

EPA/600/R-99/081
September 1999

**SUMMARY OF THE U.S. EPA WORKSHOP
ON THE RELATIONSHIP BETWEEN
EXPOSURE DURATION AND TOXICITY**

Sheraton Crystal City
Arlington, Virginia
August 5-6, 1998

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

NOTICE

This document has been reviewed in accordance with U.S. Environmental Protection Agency (EPA) policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

This report was prepared by Eastern Research Group, Inc. (Contract No. 68-D5-0028) as a general report of discussions during the Workshop on Relationship Between Exposure Duration and Toxicity. As requested by EPA, this report captures the main points and highlights of discussions held during plenary sessions. The report is not a complete record of all details discussed nor does it embellish, interpret, or enlarge upon matter that were incomplete or unclear. Statements represent the individual views of each workshop participant; none of the statements represent analyses by or positions of the National Center for Environmental Assessment or the EPA.

CONTENTS

SECTION ONE: BACKGROUND	1-1
1.1 Background	1-1
1.2 The August 1998 Workshop	1-1
SECTION TWO: OPENING PLENARY SESSION	2-1
2.1 Introductory Presentations	2-1
2.2 C × T: Historical Perspectives, Current Issues, and Approaches	2-2
2.2.1 The Risk Assessment Context	2-2
2.2.2 Haber’s Law	2-3
2.2.3 Dose Metrics	2-7
2.2.4 Historical Perspective on Dose-Response Assessment	2-12
2.2.5 Harmonization of “Noncancer” versus “Cancer” Endpoints	2-13
2.2.6 Variability and Uncertainty	2-17
2.2.7 Discussion Questions	2-17
SECTION THREE: PLENARY PRESENTATIONS—ENDPOINTS OF TOXICITY	3-1
3.1 Developmental Toxicity: The Effects of Temperature and Exposure on In Vitro Development and Response-Surface Modeling of Their Interaction	3-1
3.2 C × T and Dermal Toxicity	3-7
3.3 Neurotoxic Effects of Trichloroethylene Inhalation as a Function of Exposure Concentration, Duration, and Target Tissue Dose	3-10
3.4 Respiratory Toxicity: Coherent Response Models of Ozone Injury in Humans and Animals .	3-15
3.5 Observer Comments	3-26

SECTION FOUR: PLENARY PRESENTATIONS—STATISTICAL APPROACHES	4-1
4.1 What Can Mechanisms Tell Us About Modeling Dose-Time Relationships?	4-1
4.2 C × T Issues Related to National Ambient Air Quality Standards (Eco Effects)	4-6
4.3 Statistical Models for Assessing Dose-Rate Effects	4-9
4.3.1 Background	4-9
4.3.2 Ethylene Oxide Study	4-12
 SECTION FIVE: PLENARY PRESENTATIONS—DOSIMETRY AND MECHANISTIC MODELING	 5-1
5.1 Dosimetry: Mechanistic Determinants of Exposure-Dose-Response	5-1
5.2 Dosimetry and Mechanistic Modeling	5-11
 SECTION SIX: PLENARY PRESENTATIONS: IMPLICATIONS FOR RISK ASSESSMENT	 6-1
6.1 Implications for Risk Assessment	6-1
6.2 Integration of Approaches	6-9
 SECTION SEVEN: FUTURE DIRECTIONS—WHAT SHOULD BE ACCOMPLISHED IN THE NEXT 5 YEARS?	 7-1
 SECTION EIGHT: SUMMARIES OF BREAKOUT GROUP DISCUSSIONS	 8-1
8.1 Summary of Breakout Group One Discussions	8-1
8.1.1 Relationship Between Concentration and Exposure Duration (C × T) and Toxic Endpoint	8-1
8.1.2 Mechanistic Modeling	8-3
8.1.3 Statistical Modeling	8-5
8.1.4 Dose Metric	8-5

8.1.5	Risk Assessment	8-6
8.2	Summary of Breakout Group Two Discussions	8-7
8.2.1	Endpoints of Toxicity	8-7
8.2.2	Statistical Approaches	8-9
8.2.3	Dosimetry and Mechanistic Modeling	8-10
8.2.4	Implications for Risk Assessment	8-10
8.3	Summary of Breakout Group Three Discussions	8-11
8.3.1	Dosimetry and Mechanistic Modeling	8-11
8.3.2	Risk Assessment	8-12

APPENDIX A: WORKSHOP AGENDA

APPENDIX B: CHARGE TO PARTICIPANTS

APPENDIX C: LIST OF INVITED PARTICIPANTS AND BIOGRAPHIES, LIST OF EPA PARTICIPANTS, AND LIST OF OBSERVERS

APPENDIX D: ISSUES PAPER