United States
Environmental Protection Agency

REGION/ORD WORKSHOP ON INHALATION RISK ASSESSMENT: A SUPERFUND FOCUS

SUMMARY REPORT

September 9 - 12, 2003
Washington, DC

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FOREWORD

The U.S. EPA ORD/Regional Inhalation Risk Workshop was the thirteenth in a series of Regional Science Topic Workshops sponsored by the Office of Science Policy in the Office of Research and Development at the United States Environmental Protection Agency (EPA). Other workshops in this series have included the following:

Asthma: The Regional Science Issues
Communicating Science: Waves of the Future Info Fair
Fully Integrated Environmental Location Decision Support (FIELDS)
Non-Indigenous Species
Pesticides
Endocrine Disruptors
Emerging Issues Associated with Aquatic Environmental Pathogens
Aquatic Life Criteria
Critical Ecosystems
Air Toxics Exposure Assessment
Cumulative Risk Assessment
Emerging Pollutants

The ORD/Regional Science Topic Workshops have two complementary objectives: 1) establish a better cross-agency understanding of the science applicable to specific region-specific human health and/or ecological topics; and 2) develop a network of EPA scientists who will continue to exchange information on these science topics as the Agency moves forward in planning education, research, and risk management programs.

Each year, EPA Regions identify high priority science topics on which to conduct workshops. The workshops address the science issues of greatest interest to the regions on the selected topic areas. Each workshop is planned and conducted by a team of regional, ORD, and interested program office scientists, is led by one or more Regional Science Liaisons or ORD, and is facilitated by a regional chairperson. Participants maintain the cross-Agency science networks they establish at the workshops through planned post-workshop projects and activities such as identifying collaborative research opportunities, creating information sharing mechanisms (e.g., interactive web sites), and developing science fact sheets for regional use.

For additional information on a specific workshop or on the Regional Science Topic Workshop series in general, contact David Klauder in ORD's Office of Science Policy (202-564-6496).

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EXECUTIVE SUMMARY

The U.S. EPA ORD/Regional Inhalation Risk Workshop was hosted by EPA Headquarters and held September 9 - 12, 2003, in Washington, DC.

The workshop was organized into multiple sessions covering a number of diverse topics, all of which addressed past, current, and emerging methods for assessing human health risks through the inhalation route. The workshop culminated in an extended discussion concerning how the Superfund program might consider modifying its existing methodologies to more full reflect the state of the art in assessing human health risks at Superfund sites through the inhalation route. Workshop participants focused on the following major questions and issues:

- What methods has Superfund traditionally used to evaluate exposure and risk from chemicals through the inhalation pathway?
- What methods are recommended by the Agency's Inhalation Dosimetry approach to evaluate exposure and risk from chemicals through the inhalation pathway?
- How should exposures and risks to children be estimated? Are additional default factors needed?
- How are chronic exposure estimates using discontinuous exposure scenarios developed so as to assess chronic risk?
- Are Inhalation Unit Risks extrapolated from oral values valid for assessing inhalation risk?
- How should the issue of route-to-route extrapolation be addressed when inhalation toxicology values (RfC and IUR) are not available?
- How should aggregate exposures be evaluated?

Scientists from EPA (Regions; Office of Research and Development; Offices of Solid Waste and Emergency Response, Pollution Prevention and Toxics, Radiation and Indoor Air, and Children's Health Protection; Office of Science Policy) and invited speakers from government laboratories presented research and background information on inhalation risk methodologies, recent research results and new/ongoing initiatives, and current inhalation risk assessment practices.

According to the workshop evaluations, most participants found the workshop very useful, and many expressed interest in making such dialogs a more regular feature of ORD activity. The major planned outcome of the Workshop is development of updated guidance for conducting inhalation risk assessment at Superfund sites.

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WORKSHOP SESSION SUMMARIES

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EPA WORKSHOP ON INHALATION RISK ASSESSMENT: A SUPERFUND FOCUS
September 9-12, 2003, Washington, DC

Summary Report

INTRODUCTION

This Workshop was convened under the auspices of the Office of Research and Development's (ORD) Regional Science Program, the EPA Regional Offices, and the Office of Superfund Remediation and Technology Innovation (OSRTI).

WORKSHOP OBJECTIVES

The workshop had several overarching objectives:

- Establish a better understanding of the science used to conduct inhalation risk assessments
- Apply this science to existing Superfund inhalation risk assessment paradigms
- Assess these methods relative to those historically used by the Regions to evaluate inhalation risks at Superfund sites
- Identify keys gaps in the science
- Discuss Superfund policy issues associated with implementation of the science, and
- Take initial steps, including identification of a representative workgroup, to develop a proposal for updating Superfund inhalation risk assessment guidance.

Within these broad objectives, the Workshop focused on questions in seven specific areas:

1. What methods has Superfund traditionally used to evaluate exposure and risk from chemicals through the inhalation pathway?
2. What methods are recommended by the Agency's Inhalation Dosimetry approach to evaluate exposure and risk from chemicals through the inhalation pathway?
3. How should exposures and risks to children be estimated? Are additional default factors needed to ensure protection for children subjected to exposure in residential settings?
4. How are chronic exposure estimates using discontinuous exposure scenarios developed so as to assess chronic risk? Can the exposure equations be modified to accommodate occupational, construction worker, trespasser, and other discontinuous exposure scenarios?
5. Toxicity values for some agents predate the 1994 Reference Concentration (RfC) methodology. For these agents, Inhalation Unit Risks (IUR) were extrapolated from oral values. Are these values valid for assessing inhalation risk? In the case of gaseous agents, would the specific classification category (i.e., Category 1 or 3) make a significant difference in the assessment methodology or findings?

6. How should the issue of route-to-route extrapolation be addressed when inhalation toxicology values (RfC and IUR) are not available? Can they be derived from oral values? If so, are there limitations on the conditions under which this may be done?
7. How should aggregate exposures be evaluated? More specifically:
   - Should cancer risks from inhalation be combined with risks from oral and dermal exposure? If so, when and how should such aggregation be done? Can risks from exposure to multiple contaminants be combined?
   - Similarly, should inhalation Hazard Indices be combined with those from oral and dermal exposures to the same agent, or from multiple agents that affect the same organ?

The initial two days of the Workshop featured several sessions providing an overview and context, and a detailed review of past and current approaches to evaluating human health risks through the inhalation exposure route. The remaining time was devoted to a discussion of how to update assessment methods, with a focus on the proposed "Strawman" revisions, the estimation of risk to children, and techniques for dealing with various exposure scenarios, multiple exposure routes, and assessment data collected prior to development of the 1994 RfC dosimetry methodology.

WELCOME

Introductory presentations were given by William Farland (Deputy Assistant Administrator for Science, ORD), and Mike Cook (Director, OSRTI).

- Dr. Farland discussed the ORD's current resource levels, research priorities (e.g., human health, especially as affected by particulate matter and drinking water; water quality; and global climate change), the Regional Science Program and Science Topic Workshops, and the general objectives of the current Workshop. Mr. Cook addressed the on-going Superfund Program reorganization and noted that it would add more scientific expertise, but that major resource constraints were still an issue for management. Concurrently with trying to manage costs better and seeking to run programs on a performance basis, the Superfund program was placing greater emphasis on public health and on addressing new scientific issues, particularly those involving solvents (such as perchloroethylene and trichloroethylene), vapor intrusion, and better assessment methods.

- A presentation on the Historical Background of Inhalation Toxicology Risk Assessment, and Methods and Approaches Used Within EPA Programs, was given by Deirdre Murphy (OAR/OAQPS).

HISTORICAL BACKGROUND

- An early focus of Agency risk assessment was the oral route of exposure, in which a role for animal inhalation exposures was, in lieu of oral studies, to be "converted" to

human equivalent oral intakes using animal ventilation/ body weight scaling factors). For non-cancer assessment, Reference Doses (RfDs) typically were derived from animal oral studies (though sometimes from animal inhalation studies, as just stated). For cancer assessments, inhalation unit risk estimates (IURs) often were derived from oral slope factors, though there were some based directly on animal inhalation or human occupational data. In the mid-late 1980s, increased emphasis was placed on development of inhalation toxicity values based directly on inhalation studies and dosimetry methodology, to "translate" animal exposure concentration to human exposure concentration associated with the equivalent dose at the target tissue. This inhalation dosimetry methodology took into account the varying disposition within the body of different categories of chemicals (e.g., particles vs. gases, remote acting vs. respiratory tract toxicants).

- In the 1990s, following several Science Advisory Board reviews, the document *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* was released. The *Methods* document established a framework/hierarchy of guiding concepts for EPA inhalation dosimetry methods for use with inhalation dose-response assessment. The RfC methodology departed from the RfD approach, by accounting for the dynamics of the respiratory system (such as the portal of entry), and providing dosimetric adjustments to address the species-specific relationships of exposure concentrations to deposited/delivered doses. This methodology was then subsequently used to derive human equivalent concentrations in the development of both RfCs and IURs.

- Consistent with statements made in the 1994 document, ORD has a commitment (in the 2003 Air Toxics Multi-Year Plan) to review and update the 1994 *Methodology* document.

METHODS AND APPROACHES

Assessment in "Data-Rich" Situations

A session on Data-Rich Inhalation Risk Assessment was co-chaired by Deirdre Murphy (OAR/OAQPS) and Rob DeWoskin (ORD/NCEA). Harvey Richmond (OAR/OAQPS) gave a presentation on Exposure-Response Modeling in Ozone Risk Assessment.

- The OAR/OAQPS spokesperson discussed inhalation toxicology assessment under a "best case" situation, that is, a scenario in which a robust data base is available – the National Ambient Air Quality Assessment study of the criteria air pollutant ozone. Although few risk assessments have the "luxury" of access to such a massive database as is available for the criteria pollutants, the exercise does provide some insights and guidance for conducting more typical assessments. For example, observations from controlled human exposure studies provided information as to the relative importance of different exposure durations in characterizing acute exposures,

as well as information on the role of activity/exertion level. Additionally, the exposure modeling concepts and databases employed may have relevance to toxics assessments, and the probabilistic analysis tools facilitate characterization of uncertainty and variability and allow identification of critical parameters with broader relevance.

Physiologically Based Pharmacokinetic (PBPK) Modeling

Hugh Barton (ORD/NHEERL) made a presentation on PBPK Modeling to Determine the Human Equivalent Concentration (HEC).

- PBPK-based analyses are useful for improving extrapolation and evaluating population variability and uncertainties in risk assessments. When applied to animal and human models, PBPK approaches support conversion of external bioassay metrics to internal metrics (e.g., tissue concentration), calculation of potency based on the internal metric, and conversion of the internal human metric back to an external metric (e.g., concentration in air or water). PBPK modeling offers opportunities for improving species, life stage (e.g., children), dose, and route extrapolations.

Using Default Chemical Category-Specific Approaches: Inhalation Dosimetry in Cancer and Non-Cancer Assessments

Sarah Levinson (Region 1) and Bob Benson (Region 8) co-chaired a session on Inhalation Dosimetry Using Default Chemical Category Specific Approaches (Cancer and Non-Cancer Assessment). The principal considerations in extrapolation of animal inhalation exposures to equivalent human exposures were identified as the following:

- Where does the chemical act?
- What is the exposure in the test species at the site of action?
- What is the equivalent exposure in the human at the presumed or known site of action (i.e., what is the dose in the target tissue of the human)?

There is a preferred hierarchy of approaches to modeling inhalation dosimetry to accomplish the interspecies extrapolation for these assessments:

- Fully parameterized PBPK models
- Next, an intermediate approach, using some chemical-specific information
- Then, using a default chemical category-specific approach (most commonly employed)
- Last, using route-to-route extrapolation from an oral study (if “first-pass” effects can be ruled out or otherwise accommodated).

Superfund Traditional Approach for Calculating Risk

Sarah Levinson (Region 1) made a presentation on the Superfund Traditional Approach for Calculating Inhalation Risk. She noted that the initial approach was to determine intake (administered dose in units of milligram per kilogram per day (mg/kg-day)), then use a Slope Factor (in units of risk per mg/kg-day, or $(mg/kg\text{-}day)^{-1}$) to calculate cancer risk, and a toxicity factor (in units of mg/kg-day) to calculate non-cancer risk. In the early 1990s, the Superfund program turned to use of the IUR (which is reported as the risk per concentration, or $(mg/m^3)^{-1}$) and RfC (also reported as a concentration in terms of mg/m^3) for these risk estimates. In the mid 1990s, the current approaches, converting the IUR to an Inhalation Slope Factor (SF_i), and the RfC to an Inhalation Reference Dose (RfD_i), were put into practice. For the inhalation route of exposure, this process involves a comparison of intakes, rather than a comparison of concentrations.

Using Default Chemical Category-Specific Approaches: Deriving the HEC for Gases

Bob Benson (Region 8) made a presentation on Derivation of the HEC For Gases From Laboratory Animals and Occupational Studies. This presentation discussed the derivation of the Human Equivalent Concentration for gases. The crucial point regarding dosimetric adjustments was noted via reference to a pronouncement of the seminal 1994 NRC document *Science and Judgment in Risk Assessment*: "…the target-site dose is the ultimate determinant of risk..."

After a review of the anatomy of the respiratory tract, the major considerations in deriving an HEC were identified as the following:

- Where does the chemical act?
- What is the exposure in the test species at the site of action?
- What is the equivalent exposure in the human at the presumed or known site of action (i.e., what is the dose in the target tissue of the human)?

