Formaldehyde / Vinyl Acetate / Acetaldehyde: Toxicological Review and Risk Characterization Based on Mode of Action

Overview

Introduction

Formaldehyde, vinyl acetate, and acetaldehyde are all listed as hazardous air pollutants (HAPs) in the Clean Air Act Amendments of 1990, and each is associated with significant ambient exposures. Risk assessments are required for each chemical to support major regulatory activities of EPA program offices. All three chemicals have been listed for development of toxicological reviews to be included in the Integrated Risk Information System (IRIS), a U.S. Environmental Protection Agency (EPA or the Agency) database of human health effects that may result from exposure to various substances found in the environment. EPA's Office of Research and Development is preparing the toxicological reviews and will submit them to the EPA Science Advisory Board (SAB) for external peer review.

The purpose of this overview is to describe the scope of the required evaluation that a participant can expect to provide as an ad hoc member of the SAB. The nature of the quantitative analyses, conceptual approaches, and scientific issues involved in the three proposed risk assessments will be described so that individuals can evaluate their interest in participating in the scientific peer review and identify specific area(s) where their expertise might be best utilized.

Background

The Environmental Health Subcommittee of the SAB previously reviewed the Agency's risk assessment for formaldehyde in 1991. The 2003 revision includes responses to recommendations made at that review as well as updates reflecting the current state of the science. The 2003 revision for vinyl acetate addresses recommendations made at the 1995 external peer review workshop on the inhalation assessment. The 2003 update for acetaldehyde completely revises the 1987 hazard assessment document.

These three chemicals are all related with respect to their physicochemistry and proposed mode of action. The assessment approaches applied to the three chemicals represent significant new methods for the use of mechanistic data at various levels of biological organization (population, organism, target tissue, and subcellular components) to integrate diverse data sets and to inform an understanding of the mode of action. These assessments apply new guidance in EPA's draft Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999) and address emerging issues in risk analyses.

All three chemicals cause portal-of-entry toxicity whether administered orally (gavage or drinking water) or by inhalation exposure. The three chemicals are closely related in that they share common factors that influence their pharmacokinetic and pharmacodynamic properties. For chemicals classified under the EPA scheme for inhalation dosimetry as reactive (Category 1) gases, airflow delivery and tissue extraction dictate target tissue dose (U.S. EPA, 1994). Pharmacodynamic properties are related to metabolism and toxicant-target cell interactions. Acetaldehyde is a metabolite of vinyl acetate and related to formaldehyde both in its physicochemical and toxicological properties.

A challenge central to each of the assessments is how best to perform a dose-response assessment of a chemical that has both inflammatory or cytotoxic and mutagenic or clastogenic properties. Traditional approaches to risk assessment separate these endpoints for noncancer versus cancer evaluation. Approaches to cancer have typically used a linear low-dose risk term. A new approach is proposed for these chemicals, based on systems biology, that describes and relies on a common mode of action (MOA) to integrate the various observed endpoints. In all three cases, the mode-of-action approach serves as a platform to harmonize approaches to noncancer and cancer toxicity in the portal-of-entry. The harmonized risk characterization is based on an evaluation of the exposure-dose-response continuum and consideration of whether the epithelial changes have prognostic value and can serve as precursor lesions that are sentinel for more overt toxicity, applicable to both cancer and non-cancer effects. A priority issue for the review will be whether or not such a non-linear dose-response procedure is adequately supported by the available data on these chemicals, or if the more traditional low dose linearity default assumption should be retained where there is residual concern for mutagenicity and clastogenicity. Related to this priority issue are considerations of the data requirements necessary to conclude that such a mode of action exists, noting the precedent setting nature of these assessments, and of the application of the draft Guidelines for Carcinogen Risk Assessment in interpreting these data.

Another challenge is how best to leverage mechanistic information across the three databases. While formaldehyde has the richest data set, both the vinyl acetate and acetaldehyde approaches take advantage of pharmacokinetic and pharmacodynamic relationships to share model structures and approaches to response analysis among the three. Thus, the set represents an excellent opportunity to evaluate the limitations and advantages of dosimetry and biologically-based model applications across a range of available data and among chemicals.

