Protection, delivered a presentation on EPA's current policies for assessing children's environmental risks and how the agency would like to further develop these policies. Dr. Firestone remarked that it did not take him long after joining the Office for Children's Health Prevention to recognize the key precept around which the Office is organized: "Children are not little adults." It is an overarching goal of the Office to help others, within and outside EPA, to understand the specific ways in which children must be considered differently than adults. He provided several examples of how children differ physiologically and behaviorally from adults:

- # Children eat and drink more for their size than adults do.
- # Children play and act differently than adults do: very young children have more contact with ground surfaces than adults and engage in a great deal of hand-to-mouth activity.
- # Children's bodies are undergoing development.
- # Children may be less able to metabolize and excrete certain toxic substances.

While it has been an important first step for EPA to distinguish children from adults, further distinctions are necessary. The need for a more refined approach to considering children is apparent from the fact that some of the rapid changes in human development take place within the first few years of life—it is the purpose of the workshop to gather advice from the participants about how to take these developments into account and better assess children’s exposure. Dr. Firestone referenced an earlier comment by Dr. Lynn Goldman, Professor of Public Health at Johns Hopkins University: EPA should not consider children a “sub-population of concern” but rather a “life-stage of concern.”

The ultimate goal of exposure assessment is to develop a day-to-day model of human life that can predict the chemical exposures an individual is likely to face at any point in his or her life. While this is a laudable goal, it is not likely to be realized in the foreseeable future, so risk assessors need to develop simpler models. One way to simplify exposure models is to classify individuals into age bins, though some may be concerned that this procedure leads to over-simplification.

Different programs within EPA have been attempting to develop default approaches (including the use of age bins) to address children’s exposure when data are sparse. The different default approaches ought to be replaced by a standardized approach that is based on science and that provides justifications based on evidence. EPA has convened the workshop to gain insight and input into factors it should consider when developing such a standardized approach, as well as to identify what further scientific research may be necessary to accomplish these goals.

Recent EPA actions to improve assessment of children’s exposure include:

- # The *EPA Rule-Writer’s Guide* released in 1998. The guide is designed to help program offices incorporate children’s risks into their assessments. Under the auspices of EPA’s Science Policy Council, the Office for Children’s Health Prevention is currently reviewing the usefulness of this guide to the different program offices.

- # The *Child-Specific Exposure Factors Handbook*, which is currently undergoing peer review. In 1997, EPA issued the latest version of the *Exposure Factors Handbook*, which contains exposure factors useful for probabilistic risk modeling. EPA's Office of Research and Development (ORD) has been developing a child-specific version of the exposure factors handbook this year. This new document is presently in draft form.

Efforts, such as those described above, to estimate children's exposure are hampered by the uneven coverage of existing data sets. For example, the NHANES data on the biological monitoring of pesticide exposure include no data for children under the age of 6.

Recent EPA risk assessments have tried to address the following age groups: fetuses, infants, toddlers, children, and adolescents. There has been some variation, however, in the particular age ranges attached to some of these qualitative categories.

In conclusion, Dr. Firestone expressed particular hope that the participants would provide guidance in the following areas:

- # Defining age bins more effectively by carefully identifying the particular characteristics that distinguish them.
- # Deciding how finely EPA should subdivide the overall life stage of childhood into age bins.
- # Describing how additional factors such as sex, culture, and geography might modify the significance of standard age bins.
- # Identifying the most pressing gaps in the base of scientific knowledge that would justify age bins.

2.3.2 *Questions and Comments*

Dr. William Weil asked Dr. Firestone if he could more closely define the percentage of children that he hoped to describe in each age group. For example, was a particular age bin meant to accurately describe the average child or a range of children? If a range, was a bin meant to describe 90 percent of

the children within that age group, 95 percent, or 99 percent? Dr. Firestone replied that the EPA definitely wanted to study distributions as far out as they could be measured. The particular cutoff points used in risk assessments would depend on the particular risks being considered. Dr. Weil continued to express some confusion about how EPA intended to use age bins to summarize the widely varying development of complex organ systems. Dr. Robert Johnson suggested that it might be more appropriate to base exposure assessments directly on the relevant behavioral and physiological properties of the child rather than by generalizing from standard age categories. Dr. Firestone agreed that such a sophisticated approach might be a good long-term goal for EPA, but cautioned that it was not a realistic short-term goal. Dr. Melanie Marty suggested that while models based on age bins might often be adequate, users of age bins should be alert to the complexities that underlie them. There may be cases in which a specific factor (such as mouthing behavior) is a more significant indicator of exposure than age. Dr. Firestone agreed with this caveat.

2.4 Methods of Exposure Assessment for Children

2.4.1 Presentation

Next, Elaine Hubal of EPA's National Exposure Research Laboratory (NERL) delivered a presentation on some of the techniques presently used to assess exposure in children. Dr. Hubal began by remarking that much of her work is oriented toward defining the particular kinds of data that, if available, would be most helpful for use in exposure assessments. The definition of human exposure is the contact (at some visible, external boundary for some period of time) of an individual with a pollutant. It is important to distinguish exposure from dose, even though the two concepts are related, as individuals do not necessarily absorb into their bodies all the chemicals they are exposed to. Exposures can be measured either directly or indirectly:

- # Direct exposure assessment involves actually measuring the chemicals that an individual is exposed to, using tools like personal air monitors or techniques like duplicate diet sampling.

Biomonitoring tests are useful as indicators of direct exposure, but it is often difficult to develop quantitative exposure estimates from the results of these measurements.

- # Indirect assessments estimate exposure from data about chemical concentrations in an exposure medium (e.g., soil, toys, the floor). Concentration data are combined with information about how an individual interacts with the exposure medium, and a series of exposure factors, to arrive at an estimate of personal exposure to the chemical in the medium.

NERL is particularly interested in improving knowledge about the indirect exposure factors involved in the transfer of chemicals from contaminated exposure media to children, whether by inhalation, dermal contact, or ingestion. In general terms, these factors are the:

- # Concentration of chemical in exposure medium.
- # Contact rates of the individual with the medium.
- # Contaminant transfer efficiency from the medium to the portal of entry.
- # Contaminant uptake rates.
- # Human activity patterns.

Dr. Hubal went on to discuss some of the characteristics of children that influence exposure. With respect to physiological effects, she distinguished between those that affect a child's *susceptibility* to toxic chemicals (e.g., growth in an organ system creating a window of vulnerability) and those that affect a child's *exposure* to those chemicals (e.g., changes in food consumption, respiration, and surface area to body weight ratio). There are many kinds of specific developmental changes that are of interest to exposure assessors. When a child acquires the ability to crawl, walk, run, or manipulate objects, his or her potential exposure changes significantly. These different developmental capabilities affect the different environments to which a child has access. Changes in how and what a child eats affect his or her exposure to foodborne environmental contaminants. Other factors, such as gender, socioeconomic status, race, and ethnicity are also extremely important because they can affect the location, quality, and intensity of many other behaviors.

Dr. Hubal began summarizing the equations used to estimate children's exposure from sets of exposure factors. They are included in the document titled *Children's Exposure Assessment: A Review of Factors Influencing Children's Exposure and the Data Available to Characterize and Assess That Exposure*, which can be found in Appendix G and which has been published in the June 2000 issue of Environmental Health Perspectives (volume 8, number 6, page 475). With respect to these equations, she indicated that the exposure pathway of ingestion can be broken down further into a dietary pathway (eating) and a non-dietary pathway (placing fingers and objects in one's mouth). Dietary ingestion pathways can be broken down further to include both the contaminants present in the food itself and contaminants that get onto the food as it is consumed.

The characterization of a child's activity patterns requires several kinds of information. The first kind of information describes a child's *microenvironment*: it provides a specific and detailed description of the place a child occupies during an activity (e.g., indoors in a kitchen, outdoors on a lawn). The second kind of information is *macroactivity*: it is a general description of what a child is doing (e.g., watching television, eating dinner, taking a shower). The third kind of information is described as *microactivity*: the specific physical acts that are characteristic of a macroactivity (e.g., the number of times a child touches the floor per hour while watching television).

Children's inhalation exposure is relatively well characterized: it depends on atmospheric pollutant concentration in the particular microenvironment where a child is located, that child's rate of inhalation, and the length of time spent in the microenvironment. There are four studies that provide macroactivity data for children over a single day. These can be accessed through the Consolidated Human Activity Database (CHAD) and used to estimate inhalation exposure. There are some problems with these data: they are not longitudinal, they do not provide detailed enough microenvironment information to make it possible to estimate other kinds of exposure pathways (such as dermal exposure), and the macroactivity categories were developed for adults rather than for children.

Dermal exposure can be estimated with one of two alternative equations:

Equation 1: Macroactivity Approach. To estimate dermal exposure using the macroactivity approach, microenvironments are defined by location and surface type (e.g., indoors at home on carpet). The dermal exposure associated with a given macroactivity (e.g., actively playing in the yard) is measured and used to develop an activity- and microenvironment-specific transfer coefficient. Exposure can then be estimated individually for each of the microenvironments where a child spends time and each macroactivity that the child conducts within that microenvironment. Exposure over the 24-hour period is the sum of all of the microenvironment/macroactivity (me/ma) exposures. For each microenvironmental/macroactivity (me/ma), dermal exposure over the 24-hour period ($E_{\text{dme/ma}}$) is defined as:

$$E_{\text{dme/ma}} = C_{\text{surf}} \times TC_{\text{der}} \times ED$$

Where:

C_{surf} = total contaminant loading on surface ($\mu\text{g}/\text{cm}^2$)

TC_{der} = dermal transfer coefficient for the me/ma (cm^2/hr)

ED = exposure duration that represents the time spent in the me/ma (hr/day)

Equation 2: Microactivity Approach. To assess dermal exposure using the microactivity approach, exposure is estimated individually for each of the microactivities or events (e.g., each time a child touches a given object) from which dermal contact or non-dietary ingestion occurs. Exposure over the 24-hour period is then the sum of all of the individual exposures. For each microactivity, dermal exposure over the 24-hour period ($E_{\text{der/mi}}$) can be defined as:

$$E_{\text{der/mi}} = C_{\text{surf}} \times TE \times SA \times EF$$

Where:

$E_{\text{der/mi}}$ = dermal exposure for a given microactivity over a 24-hour period ($\mu\text{g}/\text{day}$)

C_{surf} = total contaminant loading on surface ($\mu\text{g}/\text{cm}^2$)

TE = transfer efficiency, fraction transferred from surface to skin (unitless)

SA = area of surface that is contacted (cm^2/event)

EF = frequency of contact event over a 24-hour period (events/day)

The first equation is simpler, but it has traditionally been used in agricultural rather than home environments, so it needs to be tested in the residential environment with children. It uses a single, lumped transfer coefficient to relate the contaminant loading on a surface to an individual's rate of

exposure for each hour spent in a given microenvironment/macroactivity combination. Dermal transfer coefficients must be developed empirically. To do so will require studying groups of children—it is essential that these groups be selected according to appropriate age bins in order to minimize the variability of the measurements.

The second and more complex equation is based on detailed microactivity data. Instead of a single, lumped transfer coefficient, it uses data about how often a particular surface is touched per hour, the surface area that is contacted with each touch, and the transfer efficiency of the contaminant from the surface to the skin. This methodology requires extremely detailed information that is often slow, costly, and challenging to collect.

Non-dietary ingestion exposure can be estimated through an equation similar to the second, microactivity-based dermal transfer equation:

For each microactivity resulting in non-dietary ingestion, exposure over the 24-hour period ($E_{\text{nding/mi}}$) can be defined as:

$$E_{\text{nding/mi}} = C_x \times TE_{\text{xm}} \times SA_x \times EF$$

Where:

$E_{\text{nding/mi}}$ = non-dietary ingestion exposure for a given microactivity over a 24-hour period ($\mu\text{g/day}$)

x = hand or object that is mouthed

C_x = total contaminant loading on hand or object ($\mu\text{g/cm}^2$)

TE_{xm} = transfer efficiency, fraction transferred from object or hand to mouth (unitless)

SA_x = area of object or hand that is mouthed (cm^2/event)

EF = frequency of mouthing event over a 24-hour period (events/day)

Determining indirect dietary ingestion involves measuring the detailed patterns of a food item's contact with contaminated surfaces before it is consumed.

Dr. Hubal emphasized that the actual values and distributions of exposure factors are developed in the context of specific exposure *scenarios*. An exposure scenario defines a particular source for a chemical (e.g., the use of a chemical in the home), a particular population that is potentially exposed, and the timeframes, microenvironments, and macroactivities that are associated with the exposure pathway for that chemical. Dr. Hubal concluded by emphasizing that proper selection of children's age categories will be crucial to the effective development of field studies to characterize exposure factors for different scenarios.

