

# MUSC

MEDICAL UNIVERSITY  
OF SOUTH CAROLINA

Discovering. Understanding. Healing.

GENERAL PEDIATRICS  
326 CALHOUN STREET  
2 CENTER • ROOMS 200-205  
PO BOX 250106  
CHARLESTON • SC 29425

(843) 953-8512  
FAX (843) 953-8709

J. Rault Reigart, MD  
Director

William T. Basco, MD  
Paul M. Garden, MD  
Walton L. Ector, MD  
Melissa Howard Henshaw, MD  
Patricia G. McBurney, MD  
Colleen Moran, MD  
James R. Roberts, MD  
Sara E. Schuh, MD

Patient Appointments  
General Pediatrics Clinic  
(843) 953-8444  
Primary Care Clinic  
(843) 953-8499

Framework

August 9, 2002

Dr. Paul Gilman  
Assistant Administrator  
Office of Research and Development  
USEPA Headquarters, Ariel Rios Building  
1200 Pennsylvania Avenue, NW  
Washington, DC 20460

Dear Dr. Gilman;

Over the course of the last two years, the Child Health Protection Advisory Committee (CHPAC) has evaluated a new approach to assessing health risks from environmental exposure. This health outcome approach is described in *The Children's Health Risk Matrix: Technical Background Paper*. A similar health outcome based approach is expected to appear in the report of the Office of Research and Development (ORD) sponsored International Life Sciences Institute's *Workshop to Develop a Framework for Assessing Risks to Children from Exposure to Environmental Agents*. This approach contrasts with existing EPA risk assessment approaches focusing on individual chemicals or around chemicals sharing a common mechanism of action. We believe that this innovative approach has merit, particularly when considering multi-factor health outcomes such as developmental dysfunction or chronic lung disease, and that this approach would supplement, but would not replace, exiting risk assessment approaches.

The CHPAC wishes to encourage the ORD to assess the merits of this approach and to consider incorporating this approach into EPA's formal risk assessment process. We would appreciate an opportunity for designated CHPAC members to meet with you to discuss this approach, to gain a better understanding of the Framework development process, and to understand the status of health outcome focused risk assessment within ORD. If the ORD chooses to further evaluate this approach, we would also request a briefing to the CHPAC when sufficient progress has been made to merit such an update.

Our new approach begins with selection of a health outcome of concern. One then proceeds to consider: the possible exposures which might lead to the outcome being considered, the life stages at which exposure may occur to produce that outcome, and the life stages at which that outcome may become manifest as clinical or sub-clinical disease. For example, increased risk or severity of adult lung disease, resulting from abnormal lung development, may have begun with intrauterine exposure to a particular chemical.

Without full consideration of all four factors- health outcome, exposure, exposure life stages, and outcome life stages, complete characterization of such an illness scenario is not possible. By placing these considerations into a matrix structure, a systematic approach to health outcomes and causation is facilitated.

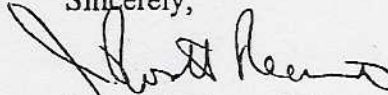
To test the application of this matrix, the Science and Research Work Group of the CHPAC undertook pilot exercises with two disease outcomes- childhood asthma and neurodevelopmental disorders. These exploratory exercises were not driven to consensus or completion and are therefore not attached. However, these exercises taught us a great deal, and CHPAC feels that these learnings, listed below and discussed at greater length in the technical background paper, are of sufficient value to merit transmittal to the agency:

- The matrix is a useful concept and assures comprehensive consideration of various agents, exposure life stages, outcomes, and outcome life stages on a systematic basis.
- The matrix works best for reasonably well-defined entities such as asthma. Diffusely defined categories of outcome, such as neurodevelopmental disorders, do not fit readily into this format as they contain a variety of sometimes poorly defined and overlapping outcomes.
- Much of the data necessary to fill in the matrix for a wide variety of agents and outcomes is not available. While this does reduce the immediate utility of the matrix for risk assessment, the matrix is still helpful in assuring systematic and comprehensive consideration of all factors related to a particular health outcome.
- The matrix may be of significant use in identifying data gaps and, perhaps more importantly, prioritizing efforts to fill those data gaps based upon reasonable scientific and policy judgment as to the likely effect of a particular agent, the disease burden of expected outcome, the life stage effected, and ultimately the anticipated size of the affected population(s).
- In many cases, agents will have similar exposures over a number of life stages, which can then be combined for purposes of risk assessment. This does not negate the value of the framework in prompting the policy maker to at least consider all exposure life stages.
- Similarly, many agents will have similar outcomes over a number of life stages, which can then be combined for purposes of risk assessment. Again, this does not negate the value of the matrix in prompting the policy maker to at least consider all outcome life stages
- A need for flexibility in application of the matrix was recognized. While the SPWG believes that there are great benefits to systematically considering all life stages independently at the outset of the hazard and risk assessment process, the risk