Toxicological Review Document — Size, Contents, and Topic Areas

This section provides an example table of contents and discusses the topic areas addressed in each chapter. Each document follows this general outline so that the chemical is denoted in the outline as “aldehyde/acetate”. The formaldehyde document is more extensive on certain topics, however, and specific differences with respect to it will be highlighted. The acetaldehyde and vinyl acetate documents are approximately 250 pages (1.5 line spacing) each, and the formaldehyde document is approximately

500 pages, table and figures inclusive.

Front Matter
Foreword
Authors, Contributors, and Reviewers
Acknowledgments
List of Abbreviations
Executive Summary

This chapter provides information on the authors and reviewers who have helped to produce the existing draft document. The executive summary provides the highlights from each of the chapters that follow.

- ***Introduction***
  Production uses and source of "aldehyde/acetate"
  Historical overview of health risk assessments for "aldehyde/acetate"
  Risk characterization and regulatory agenda
  Summary

The purpose of this chapter is to provide background information on ambient exposures and sources of the pollutant in the environment. Previous assessments performed by the Agency or other regulatory bodies are described. The basis of these assessments is outlined as a point of comparison for the new or revised assessment described in the document. The likely application of the proposed risk estimates in various regulatory actions or implementation activities is also discussed.

- ***Physicochemical characteristics***

This chapter describes physicochemical characteristics of the chemical that likely contribute to its disposition (absorption, distribution, metabolism, and elimination) and toxic properties.

- ***Hazard Characterization***
  Studies in Humans
    Inhalation exposure
    Oral exposure
  Laboratory animal studies
    Inhalation exposure
    Oral exposure

Genotoxicity
Cytogenetic effects
Mutagenic and related effects

The purpose of this chapter is to describe the available database of studies on observed health effects in both humans and laboratory animals for each exposure route. Because the objective is to derive a health risk estimate for lifetime exposures, available data on endpoints used to address various life stages are described, such as reproductive and developmental indices. Human data include ecological epidemiology and occupational and clinical evaluations. Laboratory animal studies include short-term and lifetime bioassays and some specific targeted studies such as sensory irritation and genotoxicity. General conclusions are drawn regarding the conditions of the exposure (e.g., route specific, concentration and or duration dependent) and the nature of the toxicity and its target tissue.

- ***Mode of action: Toxicokinetics, toxicodynamics and conceptual model***

Toxicokinetics and determinants of tissue dose
Respiratory tract
GI tract
Skin
Toxicant-target tissue interactions and response
Reactions with respiratory tract epithelia and cellular constituents
Reactions with GI tract epithelia and other tissues
Proposed mode of action and conceptual model
General considerations: Determinants of tissue dose and defining key events
Construction of a specific conceptual model for "aldehyde/acetate"
Additional considerations: Asthma and airway hyperreactivity
Summary: Weight-of-evidence evaluation

This chapter discusses mechanistic data on the factors governing internal tissue dose and toxicant-target tissue interactions and responses. Studies describing the uptake and metabolism of vapors in an in situ isolated upper respiratory tract (URT) or in an isolated oral cavity are described. Some in vitro studies of metabolism determinants are also included. In vivo and in vitro studies of the interaction of these chemicals or their metabolites and reaction products with cellular constituents such as proteins and DNA are also discussed.

The determinants of toxicokinetic and toxicodynamic properties of the chemical are then formalized into a conceptual model of the MOA that describes the exposure-dose-response continuum. This model starts with administered dose, determines internal dose moities associated with toxicity, and identifies critical components necessary to pathogenesis. Key events are chosen to serve as precursor lesions that are predictive of significant portal-of-entry toxicity, including tumors. A key event is defined as an empirically observable precursor that is a necessary element of the MOA or is a marker for such

an element. A weight-of-evidence evaluation concludes the chapter and summarizes considerations related to the identification of key events; the strength, consistency and specificity of the associations or linkages along the proposed MOA; evaluation of the dose-response and temporal relationships of the components or steps along the pathogenesis included in the MOA, including the role of cytotoxicity and mutagenesis; and a discussion of the overall biological plausibility and coherence of the proposed MOA; other potential MOA or an evaluation of the comprehensiveness with respect to all endpoints of the MOA; and a general conclusion with respect to the MOA model.