2.4.2 Questions and Comments

Dr. William Weil inquired whether air sampling measurements were conducted at the height of adults or children. Dr. Hubal replied that although some studies have found significant differences in chemical concentrations between adult and child heights, many have not. She still agreed with Dr. Weil that it was an important distinction to bear in mind, along with other activity pattern data. Dr. Weil asked whether or not children's air exposure factor measurements were conducted at the appropriate heights, noting that some compounds on ground surfaces have limited volatility that can create layers of airborne chemicals confined to 6 inches above the surface. Children who crawl are therefore likely to have very different inhalation exposures than children who can walk. Dr. Hubal replied that, as yet, few exposure assessment studies have been conducted that specifically consider children. The few assessments geared toward children do sample air at the appropriate heights.

Dr. Richard Fenske asked for more information about how exposure scenarios are built and about how many of them EPA puts together. They appear to be the crucial place where all the different exposure factors come together. Dr. Hubal said that she did not believe exposure scenarios were, at present, being developed systematically. She hoped that more information about age differences among children would help exposure assessors to make better decisions about when they can lump children together into a single scenario and when they need to develop separate scenarios for two different age ranges.

Dr. Fenske explained that at present, exposure assessors first identify a scenario and then develop the particular data necessary to define that particular scenario. He wanted to know whether EPA was hoping to develop a set of scenario-independent life stages with associated exposure factors. Dr. Hubal believed that was EPA's goal. She commented further that general, scenario-independent data on children's activity patterns would be an important resource for the proper development of specific scenarios of children's exposure.

Dr. Marty expressed some skepticism that toxicokinetic issues could be separated from exposure issues. Any physiological data that are available about children are inextricably linked to toxicokinetic and toxicodynamic issues. The participants, she continued, will not be able to avoid these issues when they consider age bins. There is a concern that if one ignores toxicological factors, one will pay inadequate attention to a particular exposure factor that is very important to a particular chemical exposure. Dr. Hubal replied that EPA does not mean to ignore toxicological factors—it is addressing them in another meeting and it is simply trying to focus the present workshop on issues of exposure. Dr. Firestone suggested that assessments should be developed as matrices of different developmental stages and different toxins of concern. A matrix will be filled in where exposures are particularly high and toxicological risk is particularly great. Dr. Firestone was concerned about allowing different EPA programs to define age bins in an idiosyncratic fashion. Dr. Bruce Lanphear admitted that indirect exposure assessment was valuable in cases where no direct data are available, but he expressed concern about the attitude that direct assessment is too difficult and expensive to be useful. Dr. Lanphear indicated that he did not believe direct assessments were too difficult and expensive to be conducted, at least for prevalent toxic chemicals and prevalent exposures. These studies should incorporate information about both exposure and biomarkers of exposure. Ultimately, he observed, direct assessment is needed to validate the results of the “mechanistic models” of indirect assessment. Dr. Hubal agreed with these comments but cautioned that it is not always possible to directly measure how much of a chemical an individual absorbed and how that individual absorbed it.

Dr. Gary Ginsberg asked for a sense of how well studied and standardized the process of developing transfer coefficients had become. Dr. Hubal replied that these methods are currently being developed at NERL and exposure assessors need some way of focusing and coordinating their efforts as they develop these methods. Dr. Ginsberg asked whether there were any surrogate methods that did not need to be developed by working with children. Dr. Hubal replied that there are some surrogate methods but it is currently not well understood how the results of those methods can be used in children's assessment.

Dr. Fenske expressed continuing skepticism, apparently shared by several other panelists, about the possibility of developing scenario-independent life stages for children.

2.5 Age Bins in Existing Data Sets That Are Relevant to Children's Exposure Assessment

2.5.1 *Presentation*

Next, Dr. Kimberly Thompson presented an issue paper that she developed for the workshop. The paper summarized the use of age categories in the existing collections of children's exposure data. Dr. Thompson expressed the hope that the workshop would produce guidance both about how to make the best use of existing data sets (for the short term) and about how to develop new data sets (for the long run).

Children's development, whether at the most obvious level of physical growth or in terms of social, behavioral, and psychological changes, affects the kinds of chemical exposures they are likely to experience. The issue of development is further complicated by a significant degree of variability among children's developmental pathways and exposure risks. The pediatrician's growth chart is a familiar illustration of childhood development and variation. Pediatricians also use similar standardized charts of behavioral milestones to assess behavioral development. The milestones described on these charts, while significant from a medical perspective, are often not closely suited to the characterization of

childhood exposure. As an example, Dr. Thompson said that although language and social skills are highly emphasized in pediatric medical charts, these factors are only of secondary significance to exposure assessment. Conversely, the period of teething is extremely important to exposure assessors but is not prominently defined in pediatric charts. Dr. Thompson expressed the hope that the workshop might provide an opportunity for pediatricians and risk assessors to learn more about each other's work and might help them to work together, in the future, in a more coordinated fashion.

There are both qualitative and quantitative differences between how chemical exposures affect children and adults:

- # Qualitative differences between adults and children exist when the effect of a chemical dose on a child is completely different from the effect the same dose would have on an adult. Children's organ systems are undergoing development, creating windows of vulnerability to particular chemicals.
- # Quantitative differences between adults and children exist when the effect of a chemical dose on a child is similar to the effect that the same dose would have on an adult, but is present to a greater or lesser extent.

In the absence of careful studies of the effects of a chemical on children, it is very difficult to extrapolate from adult risk profiles to child risk profiles. Comparing the effects of a particular chemical in children and adults, the chemical may act completely differently or in the same way; to lesser extent or to a greater extent. It is very important that exposure assessors know where the critical windows of vulnerability in childhood development are, so as to develop exposure data that specifically address those time periods.

The existing exposure data do use a fairly wide range of different age categories, but these choices have not been irrational. Age categories are typically defined to reflect the particular factor being studied (such as change in diet, for example). The use of existing data often becomes problematic when one wishes to make extrapolations from them—for example, when one is attempting to extrapolate from

short-term exposure studies to long-term exposure studies and vice versa. It is also unclear how one should deal with the spatial and temporal limitations of existing studies. For instance, can a study of a small group of children be taken as representative of all the children in the United States? Can a national study provide useful information about exposure in a specific socioeconomic/cultural group? Exposure assessors need to be very careful to avoid representing children in unrealistic ways. It is an open question whether it would be most efficient to answer these questions by developing new data or by learning how to better use existing data.

Dr. Thompson's report (*Changes in Children's Exposure As a Function of Age in the Relevance of Age Definitions for Exposure and Risk Assessment*) is included in Appendix H. It describes the data that feed into the exposure equations that Dr. Hubal described in her previous presentation. Dr. Thompson reiterated that there are three major routes of exposure: inhalation, dermal, and oral. The concept of the microenvironment, mentioned by Dr. Hubal earlier, was originally developed with reference to the measurement of chemical concentrations in the air. The importation of the concept of the microenvironment to the assessment of dermal and oral exposure has generated a great deal of uncertainty, since it is unclear how to characterize microenvironments in these new terms.

One of the major objectives of Dr. Thompson's paper is to describe the availability of the data necessary to use the standard set of exposure assessment equations (described in Dr. Hubal's paper) for children's exposure assessment. Another major objective is to describe the age categories that are used in the existing data relevant to assessing children's exposure. Other objectives are to characterize the extent to which the data are accessible and the extent to which the existing data age categories can be modified. A primary source of Dr. Thompson's research was the draft copy of the *Child-Specific Exposure Factors Handbook* (mentioned earlier by Dr. Firestone and provided to the participants at the workshop).

Exposure assessors are required by the Food Quality Protection Act to gauge *aggregate* exposure to particular chemicals—that is to say, total exposure from all sources, pathways, and routes. This is extremely difficult to accomplish with the present data sets because the age categories do not coincide in the different studies describing different exposure pathways.

Dr. Thompson evaluated the existing exposure factor data for children (e.g., body weight, food intake, soil ingestion), closely following pages 15 through 46 of her report. Summarizing her survey of the studies that describe the different exposure factors, Dr. Thompson concluded that assessors lack the kind of information they need to extrapolate exposure data from the particular populations that have been studied to broader or different populations. A great deal more is known about easily measurable anatomical factors, such as body weight, than is known about behavioral factors such as the mouthing of objects.

Direct, indirect, and biomarker studies can provide three independent techniques for filling in the gaps in exposure assessors' knowledge. All three techniques should be used and can validate each other. Dr. Thompson said that each of these techniques involves the taking of measurements and the use of models. In the indirect assessment approach, one must make measurements in order to build one's model. In the direct approach, one needs models in order to interpret one's data. It will not do to call for the use of either measurements or models alone because the two kinds of tools are closely interconnected.

Available exposure data describing children's surface areas, their fish consumption rates, and the duration of their mouthing behaviors are currently not used in any of the exposure assessment equations described by Dr. Hubal. Also, these equations call for pieces of data that are currently not available in the scientific literature. These missing data primarily have to do with the precise description of how children might contaminate their food by touching it with their contaminated hands or dropping it on contaminated surfaces before consuming it.

Breast milk consumption is the only exposure factor for which data have been reported by individual days of age. Water consumption, food consumption, and inhalation rates are the only factors for which data are available in age ranges of months. On the yearly scale of age ranges, there is a great deal of variability among the different age ranges that investigators have chosen for their studies.

Dr. Thompson mentioned that many aggregate exposure models are being developed to meet the demands of the Food Quality Protection Act and she gave an example from the Lifeline™ model to demonstrate the issues of how the model developers evaluated the natural breakpoints in the data to develop appropriate age bins.

Dr. Thompson went on to outline some goals for improvement in exposure assessment data. There are gaps in the data on breast feeding, the handling of food and how it relates to non-dietary exposure, fish intake rates, soil intake, and soil adherence rates. Assessors also need more information about the connections between different macroactivities, microactivities, and microenvironments. They also need to learn more about the activities of school-age children in the summertime and after school.

2.5.2 Questions and Comments

Dr. John Kissel made a comment about the use of the term “data” in reference to the information in the *Exposure Factors Handbook* (he had not looked yet at the *Child-Specific Exposure Factors Handbook*). He found that many of the numbers in this handbook are estimates based on prior data rather than actual measurements. He also thought there was more need for critical evaluation of the different degrees of certainty about the different numbers in the handbook. For example, he thought that dermal soil adherence could be measured much more accurately than soil ingestion numbers because of the different methodologies used in those two measurements. He also thought that the consequences (in terms of assessing actual dosage) of underestimating dermal soil adherence factors were far less grave than the consequences of underestimating soil ingestion factors. For both reasons,

he considers dermal soil adherence factors to be better measures than soil ingestion factors. He was perplexed, therefore, that Dr. Thompson ranked a set of soil adherence factors generated by him as being of low quality, while a set of soil ingestion factors were ranked as being of medium quality. He is concerned that exposure factors are being evaluated simply on the basis of the quantity of numbers that exist to describe them rather than on the quality of those numbers. This misevaluation, he continued, might lead to the misappropriation of resources intended to improve data quality. Dr. Thompson remarked that the assessments of quality were not hers: she took them directly from the *Child-Specific Exposure Factors Handbook*. She made her own evaluations under the heading of “Extent of generalization” and she ranked both the dermal soil adherence factors and the soil ingestion factors as “low” under that heading. Dr. Thompson invited constructive criticism from the participants about how EPA might better evaluate data quality. Dr. Kissel remarked that EPA should make it a major research priority to learn more about soil ingestion in children with pica because it represents a far greater and less well understood exposure pathway than dermal absorption through soil.

Another panelist suggested developing growth charts for different organ systems. Dr. Weil asked if Dr. Thompson had used the children’s growth charts being developed by the Centers for Disease Control and Prevention (CDC). Dr. Weil commented that CDC left out the NHANES III data for children over age 6 because they have become too fat.

Dr. Walker, a workshop observer from EPA’s National Center for Environmental Assessment, made comments and presented some empirical evidence showing that children have multiple critical growth periods, as they develop from birth to maturity (his overheads are provided in Appendix E). He defined a critical growth period as an age when the child reaches a peak growth velocity in weight or height (growth spurt).

Dr. Walker said that he was hired by EPA to develop age-specific radiation dosimetry models, but early on discovered this could not be done without devising a more adequate description of organ

masses as a function of age. He went on to say that many years were spent developing these models, using cross-sectional data that were obtained from the literature, but it was not until recently, after acquiring large sets of longitudinal height data for analysis, that he was able to develop a model that was representative of bone growth in children.

Dr. Walker showed overhead slides illustrating how well his newly published WWHLA growth model (recently published in *Growth, Development, and Aging* 2000, **64**, 33-49) fitted longitudinal height data of children from two major growth studies. He said that, although it was earlier believed that children experienced only two spurts (infantile and pubertal), his height displacement and velocity curves showed six, from birth to maturity. These spurts occurred at different times in each child. Dr. Walker named them according to the age when they reached their peak height velocity (PHV): neonatal, infantile, early-childhood, middle-childhood, late-childhood, and pubertal. His analysis revealed that the mean ages at PHV for these spurts were different in males and females (see his overheads in Appendix E). He indicated that, although the ages at PHV for the different spurts varied between the children and depended on gender and whether a child was a slow, average, or fast grower, they represented developmental milestones for height growth in children and should be considered in risk assessment. He felt that his model could be a powerful tool for better characterizing height growth in children and identifying those critical periods of rapid growth that may make children highly susceptible to xenobiotics from the environment. Dr. Walker also presented graphs showing that the kidneys and liver undergo multiple postnatal growth spurts; the periods of rapid growth in height correspond very closely to periods where peak concentration levels in the bones were found for such bone seekers as radium-226 and strontium-90.