assessor must ultimately be permitted to adapt the matrix to the specific exposure and disease process under consideration. Thus, policy should allow for the consolidation and/or adjustment of life stages, or even the designation of additional life stages, when such adjustments are necessary to most accurately assess risk.

Your time and your attention to this important issue are very much appreciated, and we look forward to the opportunity to meet with you to discuss development of this new approach to risk assessment. I have asked the OCHP to set up a meeting with you and the representatives from the CHPAC.

Sincerely,



J. Routt Reigart, MD  
Chair, Children's Health Protection  
Advisory Committee

JRR/pc

cc: Administrator Whitman  
OCHP, Joanne Rodman

## *THE CHILDREN'S HEALTH RISK MATRIX*

### *TECHNICAL BACKGROUND PAPER*

This document, describing a child risk assessment matrix, provides technical background to a letter from the Children's Health Advisory Committee to Dr. Gilman, Chief of the Office of Research and Development, the Environmental Protection Agency and copied to the Administrator, dated August 9, 2002.

#### **NATURE OF THE CONCEPTUAL MATRIX:**

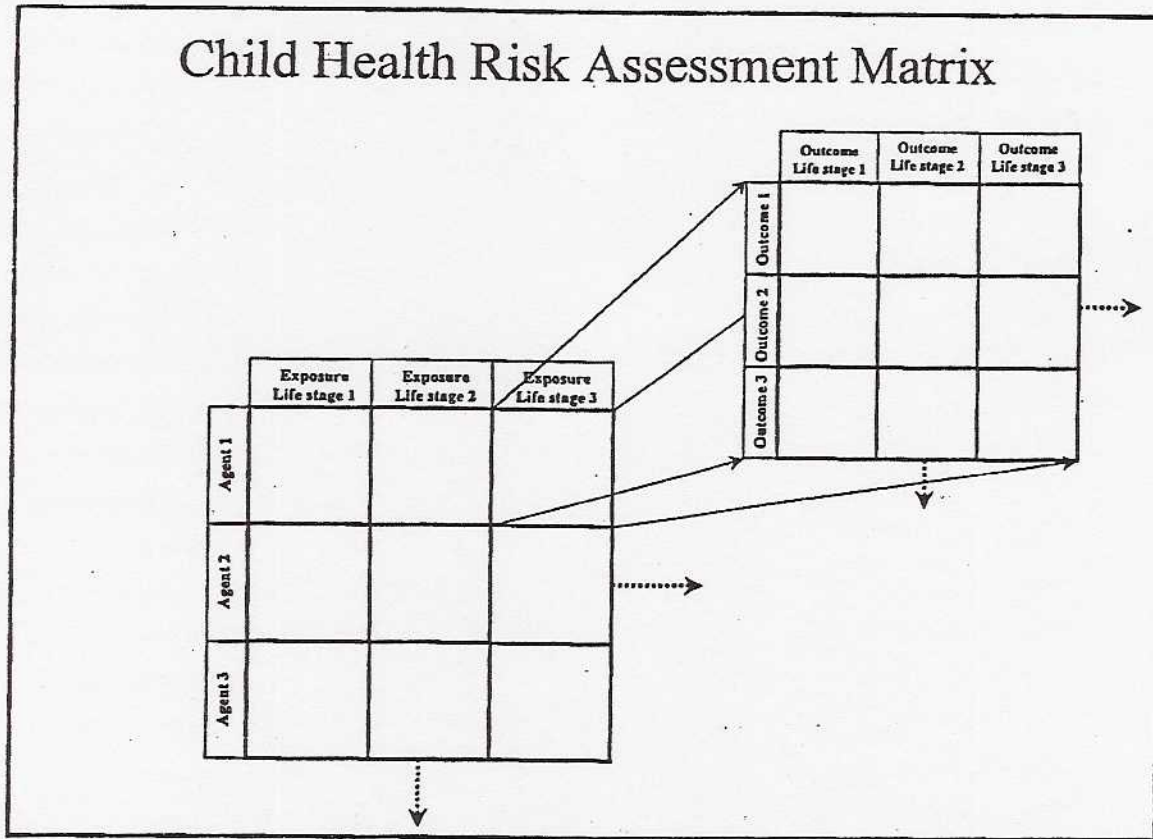
Ideally, a complete description of the outcomes of childhood exposure (in which we include prenatal and even pre-conceptual factors) would consider four factors:

- 1) The nature of the specific exposure(s).
- 2) The timing of exposure relative to critical life stages (preconceptional, embryonic, fetal, perinatal, infant..... etc.)
- 3) The nature of any adverse effects (i.e.- outcomes) resulting from this exposure.
- 4) The timing of these outcomes relative to critical life stages, including outcomes that may be manifest only in the adult or, indeed, the elderly individual.

These factors can be placed in a matrix to help conceptualize childhood hazard and risk assessment. As a four-dimensional framework is difficult to visualize, the matrix can be more conveniently constructed as illustrated below. In this illustration, there is a primary matrix considering a series of potential environmental exposures (Agent 1, Agent 2....) which may occur at any of a number of life stages (Exposure life stage 1, Exposure life stage 2....). These exposure life stages are analogous to the concept of "age bins". However, the use of chronological age is largely a matter of convenience, and the clustering of ages is largely determined by biological and behavioral changes independent of time itself, perhaps making life stages a preferable terminology.

For each compartment within the primary grid (i.e.- for each possible combination of agent and life stage of exposure) there is a secondary matrix (a "matrix within a matrix") which considers all possible outcomes (Outcome 1, Outcome 2...) and the various life stages at which these outcomes may occur (Outcome life stage 1, Outcome life stage 2.....)

# Child Health Risk Assessment Matrix



The utility of the matrix is perhaps best illustrated by a brief example using a hypothetical material that interferes with normal lung development in the embryonic stage of infant development. Such a compound would appear in the primary matrix at the intersection of:

Agent: Compound-X (hypothetical)

Exposure Life Stage: Embryo (1<sup>st</sup> trimester, organogenesis)

This hypothetical exposure might have multiple outcomes of interest, each of them relevant at a particular life stage of development. For example:

Outcome Life Stage	Outcome of Concern
Embryonic	abnormal progression of lung development.
Fetal	(No discernable effect)

Newborn- Premature	Increased risk of bronchopulmonary dysplasia (lung disease of the premature infant)
Newborn (term)	(No discernable effect)
Infant	Increased risk of serious or fatal infection with Respiratory Syncytial Virus (RSV).
Toddler	Increased risk of asthma and/or pneumonia Increased susceptibility to air pollutants
Child, Teen, Adult	No readily discernable effect (subtle abnormalities of pulmonary function are subclinical).
Elderly	Increased risk or severity of Chronic Obstructive Lung disease (COLD).

---

It was clear at the outset that much of the knowledge necessary to completely fill in the matrix for a wide variety of agents is not currently available. Not all agents will have effects in all exposure life stages or produce outcomes in all outcome life stages, and thus many "boxes" in the matrix may in fact be devoid of content. Finally, it was recognized that various effects may be shared among multiple exposure and/or outcome life stages. These various stages could then be "collapsed" or consolidated for the purposes of risk assessment.

While the SRWG undertook some discussion of how to best select appropriate life stages, this subject has been more addressed in the *Summary Report of the Technical Workshop on Issues Associated with Considering Developmental Changes in Behavior and Anatomy when Assessing Exposure to Children* (EPA/630/R-00/005, December 2000). The life stages proposed in this document appear to be a satisfactory starting point for default assessment. However, the authors point out that the "[b]ins may be useful as a guide to the development of exposure scenarios, but EPA should always keep in mind that the bins are only a crude approximation of an underlying distribution. Age bins, if used uncritically during exposure assessment, could lead to significant error."

