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Toxicological hazards

'Toxicological hazards', this is the title of a symposium held at the 14th annual meeting of the Union of the Swiss Societies for Experimental Biology (Interlaken, April 1–2, 1982). The topic was chosen in order to answer questions that are often asked today, since they are everybody's concern. What are the consequences of the steady increase of environmental pollution in the long run? To what extent does the air we breathe, the water we drink and the food we eat affect our health? Whatever the answer may be, finding it is hampered by the complexity of the problems involved. The responsible scientist can contribute to overcoming them by investigating, evaluating and commenting on toxicological hazards. In this sense the four papers presented in this symposium permit us to draw conclusions about the present situation by making the following statements:

1. More and more toxicological hazards threaten our environment; sooner or later some of them can contribute to food contamination and may finally affect human health. Consequently, the release of potentially dangerous substances into the environment and their moving along the food chain must not be regarded as isolated, nasty events; the global situation should be analyzed minutely and judged carefully.

2. It is the inevitable fate of a modern society – at least in highly industrialized countries – to live with an ever increasing load of toxic substances; many are used to achieve better efficiency in agricultural and technical production as well as for making our lives more comfortable. Therefore, a minimum knowledge of the phenomenon of toxic action and its consequences is mandatory. It is the common task of scientists and media to inform and – whenever necessary – to warn rather than frighten the public.

3. There is no general remedy against environmental pollution. However, despite an ever-increasing population density and industrial productivity, an acceptable compromise must be found. Enforcing appropriate regulations based on the far-sighted setting of priorities should be the main element in a coherent system of political decisions. For the benefit (and welfare) of present and future generations such a policy requires concessions on either side, i.e., a balance between the divergent opinions of producers and consumers. H. Aebi

Polychlorinated persistent compounds

by M. H. Bickel

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A persistent compound is defined as one having a very slow rate of metabolism or of degradation in the environment. Certain heavy metals have long been known to be persistent, and so is methyl mercury. Among organic compounds, polychlorinated hydrocarbons are the most important examples of persistent compounds. Important questions to be dealt with are:

- Why are persistent compounds persistent?
- What do we mean by saying a compound is persistent?

Major problems have been created by the large-scale use of polychlorinated compounds in the past decades. The experience gathered will be briefly summarized, and may serve as a starting point for a number of conclusions and comments according to the current state of knowledge.

DDT

The novel pesticide, DDT (fig. 1), which was discovered in 1939, had a tremendous success both in

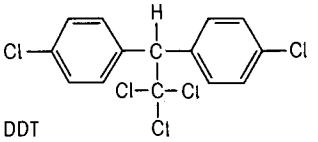


Figure 1 DDT

agriculture and in preventive medicine. However, a painful surprise followed in the 1950s when it became clear that DDT and similar organochlorine pesticides could be found in areas far remote from the places of use. Indeed, this was the first example of initially local contaminations spreading out to become a truly global contamination. In contrast to the familiar gradual dilution of wastes, what happened with DDT was a concentration in the biosphere.

This first surprise could be scientifically explained once more was known about this novel class of compounds. The high lipophilicity of DDT allows it to enter organisms and to be transferrred easily across permeation barriers like membranes. However, lipophilicity also precludes urinary excretion. In the steady state the distribution of DDT in a higher organism shows the following relative concentrations: blood/nervous tissue/adipose tissue 1/3/300, respectively.

Another important prerequisite of bioconcentration is persistence. Lipophilic xenobiotics, like drugs, for example, are metabolized by the cytochrome P-450 system in the liver. It attacks individual atom groups on the molecule which thereby becomes polar and excretable. If the metabolically vulnerable groups of the molecule are substituted with chlorine, the regular pathways of metabolism are no longer operative. Metabolism then relies on minor pathways with slow rates, and the compounds thus become persistent (fig. 1). These pharmacokinetic properties (lipophilicity, lipid accumulation, persistence) thus lead to the bioconcentration which in turn determines the ecodisposition of DDT. As a consequence, the adipose tissues of virtually all organisms contain residues of this and similar insecticides. However, since the input of DDT into the environment has been drastically restricted since the 1960s these residues are on the decrease.

PCB

Mixtures of polychlorinated biphenyls (PCB) have been industrially produced since 1929. Due to the extreme stability and other favorable properties of these compounds they were used for a wide array of technical applications, for instance as fluids for electrical and hydraulic devices, and as additives to plastic materials, paper, paints etc. The detection of PCB residues in wildlife and in the general population in 1966 came as a shock. In contrast to DDT or other pesticides, PCBs had never been introduced into the environment on purpose, and therefore must have entered it along pathways that were not yet known. In the following years it became clear that PCBs found their way into the environment by leakage, incineration, and dumping of wastes, and that any persistent compound will eventually wind up in the environment. Large amounts of PCBs in landfills and on the bottom of the sea form a pool for release for a long time to come.