2.6 Charge to the Experts

Kimberly Thompson reviewed the charge for the workshop. She urged panelists to think about the questions in the charge from a “value of information” approach. That is, they should consider how

limited resources may be most efficiently allocated to meet research needs for the future. Dr. Thompson suggested that panelists think about the different ways in which the problem of children's exposure could be subdivided. Some reasonable ways to subdivide exposure are:

- # By the class of chemicals involved in the exposure.
- # By the organ affected in the exposure.
- # By behavioral characteristics that lead to the exposure.
- # By age categories (using the following categories as a starting point: newborn, infant, toddler, young child, and adolescent).

Dr. Thompson advised the participants to think about the ways in which exposures, grouped in these different ways, do or do not fall into similar groups.

Dr. Thompson reviewed two parallel sets of questions (see Appendix C) for the two discussion groups (one concerned with anatomical development and the other concerned with behavioral development). She asked the participants to identify the kinds of problems that might be associated with the use of age bins. She also asked the participants to focus, as much as possible, on anatomical and behavioral developments that affect a child's exposure to chemicals. The participants then broke up into two discussion groups (persons named in bold italics were discussion leaders):

Anatomy Group	Behavior Group
Thomas Armstrong ExxonMobil Biomedical Sciences, Inc.	Deborah Bennett Lawrence Berkeley National Laboratory
Sophie Balk Montefiore Medical Center	Richard Fenske Department of Environmental Health, University of Washington
Jim Bruckner College of Pharmacy, University of Georgia	Lynn Goldman Johns Hopkins School of Hygiene and Public Health

Anatomy Group	Behavior Group
Michael Dinovi U.S. Food and Drug Administration	Celestine Kiss U.S. Consumer Product Safety Commission
Gary Ginsberg Connecticut Department of Public Health	Bruce Lanphear Department of Pediatrics, University of Cincinnati and Children's Hospital Medical Center
Robert Johnson Agency for Toxic Substances and Disease Registry	James Leckie Department of Civil and Environmental Engineering, Stanford University
John Kissel Department of Environmental Health, University of Washington	Mary Kay O'Rourke College of Public Health, University of Arizona
Melanie Marty California Environmental Protection Agency	P. Barry Ryan Rollins School of Public Health, Emory University
George Rodgers Division of Pediatric Critical Care, University of Louisville	Katherine Shea Consultant
Margo Schwab Johns Hopkins School of Hygiene and Public Health	Robin Whyatt Joseph L. Mailman School of Public Health, Columbia University
William Weil Department of Pediatrics/Human Development, Michigan State University	

The two groups met separately during the afternoon of the first day of the workshop and the morning of the second day. They convened briefly in a plenary session at the end of the first day to report their progress, and again during the afternoon of the second day to report their conclusions and recommendations to all participants. The discussions and conclusions of the behavior and anatomy groups are summarized in Sections 3 and 4, respectively. Section 5 summarizes the brief plenary discussion that took place at the end of the workshop.

3. CHANGE IN CHILDREN'S EXPOSURE DUE TO BEHAVIORAL DEVELOPMENT

The behavior group consisted of 10 specialists in fields relating to children's exposure, including pediatrics, risk assessment, and exposure assessment. A list of participants is provided in Section 2.6. The group was charged to consider the changes in behavioral patterns during childhood that can impact children's exposure to environmental contaminants (see Appendix C for the complete charge). The group was asked to consider questions such as:

- # Does it make sense to think about childhood behavioral development as a series of discrete events which lend themselves to characterization using age group categories or "bins?"
- # What are the most important developmental milestones in children's behavior?
- # For those behaviors that are likely to have an importance impact on exposure, is there existing exposure information that is representative of the behavior?
- # For those behaviors that are represented in existing exposure information, compare the age groups identified for the developmental milestone in question 2 with the age groups in the existing exposure information.
- # For those behaviors where the age groups reported in the exposure information are not aligned with the age groups defined by the developmental milestone, what is the best approach to representing the appropriate age groups in an exposure assessment?

The group began by carefully evaluating the use of age bins in describing children's behavior. They then discussed specific issues related to characterizing behavioral changes relevant to exposure, organizing their discussions by the three major exposure pathways (oral, dermal, and inhalation). They concluded by integrating their discussions of the different exposure pathways into a preliminary breakdown by age representing changes in constellations of behavior that could signal new categories of exposure and by compiling a list of research recommendations. The group's chair presented the group's conclusions at the workshop's final plenary session.

This section summarizes the discussions and conclusions of the behavior group. It is divided into five sections dealing with:

- # The defensibility of age bins (Section 3.1).
- # Specific behavioral factors related to oral, dermal, and inhalation exposure pathways (Sections 3.2 through 3.4).
- # Conclusions developed by synthesizing the discussions about the three exposure pathways (Section 3.5).
- # Recommendations for future research (Section 3.6).

3.1 The Defensibility of Representing Behavioral Difference in Terms of Age Bins

3.1.1 *Principal Discussion Points*

The group considered whether or not it made sense to think about children's behavioral development as a series of discrete events that can be organized into age bins. They arrived at the unanimous conclusion that it did *not* make sense to think about childhood behavioral development in that fashion. Although behavioral development follows a recognizable progression, it takes place differently between individuals and unevenly within individuals. More specifically:

- # Children begin developing behaviors at widely different times, and that development often occurs in brief spurts that are hard to predict precisely.
- # Different domains of behavioral development (e.g., language skills, motor skills, social skills) may not develop in a synchronized fashion, complicating attempts to peg an age range of children to a particular overall stage of behavioral development.
- # It is extremely difficult, sometimes even impossible, to identify where in a child's development of a particular behavior pattern ends. Many behavior patterns typically associated with small children (such as mouthing non-food items) simply become less prominent with time and persist

into adulthood. It appears that, in many cases, new behaviors do not completely replace older behaviors.

- # Modifying factors having to do with culture and socioeconomic status may substantially limit one's capacity to generalize about the specific behaviors children exhibit within particular age ranges.

Although it noted these major flaws with the practice of age binning, the group recognized the practical utility of age bins to EPA in its day-to-day decision-making. The use of age bins, while problematic, is a great improvement over not taking behavioral development into account at all. Some pediatricians within the group pointed out that it is common practice for them to use age bins as a starting point for evaluating their patients—an age bin provides a set of starting expectations for a particular child, which can help them evaluate that child's particular characteristics. There was very strong concern within the group, however, that if EPA developed age bins in an exposure assessment context, these bins might take on a "life of their own" and come to be accorded an unjustified degree of authority and precision. One panelist pointed out that when pediatricians use age bins, they use them at a screening assessment level. Such use depends upon a familiarity with the underlying continuous processes of children's development. Age bins, if used uncritically by individuals unfamiliar with the behavioral development that those bins crudely represent, could lead to significant errors of exposure assessment. EPA exposure assessors, therefore, need to become familiar with the continuous distributions that underlie any age bins they use.

The group suggested that it would make sense to focus on particular behavioral milestones that indicate the beginning of the capacity to engage in particular domains of behaviors (e.g., crawling, mouthing) that potentially lead to particular kinds of exposure. EPA should always bear in mind that the underlying expression of these domains of behavior are distributions rather than neat categories. Some panelists considered it entirely plausible, in the absence of specific evidence to the contrary, that the frequency distributions of different classes of behavior might be spread out broadly, rather than clustered, across

the range of children's ages. The usefulness of the concept of general behavioral age bins depends on the degree to which the relevant behaviors are spread out or clustered together.

In their discussion of the merits of age bins, members of the group agreed that age bins could be useful as a guide to the development of particular exposure assessment scenarios. They could serve as reminders to the developers of exposure assessment factors that these factors need to be developed for different broad age ranges among children.

The group members urged EPA to remember that the details they provided at the Workshop about specific age categories were based solely upon their general knowledge. These details require much more careful research and expert guidance before EPA can rely on them as scientifically validated facts.

3.1.2 Other Discussion Points

Concern about EPA's direction in basing children's exposure assessment on indirect exposure factors was expressed by the members of the group. A substantial number of the panelists thought that EPA was overreaching the inherent limitations of indirect exposure assessment and thought that it ought to be focusing more of its resources on biomonitoring efforts. There was some suspicion that EPA wanted to use age categories to develop a broadly generalizable model of child development rather than as a guide to better understanding the underlying elements of childhood development. One panelist broadly referred to the equations in the Hubal et al. paper as "modeling efforts" and indicated that she was worried when she heard about them, given the poor and limited data that are being used as inputs to them. She expressed strong skepticism about the results of these equations, contrasting them to "empirical data." The chair reassured the panel that EPA was interested in the underlying elements of childhood development, not modeling efforts. Another panelist indicated that he disagreed with EPA's basic approach to exposure assessment but considered "mechanistic modeling" to be adequate for addressing urgent, present day issues. He said that his cooperation with EPA was based on the

assumption that age-bin/modeling efforts would be phased out in the long run. Some members of the group, however, felt that the use of mechanistic modeling was justifiable (or even essential) in the context of studying new chemicals for which exposure pathways are not yet well understood.

Some members of the group were frustrated that EPA did not place more emphasis on epidemiological approaches to exposure assessment (as opposed to focusing primarily on what were seen as “mechanistic modeling” efforts). They felt that indirect exposure assessments might be most valuable if they were conducted simultaneously with direct exposure assessments and epidemiological studies so that the different kinds of data could be cross-referenced to each other.

Despite all these caveats, the members of the group were generally willing to suggest which domains of behavioral development were relevant to exposure assessment and to make rough approximations of when they tend to first appear. They emphasized that their conclusions should be taken as a starting point for further research and not as a definitive evaluation.

One panelist indicated that EPA could add a biological dimension to its *Exposure Factor Handbook* by including information about the distribution of behaviors and by including information about biomonitoring. Another panelist agreed. The use of distribution curves is an important tool that EPA should use if it wishes to approach exposure factors in a biological fashion.

A panelist suggested creating a field of study similar to industrial hygiene but focusing on children’s play rather than adult work.

Finally, the group emphasized that it was extremely important for EPA to look closely at fetal exposure, although it was not directly relevant to the present discussion of children’s behaviors. Transplacental exposure should really be considered a fourth exposure pathway in addition to the oral, dermal, and inhalation pathways.

3.2 Behavioral Development and Oral Exposure

3.2.1 Principal Discussion Points

The group recognized four major domains of behavioral development that affect oral exposure to chemicals:

- # *Gross motor development.* For example, the onset of mouthing, sitting, crawling, walking, rolling, climbing, bike riding.
- # *Fine motor development.* For example, the onset of behaviors involving grasping objects, placing hands in mouth, placing objects in mouth, using utensils, and opening jars.
- # *Cognitive development.* For example, the onset of understanding object permanency, understanding the meaning of the word “no,” and understanding the concepts of death, danger, and poison.
- # *Social development.* For example, the onset of willingness to follow directions, interest in risk taking, and ability to drive an automobile.

Changes in these domains of development could plausibly affect oral exposure to chemicals through the following six pathways:

In connection with this discussion of exposure pathways, the group expressed particular hope that EPA would locate existing data on when parents start feeding their children with bottles and with solid food as well as when they stop breast- and bottle-feeding their children. These statistics are likely to be highly variable between different ethnic and social subgroups and may merit closer investigation. EPA should attempt to find out at what ages children receive “exclusive” breastfeeding (i.e., breast milk is the only food source), “full” breastfeeding (i.e., breast milk is the only milk source), and “any” breastfeeding (i.e., some breast milk is consumed).

3.2.2 Other Discussion Points

One panelist expressed some confusion about which behavioral characteristics were relevant to oral exposure. Many of them, such as being able to sit or walk, are relevant in a “one-step-removed” sense—they affect whether or not a child could get into a situation in which he or she might have an oral exposure.

Another panelist mentioned it was important to distinguish whether children were ingesting non-food items or soil in particular.