The derivation of the HEC for both particles and gases first calls for the adjustment of the observed NOAEL/LOAEL values to reflect the difference between experimental intermittent exposures and continuous exposures (per RfC definition). Dosimetric adjustment factors (DAF) are then applied to adjust for interspecies differences and to account for the type of gas (particularly Category 1 or 3) to yield the HEC.

The DAF employed in deriving the HEC for gases from animal or occupational data is the Regional Gas Dose Ratio (RGDR) for both respiratory tract and remote effects. The RGDR for a category 1 gas (gases that cause effects in the respiratory tract) is based on the ventilation rate and the surface area of the affected region. The RGDR for a category 3 gas (those that cause effects remote from the respiratory tract) is based on the blood:air partition coefficient.

Using Default Chemical Category-Specific Approaches: Deriving the HEC for Particles

Gary Foureman (ORD/NCEA) gave a presentation On Derivation of the HEC for Particles from Laboratory Animal and Occupational Studies. As noted in the discussion on assessing gases, dosimetric adjustments for particle exposures also are founded on the concept that "…the target-site dose is the ultimate determinant of risk..." The DAF employed in deriving the HEC for gases from animal or occupational data is the Regional Deposited Dose Ratio (RDDR) for both respiratory tract and remote effects. Adjustments incorporate the effects of ventilation rate, surface area, and fractional deposition of the particles within the affected regions of the respiratory tract; the RDDR is then applied to the animal exposure concentration to yield the HEC. The principal technical issue that must be addressed is the highly non-uniform nature of particles and of airways both inter- and intraspecies.

Using Default Chemical Category-Specific Approaches: Frequency and Duration

Sarah Levinson (Region 1) and Bob Benson (Region 8) gave presentations on Frequency and Duration of Exposure Issues: Superfund Traditional Approach ("Non-Standard Inhalation Rates") and Derivation of the HEC.

The question posed here was the following: Do the standard Superfund exposure scenarios for the various types of chemicals fall within animal study parameters? The presentation discussed in detail the various adjustments for continuous vs. discontinuous exposures and varying durations and frequency patterns for assessing different chemical agents. It was stressed that, for site-specific risk assessments presented to the public, there is a need to explain fully the various definitions and adjustments employed.

Using Default Chemical Category-Specific Approaches: Age-Group Considerations

Sarah Levinson (Region 1) and Gary Foureman (ORD/NCEA) made presentations on Age Group Issues: Superfund Traditional Approach and Derivation of the HEC. The major issue of concern in this discussion was: Are the Agency default DAF and HEC procedures inclusive of different age groups? The particular focus of this concern was with children. The issue was addressed earlier by the EPA Risk Assessment Forum, which recommended that the Agency pursue both theoretical and experimental efforts to ensure that its assessment procedures were appropriate for all age groups. Such efforts are currently underway, some results of which were conveyed in Dr. Foureman's presentation. The presentations on this topic provided detailed discussions on factors such as age-related changes in the interaction of ventilation rate/surface area ratios for the various regions of the respiratory tract (pulmonary, extrathoracic, and tracheobronchial), and the effects of these interactions on the RGDR and the RDDR, and ultimately on the HEC.

The presenters offered several primary conclusions:

- RfC and IUR derivation already accommodate age-related differences both at the level of HEC derivation and, in the case of the RfC, at the level of application of uncertainty factors.
- Age differences in HEC derivations are likely accommodated for effects in the extrathoracic and tracheobronchial regions, and possibly for the pulmonary region.
- Age-related differences are likely accommodated for remote, or systemic, effects with regard to determinants of this calculation (blood:gas partition coefficients) and total intake via the respiratory tract.
- For particles, age-related differences in HEC derivation appear to be minor or non-existent.

Route-to-Route Extrapolations

Dan Stralka (Region 9) and Michael Sivak (Region 2) co-chaired a session on the Derivation of an Inhalation Toxicity Value (IUR/RfC) by Route-To-Route Extrapolation.

They noted that quantitative dose-route extrapolation can help the assessor in many ways, particularly by filling in gaps in the toxicity database and by providing alternatives studies for development of a toxicity value. It also can lead to better experimental design, reducing the number of laboratory animals required for a given study.

Pharmacokinetic Issues

A number of presentations were offered on pharmacokinetic issues. Elaina Kenyon (ORD/NHEERL) gave a presentation on Pharmacokinetic Issues in Route-To-Route Extrapolation; Rob DeWoskin (ORD/NCEA) on Agency Examples of Route-To-Route Extrapolation; and Bob Benson (Region 8) on the Practical Aspects Of Route-To-Route Extrapolation Issues.

Executing a route-to-route extrapolation must start with the selection of an appropriate dose metric, a critical choice. To make this choice, some knowledge of the relevant mode of action is required. Other data/conditions ideally required are the following: an “adequate” toxicology database for at least one route of exposure; toxicity remote from the contact site (i.e., a systemic, rather than portal of entry, effect (if toxicity is observed at the contact site, the feasibility of the extrapolations depends on the specific chemical involved)); sufficient confidence in the mode of action to select the appropriate dose metric (as noted above); and existence of a “functional” PBPK model (one in which the model structure can deal with the relative absorption, metabolism, binding, and excretion rates; critical parameters are appropriately estimated; and the most influential parameters can be identified via sensitivity analysis. There also must be an understanding of the interactions at the relevant “barrier” tissues (the lung, skin, gastrointestinal tract, and liver).

Route-to-route extrapolations could be improved in the future through the development of improved methodologies for addressing contact site/portal of entry effects; more refined model evaluation criteria for dose-route extrapolation; and better methodologies for route extrapolations other than oral to inhalation.

Dr. Gilman's Presentation: Risk Assessment Task Force

A presentation was made on Principles and Practices of EPA Risk Assessment by Paul Gilman, EPA Science Advisor and Assistant Administrator of ORD.

Dr. Gilman addressed the history of risk assessment at EPA, from the issuance of the National Academy of Science "Red Book" in 1983 to the current policies of extensive peer review and Information Quality Guidelines. Dr. Gilman noted that, despite the extensive efforts to improve risk assessment, there was still considerable criticism of EPA's policies and practices. He reviewed some of these criticisms, and then discussed the formation of the EPA Risk Assessment Task Force to address them. The Task Force will collect and analyze criticisms of risk assessment practices, classify them and attempt to separate facts from fiction, take a close look at current efforts, and consult with expert groups outside EPA. It was anticipated that the Task Force would make recommendations sometime in late September/October, 2003.

New Directions in Science

Technical presentations on new directions in the science of risk assessment were made in a session co-chaired by Gary Foureman (ORD/NCEA) and Lee Hofmann (OSWER). Presentations in this session included one on recommendations from the recent report from the Risk Assessment Forum on review of the RfD/C process, and another on issues in aggregating risk through the combination of risk values obtained from different media. A series of presentations were made on the state-of-the-science in areas relevant to dosimetry and risk assessment, including animal and human modeling of airway flow in the upper respiratory tract, age-related particle deposition, and nasal tract uptake of a volatile solvent in humans. An update on the activity of an interagency dosimetry project with NCEA also was presented.

Review of the RfD/RfC Processes

Carole Kimmel (ORD/NCEA) gave a presentation on Recommendations From a Review of RfD/C Processes.

The EPA review of RfD/RfC processes was initiated in response to questions arising as the Agency implemented the mandates of the Food Quality Protection Act (FQPA), especially the provisions relating to the protection of children's health. The project's original charge was to review the RfD/RfC methodology as it applied to children, but was expanded to include a more in-depth review of the entire process for setting reference values. Work started in 1999, and a final report (intended to provide recommendations, but not constituting a guidance document) was released in December, 2002.

The major findings and recommendations were as follows:

- Derive reference values (RfDs and RfCs) for multiple durations of exposure, e.g., acute, short-term, longer-term, and chronic.
- With regard to the use of uncertainty factors, provide justification for the application of the uncertainty factors for all durations of exposure, taking into consideration all of the data. Discontinue the use of the modifying factor. The current interspecies, intraspecies, and database deficiency uncertainty factors, if appropriately applied using the approaches recommended in the Review, will be adequate in most cases to cover concerns and uncertainties regarding the potential for pre- and postnatal toxicity and the completeness of the toxicology database. In other words, an additional uncertainty factor is not needed in the RfD/RfC methodology.
- EPA should recast the definition of the RfD and RfC to include designation of the exposure duration and route, and drop the phrase "with uncertainty spanning perhaps an order of magnitude." Instead, the size of uncertainly issues should be addressed in an accompanying narrative, which also would describe the extent, quality, strengths, and limitations of the database.
- Further evaluation of current dosimetric adjustments for deriving HECs should be pursued to confirm or assess the relevance for population subgroups.

Dosimetry Considerations in URT in Animals and Humans

Julia Kimbell (CIIT Centers for Health Research, RTP, NC) gave a presentation on Considerations of Dosimetry in the Upper Respiratory Tract in Animals And Humans.

The presentation on upper respiratory tract (URT) dosimetry detailed current research involving computer modelling of the URT, and its contribution to reducing uncertainty when dealing with interspecies extrapolation and dose-response issues. URT modelling will allow better understanding of the relationship between the average, and regional, delivered dose, and better estimates of the value of the regional gas phase mass transfer coefficient. This modelling can lead to better interspecies extrapolation incorporating mode of action and accounting for species-specific, localized dose effects. It also will improve our ability to deal with non-linear effects.

Particle Dosimetry in Human Lungs

Chong Kim (ORD/NHEERL) gave a presentation on Approaches for the Improvement of Particle Dosimetry in Human Lungs.

The discussion of approaches for improvement of particle dosimetry in human lungs addressed the question of assessing the internal dose of particulate matter delivered to the bronchial tract and lungs. The presentation described current research, particularly on human subjects using new experimental methods for assessing particle dose at local regions of the lung, and the use of the resulting data to develop mathematical lung deposition models. It was noted that these

models can provide information on a variety of inhalation conditions, support detailed dose analysis, enable projections from existing data, fill gaps in existing data sets, and explore various "what if" scenarios. They are still limited, however, by their use of simple geometry, assumptions about certain parameters, and the need for validation and empirical adjustments, particularly with regard to children.

Aggregate Risk Considerations

A presentation on aggregate Risk Considerations In Risk Assessment was made by Haluk Ozkaynak (ORD/NERL).

The presentation on aggregate risk considerations in risk assessment outlined in detail the issues and technical constraints encountered when attempting (or considering a decision) to aggregate risks from exposure via various routes. Several principal conclusions were presented:

- Route-specific concentrations, exposures, dose, and health risks for an individual are not necessarily independent of, or linearly related to, each other.
- Aggregate exposures and risks for each subject or cohort vary according to pollutant, exposure scenario, age, gender, behavioral factors, route-specific metabolism, and toxicity.
- It is important to evaluate contributions of each of the relevant pathways of exposure to total or aggregate human exposure and dose when assessing risks from exposures to multimedia pollutants.

Nasal Tract Uptake in Humans

Gary Foureman's presentation on this subject dealt with trials performed during which volunteers were exposed to acetone (1 ppm) via inhalation and concentration measurements were taken at the immediate exterior of the nose and in the nasopharyngeal region via a flexible probe placed therein. Detection was in real-time via mass spectrographs connected to the probes. This pilot study showed uptake of acetone by the time the acetone-laden air has passed through the head region to the level of the nasopharyngeal probe of 40-75%. When compared with literature values for rat upper airway absorption of acetone at 20-26%, the human absorption appeared to be more extensive, but not quite as extensive as predicted by the current default procedures given in the current version of the 1994 *RfC Methodology*.

Interagency Dosimetry Project

An update on this project was provided by Hugh Barton (ORD/NHEERL), who filled in for Annie Jarabek (ORD/NCEA). The Interagency Dosimetry Project's broad goals included improving default values used in RfC generation, placing more emphasis on understanding mode of action when developing new guidelines, and harmonizing cancer and non-cancer approaches. The presentation at the Workshop stressed the following points:

- The key role for dosimetry is to strengthen the inferences regarding the shape of the dose-response relationship and to extend the range of observation.
- Mode of action is important to defining the dose metric related to tissue response.
- Tiered and flexible approaches to dose-response assessment should address the following:
  - Different types of chemicals
  - Levels of biological organization
  - Mode of action

The approach to dosimetry is the same regardless of the route of exposure or cancer vs. non-cancer endpoint.

INHALATION RISK ASSESSMENT

On day three of the Workshop, the question of coordination of inhalation risk assessment across various EPA programs was addressed, and chaired by Michael Sivak (Region 2).

A panel comprised of Alec McBride (OSW), Deirdre Murphy, (OAR/OAQPS), William Burnam and Steven Weiss (OPPTS/OPP), and Brenda Foos (OCHP) discussed their programs' approaches to dealing with four specific issues:

1. Determining general inhalation exposure/risk and childhood exposure/risk
2. Developing chronic exposure estimates with discontinuous exposure scenarios
3. Evaluating aggregate exposure, i.e., exposure via inhalation, oral, and dermal pathways, for assessment of chronic risk, and
4. Performing route-to-route extrapolations when inhalation toxicology values are not available.

1. Determining general inhalation exposure/risk and childhood exposure/risk

- **OSW** generally does not conduct independent toxicity assessments or independently develop methodologies for risk assessments. The program relies on data from sources such as the EPA Integrated Risk Information System (IRIS), the National Center for Environmental Assessment (NCEA), Health Effects Assessment Summary Tables (HEAST) documents, and the California EPA. In assessing children's risk, OSW uses Monte Carlo analysis and adjusts the exposure factors for age, but does not adjust toxicity measures (RfC). An age is selected for the representative child and the exposure factors are adjusted accordingly. Risks to children are reported separately.