Because each of these chemicals is reactive in the respiratory tract to some degree, one specialty area discussed in this chapter is that of asthma and airway hyperreactivity. This section discusses the evidence for the role of chemical "aldehyde/acetate" in the development versus the aggravation of this disease. Consideration is given to how concerns for this endpoint might be best addressed at this time given the limitations of the database and of the current scientific understanding of the respiratory reactions and immunobiology necessary to characterize dose-response relationships for asthma.

- ***Development of dosimetry models to address mode of action***
  Upper respiratory tract and nasopharyngeal model
    Structure
    Parameterization
    Verification
    Internal dose metric predictions and human equivalent exposures
  Upper gastrointestinal tract model
    Structure
    Parameterization
    Verification
    Internal dose metric predictions and human equivalent exposures

This chapter presents the development of physiologically-based dosimetry models used to describe uptake and tissue dose for the chemical. These dosimetry models will be used to predict internal dose metrics with which to perform dose-response analysis and interspecies extrapolation.

In the case of formaldehyde, computational fluid dynamics (CFD) models of the airway geometry from casts of the F344 rat and human URT were used to describe airflow and flux to the airway tissue. A distributed parameter model of the lower respiratory tract was also included in the formaldehyde description. The vinyl acetate and acetaldehyde models are restricted to the URT and rely on mass transfer coefficients that derive from flux estimates provided by the CFD model developed for formaldehyde. The CFD model for formaldehyde predicts flux to the various types and numbers of cells lining the respiratory tract whereas the models for vinyl acetate and acetaldehyde rely on

compartmental analyses to arrive at an average tissue dose. Compartmental analyses were also used to describe uptake for the oral route of exposure. The compartments in the models correspond to different tissue types or anatomical entities dictated by where the toxicity of interest was observed (e.g., olfactory versus respiratory epithelium or oropharynx and forestomach).

The chapter reviews the rationale for the model structures, source of parameters in the structures, and verification exercises. Results of simulations to predict different internal dose metrics are also presented.

- ***Dose-response analyses for human health risk assessment***

  Inhalation assessment

  Key events and weight of evidence
  Dosimetric adjustment
  Point-of-departure analysis
  Application of uncertainty factors
  Operational derivation of the harmonized reference concentration
  Designation of confidence levels

  Oral assessment

  Key events and weight of evidence
  Dosimetric adjustment
  Point-of-departure analysis
  Application of uncertainty factors
  Operational derivation of the harmonized reference concentration
  Designation of confidence levels

  Summary

This chapter presents the synthesis and integration of the most relevant data discussed in the previous chapters to derive quantitative risk estimates of human health risk for inhalation and oral exposures. Based on the MOA formalized in previous chapters, an approach to dose-response analysis for each route is presented that combines non-neoplastic or pre-neoplastic endpoints with traditional measures such as tumors. Operational derivation includes identification of key events and determination of the point of departure for the procedure, choice of dose metrics associated with pathogenesis and extrapolation across species, and application of uncertainty factors to address uncertainty in model structures and their ability to capture potential variability in MOA between species and across life stages, including consideration of potential sensitive populations.

- ***Major risk characterization conclusions***

  Hazard potential
  Dose-response

Major uncertainties and research needs
Summary

This chapter draws together the major findings and conclusions from the preceding chapters to succinctly describe the hazard potential and dose-response assessment of potential health effects for both routes of each chemical. Major uncertainties and research needs are identified and their potential impact on future iterations of the risk assessment are described.

- **References**

This chapter is the bibliography of all materials cited in the document. One of the key questions to the reviewers is whether all relevant data are included.

U.S. EPA. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA/600/8-90/066F.

U.S. EPA. 1999. Draft Revised Guidelines for Carcinogen Risk Assessment. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. NCEA F-0644.