Exposure Pathway	Examples of Relevant Age-Related Developments <i>(Ages, particularly when stated as single numbers, are spontaneous approximations from the workshop and require further validation)</i>
Breast Milk/Nursing	Nursing takes place roughly from 0 to 18 months of age, though this varies by culture.
Bottle Feeding	Bottle feeding takes place roughly from 0 to 12 or 24 months.
Food	Head control (2 months), sitting (6 months), finger feeding (8 to 9 months), use of utensils (10 to 12 months), and the final shift to adult patterns of eating. Solid food, served in a bottle as a slurry, is often consumed as early as 1 month of age, but 4 to 6 months is the typical age range for beginning solid foods by themselves.
Water	Use of cups (6 to 9 months).
Mouth-Hand Contact	Prevalence of hand-to-mouth behaviors, such as thumb-sucking. Gross motor skills determine access to areas where the hand can become contaminated. Succession of gross motor milestones: rolling (4 months), creeping (6 months), crawling (8 months), walking (12 months), and climbing (18 months).
Mouth-Object Contact	The ability to interact with objects is a major factor here. The ability to grasp an object to one's mouth begins roughly at 3 to 5 months. A pincer grasp and moderate strength are achieved by 9 months. Children become aware that objects exist even when covered around 6 months but generally do not understand the meaning of the word “no” until 12 months.

There was some discussion of whether or not it was important to distinguish between mouthing and chewing of objects. There was some expression of non-specific concern about determining how to differentiate between different kinds of oral behaviors. There was disagreement about whether or not

socioeconomic status and education were effect modifiers. Panelists considered them to be confounders.

Several panelists were interested in including transplacental food consumption as an oral exposure, but the group came to the eventual conclusion that EPA should consider transplacental exposure as a sort of fourth exposure pathway rather than trying to fit it into oral exposure.

Some members of the group felt that non-food mouthing behavior was comparable to pica behavior. The chair pointed out that these were essentially two different behaviors.

One panelist suggested that the swallowing of coughed-up dusts might be considered a behavioral factor contributing to non-dietary oral exposure, but there was some disagreement within the group about whether this was an appropriate classification. The degree of exposure varies depending on whether one spits or swallows coughed-up mucus. Some panelists noted that playing in water or dusty yards might contribute to non-dietary oral exposure.

Several panelists noted that their discussion of oral exposure behaviors was primarily focusing on very young children. The chair thought this was a result of the fact that behaviors never really die out—it is simpler to point out the beginning of behaviors in early childhood than to estimate how those behaviors scale back later in childhood. An implication of this observation is that exposure assessment for older children should also incorporate nonfood mouthing behaviors.

3.3 Behavioral Development and Dermal Exposure

3.3.1 *Principal Discussion Points*

The group recognized substantial similarity between behavioral development's effects on oral exposure and its effects on dermal exposure. Thus, the previously discussed domains of gross motor development, fine motor development, cognitive development, and social development were also found to be relevant to dermal exposure. However, the group noted that these behavioral domains may have unique relationships to dermal exposure. Dermal exposure can result from behaviors that cause *any* part of the body (not just the mouth) to come in contact with contaminated surfaces.

Changes in these domains of development could plausibly affect dermal exposure to chemicals through the following six pathways:

- # Showering
- # Bathing
- # Recreational water use (e.g., swimming)
- # Surface contacts
 - Floor
 - Object
 - Ground (outdoor)
- # Skin-to-skin transfer
 - With hands
 - With other skin
- # Intentional applications to skin

The group also noted that changes in a child's clothing/diaper use throughout development would affect the amount of his or her skin available for dermal exposure, as well as the permeability of the skin.

3.3.2 *Other Discussion Points*

One participant mentioned that there is significant concern about chloroform absorption into the skin from water. Another member of the group wondered about the effects of different soaps on the permeability of the skin.

Panelists were unsure of whether or not they should distinguish between pools, lakes, rivers, and drainage ditches in terms of their dermal exposure profiles.

One panelist objected to distinguishing between soil and floor exposure in the case of dermal contact because this distinction had not been made in the case of oral exposure. The panelist wanted oral and dermal exposures to be classified in a parallel fashion.

A group member commented that children undergo a very abrupt transition from taking no showers at all to taking regular showers.

3.4 **Behavioral Development and Inhalation Exposure**

3.4.1 *Principal Discussion Points*

The group attempted to develop a list of behavioral milestones that affect inhalation exposure, but ended by concluding that behavioral effects on inhalation exposure do not change in discrete jumps marked by milestones; rather, they change in a continuous fashion because exposure by inhalation is driven substantially by activity level and exposure scenarios. The relevant domains of behavioral change were:

- # *Gross motor development.* Gross motor development is important for characterizing the atmosphere in which children breathe (i.e., their “personal clouds”). At different life stages,

children spend their time breathing in different microenvironments depending on their modes of locomotion (e.g., rolling, crawling, and walking). Also, certain gross motor skills, such as the ability to run and play sports, tend to increase overall activity levels as they develop.

- # *Activity level.* The group concluded that activity level could not be considered simply as a series of states through which a child develops, and agreed that children's broad level of development certainly affects their average activity level. For example, infants are generally relatively passive, but can exert themselves very intensely when crying. Activity level affects inhalation rate and is thus an important factor in assessing inhalation exposure.
- # *Breathing behavior.* The group considered the transition from mouth breathing to nasal breathing. They concluded that it is a significant factor in inhalation exposure, but is complex and does not lend itself to discrete cut-offs.

3.4.2 Other Discussion Points

Some members of the group suggested that one should differentiate between activities that tend to stir up dust and those that do not. This distinction determines whether one is exposed only to atmospheric gases or also to aerosol particles.

The group gave some initial consideration to using sleeping, awake but quiet, and active as behavioral stages, but the chair suggested that this was inappropriate and that activity level varies continuously in children. There was prolonged confusion about how to incorporate these terms (sleeping, quiet, and active) into a classification scheme parallel to that which was used for the other exposure pathways.

3.5 General Conclusions for Incorporating Behavioral Development into Children's Risk Assessment

3.5.1 Principal Discussion Points and Presentations

Dr. Katherine Shea, the group's chair, proposed a set of provisional behavioral age bins as a starting point for further research. The bins are as follows (see also the corresponding overheads in Appendix F):

Age Bin	Characteristics Relevant to Oral and Dermal Exposure Pathways	Characteristics Relevant to Inhalation Exposure Pathways
0 to 2 months	Breast and bottle feeding. Hand-to-mouth activities. Rapid growth makes children particularly vulnerable to chemicals.	Children spend a great deal of their time asleep.
3 to 5 months	Solid food is introduced. Contact with surfaces increases. Object-to-mouth activities increase.	Children may breathe close to floor level when placed in play pens or infant seats on the floor.
6 to 11 months	Food consumption expands. Children's floor mobility increases. Children are increasingly likely to mouth non-food items.	Development of personal dust clouds.
12 to 23 months	Children consume a full range of foods. They participate in increased play activities, are extremely curious, and exercise poor judgment. Breast and bottle feeding cease.	Children walk upright, run, and climb. They occupy a wider variety of breathing zones and engage in more vigorous activities.
2 to 5 years	Children begin wearing adult-style clothing. Hand-to-mouth activities begin to approximate adult patterns.	Occupancy of outdoor spaces increases.
6 to 10 years	There is decreased oral contact with hands and non-food items, as well as decreased dermal contact with surfaces.	Children spend time in school environments and begin playing sports.
11 to 15 years	Smoking may begin. There is an increased rate of food consumption.	Increased independence. Work outside of home begins.
16 to 20 years	High rate of food consumption continues.	Independent driving begins. Expanded work opportunities.

The group briefly discussed Question 3 of their charge (Appendix A), which asked whether or not information was presently available on the behaviors that affect exposure. Panelists could only answer this question in general terms, because they did not have the resources to provide specific examples of behavioral data. There is a definite need for more data on behavioral exposure factors, as many of the existing data are of limited quality or coverage. Some members of the group suggested that exposure factors be collected in the context of specific chemical compounds, and there was general agreement

that more work was needed on behavioral development in specific sub-populations of children (e.g., developmentally impaired, physically disabled). It is also very important, many felt, to better integrate indirect measurements of exposure factors with physiological and mass-balance measurements so as to better validate those exposure factors.

Question 4 of their group's charge asks whether existing exposure factor data have been collected in a manner that fits with the proper age bins for children. The group did not have time to review and evaluate the age distributions chosen by the different studies Dr. Thompson listed in her presentation. They did note a general lack of rich data sets describing the exposure of very young children. They suggested, furthermore, that EPA re-evaluate the raw data of past exposure studies when it appears that those studies did not organize their published results according to the best set of age categories. Such plans, of course, would have to take into account some important concerns about the cost of re-analyzing data and the continued protection of the privacy of the individuals from whom the raw data were collected.

Question 5 of the charge asks for guidance in assessing exposure to a particular age bin when existing data do not provide uniform coverage of that group. The group had no simple answers to this question and could only encourage EPA to develop more data, focusing on being as child-protective as possible and emphasizing direct, empirical data collection. With respect to the problem of aggregate exposure, EPA should note that oral and dermal exposure factors are dependent on similar behavioral parameters and that inhalation exposure follows a fairly independent set of parameters.

3.5.2 Other Discussion Points

The group generally agreed with the chair's proposal for different age categories, but one panelist suggested that they should not try to arrive at any further specificity, given the lack of data and specialized expertise to ground their discussion. Another panelist stated that EPA tends to overestimate

the universality of its activity data—it tends to generalize from one set of data to many different contexts, which may not be justified. A third panelist responded that age categories would be useful not only for collecting activity data but also for the more direct, epidemiological studies that other panelists were calling for. There is some value to mechanistic modeling, argued another panelist, when it is unclear how exposure to a new chemical is partitioned across different exposure pathways. The emerging consensus in the group was that it was reasonable for EPA to conduct indirect exposure assessment. The problem that panelists perceived, however, was that EPA does not seem to give sufficient priority either to the direct exposure assessment approach or to the validation of indirect exposure models.

The group noted that these categories do not align perfectly with the categories of cognitive development articulated by Piaget. It is unclear, however, whether cognitive development (e.g., the ability to understand the concept of death) is as relevant to exposure assessment as it is to risk management. For the purposes of scenario development, at least, the child's cognitive development is a crucial factor for risk assessors to understand. Some members of the group also briefly noted that the categories do not align perfectly with the Erickson's categories of emotional development.

3.5.3 Observer Comments

Dr. Harvey Richmond of EPA's Office of Air Quality Planning and Standards delivered some comments pertaining to the group's discussions. He argued that each behavioral age bin should include information about the amount of time children in that category spend outdoors. From his perspective, one of the most important factors in inhalation exposure is the amount of time that one spends outdoors. Dr. Richmond also noted the group's enthusiasm for conducting epidemiological studies that include biomarkers. He cautioned that, while such an approach is valuable, it is only technologically feasible for a limited number of chemicals. Among air pollutants, he ventured that it would only work for 10 percent of the chemicals EPA is concerned about (e.g., certain metals and volatile organic compounds).

He also noted that biomarker data for a chemical is of no use to exposure modeling unless the paths of exposure for that chemical are already very well understood.

3.6 Research Recommendations

The behavior group highlighted three major data gaps that it believes EPA should immediately address to improve its use of age bins. The group suggested the following measures:

- # Carefully evaluating the distribution of behaviors across different age ranges, taking into consideration the variability introduced by effect modifiers and specific sub-populations, such as particular ethnic and socioeconomic groups, developmentally impaired children, and disabled children.
- # Using integrated data sets to evaluate the relative importance of different kinds of exposure. It is important to focus time and resources on exposure pathways that are more likely associated with significant risks.
- # Collecting integrated data sets that combine information about children's behaviors, their estimated exposure, their biomarkers for particular chemicals, and their health.

Other short-term data gaps mentioned by different members of the group include the lack of information about:

- # The frequency, distribution, and duration of children's dermal and oral contact events.
- # Prenatal exposure. EPA should, perhaps, hold another conference on issues of prenatal exposure and its modifiers. The accumulation of environmental contaminants in amniotic fluid is a particular area of concern.
- # The relationship between adolescent developmental milestones and adolescent exposure.
- # The distributional properties around developmental milestones.
- # The exposure of children to household dusts and residues. Both oral and dermal exposures need to be better characterized. Such studies could be conducted either by direct exposure

measurement or by measurement of the number of contact events children have with household dusts and residues.

- # Hand-to-mouth and object-to-mouth transfer of contaminants. These exposure factors are currently very poorly understood.
- # The particular biomarkers which are most useful for measuring children's exposures to prevalent chemicals. Additional pharmacokinetic data on these chemicals may aid in the proper interpretation of biomarker data.
- # The extent to which EPA's definitions of soil ingestion (as a measure of exposure) are validated by biomarkers.
- # The relative significance of different exposure pathways for children of different ages.
- # Probability-based biomarker surveys of prevalent exposures. A good model of this sort of study is the one recently conducted on lead exposures by the National Center for Health Statistics (with the support of the U.S. Department of Housing and Urban Development).
- # The amount of time children spend near the floor or soil and how this affects their personal dust clouds.

Individual members of the behavior group also mentioned several data gaps that EPA should address in the long term. These include the lack of information about:

- # The relationship between cross-sectional studies and longitudinal studies. It is unclear to what extent cross-sectional studies can stand in for longitudinal ones. It is common research practice at present to simultaneously study the exposure of different children at different ages, but this research strategy may leave out important information about how the exposure of particular cohorts of children changes over time.
- # How exposure varies at different times of the year and among different geographical locations. For example, children may have different dermal transfer coefficients in the spring and summer, depending on how sweaty their palms are.
- # How long-term trends in child-rearing practices affect children's exposure.