- **OAQPS** performs assessments for the Criteria pollutants specified in the Clean Air Act (CAA) and for the Air Toxics named in the CAA or about which concerns have been raised. The focus of this presentation was on assessment performed for air toxics, which may be performed on both national and local

geographic scales. These risk assessments are generally supported by air quality modelling (starting from emissions estimates for sources of interest), and exposure assessment/characterization. Cancer risk assessments are reported in terms of additional lifetime cancer risk; non-cancer risks are reported as a chronic hazard quotient. Childhood exposure/risk estimates use toxicity values (RfC and IUR) usually based on the EPA inhalation dosimetry methodology. Screening assessments assume that the predicted ambient air concentration equals the exposure concentration (i.e., someone is breathing air at that location 24 hours/7 days a week for a lifetime).

When more refined deterministic exposure modeling is performed, which still presumes the predicted annual air concentration is relevant for 70 years, the childhood exposure concentration estimates reflect children's time activity pattern. With this latter approach, cancer risk estimates are derived for a full lifetime, of which childhood is a part. Similarly, hazard quotients are derived for a full lifetime, of which childhood is a part, or may be presented for a specific period of interest. When still more refined population-based (probabilistic modelling) estimates are generated, cancer risk may be derived for shorter durations of exposure (i.e., less than lifetime), of which childhood may then comprise a larger fraction.

- **OPP**'s risk assessments focus primarily on the active ingredients of pesticides. The inhalation route represents about one percent of the total exposure for most scenarios assessed by OPP. Most of the inhalation exposure data used is collected by registrants/industry groups following OPP guidelines. All inhalation exposure risk estimates follow guidelines based on standard industrial hygiene practices. These estimates are based on air sampling data that do not differentiate between gases and particles, or between different particle sizes. Estimates for children are based on air sampling data (from the adult breathing zone or area samples) and modelling methods. The breathing rate and exposure duration assumptions used are derived from the EPA Exposure Factors handbook and other published sources. OPP typically uses higher-end values for input variables (e.g., breathing rates, application rates) in short-term scenarios and average or more typical values for intermediate-term or chronic scenarios (though most scenarios evaluated by OPP are not chronic). OPP calculates and reports childhood risks separately from adult risks, but does not calculate cancer risk for childhood exposures.

- **OCHP** does not generate risk assessments of any type. The Office is concerned, however, about whether or not current practices are sufficiently protective of children. The OCHP presenter raised questions about the Dosimetric Adjustment Factor (DAF), noting that the current DAF equation is essentially a body weight scaling equation, and that (in her opinion) the body weight scaling assumption is not valid for children. She also expressed concerns about the degree of protection

provided by the interspecies uncertainty factor (UF), suggesting that it actually reflected uncertainty in the extrapolation, not in the population variability. Consequently, she believes that this uncertainty should be reflected in the pharmacokinetic portion of the interspecies UF (that currently has a default value of one). The presenter also called for considerable further research, both theoretical and experimental in nature, and that improved dosimetry for children be developed in future revisions of the *RfC Methodology*.

This presentation generated considerable discussion by Workshop participants as to what degree of protective revisions, if any, needed to be added to current practices to ensure adequate protection of children. This topic is addressed in greater detail below in the summary of the conclusions addressing the five major organizing issues of the Workshop.

2. Developing chronic exposure estimates with discontinuous exposure scenarios for assessment of chronic risk.

- **OSW** generally conducts only assessments involving continuous exposure; if intermittent (e.g., occupational) exposures are involved, the program defers to the Occupational Safety and Health Administration (OSHA).

- **OAQPS**' screening assessments assume continuous exposure for a lifetime. For more refined assessments, exposure concentrations are estimated using time activity pattern data. When single or few sources are involved, the approach may be comparable to that of the Superfund program, which assumes zero concentration away from the site(s) of concern. Depending on the scope of multiple source assessments (e.g., National-scale and community-scale assessments), there may be no such thing as discontinuous exposure (i.e., the population is always exposed to one or more pollutants from a source of interest), only variation in exposure concentration during the duration of interest.

- **OPP** typically does not encounter chronic exposure scenarios, dealing primarily with discontinuous exposures. The program classifies inhalation exposures into three broad categories: short-term (30 days or less); intermediate-term (30-180 days); and long-term (greater than 180 days). Higher-end values for inputs (e.g., application rates, breathing rates, exposure duration per day) are usually employed to estimate short-term exposure scenarios, and average values for intermediate- to long-term scenarios.

- **OCHP** does not deal with this issue.

3. Evaluating aggregate exposure, i.e., exposure via inhalation, oral, and dermal pathways.

- **OSW** typically aggregates risks across pathways for carcinogens if appropriate from the toxicological and temporal viewpoint; it does not do so for non-carcinogens.

- **OAQPS** sums inhalation and oral cancer risk estimates as appropriate (e.g., giving due attention to compatibility of exposure estimate assumptions). For non-cancer exposures, route-specific hazard quotients are derived. They may be aggregated in some circumstances, with attention to target, critical effect, and compatibility of exposure estimate assumptions.

- **OPP** aggregates exposures across routes based on the toxicological endpoints of concern. One of three optional approaches is used.
  - Option 1 is used when the No Observed Adverse Effects Levels (NOAEL) and endpoints are the same for all three routes. Aggregate exposure is the simple sum of exposure for all three routes; the Aggregate Margin of Exposure (MOE) is defined as the NOAEL ÷ Aggregate Exposure
  - Option 2 is used when all target MOE are identical. The Aggregate MOE is defined as:

$$\frac{1}{(1/MOE_{FOOD})+(1/MOE_{ORAL})+(1/MOE_{DERMAL})+(MOE_{INHALATION})}$$

  - Option 3 is used to generate an Aggregate Risk Index (ARI) when the target MOEs are not identical. The ARI for each route is defined as the quotient of the calculated MOE for each route divided by the MOE of concern for that route. The ARI is calculated as:

$$\frac{1}{(ARI_{FOOD})+(ARI_{ORAL})+(ARI_{DERMAL})+(ARI_{INHALATION})}$$

- **OCHP** had no comments on this issue.

4. Performing route-to-route extrapolations when inhalation toxicology values are not available.

- **OSW** only does such extrapolations when there are findings that indicate it is appropriate. When it is performed, the approach is similar to that used to aggregate exposures, and technical support is sought from ORD.

- **OAQPS** treats cancer and non-cancer extrapolations differently. For cancer, in lieu of an IUR from the hierarchy of sources, an IUR may be derived from an oral value, (using a rough breathing rate/body weight calculation), with recognition of

added uncertainty. No such rough extrapolation is done to create RfCs. Because the CAA list of hazardous air pollutants is heavily weighted by respiratory toxicants, such rough non-cancer route extrapolations are generally not performed because of the high probability of missing target toxicity.

- **OPP** performs route-to-route extrapolations with no distinction between cancer and non-cancer endpoints. Absorption via the inhalation route (in mg/kg/day) is considered to be equal to oral absorption. Air concentration estimates for human exposure are converted from a concentration (mg/m^3) to an average daily dose expressed as mg/kg/day so that exposure can be compared directly to oral NOAEL and LOAEL values.

- **OCHP** had no comments on this issue.

Updating Existing Superfund Inhalation Risk Assessment Guidance (RAGS)

A session on Updating the Superfund Inhalation Risk Assessment Guidance -- Focus, Goals, and Desired Outcomes – was co-chaired by David Cooper (OSWER/OSRTI), Lee Hofmann (OSWER), and Jayne Michaud (OSWER/OSRTI). Further, a presentation on the Identification of Guidance To Be Revised was given by David Cooper and David Crawford (OSWER/OSRTI).

The Workshop addressed the topic of how to update the existing Superfund Inhalation Risk Assessment Guidance (RAGS). With respect to inhalation, the RAGS have not been substantially updated since 1989.

The focus of the current effort is to examine possible updates to RAGS, Part A (leaving Part B for later efforts). The initial step in the revision process called for creating a "Strawman Proposal" for presentation and discussion at the current Workshop.

Bob Benson (Region 8) gave a presentation on the Strawman.

The single most significant change proposed in the Strawman is the revocation of the primary intake equation used for evaluating internal dose delivered via inhalation, and the consequent risk. As noted in the Strawman Proposal, the current approach essentially considers inhalation exposure (in terms of pollutant taken into body) to be a simple function of the subject's daily inhalation rate and body weight, and correspondingly implies that an inhalation value (i.e., the IUR, risk per ug/m^3 or Reference Concentration, mg/m^3) can be converted into a corresponding value with units on a pollutant mass per body weight basis. Neither of these practices is in accord with the 1994 methodological guidance on inhalation dosimetry for determining the human equivalent concentration (HEC) for calculating RfC and IUR. The Strawman suggests the following methods to replace the current RAGS intake equation approach:

Calculating Lifetime Excess Cancer Risk:

$Risk = IUR(ug/m^3)^{-1} \times CA$

Where:
CA = Air Concentration$(ug/m^3)^{-1}$

This assumes a continuous exposure for a 70 year lifetime. For less than lifetime exposure, risk is calculated as:

$Risk = IUR(ug/m^3)^{-1} \times CA \times (ET \times EF \times ED)/AT$

Where:
ET = exposure time (hours/day)
EF = exposure frequency (days/year)
ED = exposure duration (years)
AT = averaging time (70 X 365 X 24)

Calculating the Hazard Quotient (HQ)

$HQ = CA/RfC$

assuming continuous exposure for a 70 year lifetime. For a less than lifetime exposure, the calculation is:

$$HQ = \frac{CA}{RfC} \times \frac{(ET \times EF\ ED)}{AT}$$

The Strawman Proposal (and an accompanying Appendix) discusses in detail the question of the possible need for additional corrections for specific age groups (particularly children). The conclusion reached in the Strawman is that, beyond consideration of time spent in the contaminated area and changes in the exposure concentration that could be age/activity related, no additional corrections to the risk calculations for specific age groups are necessary. This conclusion is supported by examples provided in the Proposal's Appendix 1, which show that any age-related variations in the physiological parameters used to derive the HEC when following the 1994 dosimetry methodology guidance are subsumed by the default values used for the HEC.

The Proposal also cites the conservative nature of the methodology for deriving the RfC. The starting point for this derivation calls for the consideration of age group susceptibility in the choice of the toxicological effect of concern (thus accounting for known physiological differences), and consideration of uncertainty factors for database questions, and intra/interspecies variation. This combination, the Proposal asserts, provides adequate protection for all age groups. The general issue of the protection of children is addressed again below as

part of the discussion on the five major science/policy issues that occupied the remainder of the Workshop.

Estimating Exposures and Risks To Children

The first of the issues revisited in the summary discussion involved a presentation and discussion on the topic, How Are Exposures and Risks to Children Estimated? The participants examined in depth the means by which estimates of exposures and risks to children are formulated. They also discussed the non-technical, intangible aspects of risk assessment, and the perceptions of the public about Agency actions and policies. It was noted that EPA is under considerable pressure to develop more realistic assessments. At the same time, stakeholder and community acceptance of Superfund risk assessments becomes more problematic if it appears to be removing a conservative assumption presumed to protect children, particularly if it can be said that the changes are not backed by robust data.

Although no vote or "head count" was taken, it appeared that most (but not all) participants agreed with the position advanced by the Strawman Proposal that, with the proposed revisions, significant additional factors were not required to ensure adequate assessment of children. That said, there were several comments and suggestions put forward for consideration by the volunteer Working Group that would undertake the next stage of revision/development of the Proposal.

These comments/suggestions included the following:

- One participant asked if the fact that children have higher ventilation rates (breaths/minute) than adults and might achieve steady-state during exposure more quickly should be taken into consideration? (Some commented that consideration of this factor shouldn't be limited to children, but extended to any cohort with possible atypical ventilation rates, be it by age (e.g., the elderly) or occupation (e.g., construction workers).

- Should default factors be added to ensure protection of residential children?

- Another participant wondered if the default methodology for Category 3 gases is sufficiently protective, and suggested that new PBPK models which now exist for some significant Superfund-related chemicals should be investigated.

- It also was noted that the distribution of inhaled particles in the respiratory tract differs between adults and children. Consequently, the Workgroup should attempt to obtain more data on the size, distribution, and deposition of particles in children vs. adults, and the effect these factors might have on toxicity. Some consideration was given to where such data might be found. It was thought that CAT scans in hospitals might convey information on morphology, or that the Food and Drug Administration (FDA) might have collected useful information.

Regarding FDA data, however, the highly proprietary nature of information typically collected by FDA renders its use by EPA problematic.

- The volunteer Work Group was advised to consider, in addition to children, all possibly sensitive sub-populations.

Aggregating Exposure Across Routes Of Exposure

The workshop next turned to a discussion entitled, How Should Aggregate Exposure Be Evaluated? The Conference participants addressed the issue of aggregating exposure across routes of exposure. The group concluded that aggregating is generally correct, but that underlying assumptions and conditions need to be carefully evaluated.

