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Perspectives on Polyhalogenated Aromatic Compounds

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This meeting has arrived at many conclusions, often interim and perhaps to be changed as knowledge increases, and almost numberless direct or implied suggestions for more research to clarify this very complex field. It is not possible, in a brief summation, to deal adequately with all of these issues. I would prefer, therefore, to establish some perspectives as to where we are and what we need to know additionally.

A concern that started rather obscurely has now attracted the attention of scientists and public health officials around the world, not only because of real or presumed danger, but also because of the extremely challenging scientific issues it presents. In 1968 the identification, largely as a result of the efforts of our Japanese host, Dr. Kuratsune, of the special characteristics of Yusho disease was one of the signals leading to present concern. Another even more obscure one was the identification in 1966 by Swedish scientists of some unexpected gas chromatograph peaks in tissue from fish and deep-sea mammals which could not be attributed to the pesticides that were being looked for. There had also been difficulties at that time in industry which were neither widely known or understood. These small beginnings led to widespread concern and scientific interest.

I would like to comment briefly on where we are under six headings: (1) epidemiological and clinical aspects, (2) species differences and acceptable exposure, (3) biochemistry and mode of action, (4) analysis, (5) occurrence and reduction of future accumulations and (6) safe disposal. Each of these topics has had some comments here. My discussion, in many instances will assume similarity in the qualitative nature of the biological action of many of these compounds. However, this is based on a hypothesis which I recommend be tested.

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Epidemiological and Clinical Aspects

One of the interesting features of this group of compounds is the manifold effects they produce: effects on skin, respiratory system, liver, the immune system, malignant disease, reproductive organs, eye and others.

There are differences, of course, depending on the specific compounds, the nature of the exposure and its intensity. The skin effects are almost universally present; hepatic injury is a common early feature with intense exposure. Detailed clinical observations on both the Yusho and Taiwan victims are remarkably complete and appear to be in good general agreement (except perhaps porphyria). Dose-response relationships have been well demonstrated. What is still very uncertain are the late effects. It is clear that with polychlorinated biphenyl (PCB) and TCDD there is decisive recovery, especially of the dermal effects, also probably liver, eye, immune system, neurological and transplacental effects. The time scale can be long, improvement still occurring in the second 5 years after exposure to the PCBs. This improvement occurs while there is still a significant body burden. The decay of that body burden needs continuing follow-up quantitatively. What are the residual effects of this continuing remaining body burden? To what extent is malignancy a likely outcome in humans? Animal studies tell us that we should be concerned; human data so far are obscure on this issue. On the other hand, follow-up studies have involved either too short a time, too small a group, or both, to answer conclusively the issue for humans. Considering the positive findings in animal studies, it would be surprising if malignancy were not at least an occasional outcome of human exposure to these compounds. Thus it is that follow-up of exposed populations is of the utmost importance in order to resolve the question of cancer in exposed human populations.

Treatment of overt poisoning has been largely symptomatic; the fasting procedures described here are one of the possible approaches. One should add that hopefully

future acute episodes of poisoning will be very rare so that interest in treatment, although important, may dwindle with time. Search for safe and effective therapy should continue.

Species Differences and Acceptable Exposure

One of the challenges of the studies in this area is the enormous range of qualitative and quantitative differences in the effects of these compounds in different species and, indeed, in different strains of animals. To generalize here would be a mistake, since particular compounds differ in the range of species differences in sensitivity. However, for dioxin, as an example, the range of susceptibility covers several orders of magnitude insofar as lethality is concerned. There is also a wide range in the occurrence of nonlethal effects with dosage. A fuller understanding of the biological bases for these species differences can be extremely instructive for an understanding of the mode of action of these compounds and is an issue that fully merits continued study.

A very practical problem in this area which relates to the first topic, i.e., human effects, has to do with the question of acceptable limits of exposure. In respect to dioxin, it seems certain that human sensitivity and reliable estimates of acceptable limits for low level human exposure are not likely to emerge from human studies alone, considering the relatively scant human material available for study. Thus, it is that we must depend to a considerable extent on animal studies (with a full awareness of the wide range of species differences) in defining acceptable limits of exposure for humans. The establishment of acceptable levels of human exposure is of extremely vital moment, both to insure that people are not exposed to dangerous levels, but equally to avoid needless expense, worry and anxiety from concern over negligible exposures. This is an issue that faces not only the regulatory officials, but the persons who are in areas where these virtually ubiquitous compounds have been found; since the sensitivity of detection is very high, dioxins can be detected almost everywhere. Accordingly a concerted and continuing effort to define acceptable levels of exposure quantitatively is extremely urgent.