- # Whether or not the recommended interventions for environmental hazards are indeed effective. Randomized, controlled studies are needed to address this question.

4. CHANGE IN CHILDREN'S EXPOSURE DUE TO ANATOMICAL DEVELOPMENT

The anatomy group consisted of 11 specialists in fields relating to children's exposure, including pediatrics, risk assessment, and exposure assessment. A list of participants is provided in Section 2.6. The group was charged to consider the changes in anatomy during childhood that can impact children's exposure to environmental contaminants and their susceptibility to health effects from that exposure. The group was asked to consider questions such as:

- # Can anatomical development during childhood be considered as a series of discrete bins, particularly when existing information is not adequate to construct a continuous exposure function?
- # What are the most important developmental milestones for anatomical changes related to physical growth in children?
- # For those anatomical characteristics that are likely to have an important impact on exposure, is there existing exposure information that is representative of the characteristics?

The group began by discussing the charge. Some panelists questioned whether "binning" was an appropriate approach. There was initial concern that such an approach could result in a impractically large number of bins, and that the type of information provided by such an approach may have an insignificant impact compared to other uncertainties in risk assessment. Other panelists felt that binning could have merit. The group eventually agreed to pursue the possibility of binning since this was an integral part of their charge. They began by discussing the development of individual anatomical and physiological characteristics (such as body weight and skin surface area), organs, and systems (including body fat, skin, skeleton, liver, immune system, reproductive and endocrine systems, lung and respiratory system, gastrointestinal tract, renal system, cardiac system, muscle, and sensory organs). They generally limited their discussions to development after birth; fetal development and in utero exposure were not covered. They then discussed general issues related to characterizing developmental changes relevant to exposure, and concluded their discussions by compiling a list of

research recommendations. The group's chair presented the group's conclusions at the workshop's final plenary session.

This section summarizes the discussions and conclusions of the anatomy group. It is divided into three sections:

- # Individual anatomical characteristics, organs, and systems (Section 4.1).
- # General issues (Section 4.2).
- # Research recommendations (Section 4.3).

In each section, the group's conclusions, as summarized by the chair in the final plenary session, are provided first, followed by a summary of the discussion that led to those conclusions.

4.1 Individual Anatomical Characteristics, Organs, and Systems

4.1.1 Weight

Conclusions

For weight, the following preliminary bins were suggested based on changes in the rate of weight gain: 0 to 6 months, 6 to 12 months, and 1 to 2 years. From 2 to 8 years the rate of weight gain is relatively stable. It increases again at 8 years and at 10 years. After this, it peaks and then decreases at 13 to 15 years depending on gender. Skin surface area as a function of weight is a rapidly decreasing relationship until about 1 year, when it levels off. It remains stable until about age 14, when it flattens out and becomes virtually horizontal.

Discussion

The chair presented data¹ on weight gain in children. The data showed rapid but different rates of growth for three periods in early childhood: 0 to 6 months, 6 months to 1 year, and 1 to 2 years. By 2 years, weight gain continues at a relatively stable rate until about age 8, when it increases again. Weight gain also increases around age 10 or 11, then decreases at age 13 to 15, depending on gender.

4.1.2 Body Fat

Conclusions

The group considered body fat in terms of retention and mobilization of xenobiotic products. Excess fat may act as a safety factor to the extent that it serves as a sink for lipophilic chemicals. However, this potential “protection” becomes a liability during periods of weight reduction (e.g., in early adolescent boys and during dieting—which is common to adolescent girls—when lipophilic substances stored in the fat become mobilized).

The proportion of fat in the body increases during the first 18 months and then remains stable until about age 14. At age 14 in boys, it begins to decrease slightly and then increases again. At 14 in girls, it begins a more rapid increase, which continues up to adulthood.

¹The chair presented data at many points during the discussions. These data were primarily drawn from five sources:

- # Pesticides in the Diets of Infants and Children, National Research Council, 1993.
- # Research Needs on Age-Related Differences in Susceptibility to Chemical Toxicants, ILSI Risk Science Institute, November, 1966.
- # Bruckner, J.V., and Weil, W.B. 1999. Biological Factors Which May Influence an Older Child's or Adolescent's Response to Toxic Chemicals. *Regulatory Toxicology and Pharmacology*, 29: 158-164.
- # Analysis of the Michigan Department of Environmental Quality's Administered Environmental Standards to Protect Children's Health, Michigan Environmental Science Board, February, 2000.
- # Department of Labor Conference on Environmental and Occupational Risks of Adolescents.

Discussion

The chair kicked off the discussion by showing body fat data for boys and girls by age. For boys at age 20 years, there is more than a four-fold difference in body fat between the 10th percentile (in which boys have 5 kilograms of body fat) and the 90th percentile (in which boys have more than 20 kilograms of fat). For girls at that age, body fat ranges from 10 to 30 kilograms between the 10th and 90th percentiles. The chair said there is a characteristic bump in fat mass for boys just prior to adolescence, followed by a drop in body fat with the first stage of adolescence, then an increase. This bump does not usually appear in girls.

The chair also showed data from the early National Health and Nutritional Evaluation Study (NHANES); the Tecumseh, Michigan, study; and the Ten State Nutrition Survey of fat fold thickness for triceps. These data show the same bump in fat mass for boys. In boys, extremity fat is constant throughout childhood. For girls, it is fairly stable until early adolescence, when it rises and then levels off at three times preadolescent levels. The chair was not sure whether this would have any impact on exposure. However, he said, since fat is a major storage area for lipophilic materials, it plays a significant role in what happens to chemicals once they enter the body.

Another panelist said that work by the Connecticut Department of Health found that body fat at birth is low relative to older ages, but by about 1 year of age it flattens out as a percentage of body mass. This would affect various pharmacokinetic parameters, such as partitioning and how much dose is retained in the fat compartment. The panelist said the content of adipose tissue changes with maturation. It has more water content at birth than at older ages, so there is a window at least in the first year in which body composition is different enough to affect the retained dose.

The chair responded that this composition difference is due in part to the fact that there are a large number of fat cells at birth but their size is relatively small. Fat cells contain a certain amount of protein

and water, which stay relatively constant. However, the protein and water content decrease proportionally as the fat cell grows by adding more fat. This increase in fat content probably occurs somewhere between the first and second years, while the number of fat cells stays relatively constant between 2 years and adolescence. He also mentioned that the increased body water of infants is primarily extracellular water rather than intracellular water. Intracellular water varies little and if anything may be a little low, because (in theory) there may not be as many solute particles in infants' cells as in older children's. The loss of extracellular water after birth is a constant proportion of mass in species from mice to giraffes.

A panelist pointed out that while fat could increase the retained dose of a chemical, it might also act as a protective sink that lowers the chemical activity of toxic chemicals in the body. If so, leaner people would be at greater risk, since a single exposure to a chemical could overwhelm protective measures. Preadolescent males could also be at greater risk from chemical mobilization that occurs with fat tissue loss, since this is a time when they typically lose fat tissue. Also, data suggest that about 60 to 80 percent of girls diet, so they too could be vulnerable to this type of risk, particularly during the first period of dieting. Another panelist agreed that fat would not be protective when mobilized, such as during weight loss and breast feeding. The greater the exposure and amount of chemical stored, the higher would be the risk during periods of mobilization. Dr. James Walker, an EPA observer, said the some radioactive chemicals such as xenon are stored in fat, so the amount of fat a child has could be an exposure concern. A panelist pointed out that fat transport should also be considered. If there are developmental changes in how fat is transported and deposited in the fat cells, this could affect exposure.

4.1.3 Skin

Conclusions

In the premature infant, the skin as a portal of entry appears to have differential permeability with age, but members of the group did not know how long this differential permeability remained after birth. The likelihood of skin being abraded can vary with age, since children are more likely to abrade their skin as their mobility increases. Occluded skin may also be susceptible to erosion. Skin under occlusive diapers in particular might have more permeability than nonoccluded skin, especially when diaper rash is present. In later childhood, extensive eczema or acne could alter skin permeability. For the ratio of skin surface area per unit of body weight, there is a rapidly decreasing relationship until 1 year; then the ratio decreases steadily but more slowly until about age 14, when it begins to flatten out to become virtually stable.

Discussion

The chair cited data that showed a rapid decline in skin surface area to weight ratio during the first year of age, with a relatively slower but stable decrease in the ratio thereafter until about age 14. He also mentioned data showing increased skin permeability for about the first month of life. This increased permeability was a problem when hexachlorophene was used to scrub newborns. The chair said the stratum comeum begins to develop in the first month of life, and that shortly after the first year of life, skin permeability does not appear to vary with age.

Other panelists thought that there might be somewhat different data in the literature, but did not cite specific studies. One panelist speculated that there might be data on neonate absorption in the pharmaceutical literature and suggested that EPA look into this. An observer mentioned work by Fitzpatrick, which indicates that full-term infants have a complete stratum comeum, but a thinner dermis.

The stratum corneum is not necessarily complete in premature infants. A panelist pointed out that dermal thickness can be critical to absorption of chemicals, including both the rate of absorption and total absorption (since not all chemicals absorbed into the skin enter the circulatory system). Another panelist said that research has shown scrotal skin (which is in contact with occlusive diapers) to be the most permeable of all.

Panelists discussed skin conditions that may affect absorption. For example, diapers are an occlusive dressing, so they hydrate the skin and prevent the evaporation or volatilization of chemicals, which could increase absorption. This could be an issue for babies and toddlers up through toilet training. Any break in the stratum corneum can compromise the skin barrier. Children with eczema can have a significant proportion of skin that is invasively open, and thus could be a sensitive subpopulation, one panelist suggested. She also expressed concern about adolescents with acne. This might not be as great a concern, another panelist responded, because measurements of soil loadings show that the face stays relatively clean compared to hands or knees. An observer mentioned that children with atopic dermatitis have a compromised barrier, so bioavailability is much greater, and adults with psoriasis have a compromised barrier, which can make as much as a 20-fold difference. A panelist pointed out that skin shedding can be protective for highly lipophilic chemicals (greater than $\log 5 K_{ow}$), which may be sloughed off before they are absorbed in the circulatory system. Another panelist wondered whether sunburns in childhood and adolescence might have any impact on chemical exposure.

The chair mentioned that the faces and arms of young children have a greater proportion of body surface area than adults. This is true for the arms, for example, up to age 6 or 7. Exposure calculations often use adult proportions for young children, which can be off by 2 percent or so. Another panelist thought this difference was too small to have regulatory significance, given all the other uncertainties.

The panelists briefly discussed whether activities that increase blood flow to the skin (such as crying in infants) could impact absorption. This might be the case for lipophilic chemicals for which the rate at which they are transported away by the blood is slower than the rate at which they penetrate the skin.

4.1.4 Skeleton

Conclusions

Periods of bone growth can increase susceptibility to deposition of substances such as heavy metals and some antibiotics. Rapid bone growth occurs during the first year, after which the rate of growth is similar to that for the rest of the body until adolescence, when there is a period of rapid skeletal growth from approximately age 10 to 16 in girls and 12 to 18 in boys. Epiphysial closure² starts around 11 years in girls and 13 years in boys and takes approximately 6 to 7 years, depending on the site of closure. Interference with this process could shorten the length of the bone or prevent closure and result in increased bone length, which can cause long-term joint dysfunction in adult years.

Discussion

The chair presented graphs showing skeletal mass and calcium accretion. During the first year, there is rapid growth in total skeletal (bony and cartilaginous) mass. This tapers off until adolescence, when there is another significant increase in skeletal weight from about age 10 to 16 in females and 12 to 18 in males. Calcium accretion peaks at about 14 years in boys; in girls the peak is smaller and occurs earlier. During periods of rapid increase in skeletal mass, children may be more vulnerable to exposure from heavy metals. Another period of vulnerability would be the period of epiphysial closure and cessation of bone growth, which occurs during much of adolescence. This is a time when the joint

²Epiphyses are secondary bone-forming centers separated from a parent bone in early life by cartilage. When an epiphysis closes, it becomes part of the larger (parent) bone.

spaces may be susceptible to exposures that could affect the cartilage. This susceptibility is present from about 11 to 18 years in girls and 12 to 19 years in boys.

Dr. Walker, an EPA observer, said he had data showing that the uptake of some heavy metals, such as, radium and strontium, is high during the neonatal and pubertal growth periods. The chair responded that the skeletal growth rate is high during the first months of life, but (because there is so much cartilage growth during the earliest months) this is largely linear growth rather than an increase in bone mineral content. Another panelist pointed out that weight triples during the first year. Dr. Walker, said that his milestones, developed using the empirical growth model, correspond almost exactly with the ones that the group decided on for the skeleton. His model discerned a growth spurt at birth, between 8 and 12 months, between 3 and 4 years, between 6 and 7 years, at about 8 years in females and 10 years in males, and at 12 years in females and 14 years in males.