Collectively, participants identified the following specific points for consideration in performing risk aggregation:

- Toxicological endpoints should be similar, so target organ toxicity data must be available.
- If MOA are not similar, great care should be exercised.
- Aggregation could be most appropriate in initial screenings.
- Oral and inhalation risks can be aggregated, however, special care should be taken for agents that affect the lungs, with concomitant differences between oral and inhalation rates of exposure. Further, particle size may play a significant role and should be considered in deciding whether aggregation is appropriate (or adjusted for if aggregation is attempted). Region 3 may be a source of information, because it has conducted a study of differences between RfC use and inhalation/BW adjustments.
- Temporal aspects of exposure must be considered, particularly if the timing of exposure by the different routes varies.
- Risk information needs to be harmonized, because various EPA programs and Regions may use different underlying assumptions and approaches in differing situations. Specific differences among Regions 3, 6, 9, and OPP were mentioned, and it was suggested that an Agency-wide reference table be developed to provide a central data source.

Quantitative Inhalation Risk Assessments: Pre-1994

David Cooper (OSWER/OSRTI), Jayne Michaud (OSWER/OSRTI), and Lee Hofmann (OSWER) gave a presentation on Updating Superfund Inhalation Risk Assessment Guidance: Focus, Goals, And Desired Outcomes. A presentation followed on How Should Quantitative Inhalation Assessments Which Predate the 1994 RfC Dosimetry Methodology Be Handled?

Workshop participants took up the subject of dealing with quantitative inhalation risk assessments predating the 1994 RfC dosimetry methodology. The key issue here is the validity

of the some 30 IURs developed by extrapolating from oral studies. The position of the Strawman Proposal was that this issue posed primarily a science policy question. The Conference participants generally agreed with this finding, and noted also that rejecting use of extant IRIS values was unlikely. There was a suggestion, however, to ask the IRIS program to re-examine these data and the underlying assumptions used to develop published IRIS values.

There was some discussion of a suggestion to treat the agents having pre-1994 IURs as Category 3 gases. In these cases, however, the IURs were derived from animal oral ingestion data, adjusted with various scaling/interspecies factors, and extrapolated to the inhalation route. After consideration of the idea, the Workshop participants did not reach a consensus on this approach as many wanted to consider a wider range of options.

The overall position of the Workshop participants was, that for the pre-1994 agents, there was no compelling reason to not use the extant IRIS data. The use of the pre-1994 data also should be noted in the uncertainty section of any assessment using these data.

Discontinuous Exposure

A presentation was made on How Are Chronic Exposure Estimates With Discontinuous Exposure Scenarios Developed For Assessment of Chronic Risk?

The topic addressed assessing chronic exposure scenarios when dealing with discontinuous exposure. The Conference participants spent some time discussing the semantics and definitions of "chronic" and "continuous/discontinuous." Chronic exposure relates to length of time or duration of the exposure. For the discussion, seven years of exposure seemed to be adopted as a working definition for the term chronic exposure. The term discontinuous exposure refers to exposures that are intermittent throughout the exposure duration.

The issue in determining whether a discontinuous exposure scenario can be termed (and evaluated as) "chronic" is the total duration of the exposure scenario, as well as both the duration of each intermittent episode and the amount of time between each episode. It was suggested that an underlying presumption in assessing the entire scenario as chronic is that a rough steady state situation is reached with regard to the dose to the respiratory tract and/or the blood and internal organs. It was suggested that exposure scenarios in which the intermittent exposures are too infrequent for acceptance of this assumption should be assessed with some other reference value (e.g., sub-chronic or acute). The exposure scenarios assessed in a baseline risk assessment where infrequent or less than chronic exposure occur include the trespasser and the future on-site construction worker. The Strawman Proposal suggested that if, in any exposure scenario, the calculation (ET X EF X ED)/AT is less than 0.1, that scenario should not be evaluated with the chronic Hazard Quotient relationship:

$$HQ = CA/RfC \times (ET \times EF \times ED)/AT$$

without considering other toxicological endpoints from IRIS or other data sources for sub-chronic or acute reference values (e.g., ATSDR, California EPA). For on-site workers, some suggested using OSHA values. However, there is clear Superfund guidance against using OSHA occupational standards in a baseline risk assessment to evaluate risk to a future on-site construction worker.

Another approach suggested to deal with this scenario was to revisit the original study used to develop the RfC and vary the exposure time – essentially perform a sensitivity analysis – to determine how the results change. Care must be taken to not modify the results of the original study too far, and thus invalidate the underlying relationships.

Other commentators suggested that the IRIS should be revised (where possible) to provide information on when steady state is reached. This would help determine how much modification in exposure duration is credible. In addition, real-world examples of how adjustments play out would be useful. Unusual scenarios could be addressed wherein acute and chronic exposures are considered jointly. After continued discussion of the idea, the Workshop participants did not reach a consensus as to how effective or useful this information would be when conducting baseline risk assessments.

The concept of a "decision tree" or some sort of algorithm to help decision makers deal with this issue also was discussed. The participants were not optimistic about the possibility of creating such a tool. It would require extensive toxicological, MOA, and absorption, distribution, metabolism, and elimination (ADME) data, and would need to be applied on a chemical-by-chemical basis.

Formulating Route-To-Route Extrapolation in the Absence of Inhalation Toxicology Values

A presentation was made on How Should the Issue of Route-To-Route Extrapolation Be Addressed When Inhalation Toxicity Values Are Not Available?

The final question that the Conference participants considered was how to formulate route-to-route extrapolation when inhalation toxicology values are not available. More specifically in this context, can IUR and RfC be derived from oral studies?

Most participants felt the extrapolation could be done, but only when certain guidelines were met:

- If large first-pass metabolism occurs, route extrapolation would require PK modeling
- Use caution for high molecular weight or highly fat-soluble (e.g., PCB, PBB) substances
- Such extrapolation is applicable only when systemic effects exist, and
- Use caution for substances that sorb to particles (e.g., metals).

It was noted that methods to extrapolate portal of entry effects (e.g., for highly reactive gases) have not been developed, whereas existing methods are used for systemic effects.

In addition to the guidelines above, several participants emphasized that in deciding to generate a route-to-route extrapolation, the analyst must consider all the PBPK and toxicological data available, including seeking help from ORD if warranted. Data on specific agents must be considered. In the case of polynuclear aromatic hydrocarbons, for example, systemic effects are captured, but direct dermal effects may be lost; such effects need to be factored into the assessment. Other possible considerations for this topic raised by some participants included the use of additional adjustment factors, such as an uncertainty factor for metabolic effects, body weight/intake adjustments, and, as in the case of OPP, adjustments of the MOE when undertaking this extrapolation.

Finally, the participants suggested that the volunteer Work Group charged with revising the Strawman Proposal be asked to include a new appendix addressing route-to-route extrapolation in cases in which all the desired data are not available – essentially, advice on "work around" approaches.

Suggestions for Additional Items in the Strawman

A presentation was given by David Cooper (OSWER/OSRTI), David Crawford (OSWER/OSRTI), David Klauder (ORD/OSP), and Michael Sivak (Region 2) concerning a Summary and Workshop Wrap-Up.

In concluding up the Workshop, several persons suggested some additional items for inclusion in the Strawman:

- Guidance on using Central Tendency vs. the RME
- Discussion of use (or rejection) of the body weight$^{3/4}$ scaling factor in oral dosimetry
- Guidance on the use of new default values when they are issued, and
- Making a statement on the need for additional risk assessment training for EPA staff and contractors.

Appendix A

AGENDA
REGION/OSRTI/ORD WORKSHOP on
INHALATION RISK ASSESSMENT: A SUPERFUND FOCUS

Tuesday, September 9, 2003

8:00 am **Registration Opens**

8:30 am **Welcome:**
William Farland, Deputy Assistant Administrator for Science
Office of Research and Development

Mike Cook, Director
Office of Superfund Remediation and Technology Innovation

8:45 am **Introduction to the Inhalation Risk Assessment Workshop:**
Michael Sivak, Workshop Chair, Region 2

9:00 am **Historical Background:**
Deirdre Murphy, OAR/OAQPS

9:30 am **I. Data Rich Inhalation Risk Assessment Approaches:**
Co-Chairs: Deirdre Murphy, OAR/OAQPS
Rob DeWoskin, ORD/NCEA

Use of Exposure-Response Modeling in the Ozone Risk Assessment:
Harvey Richmond, OAR/OAQPS

10:15 am ***Break***

10:30 am **Physiologically-based Pharmacokinetic (PBPK) Modeling to Determine the Human Equivalent Concentration (HEC):**
Hugh Barton, ORD/NHEERL

11:15 am **II. Inhalation Dosimetry Using the Default Chemical Category Specific Approaches: Cancer and Noncancer Assessment:**
Co-Chairs: Sarah Levinson, Region 1
Bob Benson, Region 8

Superfund Traditional Approach for Calculating Inhalation Risk:
Sarah Levinson, Region 1

11:30 am **Derivation of the HEC for Gases from Laboratory Animal and Occupational Studies:**
Bob Benson, Region 8

12:30 pm ***Lunch***

2:00 pm **Derivation of the HEC for Particles from Laboratory Animal and Occupational Studies:**
Gary Foureman, ORD/NCEA

3:15 pm ***Break***

3:30 pm **Frequency and Duration of Exposure Issues: Superfund Traditional Approach ("Non-Standard Inhalation Rates") and Derivation of the HEC:**
Sarah Levinson, Region 1
Bob Benson, Region 8

4:15 pm **Age Group Issues: Superfund Traditional Approach and Derivation of the HEC:**
Sarah Levinson, Region 1
Gary Foureman, ORD/NCEA

5:15 pm **Open Discussion of Today's Topics**

5:30 pm **Adjourn for the Day**

Wednesday, September 10, 2003

8:30 am **Recap from Previous Day (Session Co-Chairs)**

9:00 am **III. Derivation of an Inhalation Toxicity Value (IUR/RfC) by Route-to-Route Extrapolation:**
Co-Chairs: Dan Stralka, Region 9
Michael Sivak, Region 2

Pharmacokinetic Issues in Route-to-Route Extrapolation:
Elaina Kenyon, ORD/NHEERL

9:35 am **Agency Examples of Route to Route Extrapolation:**
Rob DeWoskin, ORD/NCEA

10:10 am ***Break***

10:25 am **Practical Aspects of Route-to-Route Extrapolation:**
Bob Benson, Region 8

10:50 am **Panel Discussion on Route-to-Route Issues:**
Elaina Kenyon, ORD/NHEERL
Rob DeWoskin, ORD/NCEA
Bob Benson, Region 8

11:15 am **Review of Principles and Practices of EPA Risk Assessment:**
Paul Gilman, U.S. EPA Science Advisor

12:00 pm ***Lunch***

1:30 pm **New Directions in the Science of Risk Assessment:**
Co-Chairs: Gary Foureman, ORD/NCEA
Lee Hofmann, OSWER

Recommendations from AA Review of the RfD/C Processes@:
Carole Kimmel, ORD/NCEA

2:00 pm **Considerations of Dosimetry in the Upper Respiratory Tract in Animals and Humans:**
Julia Kimbell, CIIT Centers for Health Research, RTP, NC

2:45 pm **Approaches for the Improvement of Particle Dosimetry in Human Lungs**
Chong Kim, ORD/NHEERL

3:30 pm ***Break***

3:45 pm **Aggregate Risk Considerations in Risk Assessment:**
Haluk Ozkaynak, ORD/NERL

4:15 pm **Nasal Tract Uptake of Gases in Humans: A Case Study with Acetone**
Gary Foureman, ORD/NCEA

4:45 pm **The Interagency Dosimetry Project:**
Annie Jarabek, ORD/NCEA

5:30 pm **Open Discussion of Today's Topics**

5:45 pm ***Adjourn for the Day***

6:30 pm **Group Dinner at *Buca di Beppo* (1825 Connecticut Ave, N.W.)**

Thursday, September 11, 2003

8:30 am **Recap from Previous Day (Session Co-Chairs)**

9:00 am **Coordination Across Agency Programs:**
Chair: Michael Sivak, Region 2

Panel Presentations and Discussion:
Alec McBride, OSWER/OSW
Deirdre Murphy, OAR/OAQPS
William Burnam, Jess Rowland and Steven Weiss, OPPTS/OPP
Brenda Foos, OCHP

10:30 am ***Break***

10:45 am **Planning for the Guidance Session Moderators (open time for other workshop participants)**

12:00 pm ***Lunch***

1:30 pm **Updating Superfund Inhalation Risk Assessment Guidance: Focus, Goals, and Desired Outcomes:**
Co-Chairs: David Cooper, OSWER/OSRTI
Lee Hofmann, OSWER
Jayne Michaud, OSWER/OSRTI

Identification of Guidance to be Revised:
Dave Crawford and David Cooper, OSWER/OSRTI

1:45 pm **Presentation of the Strawman:**
Bob Benson, Region 8

2:45 pm ***Break***

3:00 pm **How are exposures and risks to children estimated?**
Discussion Moderator

4:15 pm **How should aggregate exposure be evaluated?**
Discussion Moderator

5:15 pm **Open Discussion of Today's Topics**

5:30 pm ***Adjourn for the Day***

Friday, September 12, 2003

8:30 am **Recap from Previous Day (Session Co-Chairs)**

8:45 am **Updating Superfund Inhalation Risk Assessment Guidance: Focus, Goals, and Desired Outcomes:**
Co-Chairs: David Cooper, OSWER/OSRTI
Lee Hofmann, OSWER
Jayne Michaud, OSWER/OSRTI

How should quantitative inhalation assessments which predate the 1994 RfC dosimetry methodology be handled?
Discussion Moderator

9:30 am **How are chronic exposure estimates with discontinuous exposure scenarios developed for assessment of chronic risk?**
Discussion Moderator

10:45 am ***Break***

11:00 am **How should the issue of route-to-route extrapolation be addressed when inhalation toxicity values are not available?**
Discussion Moderator

11:30 am **Summary and Workshop Wrap-Up:**
David Cooper, OSWER/OSRTI
Dave Crawford, OSWER/OSRTI
David Klauder, ORD/OSP
Michael Sivak, Region 2

12:15 am ***Workshop Adjourned***

Appendix B

PARTICIPANT LIST

U.S. EPA Workshop on Inhalation Risk Assessment: A Superfund Focus

September 9-12, 2003
Washington, D.C.