The basic physicochemical properties of PCBs are similar to those of DDT. There are, however, certain important differences. PCB is not a single compound, but rather a mixture of about a hundred isomers. Both the degree of chlorination and the position of the chlorine atoms decisively influence their metabolic fate. Whereas the low-chlorinated isomers are relatively rapidly metabolized and excreted, the higher-chlorinated members are persistent. From the hexachlorobiphenyls on there are virtually unmetabolizable isomers. One important example is 2,4,5,2′,4′,5′-hexachlorobiphenyl (6-CB), which is the single most abundant isomer within PCB residues (fig. 2). In fact, these were the first lipophilic unmetabolizable compounds known. Theoretically, such compounds would not be able to leave the organism, and every dose taken up by exposure would simply accumulate (table 1). Studies on the long-term pharmacokinetics of 6-CB in the rat have shown that urinary excretion is negligible and that fecal excretion extrapolated to infinite time is limited to less than 20% of a dose. The remaining 70–80% of a dose are redistributed into the adipose tissues where the compound is stored for an apparently indefinite time. The consequences of such pharmacokinetic behavior are obvious, because unmetabolizable lipophilic compounds are super-persistent and their residues in the biosphere are likely not to disappear for decades or even generations.

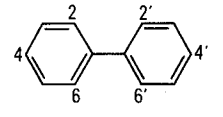
TCDD

There can be no doubt that DDT and PCBs are toxicological hazards. On the other hand, it is obvious

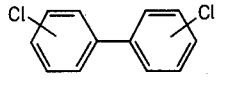
Table 1. Types of elimination of xenobiotics

Xenobiotic compounds	Elimination	
	Excretion	Metabolism
Hydrophilic	+	–
Lipophilic*	–	+
Unmetabolizable lipophilic	–	–

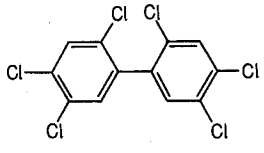
*Including persistent compounds.



Biphenyl



1 to 10 Cl,
circa 200 PCB isomers



2,4,5,2′,4′,5′-hexachlorobiphenyl

Figure 2. Polychlorinated biphenyls (PCB).

that these compounds are not potent poisons, certainly not in terms of acute toxicity. In the 1970s the discovery that extremely toxic members of the class of polychlorinated compounds do exist came as yet another surprise. The classical example of such compounds is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). This compound is not only lipophilic and persistent, and has therefore the potential for biaccumulation and global ecodisposition, but it combines these properties with excessive toxicity. In contrast to DDT and PCBs, TCDD is not a chemical purposely synthesized, but rather a trace contaminant of other polychlorinated products. It is formed in trace amounts during an industrial synthesis leading to products like the herbicide, 2,4,5-T, or the fungicide, pentachlorophenol, which are therefore contaminated with TCDD (fig. 3). Whereas these products are relatively rapidly metabolized, the persistent contaminant may accumulate in the biosphere. Being a contaminant, the compound went undetected for decades during which it had ample opportunity to enter the environment where in recent years it has occasionally been detected in trace concentrations. According to recent findings, TCDD and related compounds are also formed by incineration of municipal wastes containing chlorinated materials other than TCDD, and it may even be formed as a pyrolytic trace product in the combustion of natural products. Similar to PCBs there is a large family of polychlorinated dibenzodioxines (PCDDs) and of the corresponding dibenzofuranes (PCDFs). The acute toxicity of TCDD is such that it must be considered the most toxic synthetic compound known. Its toxicity in the guinea-pig surpasses that of nerve gases by at least an order of magnitude. As is shown in table 2 there are enormous species differences as well as differences produced by minor chemical alterations with respect of the toxicity of PCDDs. This situation creates a considerable potential for future surprises. TCDD has become a most intriguing substance with a number of outstanding biological properties. In terms of its toxicological hazards many questions remain painfully unsolved:

- waht is the cause of its toxicity and lethal action?
- what is the toxicity in humans?
- what are its long-term effects?
- is there a no-effect level?
- has it entered the ecosystem on a wide scale?