4.1.5 Liver

Conclusions

With regard to environmental agents, hepatic enzyme activity is relatively deficient during the first year of life, reaches a peak level that exceeds adult efficiency sometime during the second year of life, and then decreases to the adult range by 2 to 3 years of age. Data on developmental changes in the liver need to be evaluated.

Discussion

In previous work, two panelists had examined liver enzyme development and found that, at about 1 year of age, enzyme activity exceeds adult activity per gram of liver by about 150 percent. Enzyme activity returns to normal during the second year, after which it is relatively stable. However, liver

function during the first 6 months after birth is deficient in some respects compared to adults. Data are available to define these early deficiencies more specifically. A panelist said that much of the liver function data are fairly old and questioned how relevant they would be given more recent exposures to compounds that could be liver enzyme inducers.

4.1.6 Immune System

Conclusions

The group emphasized that the immune system was highly complex and that understanding of it is rapidly evolving. During the first few months of life, infants have greater susceptibility to certain types of infection, but by about 1 year of age most immune functions have matured.

Discussion

The group noted that the immune system is extremely complex. They pointed out that in utero exposure could have a significant impact on immune system development but that discussion was outside the scope of the group's charge. Panelists shared various facts about the immune system development in children, including the fact that breast-fed babies are less likely to develop type 1 diabetes and that infants up to about 2 months of age are more susceptible to a host of infections they are not susceptible to later, while breast-fed babies may be less susceptible to others due to maternal antibodies. Thus, the first 6 to 12 months after birth appear to be very different from the rest of childhood in terms of the potential impacts of exposure. The panelists pointed out that a number of objective measures, like white cell counts and immunoglobulin levels, are age-dependent. These could be used as markers for what is normal at particular ages, but little is known about the significance of deviations from normal levels.

The chair mentioned that though the thymus is large in infants and small in adults, thymic function appears to continue into adult life, so the gland's larger size during infancy may not be significant. One panelist wondered whether data were available on alveolar macrophage clearance of particles and how that varies with age, since slower clearance during childhood could affect dose. Another panelist pointed out that EPA and the March of Dimes held a *Workshop to Identify Critical Windows of Exposure for Children's Health* in September 1999 in Richmond, Virginia. The workshop included a work group on the immune and respiratory systems, and a report of this work group was provided in Volume 108, Supplement 3 (June 2000) to *Environmental Health Perspectives*, pages 483 to 490. This publication includes a series of articles discussing the timeline for immune system development in humans, mice, and rats. The authors suggest birth to 1 year as a significant bin for maturation of immune system competence, and 1 to 18 years as a bin for establishment of the immune system memory (i.e., induction of response to disease). He suggested that the authors might be useful sources for further information. The chair suggested that bins for immunological development should be established by specialists after thorough examination of the literature in this complex area.

4.1.7 Reproductive and Endocrine Systems

Conclusions

Hyperplasia occurs dramatically beginning at about age 8 in girls and age 10 in boys, and extending for about 8 years in each case. This could be a vulnerable time for potential mutational changes that could have long-term health impacts. The group did not have data on when the function of the thyroid, parathyroid, pancreatic islet cells, and renal cortical and medullary cells become mature. This needs to be examined.

Discussion

Panelists agreed that in utero exposure was an important concern for development of ovarian and testicular tissues (as well as other organs), but agreed that in utero exposure was outside the charge of the group. They discussed what ages would be appropriate to bracket bins for reproductive development during adolescence. The chair noted that onset of puberty varies by gender, there is substantial variability within each gender, and onset appears to be happening at earlier ages. A bin for reproductive organ development that started at age 8 for girls would likely capture about 95 percent of girls, he said. The bin for boys would need to extend to age 19 to capture 95 percent of boys. Other panelists suggested 8 to 18 for girls and 10 to 19 for boys; 8 to 15 years for girls, since few girls have menarche past age 15; and 8 to 16 years for girls, since most textbooks cite 8 years as the lower limit for breast development (the beginning of puberty in most girls) and the upper limit for onset is about 14 years, with an additional 2 years until menarche. The chair pointed out that ovulation usually does not start until about 2 years after menarche, so a bin should extend for 2 years after menarche to allow for potential effects on developing oocytes. An observer expressed concern that too broad a bin could wash out the potential for making associations. Some panelists thought that there were a lot of data in this area, which would allow graphing of distributions; this would make it possible to create bins that capture different percentiles of boys and girls.

The chair asked the group to consider the endocrine system as well, since research has shown that many thyrotoxic drugs can interfere with thyroid development and function if given to animals early in development. Also, many environmental agents have been shown to interfere with thyroid function in animals. The chair asked panelists whether they had any information on the nonreproductive components of the endocrine system, such as the pancreas, thyroid, parathyroid, and adrenals.

One panelist mentioned that perchlorate, a groundwater contaminant in many areas of the western United States, is a powerful thyroid toxin that affects iodine uptake in the thyroid. Panelists did not have any data on whether thyroid sensitivity to environmental agents was different in children than in adults. Another panelist thought that even if there are windows of developmental vulnerability for the

endocrine system, this would not necessarily affect the amount of internal or external dose per exposure event.

Dr. Walker, an EPA observer, said there are chemicals in the environment that have been shown to affect the thyroid, and since thyroid hormones affect growth, the uptake and distribution of these chemicals could be affected. The chair agreed with this and asked the group whether there were periods when those organ systems are more likely to be differentially affected by exposure than at other times. He said that studies with animals show the induction of permanent thyroid dysfunction by using an endocrine disruptor to insult thyroid anlage (the fetal tissue that will ultimately form the thyroid gland) early in life, but the same compound will not cause dysfunction if exposure occurs later in life. A panelist said that the State of California has been concerned about both prenatal and perinatal exposure to perchlorate, which is a powerful thyroid toxin. She also said that animal studies show that brain maturation is grossly affected by effects on the thyroid. The chair pointed out that children born without a thyroid will suffer permanent brain damage if the thyroid function is not replaced within a short time of birth. Another panelist added that it is well known that thyroid deficiency in childhood can have permanent devastating effects on brain development. This suggests there is differential susceptibility to thyroid dysfunction in children compared to adults.

4.1.8 Lung and Respiratory Tract

Conclusions

Changes in the ventilatory rate, alveolar surface area, and oxygen requirements all alter the rate at which volatile and particulate material enter the system through the respiratory tract. Developmental changes in the upper airways (the nasal-pharyngeal pathway and the sinuses) need further evaluation. Development of some sinuses does not begin until after birth and occurs primarily during the first 6 years of life. Gender differences in ventilatory function develop around adolescence.

Discussion

The group discussed how alveolar surface area, ventilation rate, and behavior affected children's exposure via the lung. One panelist said that, for the first 2 years of life, alveolar surface area and ventilatory rate are significantly different, so that the minute volume exchange of oxygen and other gases is significantly higher. He said that exposure to particulate matter in the lung is approximately four times higher in the infant than in the older child. Another panelist said that a study by the California EPA at their Davis facility has shown that lung surface area to body weight ratio did not change much after 12 years of age, but that infants had a much larger surface area to body weight ratio and much higher oxygen requirements. She said that ventilation rates are a key factor in the first 1 to 3 months of life and are quite different than, for example, ventilation at 1 year of age. Thus, a consideration of ventilation rates would suggest different bins than the numbers of alveoli or the surface area of alveoli. Only about 15 percent of alveoli are present at birth; the rest are acquired during the first 3 to 4 years of life. Also, although infants are not very mobile, their breathing function can be highly active when they cry and scream. A third panelist pointed out that infants take about 40 to 60 breaths per minute, compared to 12 breaths per minute in adults.

The chair noted that ventilatory rate decreases during the first 3 months, and then continues to decrease at a slower rate. He said that alveolar surface area increases until about 3 years of age, when it changes proportional to body size. He also pointed out that there are significant gender differences during adolescence with respect to vital capacity, FEV₁, (forced expiratory volume in one minute) and so on. Boys generally have higher ventilatory function than girls of the same age and weight, though part of that may be related to lean body mass rather than weight itself.

Panelists discussed the significance of nose breathing. Most children are nose breathers, unless they get a cold (which children do on average six times per year). Style of breathing likely would not impact exposure to water-soluble compounds, since these can be absorbed in the upper airways; however, it

could impact less soluble compounds, which penetrate the lower airways. A panelist wondered whether differences in the nose structure with age might be relevant. Another speculated that there might be a critical period in infancy when there is a high ventilation rate and lower surface area of the upper respiratory tract that could make infants more susceptible to exposure of less soluble air pollutants in the lung.

The chair said a lot of data are available on ventilation rate in very young children, including data on the development of alveolar surface area, on minute volume rates, and therefore on air contact with the surface of alveoli. He thought those data were referenced in Chapter 2 of *Pesticides in the Diets of Infants and Children*. A panelist thought data were missing regarding measurements for specific activities in children under 3 years of age. Another panelist said most data are for sick children and thought that there were insufficient studies of healthy children. The quality of the available data must be considered as well, another panelist pointed out, including considerations of how the data were collected, how accurate they are, whether they are up to date, and whether there is some reason why they might not be applicable (e.g., they pertain only to sick children). Many of the techniques in older studies (for example, looking at the rate of blood flow from specific tissues) are far from state-of-the-art now, said another panelist, and there is disagreement about their value. The chair said that many older morphologic studies (e.g., measuring the surface area of alveoli) were well done and the data are available in old biology handbooks.

A panelist cautioned that future research should be directed toward data that would be truly useful for exposure assessment, and should avoid areas that will not have a significant impact. For example, an analysis of breathing rate distributions shows only a two-fold difference between the 5th and 95th percentile, which is insignificant in the overall uncertainty of risk assessment. The chair pointed out that it would be difficult for the current panelists to cite specific data gaps, since they had not recently reviewed the literature, and he suggested that the quality, comprehensiveness, and significance of the data for exposure assessment would need to be reviewed carefully for data gaps. He said most of the

papers in the *Environmental Health Perspectives* review (referenced earlier) recommend more research.

The group briefly discussed the upper respiratory tract. Panelists felt that the nose and upper airways could have significance since they serve as a chemical entry point, a potential target for effects, and a potential detoxifying organ; however, the panelists were not aware of data on whether and how the nose and upper airways might differ between children and adults. A panelist pointed out that large numbers of children have allergies or adenoidal hypertrophy; when affected by these, they breathe through their mouths, bypassing the ciliary clearance mechanism in the nasopharynx. Another panelist noted that certain sinuses (frontal and sphenoid sinuses) are not formed at birth, so development of some sinus function takes place after birth. Panelists listed upper airway changes, including sinus development, as an area that should be examined.

4.1.9 Gastrointestinal Tract

Conclusions

Up to 3 months or so after birth, the infant stomach is more alkaline and has a greater capacity to absorb intact proteins and large peptides. However, the group did not know whether this difference had any significance for exposure.

Discussion

The group discussed development of the gastrointestinal tract during childhood. They noted that, during the first 1 to 3 months of life, the stomach is more alkaline and has a greater capacity to absorb intact proteins and large peptides than later. This could impact developing sensitivities to certain proteins, since they get into the system intact at a time when immune tolerance could occur. However, this

difference lasts for 1 to 3 months, and very little data are available regarding these gastrointestinal differences in babies after the first month of age. One panelist questioned whether pH differences were relevant during the first month of life, when there is little variability in diet. Another panelist responded that there are data suggesting that pH is related to development of methemoglobinemia in infants fed water with high nitrate content. A third panelist pointed out that the infant stomach may also be exposed to particles cleared from the deep lung.

The group was not aware of changes in motility of gut during childhood and had no information on how gut surface area changed. They noted that gut colonization changes with birth and again with the transition from breast milk to other foods, but probably not much after that. Colonization of breastfed and bottlefed infants is different (e.g., breastfed infants are colonized with lactobacillus rather than *E. coli*). Beyond the first year of life, even breastfed babies are exposed to so many other foods that breast milk's impact is much less significant (unless it contains significant toxicants).

A panelist said data suggest that children's excretions have a high fat content and wondered whether that was because children have a high fat diet or because they are less efficient at absorbing fat. He said that decreased fat absorption has been suggested as a mitigating factor in exposure to lipophiles in breast milk.

One panelist questioned the extent to which children with deficient diets or nutrition should be noted as a subpopulation. A panelist said there likely would not be any gender-related differences in growth rate of the gastrointestinal tract until age 8 or 9, though there could be individual differences in growth spurts.

4.1.10 Circulatory System

Conclusions

There is a protein-binding deficiency during the first 6 months of life. Fetal hemoglobin, which is present during the first few months of life, has different binding capacities than adult hemoglobin. Around age 2 years or younger, children switch from liver and spleen as a source of hematopoiesis. Extracellular fluid increases during the first 6 months or so of life and then rapidly decreases until about age 2, when it becomes more consistently related to body size. Children with G6PD (glucose-6-phosphate dehydrogenase) deficiency may be a susceptible group. There may well be other susceptible groups of children that will need to be considered as we learn more about the prevalence of genetic differences.