Daniel Axelrad
U.S. EPA OPEI
1200 Pennsylvania Avenue, NW
Mail Code 1809T
Washington, D.C. 20460
Phone: (202) 566-304
Email: axelrad.daniel@epa.gov

Hugh A. Barton
U.S. EPA ORD
10996 Alexander Drive
Mail Code B143-01
Research Triangle Park, NC 27711
Phone: (919) 541-1995
Email: barton.hugh@epa.gov

Stacy Bennett
U.S. EPA/OSWER
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460
Phone: (202) 566-1039
Email: bennett.stacy@epa.gov

Robert Benson
U.S. EPA Region 8
999 18th Street, Suite 300
Mail Code 8P-W-MS
Denver, CO 80202-2466
Phone: (303) 312-7070
Email: benson.bob@epa.gov

Mike Beringer
U.S. EPA Region 7
901 North 5th Street
Kansas City, KS 66101
Phone: (913) 551-7351
Email: beringer.michael@epa.gov

George Bollweg
U.S. EPA Region 5 Air and Radiation
77 West Jackson Boulevard
Mail Code AR-18J
Chicago, IL 60604
Phone: (312) 353-5598
Email: bollweg.george@epa.gov

Michele Burgess
Region 4
SNAFC, 61 Forsyth Street, SW
Waste Management Division
Atlanta, GA 30303
Phone: (404) 562-8667
Email: burgess.michele@epa.gov

William Burnam
OPPTS/OPP
7105 Rolling Forest
Springfield, VA 22152
Email: Burnham.William@epa.gov

S. Steven Chang
U.S. EPA OSWER/OSRTI
1200 Pennsylvania Avenue, NW
Mail Code 5204G
Washington, D.C. 20460
Phone: (703) 603-9017
Email: chang.steven@epa.gov

Weihsueh Chiu
U.S. EPA ORD/NCEA
1200 Pennsylvania Avenue, NW
Mail Code 8623D
Washington, D.C. 20460
Phone: (202) 564-7789
Email: chiu.weihsueh@epa.gov

Harlal Choudhury
U.S. EPA ORD/NCEA
26 West Martin Luther King Drive
Cincinnati, OH 45268
Phone: (513) 569-7536
Email: Choudhury.Harlal@EPA.GOV

Mike Cook
Office of Superfund Remediation and
Technology Innovation

David Cooper
OSRTI
1200 Pennsylvania Avenue, NW
Mail Code 5204G
Washington, D.C. 20460
Phone: (703) 603-8763
Email: cooper.davide@epa.gov

Dave Crawford
U.S. EPA OSWER/OSRTI
1200 Pennsylvania Avenue, NW
Mail Code 5202G
Washington, D.C. 20460
Phone: (703)603-8891
Email: Crawford.Dave@epa.gov

Kerry Dearfield
U.S. EPA ORD/OSP
1200 Pennsylvania Avenue, NW
Mail Code 8103R
Washington, D.C. 20460
Phone: (202) 564-6486
Email: dearfield.kerry@epa.gov

Rob DeWoskin
U.S. EPA ORD/NCEA/HPAG
Mail Code B243-01
Research Triangle Park, NC 27705
Phone: (919) 541-1089
Email: dewoskin.rob@epa.gov

David Eng
OSWER/OSRTI
1200 Pennsylvania Avenue, NW
Mail Code 5204G
Washington, D.C. 20460
Phone (703) 603-8827
Email: eng.david@epa.gov

William Farland
Science Office of Research
And Development

Lynn Flowers
U.S. EPA ORD
1200 Pennsylvania Avenue, NW
Mail Code 8601D
Washington, D.C. 20460
Phone: (202) 564-1537
Email: flowers.lynn@epa.gov

Brenda Foos
OCHP

Stiven Foster
U.S. EPA ORD/NCEA
1200 Pennsylvania Avenue, NW
Mail Code 8601D
Washington, D.C. 20460
Phone: (202) 564-2239
Email: foster.stiven@epa.gov

Gary L. Foureman
NCEA-RTP
Mail Code B-243-01
Research Triangle Park, NC 27711
Phone: (919) 541-1183
Email: foureman.gary@epa.gov

Martin Gehlhaus
ASPH/EPA
Fellow – NCEA
3285 Kaiser Drive
Ellicott City, MD 21043
Phone: (202) 564-1596
Email: Gehlhaus.Martin@epamail.epa.gov

Paul Gilman
U.S. EPA Science Advisor

Barbara Glenn
U.S. EPA ORD/NCER
1200 Pennsylvania Avenue, NW
Mail Code 8723R
Washington, D.C. 20460
Phone: (202) 564-6913
Email: glenn.barbara@epa.gov

Jo Ann Griffith
OSWER OSRTI
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460
Phone: (703) 603-7774
Email: Griffith.Joann@epa.gov

Belinda Hawkins
NCEA
1200 Pennsylvania Avenue, NW
Mail Code 8601D
Washington, D.C. 20460
Phone: (202) 564-3328
Email: hawkins.belinda@epa.gov

Ofia B. Hodoh
U.S. EPA Region 4
61 Forsyth Street, SW
12th Floor
Atlanta, GA 30303
Phone: (404) 562-9176
Email: hodoh.ofia@epa.gov

Lee Hofmann
U.S. EPA OSWER
1200 Pennsylvania Avenue, NW
Mail Code 5103
Washington, D.C. 20004
Phone: (202) 566-1928
Email: hofmann.lee@epa.gov

Freeman Holifield
OSRTI
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460
Phone: (703) 603-9133
Email: Holifield.Freeman@epa.gov

Jennifer Hubbard
U.S. EPA Region 3
1650 Arch Street
Mail Code 3HS41
Philadelphia, PA 19103
Phone: (215) 814-3328
Email: hubbard.jennifer@epa.gov

Annie Jarabek
ORD/NCEA

Amaris Johnson
Office of Solid Waste
& Emergency Response
EPA Headquarters
Washington, D.C. 20003
Phone: (202) 566-1927

Meghan Keaney
OPEI
1410 N. Scott Street
Arlington, VA 22201
Phone: (202) 566-2364
Email: megkeaney@yahoo.com

Elaina Kenyon
U.S. EPA ORD
109 T.W. Alexander Drive
Mail Code B143-01
Research Triangle Park, NC 27711
Phone: (919) 541-0043
Email: kenyon.elaina@epa.gov

Chong S. Kim
NHEERL
109 T.W. Alexander Drive
Mail Code MD-58B
Reaserch Triangle Park, NC 27711
Phone: (919) 966-5049
Email: kim.chong@epa.gov

Julia S. Kimbell
CIIT Centers for Health Research
6 Davis Drive
P.O. Box 12137
Research Triangle Park, NC 27709
Phone: (919) 558-1364
Email: kimbell@ciit.org

Carole Kimmel
U.S. EPA ORD
1200 Pennsylvania Avenue, NW
Ariel Rios Building NCEA-W (8623D)
Washington, D.C. 20460
Phone: (202) 564-3307
Email: kimmel.carole@epa.gov

David Klauder
U.S. EPA ORD
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460
Phone: (202) 564-6496
Email: klauder.david@epa.gov

Kevin Koporec
U.S. EPA Region 4 SNAFC
61 Forsyth Street, SW
Atlanta, GA 30303
Phone: (404) 562-8644
Email: koporec.kevin@epa.gov

Richard Leukroth
U.S. EPA OPPT
1200 Pennsylvania Avenue, NW
Chemical Control Division (7405M)
Washington, D.C. 20460
Phone: (202) 564-8167
Email: leukroth.rich@epa.gov

Sarah Levinson
U.S. EPA Region 1
1 Congress Street
Boston, MA 02114
Phone: (617) 918-1390
Email: levinson.sarah@epa.gov

Mary Manibusan
ORD/NCEA
1200 Pennsylvania Avenue, NW
Mail Code 8601D
Washington, D.C. 20460
Phone: (202) 564-1534
Email: manibusan.mary@epa.gov

Karen L. Martin
U.S. EPA OSWER/OSRTI
1200 Pennsylvania Avenue, NW
Mail Code 5204G
Washington, D.C. 20460
Phone: (703) 603-9925
Email: martin.karenl@epa.gov

Alec McBride
U.S. EPA OSW
1200 Pennsylvania Avenue, NW
Mail Code 5307W
Washington, D.C. 20460
Phone: (703) 308-0466
Email: mcbride.alexander@epa.gov

Julie McPherson
U.S. EPA Region 2
290 Broadway
New York, NY 10007
Phone: (212) 637-4159
Email: mcpherson.julie@epa.gov

Jayne Michaud
OSRTI
1200 Pennsylvania Avenue, NW
Mail Code 5202G
Washington, D.C. 20460
Phone: (703) 603 8847
Email: michaud.jayne@epa.gov

Greg Miller
U.S. EPA OPEI/NCEE
1200 Pennsylvania Avenue, NW
Mail Code 1809T
Washington, D.C. 20460
Phone: (202) 566-2310
Email: miller.gregory@epa.gov

Amy Mills
ORD/NCEA
1200 Pennsylvania Avenue, NW
Mail Code 8601D
Washington, D.C. 20460
Phone: (202) 564-3204
Email: mills.amy@epa.gov

Deirdre Murphy
OAQPS
Mail Code C404-01
Research Triangle Park, NC 27711
Phone: (919) 541-0729
Email: murphy.deirdre@epa.gov

Marian Olsen
U.S. EPA Region 2
290 Broadway
New York, NY 10007
Phone: (212) 637-4313
Email: olsen.marian@epa.gov

Cheryl Overstreet
U.S. EPA Region 6
1445 Ross Avenue
Dallas, TX 75202
Phone: (214) 665-6643
Email: overstreet.cheryl@epa.gov

Haluk Ozkaynak
EPA/ORD/NERL
1200 Pennsylvania Avenue, NW
Ariel Rios Building (MC-8601D)Room 400W22
Washington, D.C. 20460
Phone: (202) 564-1531
Email: ozkaynak.haluk@epa.gov

Dr. Solomon Pollard, Jr.
U.S. EPA Region 4 ATAIS
61 Forsyth Street, SW
Atlanta, GA 30303
Phone: (404) 562-9180
Email: pollard.solomon@epa.gov

Resha Putzrath
ORD/Risk Assessment Forum
1200 Pennsylvania Avenue, NW
Mail Code 8601D
Washington, D.C. 20460
Phone: (202) 564-3229
Email: putzrath.resha@epa.gov

Harvey Richmond
OAQPS
Mail Code C539-01
Research Triangle Park, NC 27711
Phone: (919) 541-5271
Email: richmond.harvey@epa.gov

David Riley
U.S. EPA Region 6
1445 Ross Avenue
Mail Code 6SF-LT
Dallas, TX 75202
Phone: (214) 665-7298
Email: riley.david@epa.gov

Henry Roman
Industrial Economics
2067 Massachusetts Avenue
Cambridge, MA 02140
Phone: (617) 354-0074
Email: har@indecon.com

Henry Schuver
U.S. EPA OSW
1200 Pennsylvania Avenue, NW
Mail Code 5303W
Washington, D.C. 20460
Phone: (703) 308-8656
Email: schuver.henry@epa.gov

Michael Sivak
U.S. EPA Region 2
290 Broadway
18th Floor
New York, NY 10007
Phone: (212) 637-4310
Email: sivak.michael@epa.gov

MaryBeth Smuts
Region 1, Air Permits and Toxics
One Congress Street, Suite 1100, CAP
Boston, MA 02114
Phone: (617) 918-1512
Email: smuts.marybeth@epa.gov

John Stanek
NCEA-RTP
Mail Code B 243-01
Research Triangle Park, NC 27711
Phone: (919) 541-1048
Email: Stanek.John@epa.gov

Daniel Stralka
U.S. EPA Region 9
75 Hawthorne
Mail Code SFD-8-B
San Francisco, CA 94105
Phone: (415) 972-3048
Email: stralka.daniel@epa.gov

Timothy Taylor
OSWER
1200 Pennsylvania Avenue, NW
Mail Code 5307W
Washington, D.C. 20460
Phone: (703) 308-8451
Email: taylor.timothy@epa.gov

Pat Van Leeuwen
U.S. EPA Region 5
77 West Jackson Boulevard
Mail Code SR-6J
Chicago, IL 60604
Phone: (312) 886-4904
Email: vanleeuwen.patricia@epa.gov

Winona Victery
U.S. EPA Region 9
75 Hawthorne Street PMD1
San Francisco, CA 94105
Phone: (415) 972-3736
Email: victery.winona@epa.gov

Chau Vu
U.S. EPA Region 1
1 Congress Street, Suite 1100
HBS
Boston, MA 02114
Phone: (617) 918-1446
Email: vu.chau@epa.gov

Steven Weiss
Office of Pesticide Programs/HED
1200 Pennsylvania Avenue, NW
Ariel Rios Bldg Code 7509C
Washington, D.C. 20460
Phone: (703) 308-8293
Email: weiss.steven@epa.gov

