Dioxin Toxicity: Advances Over the Past 25 Years

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Introduction

The first meeting on "Chlorinated Dioxins and Related Compounds" was part of a workshop held at the Instituto Superiore di Sanita in Rome, Italy, between October 22-24, 1980. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) had been a major public health focus in several countries due to numerous industrial accidents, concerns regarding birth defects and other adverse health effects associated with herbicide spraying in agricultural areas, and the use of Agent Orange in Vietnam. In Italy, the explosion in the ICMESA plant resulted in the atmospheric release of TCDD, and the subsequent contamination of Seveso. The environmental and human impacts of this industrial accident were considerable, and this was a major factor in holding the first Dioxin Conference/Symposium in Italy.

The presentations at this meeting reflected the multidisciplinary approach required for addressing the problems associated with TCDD and related halogenated aromatics (HAs). THe meeting was divided into six sections which included: (i) Analytical Methodology, (ii) Environmental Fate and Levels, (iii) Incineration Story, (iv) Biochemical Toxicology and Metabolism, (v) Animal Toxicology, and (vi) Observations in Man. Attendance at the meeting was less than 150, and this represents a major difference with recent Dioxin Conferences in which there may be 800 to 1000 attendees and several parallel sessions. In contrast, at Dioxin 80, it was reported that "Despite the very intense program (52 papers in three days), all lectures were attended by most participants which means that chemists must have listened to toxicologist and vice-versa" .[1]

Toxicology of TCDD and Related Compounds: Advances from 1980 - Present

Current research on TCDD and related compounds relies on the explosion of new techniques and concepts in molecular biology, and this has greatly expanded the knowledge base for these compounds. However, even in 1980, several critical elements of the dioxin story were already known. Poland and coworkers had described the isolation of the aryl hydrocarbon receptor (AhR) from mouse hepatic cytosol.[2] Structure-binding and structure-activity relationships among the polychlorinated dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), biphenyls (PCBs), and other HAs had been determined.[3] Moreover, studies in genetically inbred strains of mice and in other species had clearly defined differences in Ah-responsiveness between species that may be related, in part, to differences in the AhR.

However, since 1980, thousands of papers on the toxicology/molecular biology/mechanism of action of TCDD, and related compounds have been published and selection of the important advances would vary with each individual scientist. In my opinion, the key mechanistic/molecular biology discoveries include: (i) cloning of the AhR gene[4,5], (ii) cloning of the AhR nuclear translocator (Arnt) gene[6], (iii) generation of the AhR knockout mouse[7], and (iv) development of the molecular mechanisms of action of the nuclear AhR complex using the CYP1A1 gene as a model.[8] One of the important toxicological studies was the report that in utero exposure of pregnant female rats to exceedingly low doses of TCDD resulted in gene reprogramming which affected physiological function in the offspring.[9] This study by Peterson and coworkers also formed an underpinning for the endocrine disruptor hypothesis which has subsequently generated significant scientific, regulatory and public attention. Mechanism-based risk assessment and development of toxic equivalency factors (TEFs) and toxic equivalents (TEQs) was derived from early and later structure-activity studies of PCDDs and PCDFs. Research in my laboratory contributed to this concept and this included identification of mono- and diortho-substituted PCBs as AhR agonists[10] and subsequently as antagonists. These are only some of the advances in this field, and it is clear that these Dioxin Symposia coupled with ongoing research in this field has resulted in decreased emissions/environmental levels of these compounds and increased surveillance for new HA contaminants. (Supported by NIEHS ES09106 and ES04917)

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