Discussion

Panelists discussed features of the circulatory system that might distinguish children from adults. For example, with regard to blood chemistry during the first 6 months, there are many more protein-binding displacers relative to protein-binding sites, which means that there is excess bilirubin. Also, there are fewer basic and acidic binding sites, so there is more drug displacement. This suggests that the effective dose in the central compartment for chemicals that are significant protein binders will be different in younger children compared to older age groups. A panelist estimated that protein binding probably was an issue for the first 6 months of life. Another panelist said that infants have more fetal hemoglobin, which makes them susceptible to methemoglobinemia. A panelist pointed out that the hematopoietic capabilities of the marrow change during the first year, but he did not know if this had any toxicological significance. Also, extramedullary hematopoiesis (i.e., the liver and spleen producing hematopoietic tissue rather than just bone marrow) is very significant in the first year of life. After the first year, only bone marrow produces new blood cells. A panelist said that total body water in infants was higher, which affects volume, distribution, and clearance. Another panelist mentioned that G6PD deficiency, a genetic condition that can result in anemia, could characterize a susceptible subpopulation. Another panelist pointed out that the genetic polymorphism issue overlays the entire discussion.

4.1.11 Renal System

Conclusions

Before 6 months, renal function (in terms of parameters such as glomerular filtration rate and tubular maximum) is less than would be predicted by surface area, but by about 6 months of age, those functions have approached adult values per unit of surface area. So after about 6 months, renal function can be scaled by surface area.

Discussion

The chair mentioned a paper he had written showing that kidney function is practically normal at birth, and essentially reaches adult values per unit of surface area by age 6 months. This suggested there should be a bin for the first 6 months after birth, since there is still recognizable immaturity in renal function during that time. After 6 months a separate bin for the kidney likely is not necessary. Another panelist said that, while it is generally accepted that metabolic rate (P-450 metabolism) is substantially greater after the first year and throughout childhood, he has seen recent information suggesting it is not. These data (which have been criticized) do however indicate that there are differences in the rate of clearance of drugs but no differences in the rate of metabolism compared to adult levels. This opens to question the commonly accepted notion that rates of metabolism and renal clearance are higher during childhood and then gradually diminish to adult levels during adolescence. A third panelist discussed allometric scaling. He pointed out that many of the P-450 and conjugation systems mature somewhere between 6 months and 1 year, at which point they can be allometrically scaled to surface area. For example, physicians can use this scaling to predict blood flow to the liver based on surface area when prescribing drugs. The fact that the liver system is immature during the first 6 months and the fact that allometric scaling cannot be done for that period together argue for a bin covering the first 6 months.

4.1.12 Cardiac System

Conclusions

The group had little information about the changes in circulatory dynamics in the heart. They recommended that EPA examine whether there are any significant changes in cardiac output and regional blood flow during childhood.

Discussion

The chair kicked off the discussion by saying that the heart generally appears to be fairly mature at birth, and that he was not aware of any significant changes in shape or function after birth. A panelist questioned whether blood flow to tissues or organs could change as a function of age. Panelists were not aware of significant changes to the cardiac system, but thought it would be useful for EPA to examine whether there are any significant changes in cardiac output and regional blood flow during childhood.

4.1.13 Central Nervous System (CNS)

Conclusions

The central nervous system changes rapidly during early development and likely is the system that needs the most bins. Very little information is available about the duration and variability of periods of change. Neuronal migration occurs during the first 6 months of life, followed by rapid myelination, much of which is completed by 2 years of age. At about age 10 years, certain synapses change and atrophy. This is probably reasonably complete by age 20. The blood-brain barrier also changes during childhood, though the group did not know when this occurs, and this could be significant.

Discussion

The chair said that the *Environmental Health Perspectives* supplement (referenced earlier) contained a paper by Deborah Rice and Stan Barone, Jr. (pages 511 through 533), with a figure on the development of the nervous system, which showed that the various areas of the brain continue developing until age 19. The paper also had data showing that the order in which nervous system components develop is not necessarily the same in rats as in humans, so there is difficulty extrapolating from rats to children. Historically scientists have thought that most brain development takes place by 1 year of age, and brain size by age 2 is about 90 percent of adult size. However, research on synaptogenesis indicates that children lose a lot of synapses in early or mid adolescence in order to develop an adult brain configuration. This and other research suggests that brain development is not static during childhood, so it is difficult to know what might be critical periods. A panelist said that for some toxins like lead, the first 2 to 5 years are critical because this is the period when brain growth is rapid.

The chair said the fact that neonatal deficiency in thyroid function or PKU (phenylketonuria) can rapidly lead to permanent brain damage suggests that the first 6 or so months of life can be a very sensitive time. Also, the maturation of the blood-brain barrier would affect the internal dose to the central nervous system. The window for that maturation is approximately the first year of life. The chair mentioned concern about the effect of thimerosal, a mercuric component of vaccines. The effects of vaccination on the central nervous system may have increased as the age of vaccination has decreased. Though the mechanism for these effects is not known, their existence suggests that the nervous system is more vulnerable in younger children. He also mentioned that there are increasing neuropsychiatric disorders for birth to adolescence at varying times; however, it can be difficult to identify peaks in these disorders with age because the way in which these diseases are defined and diagnosed at different ages has changed over time.

4.1.14 Muscle

Conclusions

Muscle goes through the same periods of hyperplasia and hypertrophy that other tissues do, but little is otherwise known about the development of muscular tissue.

Discussion

Panelists discussed data that might suggest critical periods for muscle development in children. The chair showed data on creatinine coefficient (a surrogate for muscle mass/development) by age and gender. These data showed that the muscle mass of boys and girls began to differ around 12 to 14 years of age. Dr. Walker, an EPA observer, said that lots of data are available on lean body mass as a function of age. These data show growth spurts as children develop and are important for assessing the effects of chemicals like cesium, which target muscles in the body. He also said the size of the muscle compartment is important, because it determines how much of the chemical is stored. A panelist agreed, saying that while muscle had low perfusion and metabolism compared to other organs, it is a significant large reservoir for storage of chemicals in the body. The size of the muscle compartment is a sensitive parameter in PBPK modeling. It would therefore be an important variable for neonates because they have a relatively large muscle compartment.

The chair showed data for lean body mass in boys and girls. He pointed out that changes in body mass during childhood reflect changes in surface area and weight, and that there are gender differences. Dr. Walker pointed out that there are racial/ethnic differences in these parameters. For example, African-Americans have higher bone densities than other groups, and Caucasians have higher lung capacities than African-Americans. He thought that genetic or racial differences should be considered. The chair asked whether data were available for children. A panelist responded that there was a difference of

about 10 to 15 percent in lean body mass in children, though other panelists felt this was too small to be significant.

A panelist discussed the role of creatinine in dose assessment. Dose assessors routinely use creatinine as a corrector for hydration state when evaluating dose for various compounds that are excreted in urine. The assumption has been that daily creatinine output is constant in children, but the panelist's (and others') research suggests this is not so. He felt that creatinine output and variability in children should be better studied, given creatinine's role in dose estimation. The chair expressed surprise at this finding, since many studies on urinary excretion assume that creatinine clearance is a constant unless the subject is dehydrated.

Dr. Walker, an EPA observer, showed a graph illustrating how cancer incidence rates for rhabdomyosarcomas vary with age. The curves showed that the rates peaked during the neonatal and pubertal growth periods. He said this corresponded very closely to what is normally found in height and muscle velocity curves and suggests an association between muscle growth rates and soft tissue cancers in children. The chair pointed out that this raises the issues of hyperplasia and hypertrophy in all tissues. Cells are more susceptible to mutation when they are multiplying (i.e., during hyperplastic periods) than when they are simply enlarging (i.e., during hypertrophic periods). Hyperplastic multiplication tends to occur early in development and continue for some time; how long it continues varies with the tissue. After that, growth is largely hypertrophic until adolescence, when hyperplastic growth occurs again. Identifying periods of hyperplastic growth specific to the various organs and tissues (generally sometime during infancy and early adolescence) could provide important information about periods of susceptibility. A panelist agreed this was important and said the State of California was trying to identify hyperplastic time periods in order to "weight" age at exposure for risk assessments.

Another panelist said that the first year or two of life, when the exposure measures change rapidly, would be much more important in terms of exposure assessment than the later years of childhood, when exposure measurement would not vary by age. A different panelist responded that occupational exposures would start to occur in later adolescence; these exposures should be considered in a risk assessment. The chair pointed out that muscle mass increases before strength in adolescence, so adolescents are vulnerable to occupational injury because they are not as strong as they look.

4.1.15 Sensory Organs

Conclusions

The group reported no conclusions for this area.

Discussion

Panelists briefly discussed the eyes and ears. A panelist said that some toxins do enter through the eyes and ears, but he did not know whether children were more susceptible than adults. Other panelists pointed out that environmental tobacco smoke is associated with recurrent otitis media, and recurrent ear infections in early childhood can cause learning disabilities and lifelong difficulty. Another panelist mentioned data suggesting that young children are more susceptible to drug toxicity in the middle ear.

4.2 General Issues

Conclusions

- # The critical periods for exposure and impact on organs and systems need to be evaluated. The scientific data are not readily available as to exactly what those periods are, when they occur, and how sharply defined they are. Research should be done to gather available data and evaluate their methodology, reliability, sample size, relationship to current exposure conditions,

and variability. Where no data are available, where the methods are antiquated, or where the data do not cover the age groups, research should be conducted to gather the data.

- # Regarding bins for physiological development, the following general bins could be used as a very preliminary starting point: 0 to 6 months, 6 to 12 months, and 1 to 3 years for boys and girls; 3 to 8 years and 8 to 16 years for girls; and 3 to 9 years and 9 to 18 years for boys. The 0 to 6 month bin will likely need to be further subdivided; possible appropriate subdivisions might be 0 to 1 month, 1 to 3 months, and 3 to 6 months. The bins should be correlated with behavior. Bins do not make sense unless there are real data to back them up, so research should be conducted as mentioned above to gather and evaluate existing data to confirm or refine these bins, and data should be developed where they do not exist.
- # Almost all systems start with cell growth in number (hyperplasia) and then go to cell growth in size (hypertrophy). Periods of hyperplasia have the greatest likelihood of mutational changes. So many of the early bins reflect the period of cellular hyperplasia. This becomes particularly obvious historically in studies of body fat, but is also true of other systems.
- # Both premature and low birth weight babies are sensitive subpopulations that need to be considered separately. With very premature babies (under 1,500 grams), there is even more concern, since their health status continues to differ from term babies even when they reach what would have been term. Other susceptible populations should be considered. The group did not discuss the fetus, but they did emphasize its importance because so much critical development that can affect the impact of environmental agents takes place during the fetal period.
- # Variability is an important issue that must be considered. Variability is greater during periods of rapid change and may also be related to gender, age, ethnicity, and genetic polymorphism.
- # The agency should continue to involve pediatricians in further discussion about children's exposure.

Discussion

Several panelists noted that there are critical periods for children's health when developing target organs and systems might be particularly vulnerable to toxic effects from exposure to environmental chemicals. These periods would need to be overlaid with behavioral data to show whether significant exposure could occur. Ages of particular concern would be those at which exposure correlates with a

critical period for developmental physiology. A panelist wondered whether these periods were more relevant to hazard identification than exposure assessment, and suggested the group might want to confine its discussion to physiological changes that affect portals of entry for exposure to environmental chemicals. Others disagreed, saying that data on vulnerable periods would help assessors understand where they needed to refine their exposure estimates.

Members of the group emphasized that the bins they had indicated for individual organs and systems were highly preliminary. Data that panelists are aware of suggest there are critical periods for effects in children, but this needs to be evaluated. They recommended that research be conducted to systematically review the literature, gather data relevant to defining critical periods in target organs, and evaluate these data for reliability, applicability, and relevance to current exposure and lifestyle factors. Such a search would likely reveal many data gaps in which additional research would be needed to identify and define critical periods.

The group discussed whether overarching bins or breakpoints could be developed for childhood based on similarities in the bins for the individual organ systems. A panelist suggested the following general bins: 0 to 6 months; 6 to 12 months; 1 year to 2 or 3 years; 2 or 3 years to early adolescence (8 or 9 years depending on gender); and 8 or 9 years to the end of adolescent growth. Another panelist thought that 0 to 1 month might be a separate bin because so much change happens during that first month. A third panelist said there would be substantial variability during the first year, so that at least two bins if not more would be appropriate. Another panelist expressed concern that too many bins might create a nightmare for the regulatory community, who could be asked to provide data for each bin.