John Whalan
U.S. EPA ORD/IRIS
1200 Pennsylvania Avenue, NW
Mail Code 8601D
Washington, D.C. 20460
Phone: (202) 564-1536
Email: Whalan.john@epa.gov

Diana Wong
U.S. EPA ORD
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460
Phone: (202) 564-3201
Email: wong.diana-M@epamail.epa.gov

Jeanmarie Zodrow
NCEA/IRIS
1200 Pennsylvania Avenue, NW
Mail Code 8601D
Washington, D.C. 20460
Phone: (202) 564-3389
Email: zodrow.jean@epa.gov

APPENDIX C
SLIDES FROM PRESENTATIONS

These slides can be found at:
http://intranet.epa.gov/ospintra/scienceportal/htm/inhalpre.htm

Presentation Title	Presenter(s)
Welcome	William Farland Mike Cook
Introduction to the Inhalation Risk Assessment Workshop	Michael Sivak
Historical Background	Deirdre Murphy
Use of Exposure-Response Modeling in the Ozone Risk Assessment	Harvey Richmond
Physiologically-based Pharmacokinetic (PBPK) Modeling to Determine the Human Equivalent Concentration (HEC)	Hugh Barton
Inhalation Dosimetry Using the Default Chemical Category Specific Approaches: Cancer and Noncancer Assessment	Sarah Levinson Bob Benson
Superfund Traditional Approach for Calculating Inhalation Risk	Sarah Levinson
Methodology for Deriving Human Equivalent Concentrations for Gases	Bob Benson
Derivation of the HEC for Particles from Laboratory Animal and Occupational Studies – the RDDR	Gary Foureman
Frequency and Duration of Exposure: Superfund Traditional Approach	Sarah Levinson
Frequency and Duration of Exposure	Bob Benson
Age Group Issues: Superfund Traditional Approach and Derivation of the HEC	Gary Foureman
Age Group Issues: Superfund Traditional Approach ("Non-Standard Inhalation Rates")	Sarah Levinson
Pharmacokinetic Issues in Route-to-Route Extrapolation	Elaina Kenyon
Agency Examples of Route to Route Extrapolation	Rob DeWoskin
Practical Aspects of Route-to-Route Extrapolation	Bob Benson
Evaluation of EPA Risk Assessment Principles and Practices	Paul Gilman
New Directions in the Science of Risk Assessment	Gary Foureman Lee Hofmann
Recommendations from a Review of the RfD/C Processes	Carole Kimmel
Considerations of Dosimetry in the Upper Respiratory Tract in Animals and Humans	Julia Kimbell
Approaches for the Improvement of Particle Dosimetry in Human Lungs	Chong Kim
Aggregate Exposure Considerations in Risk Assessment	Haluk Ozkaynak
Nasal Tract Uptake of Gases in Humans: A Case Study with Acetone	Gary Foureman
Interagency Dosimetry Project	Annie Jarabek
OSW Regulatory Risk Assessments	Alec McBride
OAQPS: Inhalation Assessments of Air Toxics	Dierdre Murphy Roy Smith
Office of Pesticide Programs Approach for Estimating Inhalation Risk	Steven Weiss
Program Perspectives: Office of Children's Health Protection	Brenda Foos
Strawperson Guidance	Bob Benson
Updating Superfund Guidance	Jayne Michaud

Appendix D

Draft "Strawman" Inhalation Risk Assessment Guidance

Author: Bob Benson Third Draft - August 2003 Directive xxxxxxx

MEMORANDUM

SUBJECT: Transmittal of Directive for Calculation of Cancer and Non-cancer Risk from Inhalation

FROM: Some High Official in HQ/Superfund-RCRA

TO: Regional Waste Management Directors

Purpose
This directive transmits guidance on how to calculate cancer and non-cancer risk from exposure to a contaminant through the inhalation route. The directive specifically withdraws a section of RAGS, Part A and replaces it with guidance for calculating these risks using methodology that is scientifically consistent with the procedures used to derive the Reference Concentration and Inhalation Unit Risk.

Background
RAGS, Part A (1989) outlines an approach for calculating cancer and non-cancer risk from chemicals that are inhaled. See sections 6.6.3, 7.2.3, 7.3.3, and 8.2. The approach is based on the assumption that cancer risk was determined by the chronic daily intake of the chemical from the air multiplied by the cancer slope factor for inhalation and that the Hazard Quotient (HQ) was determined by the intake of the chemical divided by the reference dose for inhalation. The intake of the chemical is calculated as a function of the concentration of the chemical in air, inhalation rate, the body weight, and the exposure scenario. Often an age-adjusted factor is used to accommodate the difference in breathing rate and body weight of children compared with adults. The equations are:

Intake = CA x (IR/BW) x (ET x EF x ED)/AT
Risk = CSF_i x Intake
HQ = Intake/RfD_i
Where:
CSFi = Cancer Slope Factor for Inhalation $(mg/kg\text{-}day)^{-1}$
RfDi = Reference Dose for Inhalation (mg/kg-day)
CA = Contaminant Concentration in Air (mg/m^3)
IR = Inhalation Rate (m^3/hr)
BW = Body Weight (kg)
ET = Exposure Time (hours/day)
EF = Exposure Frequency (days/year)
ED = Exposure Duration (years)
AT = Averaging Time (period over which exposure is averaged - days)

This approach was developed before EPA adopted the inhalation dosimetry methodology (US EPA, 1994) and before there were any Inhalation Unit Risk (IUR) factors and Reference Concentrations (RfC) and there were some Cancer Slope Factors for Inhalation on EPA's Integrated Risk Information System (IRIS).

In 1991 all the Cancer Slope Factors for Inhalation were withdrawn from IRIS. In 1994 EPA adopted methodology for developing the Human Equivalent concentration (HEC) from inhalation studies in laboratory animals or from occupational studies in humans where exposure if from the air. See Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, EPA 1994, EPA/600/8-90/066F. The RfC is calculated from the HEC by dividing the HEC by uncertainty factors. The IUR is typically calculated by dividing the lowest effective dose for a 10% incidence of tumors by the HEC. If some other procedure is used to calculate the RfC or IUR, that procedure will be described in the IRIS file.

The Superfund Program has not updated its methodology for calculating risk that is scientifically compatible with the inhalation dosimetry methods now used to derive IURs and RfCs.

What specific guidance is being changed by this directive?
The intake equation (exhibit 6-16, page 6-44, RAGS, Part A, 1989) is no longer to be used when evaluating risk from the inhalation pathway. Withdrawing this equation from RAGS, Part A will also require complementary changes in RAGS, Part B, Section 3.3 (Volatilization and Particulate Emission Factors); RAGS, Part D, Tables 5.2, 6.2, 7, and 9; and some Regional tables used to calculate Preliminary Remediation Goals. No changes are required in the equations pertaining to risk from inhaled chemicals in the Soil Screening Guidance (1996), Section 2.4, or the Supplemental Soil Screening Guidance (2001), Sections 4.2.3, 5.3.2 and Appendix B other than to clarify that the IURs and RfCs used in the equations are based on continuous exposure (24 hours per day). If the exposure scenario of interest is less than 24 hours per day, a correction factor is needed in the equation. That factor is determined by the actual exposure time in hours divided by 24 hours.

Why is the intake equation being withdrawn?
As the internal dose to a chemical from the inhalation pathway is not a simple function of the inhalation rate and body weight, this intake equation (RAGS, Part A, Exhibit 6-16) does not comply with the principles of EPA's inhalation dosimetry procedures (US EPA, 1994) used to determine the human equivalent concentration (HEC) for calculating a Reference Concentration (RfC) or Inhalation Unit Risk (IUR).

How is the lifetime excess cancer risk calculated?
The lifetime excess cancer risk for the inhalation pathway will be calculated with the following equation:

$$\text{Risk} = \text{Inhalation Unit Risk [IUR]}\ (\mu g/m^3)^{-1} \times \text{CA}\ (\mu g/m^3) \qquad \text{(Eq 1)}$$

This equation assumes a continuous exposure, 24 hours/day for a lifetime of 70 years. The equation is modified when the exposure is for less than a lifetime. The standard approach is shown in equation 2.

Risk = IUR x CA x (ET x EF x ED)/AT (Eq 2)
Where CA = Contaminant Concentration in Air ($\mu g/m^3$)
ET = exposure time (hours/day)
EF = exposure frequency (days/year)
ED = exposure duration (years)
AT = averaging time (70 years x 365 days/year x 24 hours/day)

The default exposure factors (found elsewhere) can be replaced with more representative values for a site specific risk assessment. This would typically require some demographic information for the specific site or the use of professional judgment.

For the standard occupational scenario, ET (hours/day) is replaced with ½ and 24 hours/day is eliminated from the AT term. These adjustments are made because sit is likely that a higher exposure will occur during a normal 8 hours work shift due to increased physical activity and rate of inhalation. Using an 8 hour/24 hour for adjustment would likely underestimate exposure to workers from the chemical. This approach is consistent with the procedure used to derive the HEC from an occupational study. The equation is:

Risk = IUR x CA x ½ x (EF x ED)/AT (Eq 2A)
Where CA = Contaminant Concentration in Air ($\mu g/m^3$)
EF = exposure frequency (days/year)
ED = exposure duration (years)
AT = averaging time (70 years x 365 days/year)

In a situation where the calculated cancer risk exceeds 0.01, risk should be calculated using an equation of the form risk = 1 - exp(-IUR x CA). See RAGS, Part A, Section 8.2.1, page 8-11.

How is the Hazard Quotient calculated?

The Hazard Quotient (HQ) for the inhalation pathway will be calculated with the following equation:

HQ = CA (mg/m^3)/Reference Concentration (RfC) (mg/m^3) (Eq 3)

This equation assumes a continuous exposure, 24 hours/day for a lifetime of 70 years. The equation is modified when the exposure is for less than lifetime. The standard approach is shown in equation 4.

HQ =CA/RfC x (ET x EF x ED)/AT (Eq 4)
Where CA = Contaminant Concentration in Air (mg/m^3)
ET = exposure time (hours/day)
EF = exposure frequency (days/year)
ED = exposure duration (years)
AT = averaging time (ED in years x 365 days/year x 24 hours/day)

The default exposure factors (found elsewhere) can be replaced with more representative values for a site specific risk assessment. This would typically require some demographic information for the specific site or the use of professional judgment.

For the standard occupational scenario, ET (hours/day) is replaced with ½ and 24 hours/day is eliminated from the AT term. These adjustments are made because sit is likely that a higher exposure will occur during a normal 8 hours work shift due to increased physical activity and

rate of inhalation. Using an 8 hour/24 hour for adjustment would likely underestimate exposure to workers from the chemical. This approach is consistent with the procedure used to derive the HEC from an occupational study. The equation is:

$$HQ = CA/RfC \times \frac{1}{2} \times (EF \times ED)/AT \qquad \text{(Eq 4A)}$$

Where CA = Contaminant Concentration in Air (mg/m^3)
EF = exposure frequency (days/year)
ED = exposure duration (years)
AT = averaging time (ED in years x 365 days/year)

Are additional corrections for specific age groups (e.g., children) necessary?
Exposure information, specifically information related to activity patterns (e.g., exposure time, frequency, and duration, as well as contaminant concentration) may vary across age groups and other population groups. Consequently, such variation should be taken into account in deriving both lifetime excess cancer risk and hazard quotient estimates for scenarios that depart from a residential scenario. For example, due to outdoor play patterns, children may spend more time near the source of contamination than adults. Consequently, the exposure time or frequency values for children may be higher than for adults living in the same location.

Beyond the consideration of time spent in the area of contamination and any change in concentration of the contaminant in that area, no additional corrections to the risk calculations for specific age groups are necessary. As shown in Appendix 1, the lack of significant age-related variation in the physiological characteristics relied on in the derivation of the human equivalent concentration using EPA's Inhalation Dosimetry Methodology (US EPA, 1994) and the conservative values used in the default calculations generally accommodate any variation in exposure observed as a function of activity level or body size. In the case of the RfC derivation, the consideration of age group susceptibility in the selection of the toxicological effect used as the starting point for the derivation of the RfC and consideration of uncertainty factors for database, intraspecies variation and any remaining interspecies variability provide adequate protection for all age groups.

The use of the normal exposure duration (9 to 30 years) in the Superfund Program precludes significant underestimation of the duration adjusted exposure concentration for calculation of cancer and non-cancer risk for any age groups. EPA is developing Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens (US EPA, 2003) to consider cancer risk from a short duration exposure in childhood. When this guidance is final, it will be incorporated into Superfund methods, as will any updates to the Inhalation Dosimetry Methodology.

Do these new equations apply to all exposure scenarios for inhalation evaluated in a typical site specific risk assessment?
The issue to consider is whether the exposure scenario being evaluated is chronic exposure. The factors considered are the exposure time (hours per day), exposure frequency (days per years), and exposure duration (years). The RfC and IUR apply to a continuous exposure for a lifetime. Another assumption of inhalation dosimetry is that the dose to the cells of the respiratory tract or the internal dose to blood and organ systems has reached some form of "steady state."