Table 2. Oral LD_{50} of polychlorinated dibenzodioxins (μg/kg)

Chlorination	Guinea-pig	Rat	Dog	Monkey
2,3,7,8(TCDD)	1	20	1000	2
1,2,3,4		800		
2,4,8		5000		
2,3,7	29400			
2,8	300000			
1,2,4,7,8	1125			
1,2,3,4,6,7,8,9		1000		

Conclusions

The experiences with polychlorinated persistent compounds have demonstrated that it does not suffice to ask how toxic a substance is, but that this must be supplemented by the additional questions of how long-lived and how wide-spread the substance is. The ecotoxicological situation is closely related to the ecodisposition which in turn is directly related to the pharmacokinetics of the substance, i.e., its fate in organisms.

The polyhalogenated hydrocarbons manufactured since the end of the last century are in fact a novel type of organic compound which does not occur in nature. They are exceptional in that they are lipophilic and yet cannot be normally metabolized by the classical drug metabolizing enzyme systems. In a wider context, we must acknowledge that by liberating molecular chlorine from the naturally occurring inorganic chlorides many problems have been creat-

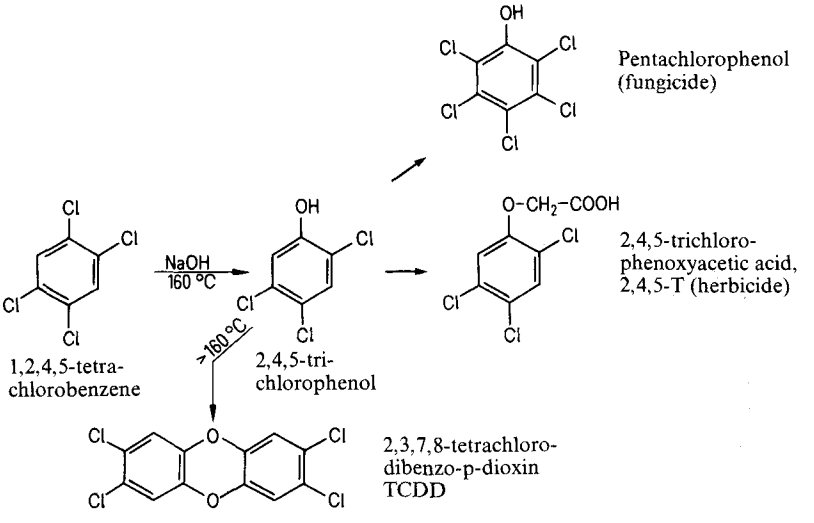


Figure 3

ed. In addition to all the ecological problems with polychlorinated organic compounds one should not forget the use of chlorine as a chemical weapon in early 20th century wars, and even chlorination of municipal water, important as it is in terms of public health, is creating problems according to recent reports. Concerning the situation with polychlorinated compounds, TCDD will not necessarily have been the last surprise. The past surprises have been caused by lack of knowledge. In order to avoid them in the future, information is urgently needed with respect of aspects such as the toxicity of individual compounds, extrapolation of toxicological data to men, long-term effects, risk assessment, and interactions with biological systems. However, to sit and wait for more information is not enough. Action must be taken, and this must be done on an international scale since contamination does not respect national boundaries. A concrete, if radical proposal would be to stop production of polychlorinated compounds altogether. This may not be unrealistic in light of the successful restriction in the use and production of DDT in the 1960s and PCBs in the 1970s and their substitution by second-generation products.

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Genetic hazards

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Among toxic effects on humans the non-reversible ones are of particularly great concern. Important effects of this kind are damage to the eye lens and to the nervous system, and the teratogenic, carcinogenic and mutagenic effects. The last group is characterized by a long latency period between initiation of the damage and the phenotypic manifestation of the induced change. In particular, genetic damage, when present in cells of the germ line (mitotically dividing pre-meiotic cells and germ cells), may be expressed many generations after the primary induction of the genetic change, the mutation. Genetic injuries to somatic cells, even though they may exhibit very strong effects, e.g. play a so far not yet well understood role in the initiation of malignant transformation and tumor formation, will not add to the genetic load of future generations. They disppear from the population with the death of the carrier.

Has the chemical induction of mutations been proved for human cells? Are chemical mutagens known which can alter the human genetic material? For somatic cells this is proved daily by the therapeutic effects of genotoxic carcinostatic drugs. In this case human cancer cells are killed as a result of the chromosomal damage induced by the drugs. Mutagenic effects from a number of causes are also known for other human cells, e.g. peripheral lymphocytes (Natarajan and Obe, 1980). In contrast to this, chemically induced mutations in germ cells have not yet been proved. This lack of scientific proof of induced human germ line mutations results primarily from the tremendous technical difficulties which, at the present time, do not allow one to distinguish between rare spontaneous and rare induced mutations. On the other hand, even if direct proof is lacking, there is no scientific basis for rejecting the