Panelists discussed the issue of variability. They noted that each bin, rather than being discrete or fixed, represents a distribution. The larger the variability within a bin, the greater the concern about using a median or central tendency value for that bin. Even a small bin, for example for the first month after

birth, could have great variability if dramatic developmental changes are occurring, such as developments in lung function. Since children are a much more variable population than adults, robust data sets are needed to generate bins small enough to adequately characterize, and minimize the variability in, the groups the bins represent. Variability is greater during periods of rapid change (e.g., growth spurts) and may also relate to gender, age, ethnicity, and genetic polymorphism. Sufficient data are needed to capture the range of variability and ensure that each bin is small enough to minimize variability. Good statistical data on distribution within the bin are important, because they make probabilistic analysis possible; this in turn makes it possible for an analysis to reflect the full spectrum of the parameter, rather than a single-point estimate that may bias the results. Panelists generally agreed that, in cases of high variability, distributional data would be very valuable.

Panelists discussed premature and low birth weight babies. A number of panelists felt it important to consider exposure of premature infants. For example, said one panelist, premature infants are highly exposed to phthalates. Several panelists suggested that premature babies represent a special subpopulation, particularly very small premature infants (e.g., under 1,500 grams). Premature infants during the first month or two of life are quite different from full-term infants in terms of hepatic clearance and other systems. The chair suggested that the bin for premature infants could go up to the expected time of birth, at which point they are similar to full-term infants unless they are sick.

Several other panelists said that low birth weight babies (less than 2,500 grams) should also be considered a special population. Since mortality and birth weight are a straight line, all low birth weight children, even at term, are susceptible.

The chair suggested that weight in relation to gestational age should be considered. For example, a premature infant with a low birth weight (e.g., 1,800 grams) could be more vulnerable than an infant of the same weight born after 37 weeks of gestation. He suggested that infants with a weight too low for

gestational age be considered a separate group from infants with a weight appropriate for gestational age.

Another panelist pointed out that the reason why a child had low birth weight was also important. Low birth weight due to a congenital infection would likely be a greater concern than low birth weight due to maternal reasons such as placental insufficiency, hypertension, or smoking, which probably would not affect growth once the baby was born. Babies and children of any age with chronic illness should also be considered a special subpopulation, the chair said. Around 10 percent of children will have some kind of chronic illness (e.g., asthma, cerebral palsy) at some point in their life that seriously interferes with their daily activities.

Panelists mentioned that concurrent exposures to other chemicals could potentially be a problem at any time during childhood. Concurrent exposure to recreational drugs could be a particular problem in adolescence.

A panelist suggested that, for longer-term research, a longitudinal study to develop a data base to model growth would be useful. Some other panelists questioned the value of longitudinal studies. They said that these studies are very expensive and that the results from following individuals over time are not different enough from cross-sectional data for different ages to make them worth doing. Another panelist pointed out that the factors that influence exposure and development (e.g., activity patterns, types of food consumed) change over time. For this reason, contemporary cross-sectional data would be more valuable than longitudinal data because they would reflect current conditions.

Dr. Walker, an EPA observer, said that cross-sectional data do not allow identification of discrete critical growth periods, whereas longitudinal data do. He also said that a database on developmental variables in childhood would be very helpful for risk assessment. The agency, he said, needs to better characterize anatomical and physiological parameters, determine whether sufficient data are available to

define critical periods, and develop a scientific basis for defining critical periods. Ideally, sufficient information ultimately will be available to replace each bin with a continuous function/model from infancy to maturity.

4.3 Research Recommendations

At the end of the discussion, panelists were asked to *individually* compile a list of the research needs for children's exposure they felt were most important. Panelists listed the following needs. (Note that since these needs were suggested by individual panelists, they do not necessarily represent the views of more than one panelist.)

4.3.1 Short-Term Research Needs

- # EPA should critically evaluate the existence and quality of data bases for organ system functional development with respect to bins and should particularly identify areas where there are no data. Variability within the bins should be characterized. A database for system development through childhood, from birth to maturity, should be developed.
- # Research is needed to improve our understanding of exposures in the 0 to 6 month bin (particularly for inhalation) and the 6 to 12 month bin (particularly for nondietary consumption) because so much change takes place during this time. Also, adolescence appears to be an important physiological window for which further research may be needed.
- # The development of the gastrointestinal tract and its impact on bioavailability for several classes of compounds should be studied. There is significant uncertainty about degree of nondietary ingestion and how age and development impact absorption.
- # A prospective study (perhaps of siblings) would be useful to better understand sex differences in lipophilic absorption and mobilization and differences in plasma levels for lipophilic substances. This would be particularly important to a better understanding of the impact of absorption during adolescent growth spurts.
- # Research is needed to evaluate common modes of action for pesticides and to develop and validate biomarkers of exposure that may be useful for a broad spectrum of pesticides.

- # Data on food and water intake should be examined to determine their adequacy in covering intake for each age group. More people should be surveyed and the surveys should cover more than 2 days. Development of an algorithm to determine the ideal duration of sampling (i.e., the minimal number of days needed to provide data relevant to a long-term average) would be useful. Optimal duration may vary with age. For example, what food is eaten in early life varies much less than what food is eaten at older ages. The length of the study may need to increase as food intake and variability increase.
- # Research is needed to improve the general exposure assessment (measuring and modeling) techniques to improve the power of epidemiologic data for the dose-response component of risk assessment.
- # Research is needed to improve understanding of differences in exposure in critical time periods for different socioeconomic and ethnic groups.
- # Research is needed to improve our understanding of, and ability to measure, what specific contaminants are present in various environmental media to which children are exposed, including dust, soil, medicines, and vaccines.
- # In the area of inhalation exposure, research is needed into upper respiratory function during the first 2 years of life, including scrubbing capability, transport, and ciliary function.
- # Research is needed to clarify and generate new data on the lung, including the major factors that influence absorption in the lung (e.g., surface area, cardiac output), respiratory rate, and flow rates of water-soluble and lipid-soluble compounds for the deep lung and upper respiratory tract. Since almost all studies of respiratory situations have been done with people at rest, respiratory function during exercise appears worth looking at. In general, the state of the art for measuring absorption in lung of children for different classes of chemicals needs to be improved.
- # Research is needed into pulmonary clearance in children, particularly both ciliated and macrophage clearance of particles from the deep lung in very young children.
- # Research is needed into the upper respiratory barrier, including the sinuses, oral pharynx, nasal physiology and scrubbing activity, and the distribution of chemical flow pathways in the nose (the relationship of flow change to surface area).
- # More information is needed on liver clearance functions. Data related to liver clearance mechanisms and enzyme levels (except, possibly, for recent P-450 data) should be reexamined.

- # More information is needed on cardiac output.
- # More information is needed on skin permeability in children with or without occlusion. For example: At what age does the rate of skin absorption in children match adult values?
- # Information on dermal transfer efficiency and absorption kinetics of chemicals such as pesticides is grossly inadequate. Better information is needed on transfer efficiency and absorption kinetics to skin.
- # Research is needed into lipophilic and nonlipophilic substances in breast milk and what kind of transfer rates exist between milk and the neonatal gut, given the gut pH and developmental changes. These transfer rates likely vary with time as the gut starts maturing. Current breast milk models focus on lipophilic toxics. There is a pH difference between plasma and breast milk, so breast milk is a sink for some chemicals, depending on the pharmacokinetics. Research should examine factors other than lipid solubility that determine what enters breast milk. Also, there is a need for better measurements of breast milk contaminants (for example, better data are needed on metals). Breast milk data primarily cover white upper middle class women; better data may be needed for other socioeconomic groups.
- # On the behavioral side, research is needed into transfer rates and efficiencies between surfaces and the skin, such as hand- or toy-to-mouth transfer rates. In general, better data are needed on the transfer efficiency for mouthing.
- # Research is needed to better define rates of consumption of game fish in children of different cultures. There are significant cultural differences in how much fish people eat.
- # Information on soil ingestion rates in children is not adequate. Both incidence and prevalence data are needed. Also, better understanding is needed of what fraction of soil ingestion might be house dust, which could have higher concentrations of some contaminants.
- # Better information is needed on consumption and content of folk and herbal medicines. Data suggest that about 60 percent of the U.S. population uses these medicines. Some of the medicines contain toxic components, such as lead.
- # Data are needed on the incidence and prevalence of children accompanying parents to farm fields during periods of farm activities.

4.3.2 *Long-Term Research Needs*

- # Panelists debated whether a longitudinal correlative study of children starting at birth and following them for about 20 years would be useful. Some felt such a study would be useful, while others felt it would too expensive and yield results that might be out of date by the time the study was completed. However, somewhat longer-term exposure information may be needed than the short-term/cross-sectional data currently available. In particular, longitudinal data through first year or two of life could be useful, and differences due to socioeconomic status or ethnicity should be noted.
- # Long-term research should include research on critical periods and possible exposure differences in fetal development.
- # Ultimately, sufficient data should be gathered to develop a continuous multivariate model that can replace bins. Over the long term, EPA should work to develop this type of model.³

³In a post-meeting comment, one panelist noted that he strongly dissented with this recommendation and felt that it would not be a worthwhile line of research. Given the variation in the physical-chemical behavior of agents of interest and the multiplicity of exposure scenarios and toxicological endpoints EPA must deal with, he felt that a single model would not be feasible.

5. FINAL PLENARY DISCUSSION

Kimberly Thompson delivered some summary remarks to synthesize the findings of the two discussion groups and introduce the plenary session of the workshop. It is clear, she gathered, that there is a great deal of work that remains to be done in learning how to assess children's exposure. The discussions of the two groups have highlighted the basic fact that it is inadequate to lump children into a single category when conducting risk and exposure assessment. They have also pointed out that there are existing data sources that could tell us a great deal about children's exposure factors if they are only properly analyzed or re-analyzed. There ought to be a comprehensive review of the data that have not been adequately analyzed.

The behavior group, which addressed the question of whether or not age bins were really accurate representations of childhood development, indicated that bins should be replaced by some other analytical framework in the long run. For the short term, while one must use age bins, it is encouraging to note that there is substantial overlap between the provisional binning systems developed by the anatomy and behavior groups. There are, however, some inconsistencies to be worked out in the age ranges between 2 and 15 years. One panelist reiterated the point that users of bins should understand the underlying distributions of behavior that those bins are approximating. Another panelist pointed out that there was no reason to use a fixed set of bins for all children's exposure assessment. One could use a different set of exposure bins for the different organ systems targeted by a chemical, so as to make sure that the bins were firmly centered around the relevant windows of vulnerability.

One panelist asked whether the present exposure factor data were sufficiently copious that they could be re-analyzed and broken down into more detailed age bins. Dr. Shea, chair of the behavior group, stated that the answer to that question is unknown, but estimated that the adequacy of present data sets would be highly variable. In some exposure scenarios, children could be rebinned, but in others one would create sample sizes that would be too small (e.g., less than 10 children) if one broke age

categories down more finely. Another panelist seconded the point that exposure factors should be evaluated in a chemical-specific or exposure-specific fashion.

Several panelists inquired about the next steps that EPA would take in connection with the issues raised at the workshop. William Wood suggested that EPA might produce a supplement to the 1992 *Exposure Assessment Guidelines* that would incorporate some of the conclusions from the workshop. He also indicated that EPA was organizing a workshop on children's pharmacokinetics. One panelist suggested that EPA use the *ToxProfile* document as a guide to organize data well.

Pediatricians among the panelists were interested in continuing and strengthening the partnership between the risk assessment community and the pediatric community that they saw developing at the workshop. One panelist suggested that EPA reach out to pediatric specialists who might be able to provide more specific answers to its questions about behavioral and physiological child development. The EPA should also start to actually use age-specific exposure factors in its risk assessments.

Dr. Thompson asked the panelists and observers to suggest important lessons for EPA that emerged from the workshop. Individual panelists and observers suggested that EPA:

- # Draw on the knowledge of experts in developmental biology, physiology, pharmacology, and toxicology.
- # Identify three or four epidemiologists to serve on an *ongoing* basis as risk assessment advisors.
- # Carefully verify the general conclusions of the panelists by going back to the specific exposure data. EPA should realize that the panelists did not have access to this data while forming their conclusions—they were working solely from their general knowledge.
- # Use a group like the International Life Sciences Institute or the National Academy of Sciences to pull together the necessary experts on a long-term basis to address children's exposure issues.

- # Work in the context of specific exposure scenarios.
- # Gather new exposure factor data to flesh out the new age bins that are created.
- # Evaluate the variability within particular age bins and study how different exposure pathways might require different age bins.
- # Carefully distinguish behavioral data from other kinds of data and avoid exaggerating their precision. There is a particular temptation to treat quantified behavioral data as if they were engineering data, simply because they are expressed in numbers.
- # Be careful to reflect ethnic variability.

Some panelists indicated they were not adequately notified that they would be asked to come up with short-term research goals at the workshop. Therefore, EPA should not take the suggestions offered at the workshop to be comprehensive—panelists might have come up with more suggestions if they had had more notice.

Dr. Thompson thanked the panelists for their participation and hard work in connection with the workshop. Jan Connery thanked the panelists on behalf of ERG and adjourned the meeting.