Most of the inhalation studies in laboratory animals used to derive the RfC and IUR involve exposure of 4 to 6 hours per day for 13 weeks or more (equivalent to 10 % or more of the lifetime of the animal). The exposure in this study is mathematically adjusted to a continuous exposure (24 hours per day, 7 days per week). For example, if exposure in the study was 6 hours/day, 5 days/week, the experimental exposure is multiplied by 6/24 x 5/7 to calculate the equivalent continuous exposure. The assumption is that if an adverse effect occurs from a chemical at an exposure of 6 hours per day at 40 ppm that same adverse effect will occur at an exposure of 24 hours/day at 10 ppm. If some other procedure was used to calculate the continuous exposure, that procedure will be fully discussed in the IRIS file for the chemical. For additional discussion see US EPA (1994), Section 4.3.2 and US EPA (2002), Section 4.4.2.1. Any adjustments for less than continuous exposure in a site specific risk assessment must be made with a procedure consistent with that used in the derivation of the RfC or IUR.

The typical residential scenario (exposure for 24 hours per day for 9 to 30 years) is consistent with the studies and surrounding framework of the RfC and IUR derivation (i.e., chronic duration of exposure). A residential exposure scenario with exposure less than 24 hours/day (for example, 16 hours/day for 9 to 30 years) is also consistent with the studies and surrounding framework of the RfC and IUR derivation. Consequently, it is appropriate to use equation 2 and equation 4 for calculations of cancer and non-cancer risk for these scenarios.

The typical commercial/industrial occupational scenario (exposure for 8 hours per day for 5 to 25 years) are consistent with the studies and surrounding framework of the RfC and IUR derivation (i.e., chronic duration of exposure). Consequently, it is appropriate to use equation 2A and equation 4A for calculations of cancer and non-cancer risk for these occupational scenarios.

A construction worker scenario (8 hours per day for 1-2 years or less), however, does not meet the definition of a chronic exposure because the duration of exposure is less than 10% of the lifetime. Thus, this exposure scenario would be best assessed using an RfC for sub-chronic exposure, if available. However, as the equation used to calculate the HQ sets averaging time equal to the exposure duration, a calculated HQ less than 1 using equation 4A will provide protection for any adverse health effect for the duration of exposure of 1-2 years. Using equation 2A to quantify cancer risk for partial lifetime exposure for a construction worker is acceptable because the cancer risk calculation is based on the concept of lifetime average daily exposure and the IUR has been derived to calculate lifetime risk associated with cumulative lifetime exposure.

A typical trespasser or recreational scenario (for example, 1 to 2 hours per day, 100 days per year or less, for 2-5 years) is not consistent with the scientific approach used to derive the RfC. In these scenarios, the daily exposure time is short relative to the time necessary to reach steady state for a typical gas or particle. The exposure frequency and exposure duration also do not reasonably match the definition of chronic exposure. The RfC and equation 4 should not be used to evaluate risk for these scenarios. The IUR and equation 2 can be used to quantify cancer risk because the cancer risk calculation is based on the concept of lifetime average daily exposure

and the IUR has been derived to calculate lifetime risk associated with cumulative lifetime exposure.

As a general rule, any exposure scenario where (ET x EF x ED)/AT is less than 0.1 should not be evaluated using equation 4 without investigation of the other toxicological endpoints noted in the IRIS file for the chemical. It is possible that an adverse effect other than that used to derive the RfC and with a different exposure-response relationship could occur under these exposure scenarios. This could be especially important in situations where equation 4 is used to calculate Preliminary Remediation Goals as screening values for a site. In most cases, it is more appropriate to evaluate risk from trespasser and recreational scenarios using an acute, a shorter-term, or a sub-chronic reference value if one is available for the chemical. If no suitable shorter term reference value is available, only a qualitative risk assessment should be conducted.

How is the inhalation pathway assessed when no inhalation toxicity values are available? Consistent with RAGS, Part A, Section 7.5.1, for cases in which RfC and IUR values are not available on IRIS, but RfD and Cancer Slope values are available, the risk assessor should contact the Superfund Technical Support Center for guidance regarding the appropriateness of using route-to-route extrapolation to determine a risk value. If no quantitative toxicity information for the inhalation route is available, the risk assessor should conduct only a qualitative evaluation of this exposure route. The risk assessor should discuss in the uncertainty section the implications of the absence of this exposure route for this chemical from the quantitative risk estimate.

All of the RfC's on IRIS were developed from inhalation studies using the 1994 inhalation dosimetry approach. However, there are some IUR's on IRIS that were calculated from oral values using a default ventilation rate and body weight (31 chemicals as of June 2003, see Appendix 2). All except two of these values (for chlordane and polychlorinated biphenyls) were developed before EPA adopted the inhalation dosimetry methodology. These chemicals cause tumors remote from the respiratory tract and should be treated as other category 3 gases with the ratio of the partition coefficients equal to 1. These IUR's are to be used with equation 2 and 2A without additional modification for calculation of cancer risk by the inhalation route of exposure. It is not appropriate to made adjustments based on ventilation rate and body weight using the intake equation because the internal dose of the chemical from the inhalation pathway is not a simple function of the inhalation rate and body weight.

[Note: I have been unable to track down the reason the IURs for these 31 chemicals were retained on IRIS. I think that most who are knowledgeable about the pharmacokinetics involved in route to route extrapolation would discourage using the values in a quantitative risk assessment. However, Superfund has been using these values for years. In addition using these values is consistent with the hierarchy of toxicological values used - "use any value on IRIS." If Superfund wants to advocate not using these 31 IURs, then HQ will have to modify the toxicity hierarchy directive based on a policy decision.]

The Vapor Intrusion Guidance, Appendix D, page D-2, and Table D-1, page D-8, uses extrapolation based on the default ventilation rate and body weight from the RfD or Cancer

Slope Factors whenever the RfC or IUR is not available on IRIS. These values are then used for screening sites but are not used for a quantitative risk assessment. The analysis in Appendix 3 supports the use these extrapolated values for screening purposes.

How is risk from multiple routes of exposure and from multiple chemicals calculated using the new methodology?

The guidance in RAGS, Part A, Section 8.2.2 and 8.3 remains in effect. See also Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures (US EPA, 2000). The appropriate way of calculating cancer risk or the hazard quotient from exposure via multiple routes to the same chemical is to first calculate cancer risk and hazard quotient for each pathway and then sum the risk or hazard estimates across the multiple pathways and routes when it is appropriate to do so.

References

[to be added later]

Appendix 1. Analysis of Default Procedure to Derive the RfC for Different Age Groups

EPA's inhalation dosimetry procedure (US EPA, 1994) recognizes a hierarchy of approaches to determine the Human Equivalent Concentration (HEC) used for the derivation of the RfC or IUR. The preferred method is to use a physiologically based pharmacokinetic model to determine the HEC. Because of the large amount of data necessary to construct a valid model, this approach is rarely used. The one example on IRIS is the vinyl chloride file. The next most preferred method to use some chemical specific and physiological information to determine the HEC. The most common method is the default chemical category specific method. This approach is discussed in more detail below. The least favored method is route-to-route extrapolation from an oral study using the default ventilation rate and body weight. A preferred approach for this route–to-route extrapolation is with a physiologically based pharmacokinetic model to calculate the equivalent internal dose . This latter approach is appropriate only when the chemical does not cause effects in the respiratory tract and any first pass effects in the liver or respiratory tract can be ruled out.

Category 1 Gas, Extrathoracic Effects, Acrolein

The Dosimetric Adjustment Factor for a Category 1 gas, the Regional Gas Dose Ratio (RGDR), is based on the ratio of the animal ventilation minute volume (Ve) divided by the surface area (SA) of the region of the respiratory tract where the effect occurs to those same variables for the human. For acrolein the effect occurs in the extrathoracic region (ET) and the equation is:

$$RGDR_{ET} = [Ve/SA_{ET}]_{animal}/[Ve/SA_{ET}]_{human}$$

The Ve and SA_{ET} for the rat are 0.1413 L/minute (after correcting for the body weight of Wistar rats, the animals in the principal study on acrolein) and 15 cm^2, respectively, giving a value of Ve/SA_{ET} of 0.00942 L/min-cm^2. EPA currently does not have values for ventilation minute volume (Ve) and surface area for the extrathoracic region (SA_{ET}) in all age groups. However, scaled estimates of the ventilation rate to surface area ratio for humans at different ages are available in the ICRP publication "Human Respiratory Tract Model for Radiological Protection" (ICRP Publication 66, 1994). From ICRP values for the mass of extrathoracic target tissue and an estimate of the thickness of the extrathoracic target tissue, one can calculate the SA_{ET} and the Ve/SA_{ET} ratio for humans at different ages. The Regional Gas Deposition Ratio for the extrathoracic region ($RGDR_{ET}$) is then calculated using the values for the rat and the human. In the laboratory animal study on acrolein, the $LOAEL_{adj}$ is 0.16 mg/m^3 (see the IRIS file on acrolein). The $LOAEL_{HEC}$ is the $LOAEL_{ADJ}$ multiplied by the $RGDR_{ET}$.

Calculation of $LOAEL_{HEC}$ Values for Humans of Different Ages and Activity Patterns

	Total Ve (L/min)	ET (cm^2)	$(Ve/SA)_{human}$ (L/min-cm^2)	$RGDR_{ET}$	$LOAEL_{HEC}$
Outdoor Worker M	17.5	470.0	0.0372	0.253	0.041
Sedentary Worker M	15.4	470.0	0.0328	0.287	0.046
Sedentary Worker F	12.3	407.0	0.0302	0.312	0.05
15 year M	14.0	439.0	0.0319	0.295	0.047
15 year F	10.9	397.0	0.0275	0.343	0.055
10 Year	10.6	293	0.0362	0.26	0.042
5 Year	6.1	198.3	0.0308	0.306	0.049
1 Year	3.6	97.1	0.0371	0.254	0.041
3 month	2.0	65.8	0.0304	0.31	0.05
HEC-default	13.8	200	0.069	0.137	0.022

As can be seen, when the proper dosimetric adjustment factor is used to calculate the human equivalent concentration, there is little variation in $LOAEL_{HEC}$ across age groups. The default procedure provides a lower $LOAEL_{HEC}$ value and is, therefore, health protective for all age groups.

Category 1 Gas, Pulmonary Effects, Hypothetical Chemical

The Dosimetric Adjustment Factor for a Category 1 gas with an effect in the pulmonary region (PU) is based on the ratio of the animal ventilation minute volume (Ve) divided by the surface area (SA) of the pulmonary region to those same variables for the human. The equation is:

$$RGDR_{PU} = [Ve/SA_{PU}]_{animal}/[Ve/SA_{PU}]_{human}$$

The Ve and SA_{PU} for the rat are 0.1413 L/minute (after correcting for the body weight of Wistar rats as above) and 3400 cm^2, respectively, giving a value of Ve/SA_{PU} of 4.15E-5 L/min-cm^2. EPA currently does not have values for ventilation minute volume (Ve) and surface area for the pulmonary region (SA_{PU}) in children. As discussed above, the values for the Ve and the surface area of the pulmonary region were taken from the ICRP publication. From ICRP values for the pulmonary region, one can calculate an SA_{PU} and the Ve/SA_{PU} ratio for humans at different ages. It is acknowledged that there are limited data and, therefore, uncertainty on the values for the surface area of the pulmonary region as a function of age. Because there are no chemicals on IRIS where the effect is in the pulmonary region, a hypothetical chemical is used for the calculation. Assume the chemical was tested in Wistar rats (as acrolein) and gave a $LOAEL_{ADJ}$ of 0.16 mg/m^3.

Calculation of $LOAEL_{HEC}$ Values for Humans of Different Ages and Activity Patterns

	Total Ve (L/min)	PU (cm^2)	$(Ve/SA)_{human}$ (L/min-cm^2)	$RGDR_{PU}$	$LOAEL_{HEC}$
Outdoor Worker M	17.5	627000	0	1.49	0.24
Sedentary Worker M	15.4	627000	0	1.69	0.27
Sedentary Worker F	12.3	627000	0	2.12	0.34
15 year M	14.0	433500	0	1.29	0.21
15 year F	10.9	433500	0	1.65	0.26
10 Year	10.6	333000	0	1.31	0.21
5 Year	6.1	212300	0	1.45	0.23
1 Year	3.6	70700	0.0001	0.81	0.13
HEC-default	13.8	540000	0	1.63	0.26

As can be seen, when the appropriate dosimetric adjustment factor is used to calculate the human equivalent concentration, there is little variation across most age groups. An exception is the 1 year group. In this case, the human equivalent concentration for the 1 year old is approximately one-half of the value calculated using the default procedure. This variation, however, is well within the uncertainty factor of 10 used for intraspecies variability when deriving the RfC. Application of the normal procedure for determining the RfC will provide an RfC that is protective. In addition, it is important to note that the RfC is developed for chronic exposure and its appropriate application will involve an exposure for multiple years. The procedure for deriving the IUR does not incorporate an intraspecies uncertainty factor. Use of the IUR on IRIS will underestimate the risk for the 1 year age group if risk to that group is calculated separately.

Category 3 Gas

The Dosimetric Adjustment Factor for a Category 3 gas is based on the ratio of the animal blood:air partition coefficient and the human blood:air partition coefficient. The equation is:

$$DAF = (H_{b/g})_{animal}/(H_{b/g})_{human}$$

The blood:air partition coefficient is primarily determined by the solubility of the gas in an aqueous medium and the protein and lipid content of the blood. There is little reason to suspect that the blood:air partition coefficient will vary greatly across the human population. The limited data available indicate no difference in the blood:air partition coefficient with age for dichloromethane (Thomas et al., 1996) and halothane and nitrous oxide (Balagopal and Krishnan, 2003). Any variability in the blood:air partition coefficient with age will be well within the uncertainty factor of 10 used for intraspecies variability when deriving the RfC. Any variability in the blood:air partition coefficient with age is also not expected to cause a large overestimate or underestimate in the calculated cancer risk.