These limitations notwithstanding, conceptualizing environmental exposures in a comprehensive, systematic manner assures that all potential opportunities for exposure and all potential outcomes of the exposure are considered at all stages throughout the life of the individual. The matrix could, for example, also be used to identify multiple agents

which, although disparate in nature and in timing of exposure, may contribute to a common outcome.

#### TEST APPLICATION OF THE CONCEPTUAL FRAMEWORK:

To assess the utility of the conceptual matrix, SRWG decided to look at two broad categories of concern: neurodevelopmental abnormalities and asthma. The former topic was chosen, in part, because of the availability of many examples of teratogens and developmental neurotoxicants which could be utilized to partially fill and thus explore the matrix. Asthma was chosen as an example of an illness of clearly multifactorial cause for which the relevant environmental triggers are still only partially characterized, but which clearly has impacts on health and well-being throughout life. The intent of the SRWG was to develop brief white papers on both of these subjects, including review of the conceptual matrix.

An outline of the neurodevelopmental paper was prepared by an ad-hoc subgroup of the SRWG under the leadership of Dr. Peter Spencer, who has extensive experience in this area. The SPWG subsequently determined that little additional knowledge regarding the matrix would be gained by actually writing the neurodevelopmental review. The asthma review was performed by Dr. Robert Wood, pediatric allergist at the Johns Hopkins University School of Medicine.

Development of the neurodevelopmental outline did provide some insight into the utility of the matrix. It was clear that, while some materials have effects clearly limited to a specific window of exposure (e.g., thalidomide induced limb defects), other materials have effects over the entire interval of neurological development (e.g., retinoids). Further, some syndromes (e.g., methyl mercury, fetal alcohol syndrome) are well described and characterized primarily at birth while others (e.g., low-level lead poisoning) are not generally recognized at birth but have a variety of clinical manifestations recognizable in later life stages. In spite of this variety, the matrix functioned well to accommodate the variety of toxins. Overall, the matrix appeared to have a high utility for the well-defined examples listed here.

However, discussion of how to structure a neurodevelopmental matrix in detail did identify some difficulties. Neurodevelopmental abnormalities are complex and are not, in many cases, readily broken down into clearly defined or agreed-upon outcome categories. Further, neurodevelopmental disorders almost invariably span multiple outcome life stages, necessitating either arbitrary categorization or the broad lumping of outcome life stages. Finally, severe neurodevelopmental abnormalities may themselves distort the age categorization of exposure, i.e., a normal 6 year old may be up off the floor and have reduced hand-mouth contact relative to a younger child, but a badly delayed 6 year old may have an exposure pattern more akin to that of a 3 year old. Thus, some flexibility is required in implementation of the matrix.

- 3) Presently, much of the fundamental data necessary to fill in the matrix is not available. While this does reduce the immediate utility of the matrix for risk assessment, the current lack of data in no way diminishes the utility of the matrix as a conceptual tool assuring systematic and comprehensive assessment.
- 4) The matrix may be of significant value in identifying data gaps and, perhaps more importantly, prioritizing efforts to fill those data gaps based upon reasonable scientific and policy judgment as to the likely effect of a particular agent (or cluster of agents), the severity of expected effect, the life stage affected, and ultimately the anticipated size of the affected population(s).
- 5) In many cases, agents will produce similar outcomes following exposure at a number of life stages. Similarly, many agents will have similar outcomes over a number of life stages. These exposure and outcome life stages can be combined for purposes of risk assessment. This does not negate the value of the matrix in prompting the policy maker to at least consider all exposure life stages.
- 6) The need for flexibility in application of the matrix was recognized independently by the SRWG, Dr. Wood, and by the authors of the *Summary Report of the Technical Workshop on Issues Associated with Considering Developmental Changes in Behavior and Anatomy when Assessing Exposure to Children*. While the SPWG believes that there are great benefits to systematically considering all life stages independently at the outset of the hazard and risk assessment process, the risk assessor must ultimately be permitted to adapt the matrix to the specific exposure and disease process under consideration. Policy should allow for the consolidation and/or adjustment of life stages, or even the designation of additional life stages, when such adjustments are necessary to most accurately characterize and assess the impact of environmental exposure on human health.