

# **TOXICOLOGY of HALOGENATED HYDROCARBONS**

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*Health and Ecological Effects*

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Edited by  
**M.A.Q. Khan**  
**R.H. Stanton**

**PERGAMON PRESS**

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Drs. Robert L. Metcalf and David P. Rall

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## PREFACE

Halogenated organic chemicals have added much to our modern living and have become an important part of every day life. Because of their production on a massive scale, and widespread usage for the last thirty years or more, many of these persistent chemicals such as DDT, cyclodienes, PCBs, etc., are commonly present in the environment and its biota, including humans.

The concern about the health and ecological effects of these persistent lipophilic chemicals is due to their high toxicity e.g. 2,3,7,8-TCDD, cyclodienes, and carbon tetrachloride, or low toxicity which results in high body burdens e.g. PCBs, chlorinated benzenes, and halogenated alkyls. Some of these chemicals have caused severe local problems such as PBBs in Michigan, Kepone in James River, chlorinated phenols and hexachlorocyclopentadiene in Love Canal, and PCBs in the Hudson River and in Lake Michigan.

The toxicological and ecological effects of these chemicals have been studied extensively in many laboratories. In humans, these chemicals can cause nonspecific effects such as chloracne, porphyria, and liver enlargement which makes the diagnosis of the disease difficult. Since the contamination with these chemicals is very extensive and our resources are very limited, the toxicology of these substances is still only poorly understood. However, knowledge about their effects on laboratory mammals and other animals is advancing rapidly. More is known now about the biochemical and cytological basis of the toxicity, carcinogenicity, teratogenicity, neurotoxicity, and mutagenicity of these toxicants than ever before. This is contributing to the understanding of the interactions between organisms (metabolism, storage, excretion of chemicals, etc.) and these toxicants (toxicity, chemical structure, etc.).

This symposium at the Second Chemical Congress of the North American Continent was organized with the intention of updating and adding to fine publications, which have preceeded this volume in the rapidly advancing area of the toxicology of environmental chemicals. This book is centered around human health and most of the information deals with human (epidemiology), laboratory mammals or their systems, cell lines or enzymes. This presents the growth of knowledge on various aspects of the toxicology of halogenated hydrocarbons, including dynamics (toxicokinetics biotransformations) and effects (both short- and long-term) with emphasis on mechanisms.

The book is divided arbitrarily into five sections. There is some overlap between sections and some of the chapters could be included in more than one section. The organization should give a coherent view and review of the toxicology of halogenated hydrocarbons. Only a small amount of material on environmental aspects is included; inclusion of more such material would have changed the theme of the book.

Section I includes some natural sources of halogenated hydrocarbons, epidemiological studies of residents and occupationally exposed human populations, with regards to general and specific health and residue burdens of these toxicants. Human studies are the ultimate in the interpretation of laboratory findings of health effects and serve as valuable source of information for human society.

Section II includes chapters on effects of these chemicals on the liver. Most of these chemicals cause ultrastructural and biochemical changes in liver. These changes, especially the induction of hepatic drug metabolizing enzymes and other detoxication systems, have been studied more thoroughly than any other effects. Their toxicological interpretation is one of the most fascinating areas of toxicology! The recognition of the relationship between chemical's structure and

induction of specific forms of cytochrome P-450 and their catalyzed reactions, their binding to the cytosolic receptors transferring them to the genetic mechanisms, and the genetics of these interactions are very proud presentations of this book. The chapter on the toxicology of polyhalogenated biphenyls is an excellent model to show that toxicity can affect more than one organs/systems. The relationship of epigenetic and genotoxic effects with liver carcinogenicity of chlorinated hydrocarbons is explained very clearly.

There is a continuation of this material in section III. The identification of the cytosolic receptor for 2,3,7,8-TCDD to initiate induction and other effects in liver is an outstanding contribution. This section (III) has excellent papers on cytotoxicity, teratogenesis, mutagenicity, neurotoxicity, and effects on immune system(s) of halogenated hydrocarbons and haloalkanes. Both these sections (II and III) have focused on the mechanisms of actions of these toxicants at cellular and biochemical levels. Some of these areas are rather new, challenging, and controversial. These and similar continued efforts will bring us closer to the understanding of the basis of such toxic manifestations.

The systemic effects of halogenated hydrocarbons are related with their dynamic behavior in the body. This section (IV) shows how these chemicals are stored (where and for how long), biotransformed, and disposed of, whether the biotransformations produce more toxic and reactive or less active products. This section provides information on the behavior in the body, of extremely toxic 2,3,7,8-TCDD and cyclodienes including kepone, and some less toxic compounds such as PCBs, hexachlorobenzene, chlorinated benzenes, and hexachlorocyclopentadiene. The factors that affect these dynamics are discussed in a lucid manner and attempts have been made to use chemical structures and organ/system models to understand metabolism, storage, and excretion of these chemicals. The metabolism of the most toxic of these chemicals, 2,3,7,8-TCDD, a very difficult task to be done, has been studied both in vivo and in vitro. Significance of the fate of the environmentally transformed cyclodienes has been discussed in mammals and fish.

The last, but not the least, of these section (V) is environmentally oriented. It deals with the toxicity of PCBs, PBBs, hexachlorocyclopentadiene, and cyclodienes to sensitive animals as well as with the fetotoxic effects of the halogenated biphenyls on ferrets and minks. The last chapter shows how activated carbon, which is now commonly used as a decontaminating adsorbent, has been and can be successfully used in reducing the hazards of persistent halogenated hydrocarbons.

While this publication brings the reader uptodate on various complex aspects of the toxicology of halogenated hydrocarbons -- it also is a way of expressing our admiration of the dedicated efforts of contributing scientists and their associates to bring us closer to the insight of what and how these chemicals cause or can cause damage to our life, biota, and environment.

We are grateful to Drs. R.A. Neal, H.B. Matthews, R. Haque, F. Matsumura, S. Aust, R.K. Ringer, L.G. Hansen, J.J. Lech, L. Keith, and H. Allen for their advice and guidance regarding the program of the symposium. Dr. L. Keith's help in organizing the symposium is very much appreciated. Most of all we, and the readers who will benefit from this book, are deeply grateful to all the scientists whose excellent contribution has made this publication such a success.

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