Biochemistry and Mode of Action

The mode of action of these compounds cannot be properly dealt with in general terms, although space permits only such an approach here. It is clear that these compounds, especially the dioxins and dibenzofurans, must involve some of the most vital biological processes in the body, leading as they do to widespread disturbances in the function of a series of systems throughout the organism.

One of the leading concepts at the present time suggests that there are receptors in the cell wall performing a series of vital functions which when occupied by one of these compounds are unable to perform these vital functions. It appears that the structural similarities of certain members of this group of compounds determine the effectiveness with which they occupy and prevent the normal function of the receptor.

Whether these receptors in turn control and modulate gene expression is uncertain and merits intense study.

Many studies are now being conducted on the induction of cancer in experimental animals with dioxin and related compounds. It appears probable that the effect is primarily one of promotion rather than initiation, although at this time the possibility of initiation cannot be excluded. The extreme sensitivity of the promoting action in experimental animals necessarily brings concern about low level exposure of humans, especially since opportunities for spontaneous initiation, i.e., mutation, or initiation from a host of environmental agents cannot be excluded. The mode of action of these compounds in the carcinogenic process clearly deserves urgent study, including additional whole-animal studies on initiation and promotion.

Among other characteristics, these compounds frequently have the property of being extremely potent enzyme inducers which is certainly related to some of the very diverse biological changes that occur throughout the body. The combination of these profound biological effects with the very long persistence in the body, i.e., the low rate of excretion and metabolism, provides the basis for continuing biological action over very long time spans. There are many gaps which need filling in our understanding of species differences in such issues as enzyme induction and the pharmacokinetics of persistence and movement within the organism.

Growing understanding of different presences of congeners and their development with usage has substantially aided in distinguishing one pattern of exposure from another and the relation of structure to biological effect.

This group of compounds, the PCBs, the PBBs, the quaterphenyls, dioxins and dibenzofurans appear to have certain common features in their biological effects. They also have some commonality of structure. The extent to which this commonality of structure provides a basis for generalization within this group of compounds and extention to other related compounds is at this time uncertain but serves to clearly define an area of ignorance which will require full examination.

These very fascinating hypotheses are attracting some of the best talent in biochemistry and cell biology throughout the world. It is thus that a study of these compounds is not only of very practical importance for the issue of poisoning *per se*, but may be of deep basic consequence in our understanding of the biology of the cell. The study of the mode of action of these compounds can have benefits going far beyond the issue of their toxicity.

Analysis

There has been a most remarkable improvement in the sensitivity and specificity of the analytical methods for these compounds over the last 20 years. It is unfortunate that some of these techniques were not available earlier for more refined analysis of the human exposures (especially to the dioxins); this could have made studies of those exposures more rewarding. Of all aspects in this difficult field, it is perhaps in the field of analytical techniques that the most progress has been made. There is, nevertheless, room for improvement by refinement, simplification and cost reduction of analytical procedures. Only a limited number of laboratories can now undertake these highly specialized analytical techniques. Wider availability of refined and simplified techniques would be a decided advantage.

Environmental Occurrence and Reduction of Future Accumulations

These analytical techniques have been of great utility in identifying the widespread occurrence of these chemicals. Although these are largely residues of the past, they will be with us for many years; others will continue to face us in the future as accidents occur with existing equipment using these compounds in transformers, heat exchangers, and so forth. The inventory of environmental occurrence of these compounds should continue.

Continuing challenges will be the replacement of PCBs with safe substitutes and the refinement of manufacturing processes of which the dioxins are by-products in order to insure minimum amounts of toxic contamination.

Disposal

Safe disposal of these dangerous and persistent compounds is still elusive and inadequately available in the face of a very widespread need. Disposal can take the form of using nature for photodisintegration, incineration (a very demanding process which can, if improperly conducted, increase the problem rather than lessening it) or chemical conversion to innocuous products. The technology for optimizing these varying approaches, each of which has certain appropriate realms of usage, is not yet here. Clearly, safe disposal merits intensive study and development.

This brief and necessarily superficial survey has attempted to identify some practical problems and also to point toward the challenging scientific by-products of broad applicability that may come from research on these compounds. It seems very clear that we will continue to have problems that will claim our attention for some years to come. Accordingly, it is not possible at this time to measure and identify the true "perspectives and dimensions" of this problem.