Because of the limited data available, the inhalation dosimetry methodology makes the science policy decision to use a value of 1 for the ratio of the partition coefficients when the animal to

human ratio exceeds 1 or when the animal or human value is unknown. For chemicals for which the animal and human partition coefficients are known, the ratio always exceeds 1.

Particle Deposition in Age Groups

The Dosimetric Adjustment Factor for a particle causing an effect in the respiratory tract is based on the ratio of the animal ventilation minute volume (Ve) divided by the surface area of the region where the effect occurs times the fractional deposition of the particle in that region to those same variables for the human. Inherent in this derivation is the assumption that 100% of the deposited dose remains in the respiratory tract and any clearance mechanisms are not considered. The general equation is:

$$RDDR = [Ve/SA_r \times F_r]_{animal}/[Ve/SA_r \times F_r]_{human}$$

The Dosimetric Adjustment Factor for a particle causing an extra-respiratory effect is based on the ratio of the animal ventilation minute volume (Ve) divided by the body weight times the total deposition of the particle in the entire respiratory tract to those same variables for the human. The assumption is that 100% of the deposited dose in the entire respiratory tract is available for uptake to the systemic circulation. The general equation is:

$$RDDR = [Ve/BW \times F_{total}]_{animal}/[Ve/BW \times F_{total}]_{human}$$

The information on particle deposition in various age groups is quite limited. A discussion of the current state of the science can be found in the Fourth External Review Draft of Air Quality Criteria for Particulate Matter (June, 2003), Volume II, Section 6.2 (US EPA, 2003a).

Some experimental results indicate that there is no difference between 6-12 and 7-14 year olds versus adults in total deposition of particles in the respiratory tract for particles of 1 - 2 microns (Bennett and Zeman, 1998; Schiller-Scotland, 1992). For particles of 2 and 3 microns, there was a two to three fold higher total deposition of particles in 6-12 year olds versus adults (Schiller-Scotland, 1992).

Modeling results with 1 - 2 microns particles suggest a 1.5 to 2- fold higher total deposition or deposition in the tracheobronchiolar region for particles in resting 8 year olds versus adults, but a 40-50% lower total deposition of particles under conditions of exercise (Hofmann et al., 1989). The modeling results of Musante and Martonen (2000) using 2 micron particles predicted a 3-fold higher deposition of particles in the pulmonary region for 7 month olds versus adults. The modeling results of Phalen and Oldham (2001) predicted no difference in total deposition of particles in 2 year olds versus adults, but a somewhat higher (10-80%) deposition of particles in the tracheobroncholiar region and a lower deposition of particles in the pulmonary region.

Conclusion

The results with gases indicate that the default approaches for derivation of human equivalent concentration for a category 1 gas with effects in the extrathoracic region and for a category 3 gas suitably accommodate all age groups. With regard to a category 1 gas with an effect in the pulmonary region, this is not as clear. The estimates of pulmonary surface area, however, are

highly uncertain, thus precluding strong conclusions regarding the potential for a higher exposure of the 1-year old age group than the default HEC would yield. It is important to note that the RfC is developed for chronic exposure and its appropriate application will involve an exposure for multiple years.

Experimental and modeling results with particles suggest the potential for small differences in deposition of particles in the respiratory tract as a function of age. It is noted however, that the assumption of 100% of the deposited dose being available for uptake into the systemic circulation (for remove acting toxicants), or for activity in the respiratory tract (for local toxicity) is considered likely to result in an overestimation of dose to the target tissue. Any small variation in deposition among age groups should be considered against the potential magnitude of such overestimation. Additionally, these differences in calculated deposition are small relative to the 10-fold uncertainty factor used for intraspecies variability in the derivation of the RfC. No additional correction for exposure to these age groups is needed when the RfC is used in a risk assessment. With regard to cancer risk assessment, any variation in calculated cancer risk is expected to be minimal and will be further minimized when cancer risk is calculated for a long duration of exposure. With regard to short duration exposures in childhood, EPA is developing Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens (US EPA, 2003b). When this guidance is final, it will be incorporated into Superfund methods.

However, it should be noted that only limited data are available to support these conclusions. In keeping with the recommendation of the RfD/RfC Technical Panel (US EPA, 2002), issues involving exposure to the young from inhalation should be pursued both theoretically and experimentally. This is especially important because of the significant developmental changes that occur in the lung from birth well into adolescence (Pinkerton and Joad, 2000). Our knowledge of the effect on exposure of these developmental changes is incompletely understood.

References

[to be added]

Appendix 2. Chemicals on IRIS with the Inhalation Unit Risk calculated by extrapolation using the default ventilation rate and body weight from the Oral Cancer Slope Factor. Also listed is the year EPA verified the cancer assessment. The list was compiled in June 2003.

Acrylamide, 1988
Aldrin, 1987
Aramite, 1991
Azobenzene, 1988
Bis(chloroethyl)ether, 1986
Bromoform, 1989
Chlordane, 1997
Chloroform, 1987 (under review to replace the IUR)
DDT, 1987
1,2-Dichlorethane, 1986
Dieldrin, 1987
1,2-Diphenylhydrazine, 1986
Heptachlor, 1987
Heptachlor epoxide, 1987
Hexachlorobenzene, 1989
Hexachlorobutadiene, 1986
Alpha-hexachlorocyclohexane, 1986
Beta-hexachlorocyclohexane, 1986
Technical-hexachlorocyclohexane, 1986
Hexachlorodibenzo-p-dioxin mixture, 1987
Hexachloroethane, 1986
N-nitroso-di-n-butylamine, 1986
N-nitroso-diethylamine, 1986
N-nitroso-dimethylamine, 1986
N-nitroso-pyrrolidine, 1986
Polychlorinated biphenyls, 1996
1,1,2,2-Tetrachloroethane, 1986
1,1,1,2-Tetrachloroethane, 1988
toxaphene, 1987
1,1,2-Trichloroethane, 1986
2,4,6-Trichlorophenol, 1989

Appendix 3. Comparison of RfC to $RfC_{R/R}$ and IUR with $IUR_{R/R}$ June 2003

The Vapor Intrusion Guidance uses extrapolation based on the default ventilation rate and body weight whenever the RfC or IUR is not available. These values are then used for screening sites. To determine the degree to which this procedure over- or under-estimates the RfC and the IUR, the IRIS files were examined. Chemicals with an RfC or an IUR derived from an inhalation study were compared to the RfC or IUR calculated by extrapolation based on the default ventilation rate and body weight from oral values. The selection process used and the results of the analysis are presented below. The analysis generally supports the use of route-to-route extrapolation to derive screening values.

Selection of Chemicals from IRIS

67 chemicals have RfCs. 27 of these chemicals have RfCs based on respiratory effects. 24 of these chemicals have no RfDs. One chemical (benzene) has an RfD based on a modified extrapolation using the default inhalation rate and body weight. Two chemicals (chlordane and manganese) have an RfC using a study with particles. One chemical (vinyl chloride) has the RfC and RfD based on a physiologically based pharmacokinetic model taking into account differential absorption and metabolism and is therefore not included in the analysis. 12 chemicals remain for analysis.

54 chemicals have IURs. 31 of these chemicals have IURs already based on extrapolation based on the default ventilation rate and body weight from the oral cancer slope factor and are not considered further. 11 of these 54 chemicals have IURs derived from occupational studies and are not considered further. 12 of these 54 chemicals have IURs derived from inhalation studies in laboratory animals. Of these 12 chemicals, 9 show tumors in the respiratory tract and are not considered further. One chemical (vinyl chloride) has the IUR and oral cancer slope factor based on a physiologically based pharmacokinetic model taking into account differential absorption and metabolism and is therefore not included in the analysis. Two chemicals remain for analysis.

Calculation of $RfC_{R/R}$ and $IUR_{R/R}$

The calculation assumes that a 70 kg person breathes 20 m^3/day, that absorption of the chemical across the lung is equivalent to the absorption of the chemical across the intestine, and that the dose to the target tissue is equal regardless of route of exposure. The specific equations are:

$$\text{RfD (mg/kg-day)} \times 70 \text{ kg} \times 1 \text{ day}/20 \text{ m}^3 = RfC_{R/R} \text{ (mg/m}^3\text{)}$$

$$\text{CSF (mg/kg-day)}^{-1} \times 1/70 \text{ kg} \times 20 \text{ m}^3/\text{day} = IUR_{R/R} \text{ (mg/m}^3\text{)}^{-1}$$

Results

Chemical	$RfC/RfC_{R/R}$	Chemical	$RfC/RfC_{R/R}$
Hydrogen cyanide	0.04	Cumene	1.1
Xylenes	0.14	1,1-DCE	1.1
Dichlorvos	0.29	Styrene	1.4
Phosphine	0.29	Carbon disulfide	2.0
Methylethyl ketone	0.48	Ethylbenzene	2.9
Toluene	0.57	EGBE	7.4

Chemical	$IUR/IUR_{R/R}$
Dichloromethane	0.22
Carbon tetrachloride	0.41

APPENDIX E: PARTICIPANT EVALUATION SUMMARY

Seventeen written workshop evaluation forms were received at the close of the workshop, containing variable amounts of feedback. Meeting participants agreed that the Inhalation Risk Workshop was a valuable opportunity to gain new information and insights about emerging issues, make valuable contacts, and exchange perspectives.

All responding participants rated the workshop either as "good" or "excellent" and all but one offered similar ratings for the major workshop components (Data-Rich Inhalation Risk Assessment Approaches, Inhalation Dosimetry Using the Default Chemical Category-Specific Approaches, Derivation of an Inhalation Toxicity Value (IUR/RfC) by Route-to-Route approaches, New Directions in the Science of Risk Assessment, Coordination Across Agency Programs, Updating Superfund Inhalation Risk Assessment Guidance). Regarding workshop accommodations and logistics, responding participants rated all categories (Meeting Materials, Registration Process, Hotel Accommodations, Helpfulness of Meeting Staff, and Meeting Room) as "good" or "excellent" with the exception of four individual "fair"ratings, two of which addressed the conference materials. Ratings were generally split fairly evenly between "good" and "excellent" for the Hotel Accommodation and Conference Materials categories. Ratings of the remaining three categories ran at about a 3:1 excellent:good ratio. Comments suggested that a more moderate room temperature and more legible handouts would improve the quality of future workshops.

Substantively, the information provided on inhalation dosimetry was viewed by many (6 of 17) participants as the most valuable. Many other topics were singled out as being of value by individual workshop participants. Some respondents made particular note of the value provided by being able to better understand the state of existing Agency science regarding inhalation risk assessment, and many expressed strong interest in and support for developing revised EPA guidance on this topic. Others expressed concerns that most of the participants with real decision making authority within EPA remained in the workshop for only a short period. On a related point, several participants emphasized the need for concrete follow-up (e.g., milestones, schedules) on the steps identified during the Workshop (e.g., dissemination of improved procedures, better cross-program interaction and consistency).

Many participants expressed appreciation for the opportunity to engage in dialog with Agency peers and counterparts on important risk assessment issues, and numerous suggestions were offered that this type of dialog be either continued. Some suggested that external stakeholders (e.g., industry) be included in future Agency dialog on inhalation risk issues. In addition to completing the new guidance, many respondents also suggested one or more mechanisms by which ongoing communication could/should be fostered among workshop participants and their respective organizations. Specific examples included the following: ensuring that the topic be included in forthcoming major meetings and conferences, regular update, meetings and/or teleconferences, maintaining list-serves, and supporting various approaches to less formal networking.

U.S. EPA Region/OSRTI/ORD
Workshop on Inhalation Risk Assessment
September 9-12, 2003 - Washington, DC

Evaluation Form

Please take a few moments to evaluate the meeting. Your completion of this form will assist us in our future planning. Thank you in advance for your comments.

Rate the following on a scale of 1 (Poor) to 4 (Excellent).

	Poor	Fair	Good	Excellent
Overall Impression of Meeting	1	2	3	4
Data Rich Inhalation Risk Assessment Approaches	1	2	3	4
Inhalation Dosimetry Using the Default Chemical Category Specific Approaches	1	2	3	4
Derivation of an Inhalation Toxicity Value (IUR/RfC) by Route-to-Route Extrapolation	1	2	3	4
New Directions in the Science of Risk Assessment	1	2	3	4
Coordination Across Agency Programs	1	2	3	4
Update Superfund Inhalation Risk Assessment Guidance	1	2	3	4

The most informative session was: _____
This session was helpful because:

The least informative session was: _____
This session failed to meet my expectations because:

General Comments:

What did you learn that you are most likely to take back and share with staff?

_____

_____

_____

OVER

If you had planned this meeting, what would you have done differently?

_____
_____
_____
_____

What follow-up activities would you like to see from this workshop?

_____
_____
_____

What could be done to facilitate your continued interaction with the people you met at the workshop concerning the science issues important to you?

_____
_____
_____

Additional comments:

_____
_____
_____

Please provide your overall rating on a scale of 1 (Poor) to 4 (Excellent).

	Poor	Fair	Good	Excellent
Meeting Materials	1	2	3	4
Registration Process	1	2	3	4
Hotel Accommodations	1	2	3	4
Helpfulness of Meeting Staff	1	2	3	4
Meeting Room (sound, space, lighting)	1	2	3	4

Thank you for completing this evaluation.

Please put this form in the Evaluation Box at the Registration area at the conclusion of the meeting.